Appendix A: Background Information for 1,1,1-Trichloroethane

A.1 Toxicokinetics

As reviewed by ATSDR (1995), results from human and animal studies indicate that 1,1,1-trichloroethane is rapidly and efficiently absorbed by the respiratory tract, the gastrointestinal tract, and skin. For example, when human subjects held single breaths of air containing radiolabeled 1,1,1-trichloroethane for 15–40 seconds, alveolar concentrations decreased to between 10 and 20% of initial concentrations (Morgan et al. 1972a, 1972b), and 1,1,1-trichloroethane was detected in arterial blood of men within about 10 seconds after exposure to 240 or 350 ppm (Astrand et al. 1973). Several experiments with rats or mice administered oral doses of radiolabeled 1,1,1-trichloroethane found that recovered radioactivity in urine, expired air, and selected tissues accounted for between 88 and 99% of administered doses, indicating nearly complete absorption by the gastrointestinal tract (Mitoma et al. 1985; Reitz et al. 1988). In human subjects exposed to undiluted 1,1,1-trichloroethane by thumb or hand immersion or by topical application to the hand or forearm, 1,1,1-trichloroethane was quickly detected in alveolar air and/or in blood, indicating rapid absorption from the skin (ATSDR 1995). In rats, approximately 30% of undiluted 1,1,1-trichloroethane was absorbed within 24 hours of application to the skin under occluded conditions, whereas 12, 13, and 10% of saturated, two-thirds saturated, and one-third saturated aqueous solutions were absorbed under the same conditions (Morgan et al. 1991). Once absorbed, 1,1,1-trichloroethane is widely distributed throughout the body with preferential distribution to fatty tissue (ATSDR 1995). Regardless of route of exposure, 1,1,1-trichloroethane is predominately eliminated from the body via exhalation of the unchanged chemical (ATSDR 1995). It is rapidly cleared from the body; only trace amounts remain in tissues within days of termination of exposure of humans (Nolan et at. 1984) and animals (Mitoma et at. 1985).

1,1,1-Trichloroethane is metabolized at low rates via initial oxidative catalysis by CYP oxygenases to the predominant metabolites, trichloroethanol and trichloroacetic acid (ATSDR 1995). Phenobarbital-inducible CYP isozymes (CYP2B1/2) and ethanol-inducible isozymes (CYP2E1) are involved in the initial steps. Ethanol pretreatment of rats caused increased levels of hepatic CYP, increased rates of 1,1,1-trichloroethane metabolism (substrate disappearance) by hepatic microsomes, and increased rates of urinary excretion of trichloroacetic acid and trichloroethanol (Kaneko et at. 1994). Induced rates of 1,1,1-trichloroethane metabolism and urinary excretion of metabolites were much lower than rates for the highly metabolized halogenated hydrocarbon, trichloroethylene (Kaneko et al. 1994). Rates of

1,1,1-trichloroethane metabolism were also increased in rats pretreated with phenobarbital compared with untreated rats (Ivanetich and van den Honert 1981). Experiments with human liver microsomes and a CYP2E1-specific inhibitor indicate that CYP2E1 is the predominant CYP isozyme involved in metabolism of 1,1,1-trichloroethane and other chlorinated hydrocarbon solvents (Guengerich et at. 1991). Results from rat studies indicate that, under conditions of low oxygen supply, 1,1,1-trichloroethane can be reductively dechlorinated by phenobarbital-inducible CYP2B1/2 to reactive radical intermediates and eventually to acetylene, but this pathway appears to account for <1% of metabolized 1,1,1-trichloroethane and does not appear to represent a toxicologically significant pathway (Durk et al. 1992).

Results regarding the ability of 1,1,1-trichloroethane to induce its own metabolic machinery or induce hepatic levels of CYP isozyme are not consistent, but the weight of the available evidence reviewed in this paragraph suggests that repeated inhalation exposure to 1,1,1-trichloroethane will not markedly alter hepatic metabolism initially mediated by CYP isozymes, especially at administered dose levels below 500 mg/kg/day. Evidence that inhalation exposure to 1,1,1-trichloroethane induces hepatic CYP isozyme levels has been reported in rats exposed to 2,500–3,000 ppm for 24 hours (Fuller et al. 1970), rats exposed to 200–800 ppm for 240 hours (Koizumi et al. 1983), and mice exposed to about 3,000 ppm for up to 96 hours (Lal and Shah 1970). The degree of apparent induction was less than 2-fold in the rats and mice exposed to 2,500–3,000 ppm (Fuller et al. 1970; Lal and Shah 1970) and ranged from about 3- to 7-fold in rats exposed to 200–800 ppm (Koizumi et al. 1983). In contrast, no significant induction of hepatic CYP isozyme levels was found in rats exposed to 200 ppm, 6 hours/day for 5 days (Savolainen et al. 1977), or in rats exposed to 800 ppm, 6 hours/day, 5 days/week for 4 weeks (Toftgard et al. 1981). Schumann et al. (1982a, 1982b) reported that repeated inhalation exposure of rats or mice to 1,500 ppm 1,1,1-trichloroethane for 16 months did not alter the routes of excretion, the extent of metabolism, or the concentration of radioactivity in tissues after a 6-hour inhalation exposure to 1,500 ppm radiolabeled 1,1,1-trichloroethane, compared with rats exposed to radiolabeled chemical without pretreatment. In rats given oral doses of 0, 0.1, 0.5, 5.0, or 10.0 g/kg 1,1,1-trichloroethane for up to 12 days, hepatic microsomal activities of CYP2E1 (hydroxylation of p-nitrophenol to 4-nitrocatechol) and CYP2B1/2 (pentoxyresorufin-O-dealkylase) were induced only by the two highest doses, but none of these dose levels significantly changed hepatic levels of total CYP (Bruckner et al. 2000). In this study, the induction of CYP2E1 and CYP2B1/2 by the high doses (which also caused early mortalities in the rats), was modest (2- to 3-fold increases were observed) and transitory in time. Based on these observations Bruckner et al. (2000) concluded that induction of hepatic CYP isozymes by 1,1,1-trichloroethane, especially at administered dose levels <500 mg/kg/day, appears to be of limited toxicological significance to environmental or occupational exposures experienced by humans.

Metabolites of 1,1,1-trichloroethane are excreted in the urine, but, regardless of route of exposure, urinary elimination of metabolites represents only small fractions of absorbed doses (ATSDR 1995). For example, after rats ingested 116 mg /kg 1,1,1-trichloroethane in drinking water, the primary route of excretion was rapid elimination of unchanged parent material, with only 3% of the ingested dose accounted for by metabolism (Reitz et al. 1988). In another study with rats and mice given gavage doses of 1,1,1-trichloroethane, >85% of the administered dose was excreted unchanged in expired air (Mitoma et al. 1985). In humans exposed to 35 or 350 ppm for 6 hours, >91% of absorbed 1,1,1-trichloroethane was excreted unchanged in exhaled breath, 5–6% was metabolized and excreted as trichloroethanol and trichloroacetic acid, and <1% remained in the body after 9 days (Nolan et al. 1984).

Physiologically based pharmacokinetic models have been developed to describe the behavior of 1,1,1-trichloroethane in mice, rats, and humans (Bruckner et al. 1989; Dallas et al. 1989; Reitz et al. 1988). Linking of 1,1,1-trichloroethane PBPK models to PBPK models for other chemicals holds promise for predicting toxicological interactions, but awaits further research and development.

A.2 Health Effects

Central nervous system depression is the predominant health effect associated with acute high-level inhalation exposure of humans and animals to 1,1,1-trichloroethane. Impaired performance in neurobehavioral function tests has been observed in humans at moderate air concentrations above about 175 ppm (Gamberale and Hultengren 1973; Mackay et al. 1987). Dizziness and initial signs of loss of coordination at concentrations are reported above 500 ppm, with general anesthesia at concentrations above 10,000 ppm (ATSDR 1995). Subtle residual neurological effects associated with repeated occupational exposures include impaired memory and deficits in balance in chronically exposed workers (Kelafant et al. 1994). In addition, changes in brain chemistry have been reported in animals exposed for intermediate durations (Rosengren et al. 1985). Neurological effects observed in animals exposed orally to 1,1,1-trichloroethane include hyperexcitability and narcosis in rats exposed to 5,000 mg/kg and changes in flash-evoked potentials and electroencephalographic patterns in rats exposed to 700 mg/kg for 4 days (ATSDR 1995). Peripheral neuropathy in several women has been associated with frequent and prolonged dermal occupational contact with 1,1,1-trichloroethane (ATSDR 1995).

Cardiac arrhythmias, associated with acute high-level inhalation exposure of humans and animals to 1,1,1-trichloroethane, are thought to involve sensitization of the heart to epinephrine (ATSDR 1995).

Acute high level exposure to 1,1,1-trichloroethane has also been associated with depressed blood pressure and transient myocardial injury (Aoki 1997; ATSDR 1995; Herd et al. 1974; Kobayashi et al. 1987).

Signs of liver damage, including increased serum levels of bilirubin and enzymes released from liver cells, have been observed in humans following high-level inhalation or oral exposure to 1,1,1-trichloroethane (ATSDR 1995). Studies of animals acutely or repeatedly exposed to high concentrations in air (>1,000 ppm) or high oral doses (>1,330 mg/kg) indicate that mild damage to liver tissue (e.g., increased serum ALT or AST levels or fatty changes associated with swelling of centrilobular hepatocytes) can be produced by exposure to 1,1,1-trichloroethane (ATSDR 1995). In male rats exposed to oral doses that produced about 30 or 50% mortality within 50 days of dosing (2.5 or 5.0 g/kg/day, respectively), pulmonary congestion was the only anomaly noted at necropsy and serum enzymes indicative of liver injury at 2 or 4 weeks were elevated to a small, but statistically significant extent, only at 5 g/kg/day (Bruckner et al. 2000). Rats exposed to 0.5 g/kg/day for 90 days showed no increased incidences of mortality or hepatic histopathological lesions (Bruckner et al. 2000). Results from a well-designed inhalation study of animals found no evidence for carcinogenic responses to 1,1,1-trichloroethane (Quast et al. 1988). Inconclusive results regarding 1,1,1-trichloroethane carcinogenicity were obtained in oral exposure studies of animals due to study limitations (ATSDR 1995).

Studies of women occupationally exposed to solvents, including 1,1,1-trichloroethane found no evidence for associations between exposure and adverse pregnancy outcomes, but minor fetotoxic effects (such as decreased fetal weights, increased minor soft tissue and skeletal anomalies, and delayed ossification) were observed in rats and rabbits exposed to moderate to high concentrations (>800 ppm) associated with maternal toxicity (ATSDR 1995). ATSDR (1995) suggested that additional developmental studies examining neurological endpoints in offspring may be warranted, but noted that a well-conducted study of rats exposed by gavage to doses as high as 750 mg/kg/day during gestation and lactation found no significant exposure-related changes in offspring examined at up to 2 months of age with a battery of neurobehavioral and neurophysiological tests (Dow 1993).

A.3 Mechanisms of Action

Like other small molecular weight halogenated hydrocarbons, which are lipophilic, rapidly absorbed upon various routes of exposure, and eliminated readily upon cessation of exposure, 1,1,1-trichloroethane crosses cellular membranes by passive diffusion (ATSDR 1995).

Nervous system depression from 1,1,1-trichloroethane and other lipophilic solvents is thought to involve reversible intercalation (of the parent material and not metabolites) in lipid bilayers of nerve membranes (yielding changes in membrane fluidity) and/or reversible interactions with membrane proteins (yielding conformational changes) leading to altered ion transport, enzymic activities, and neurotransmitter receptor functions necessary for normal nerve impulses and regeneration of action potentials (ATSDR 1995; Balster 1998; Cruz et al. 1998; Engelke et al. 1996; Evans and Balster 1991; Franks and Lieb 1985, 1987; Korpela 1989; Mihic et al. 1994; von Euler 1994). The cardiac arrhythmias associated with acute high-level exposures are thought to involve parent material sensitization of the heart to epinephrine (ATSDR 1995). Other cardiotoxic effects of acute, high-level exposure to 1,1,1-trichloroethane, such as depressed blood pressure due to decreased heart rate, myocardial contractility, increased peripheral vascular dilation (i.e., decreased peripheral vascular resistance), or transient disturbance of pulmonary blood flow, have been hypothesized to involve parent material disruption of membrane-mediated processes regulating intracellular calcium levels or damage to pulmonary interstitium (Aoki et al. 1997; ATSDR 1995; Herd et al. 1974; Kobayashi et al. 1987).

The mechanism by which 1,1,1-trichloroethane may damage liver tissue is thought to be similar to that hypothesized to be involved in liver effects from other halogenated alkanes that are more potent hepatotoxic agents, such as 1,1,2-trichloroethane and carbon tetrachloride (ATSDR 1995). It has been proposed that the production of free radical metabolic intermediates formed by the oxidative catalytic action of CYP isozymes is responsible for the tissue damage via cleavage of the carbon-chlorine bond (ATSDR 1995). The free radicals are thought to react with unsaturated lipids and proteins in the endoplasmic reticulum of hepatocytes leading to morphological and functional changes in the organelle and eventually to cellular dysfunction (triglyceride accumulation) and necrosis. This hypothesis is supported by associated differences in metabolism and toxicity between 1,1,1-trichloroethane, which is poorly metabolized and has low toxic potency, and its isomer, 1,1,2-trichloroethane, which is extensively metabolized and has relatively high potency. Illustrating this difference in metabolism and potency, urinary excretion of metabolites accounted for >70% of administered doses of the potent 1,1,2-trichloroethane, whereas >85% of 1,1,1-trichloroethane was excreted unchanged in expired air (Mitoma et al. 1985).

It is unlikely that alteration of 1,1,1-trichloroethane metabolism will significantly change 1,1,1-trichloroethane hepatotoxicity or carcinogenicity given that the metabolism of 1,1,1-trichloroethane is so slow, that downstream enzymes may prevent the elevation of hepatic concentrations of any toxic metabolites formed, and that repair mechanisms may efficiently fix any damage to cellular macromolecules.

Furthermore, results from studies in which animals have been pretreated with phenobarbital or ethanol to enhance hepatic metabolism of 1,1,1-trichloroethane have not found consistent evidence that a potentiation of 1,1,1-trichloroethane hepatotoxicity may occur. In one study, pretreatment of rats with phenobarbital increased serum levels of AST and ALT following a 2-hour exposure to 11,600 ppm 1,1,1-trichloroethane compared with exposure without pretreatment (Carlson 1973). In contrast, Cornish et al. (1973) reported that phenobarbital pretreatment did not significantly increase serum AST levels after intraperitoneal injection of single doses of 1,1,1-trichloroethane (0.3–2.0 mL/kg) compared with exposure without pretreatment. Kaneko et al. (1994) showed that ethanol pretreatment of rats induced hepatic levels of total CYP (presumably CYP2E1, Lieber 1997) and increased rates of 1,1,1-trichloroethane metabolism, but the induced rates of 1,1,1-trichloroethane metabolism were still much lower than that of other more potent halogenated hydrocarbons (specifically trichloroethylene). Whereas ethanol induction of CYP2E1 increased rates of 1,1,1-trichloroethane metabolism at low exposure levels, it only affects rates of metabolism of trichloroethylene, a well-metabolized chemical, at high exposure levels (Kaneko et al. 1994).

A.4 Health Guidelines

ATSDR (1995) derived an acute inhalation MRL of 2 ppm for 1,1,1-trichloroethane based on a LOAEL of 175 ppm for performance deficits in tests of psychomotor skills in humans exposed to controlled airborne concentrations of 1,1,1-trichloroethane for 3.5 hours (Mackay et al. 1987) and an uncertainty factor of 100 (10 for the use of a LOAEL and 10 to account for human variability).

ATSDR (1995) derived an intermediate-duration inhalation MRL of 0.7 ppm for 1,1,1-trichloroethane based on a NOAEL of 70 ppm and a LOAEL of 210 ppm for brain astrogliosis (increased brain levels of glial fibrillary acid protein) in gerbils exposed continuously for 3 months to vapors of 1,1,1-trichloroethane (Rosengren et al. 1985) and an uncertainty factor of 100 (10 for extrapolating from rats to humans and 10 to account for human variability).

ATSDR (1995) did not derive a chronic inhalation MRL or any oral MRLs for 1,1,1-trichloroethane due to the lack of appropriate studies (e.g., studies of subtle neurological effects associated with chronic inhalation exposure).

EPA does not list an RfD or an RfC for 1,1,1-trichloroethane on its IRIS database (IRIS 2001). EPA classified 1,1,1-trichloroethane as a Group D chemical (Not Classifiable as to Human Carcinogenicity)

based on no human data and the lack of demonstrated carcinogenic effects in a chronic-duration, gavage-exposure rat study and an intermediate-duration, inhalation-exposure rat study. 1,1,1-Trichloroethane is not on the NTP (2001) list of chemicals known to be or reasonably anticipated to be human carcinogens. IARC (1999) assigned 1,1,1-trichloroethane to Cancer Group 3, *not classifiable as to its carcinogenicity to humans,* due to inadequate evidence in humans and experimental animals.

Appendix B: Background Information for 1,1-Dichloroethane

B.1 Toxicokinetics

Results from animal studies indicate that 1,1-dichloroethane is well absorbed in the pulmonary and gastrointestinal tracts and absorbed by the skin to some undetermined extent (ATSDR 1990). Results from studies with animals given intraperitoneal injections of radiolabeled 1,1-dichloroethane indicate that once absorbed, it can be distributed to tissues throughout the body. 1,1-Dichloroethane is poorly metabolized in the body and is rapidly excreted predominately unchanged in expired breath. For example, 48 hours after administration of high oral doses to rats (700 mg/kg) and mice (1,800 mg/kg), metabolism accounted for only about 7 and 29% of the administered doses, respectively (Mitoma et al. 1985). More than 90% of the administered dose in each species was exhaled unchanged or as carbon dioxide with 48 hours. It is likely that, at these high exposure levels, the metabolic capacity of the liver to metabolize 1,1-dichloroethane was saturated.

Studies with liver microsomes indicate that acetic acid is the major metabolite, and that 2,2-dichloroethanol, mono-, and dichloroacetic acid are minor metabolites of 1,1-dichloroethane (McCall et al. 1983). *In vitro* rates of production of acetic acid from 1,1-dichloroethane in rat hepatic microsomes were >1,000-fold higher than rates of production of the minor metabolites (McCall et al. 1983). Phenobarbital or ethanol pretreatment of rats produced increased rates of 1,1-dichloroethane metabolism (McCall et al. 1983; Sato et al.1980) suggesting that metabolism involves both CYP2B1/2 and CYP2E1 isozymes (Nakajima 1992). Metabolic steps have been proposed to involve initial hydroxylations at both of the carbons in 1,1-dichloroethane by CYP isozymes (McCall et al. 1983). Hydroxylation at the C-2 carbon is the minor pathway leading to, sequentially, 2,2-dichloroethanol, dichloroacetaldehyde, and dichloroacetic acid. Hydroxylation at the C-1 carbon, the major pathway, is expected to produce an unstable alpha haloalcohol that rearranges to form reactive acyl chlorides (acetyl chloride or chloroacetyl chloride), which have been proposed to react with cellular constituents leading to cellular dysfunctions (ATSDR 1990; McCall et al. 1983). No information was located to indicate whether the major and minor pathways for 1,1-dichloroethane may be mediated by different CYP isozymes. Under hypoxic conditions, reductive dechlorination of 1,1-dichloroethane can occur (presumably via CYP isozymes), leading to free radicals that can damage tissue, but the rates at which this occurs with 1,1-dichloroethane appear to be less than those associated with other more potent hepatotoxic chlorinated hydrocarbons such as carbon tetrachloride (ATSDR 1990).

B.2 Health Effects

High level inhalation exposure to 1,1-dichloroethane is known to cause reversible nervous system impairment, and it has been used in the past as a gaseous anaesthetic agent (ATSDR 1990). Its use as an anesthetic agent was discontinued after it was discovered to induce cardiac arrhythmias at anesthetic doses (ATSDR 1990). Studies of rats, rabbits, guinea pigs, and cats intermittently exposed to vapor concentrations as high as 1,000 ppm for intermediate durations found no changes in several liver endpoints except for an increase in relative liver weight (ATSDR 1990). Evidence of renal toxicity (increased serum urea and creatinine, and crystalline precipitates in and dilation of kidney tubules) was found in cats exposed to 1,000 ppm, but not 500 ppm, in these studies. No renal toxicity was found in any of the other species (ATSDR 1990). In 78-week oral gavage studies with rats and mice, 1,1-dichloroethane produced increased incidences of hemangiosarcomas at various sites and mammary carcinomas in female rats exposed to 475 mg/kg/day, and liver carcinomas in male mice and benign uterine polyps in female mice exposed to 3,331 mg/kg/day (ATSDR 1990; IRIS 2001). These studies, however, were limited by low survival rates in all exposure and control groups, possibly due to pneumonia (IRIS 2001). Delayed skeletal development associated with maternal toxicity was the only effect noted in a study of pregnant rats exposed to up to 6,000 ppm, 7 hours/day during gestation days 6–15 (Schwetz et al. 1974).

B.3 Mechanisms of Action

1,1-Dichloroethane, like other low molecular weight lipophilic halogenated hydrocarbons, is rapidly absorbed from the lungs and gastrointestinal tract, and eliminated rapidly upon cessation of exposure, since it readily crosses cellular membranes by passive diffusion (ATSDR 1990).

Like other agents that produce reversible anesthetic effects with high level inhalation exposure, nervous system impairment from acute exposure to 1,1-dichloroethane is expected to be caused by the interaction of the parent compound with components (e.g., phospholipids and/or proteins) of neuronal system membranes. The cardiac arrhythmias observed in humans inhaling high levels of 1,1-dichloroethane are likely caused by the parent compound sensitizing the heart to endogenous catecholamines, such as epinephrine, based on analogy to other low molecular weight chlorinated hydrocarbons (ATSDR 1990, 1995, 1997a, 1997b; Snyder and Andrews 1996).

The difference in hepatotoxic, renotoxic, and carcinogenic potency between 1,1-dichloroethane and its more potent isomer, 1,2-dichloroethane, appears to be associated with differences in metabolic disposition

for the two isomers (McCall et al. 1983). Both isomers can be hydroxylated by CYP isozymes on either of the carbon atoms, but the 1,2-isomer can be conjugated with glutathione via glutathione transferases, leading to a reactive intermediate that is thought to be key to its toxic nature (McCall et al. 1983). The formation of reactive intermediates from conjugation of 1,1-dichloroethane with glutathione does not appear to occur; in contrast, glutathione conjugation may be a detoxification pathway for 1,1-dichloroethane (ATSDR 1990).

Hydroxylation of 1,1-dichloroethane at the C-1 carbon is hypothesized to produce an unstable alpha haloalcohol that rearranges to form reactive acyl chlorides (acetyl chloride or chloroacetyl chloride), which can react with cellular constituents leading to cellular dysfunctions (ATSDR 1990; McCall et al. 1983). Studies designed to examine if induction of hepatic CYP isozymes would influence the toxicity of 1,1-dichloroethane were not located, although phenobarbital pretreatment of rats has been demonstrated to enhance covalent binding of 1,1-dichloroethane metabolites to cellular macromolecules and increase rates of 1,1-dichloroethane metabolism in hepatic microsomes (Colacci et al. 1985). The role of glutathione conjugation as a detoxification pathway for 1,1-dichloroethane is consistent with the observation that addition of reduced glutathione to hepatic microsomal systems suppressed covalent binding of 1,1-dichloroethane metabolites to macromolecules (Colacci et al. 1985).

B.4 Health Guidelines

ATSDR did not derive inhalation or oral MRLs for 1,1-dichloroethane due to the lack of appropriate data.

EPA does not list an RfD or an RfC for 1,1-dichloroethane on its IRIS (2001) database. EPA (IRIS 2001) classified 1,1-dichloroethane as a Group C chemical (Possible Human Carcinogen) based on no human data and limited evidence of carcinogenicity in two animal species (rats and mice) as shown by an increased incidence of mammary gland adenocarcinomas and hemangiosarcomas in female rats and an increased incidence of hepatocellular carcinomas and benign uterine polyps in mice. 1,1-Dichloroethane is not on the NTP (2001) list of agents known to be or reasonably anticipated to be human carcinogens. IARC (2001) has not assigned 1,1-dichloroethane to a cancer classification group.

Appendix C: Background Information for Trichloroethylene

C.1 Toxicokinetics

Studies of humans and rats indicate that inhaled trichloroethylene is rapidly and efficiently absorbed (ATSDR 1997a). Initial rates of uptake are high, but decrease as steady state conditions are approached. Studies in humans indicated that 37–64% of inhaled trichloroethylene was absorbed. Ingested trichloroethylene is rapidly and completely absorbed by the gastrointestinal tract (ATSDR 1997a). Fasted rats given gavage doses of 5–25 mg/kg trichloroethylene displayed peak blood concentrations within 6–10 minutes and absorbed >90% of the dose within 9 hours (D'Souza et al. 1985). Dermal absorption is rapid as indicated by observations of peak blood and exhaled air concentrations occurring within 5 minutes after a human subject immersed one hand in a trichloroethylene solution (ATSDR 1997a). Once absorbed, trichloroethylene is widely distributed to organs throughout the body (including the developing fetus) and, due to its lipophilic properties, can accumulate in fat to a limited degree (ATSDR 1997a). For example, 17 hours after a 6-hour/day, 4-day exposure of rats to 200 ppm, trichloroethylene was detected in perirenal fat and blood, but was not detected in other tissues (Savolainen et al. 1977).

Studies of humans and rodents indicate that inhaled trichloroethylene is eliminated from the body predominately in the urine as metabolites and to a lesser degree in exhaled breath as the parent chemical or other volatile metabolites such as trichloroethanol and carbon dioxide (ATSDR 1997a). For example, following single or sequential daily exposures of human subjects to 50–380 ppm, 11 and 2% of the dose was eliminated as trichloroethylene and trichloroethanol in exhaled breath; 58% was eliminated as urinary metabolites; and 30% was unaccounted for (Monster et al. 1976, 1979). Trichloroethylene was detected in exhaled breath of humans 18 hours after exposure ended due to the relatively long elimination half-life of trichloroethylene in fatty tissue (3.5–5 hours) compared with other tissues. Following inhalation exposure to radiolabeled trichloroethylene, mice excreted 75% of radioactivity in the urine and 9% as carbon dioxide in exhaled breath (Stott et al. 1982). Similar patterns of elimination were observed in mice and rats following oral administration of trichloroethylene (Koizumi et al. 1986).

The principal urinary metabolites of trichloroethylene in humans and animals are trichloroethanol, trichloroethanol-glucuronide, and trichloroacetic acid (ATSDR 1997a; Lash et al. 2000). Trichloroethylene is principally metabolized in the liver, but metabolism can also occur in Clara cells of the lungs and in the kidney. The principal pathway in humans and animals involves initial oxidation catalyzed by CYP isozymes (CYP2E1 and 2B1/2). It has been proposed that this reaction forms an epoxide intermediate

(trichloroethylene oxide) that rapidly converts to chloral hydrate, but an alternative proposal indicates that chloral hydrate formation involves chlorine migration in an oxygenated trichloroethylene-CYP transition state (Lash et al. 2000). Chloral hydrate can be oxidized to trichloroacetic acid via chloral hydrate dehydrogenase or reduced to trichloroethanol via alcohol dehydrogenase. Trichloroacetic acid is a strong inducer of peroxisome proliferation and has been associated with hepatocarcinogenicity in rodents. Trichloroethanol can be conjugated with glucuronic acid via glucuronyl transferase to form trichloro-ethanol-glucuronide. Studies with human hepatic microsomes indicate that CYP2E1 is the predominant isozyme responsible for the initial steps in trichloroethylene metabolism, although there is evidence that CYP isozymes induced by phenobarbital (i.e., CYP2B1/2) may also be involved. At high exposure levels, enzymes involved in the main oxidative metabolic pathway can be saturated, leading to conjugation with glutathione to produce S-(1,2-dichlorovinyl)glutathione (DCVG). DCVG is acted on by γ-glutamyl transferase to remove glutamine, and the glycine is removed by the action of dipeptidases to yield S-(1,2-dichlorovinyl)-L-cysteine (DCVC). Cleavage of the cysteine by β-lyase in the kidney can lead to intermediates with reactive thiol groups that can react with cellular macromolecules leading to renal cytotoxicity and carcinogenicity.

Minor metabolic pathways arising from the initial intermediate, trichloroethylene oxide or the trichloro-ethylene-CYP transition state, include: (1) transformation to dichloroacetic acid through a dichloroacetyl chloride intermediate (this path appears to be more important in rodents than humans); (2) hydrolytic dechlorinations to form formic acid and carbon monoxide; and (3) hydrolytic dechlorinations to form carbon dioxide via, sequentially, glyoxylic acid chloride, glyoxylic acid and oxalic acid (ATSDR 1997a; Lash et al. 2000). Dichloroacetic acid can be conjugated with glutathione followed by sequential removal of glutamine and glycine to form dichlorovinyl-cysteine. Dichlorovinyl-cysteine can be transported to the kidney, where cleavage by β-lyase produces an intermediate with a reactive thiol group that can react with proteins and DNA leading to kidney cytotoxicity and kidney tumor development.

PBPK 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 (ATSDR 1997a; Clewell et al. 2000; Fisher 2000). The models are being used to aid assessment of noncancer and cancer human health risks based on rodent exposure-response data (Barton and Clewell 2000; Rhomberg 2000).

C.2 Health Effects

Results from studies of trichloroethylene-exposed humans and animals indicate that the primary targets for trichloroethylene noncarcinogens toxicity are the nervous system, liver, heart, and kidneys (ATSDR 1997a). The critical target (i.e., the target in which effects occur at the lowest exposure level) is expected to be the nervous system. Studies involving acute- or intermediate-duration inhalation or oral exposures have observed changes in neurobehavior in humans and animals at lower exposure levels (50–200 ppm) than those associated with liver effects (liver enlargement and cellular hypertrophy) and kidney effects (increased kidney weights and cytomegaly and karyomegaly in renal tubular epithelial cells) observed in animal studies (ATSDR 1997a). For example, Stewart et al. (1970) found no changes in liver function tests in humans who were exposed to 200 ppm for 7 hours/day for 5 days and reported experiencing headache, fatigue, and drowsiness. Effects on the heart appear to be restricted to cardiac arrhythmias due to trichloroethylene sensitization of the heart to epinephrine and other catecholamines.

Occupational exposure to trichloroethylene has been widespread due to its use in dry cleaning, for metal degreasing, and as a solvent for oils and resins. 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. Elevated relative risks, ranging from 1.1 to 2.0, have been reported for kidney cancer, liver cancer, and non-Hodgkin's lymphoma in several cohorts of workers repeatedly exposed to trichloroethylene in workplace air (see Wartenberg et al. 2000). 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. Reflecting this assessment, IARC (1995) earlier concluded that the human evidence for trichloroethylene carcinogenicity is limited.

Chronic-duration animal studies have shown that cancer can be caused by inhalation or oral exposure to trichloroethylene, but do not point to a single target organ for increased tumor incidence. Carcinogenic responses have been observed in the liver, kidney, testes, lymphatic system, and lung, but the observed responses are not consistent across studies of different species and strains of animals (ATSDR 1997a).

In general, carcinogenic responses to trichloroethylene are thought to involve trichloroethylene metabolites (Bull 2000; Green 2000; Lash et at. 2000). This hypothesis is supported by observations that mice appear to be uniquely susceptible to trichloroethylene-induced liver and lung tumors and display

higher rates of trichloroethylene metabolism than do rats. In contrast, rats appear to be uniquely susceptible to trichloroethylene-induced kidney damage and tumors. Based on its review of available data, ATSDR (1997a) concluded that there is adequate evidence to indicate that trichloroethylene is carcinogenic in mice, that the evidence for trichloroethylene carcinogenicity in rats is equivocal, and that further study is required to determine whether or not the processes that induce liver cancer in mice also operate in the human liver. EPA supported monographs on trichloroethylene health risks have been recently published and are being used to develop updated EPA health risk characterizations for trichloroethylene (Scott and Cogliano 2000).

C.3 Mechanisms of Action

Like other solvents, nervous system effects from trichloroethylene are likely to involve disruption of neural membranes by the parent chemical, but trichloroethanol is also involved. In support of this hypothesis, Mikiskova and Mikiska (1966) reported that intraperitoneally administered trichloroethanol was 5–6 times more effective than trichloroethylene in altering electrophysiological variables associated with central nervous system depression in guinea pigs.

Trichloroethylene-induced cardiac arrhythmias are thought to involve parent-chemical sensitization of the heart to epinephrine-induced arrhythmias (ATSDR 1997a). 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.

Metabolism of trichloroethylene is expected to produce cytotoxic and carcinogenic metabolites, including trichloroacetic acid, dichloroacetic acid, chloral hydrate, and 2-chloroacetaldehyde (ATSDR 1997a). Drinking water administration of trichloroacetic acid to rodents has produced carcinogenic changes in the liver that are associated with the proliferation of peroxisomes. Reactive oxygen species produced by peroxisomes are thought to be involved in a sequence of DNA damage, cytotoxicity, regenerative cell growth, and tumor development. Phenobarbital pretreatment and induction of hepatic CYP isozymes appear to be associated with enhancement of acute trichloroethylene hepatotoxicity in rodents (Allemand et al. 1978; Carlson 1973; Moslen et al. 1977; Nakajima et al. 1990), providing further support for the idea that metabolites are responsible for the hepatotoxicity of trichloroethylene. Trichloroethylene-induced liver cancer and peroxisomal proliferation have been associated with rapid metabolism of trichloroethylene to trichloroacetic acid in mice, but this metabolic pathway appears to be limited in rats and humans. Dichloroacetic acid has also been shown to produce liver cancer in mice, but its

hepatocarcinogenicity has been hypothesized to involve some other, as yet unspecified, mechanism of action. The mouse liver displays much higher rates of metabolism of trichloroethylene, and is more susceptible to the hepatotoxicity and hepatocarcinogenicity of trichloroethylene, than do the livers of rats and humans. With chronic oral exposure to high doses of trichloroethylene by gavage, increased incidence of toxic nephrosis and renal tumors occurred in male rats, but in female rats the nephrosis was not accompanied by an increase in kidney tumors. 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 macromolecules and lead to cell damage. In support of this mechanistic hypothesis, chemical agents that inhibit β-lyase protected against dichlorovinyl-cysteine nephrotoxicity in rats (ATSDR 1997a).

C.4 Health Guidelines

ATSDR (1997a) derived an acute inhalation MRL of 2 ppm 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 (Stewart et al. 1970) and an uncertainty factor of 100 (10 for the use of a LOAEL and 10 to account for human variability).

ATSDR (1997a) derived an intermediate-duration inhalation MRL of 0.1 ppm for trichloroethylene based on a LOAEL of 50 ppm for decreased wakefulness during exposure, and decreased postexposure heart rate and slow-wave sleep in rats exposed for 8 hours/day, 5 days/week for 6 weeks (Arito et al. 1994), and an uncertainty factor of 300 (10 for using a LOAEL, 3 for extrapolating from rats to humans, 10 to account for human variability).

ATSDR (1997a) did not derive a chronic inhalation MRL for trichloroethylene due to the lack of suitable data.

ATSDR (1997a) derived an acute oral MRL of 0.2 mg/kg/day for trichloroethylene based on a LOAEL of 50 mg/kg/day for reduced rearing rate in rats 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]). The rats were exposed for 7 days beginning at 10 days of age and evaluated for locomotion, rearing, and total activity at 17 and 60 days of age (Fredriksson et al. 1993).

EPA's IRIS database (IRIS 2001) does not list an RfD, an RfC, or a carcinogenicity assessment for trichloroethylene. As reviewed by ATSDR (1997a), the EPA Scientific Advisory Board in 1988 offered the opinion that the weight of evidence for trichloroethylene carcinogenicity was on a Group B2/C continuum (i.e., on the border between Group B2 and Group C). EPA has yet to present a more recent position on the weight-of-evidence classification for trichloroethylene carcinogenicity, but is currently evaluating several approaches to extrapolating from the animal tumor data for trichloroethylene to derive estimates of human cancer risks at environmentally relevant exposure levels (see Scott and Cogliano 2000). 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. IARC (1995) noted that 1) although a hypothesis linking the formation of mouse liver tumors with peroxisome proliferation is plausible, trichloroethylene also induced tumors at other sites in mice and rats, and 2) several epidemiological studies showed elevated risks for cancer of the liver and biliary tract and for non-Hodgkin's lymphoma.

Appendix D: Background Information for Tetrachloroethylene

D.1 Toxicokinetics

Results from human and animal studies indicate that inhaled tetrachloroethylene is rapidly and efficiently absorbed by the lungs (ATSDR 1997b). For example, in rats given nose-only inhalation exposures to 50 or 500 ppm for 3 hours, near steady-state exhaled breath concentrations were attained within about 20 minutes and were proportional to concentration (Dallas et al. 1994b). Total uptake of tetrachloroethylene increased with exposure concentration, but was not linearly proportional to concentration, consistent with an influence of saturable metabolism on pulmonary uptake. Studies with rats, mice, and dogs indicate that ingested tetrachloroethylene is rapidly and completely absorbed (Dallas et al. 1994a, 1995; Frantz and Watanabe 1983; Pegg et al. 1979). When applied to the skin as a liquid, tetrachloroethylene also is rapidly absorbed. Tetrachloroethylene was detected in exhaled breath of humans shortly after immersion of one thumb in liquid tetrachloroethylene; a peak concentration was attained after about 40 minutes of exposure (Stewart and Dodd 1964). Other human studies indicate, however, that skin absorption of tetrachloroethylene vapor contributes only a small portion of absorbed body burden compared with pulmonary absorption.

Once absorbed, tetrachloroethylene is distributed widely throughout the body with preferential distribution to fatty tissue including maternal breast milk. Tetrachloroethylene is capable of crossing the placenta and reaching the developing fetus (ATSDR 1997b). Estimated partition coefficients for tetrachloroethylene in human tissues and liquids are 10–20 for blood/air, 1,450–1,650 for fat/air, and 125–159 for fat/blood; these values are consistent with ready partition into blood from air and preferential distribution to fatty tissue. In humans exposed to airborne concentrations up to 144 ppm for 4 hours, exhalation of unmetabolized tetrachloroethylene was the predominant route of elimination (Monster et al. 1979). Urinary excretion of metabolites represented a small percentage (1–2%) of absorbed doses. Half-lives of tetrachloroethylene in highly perfused tissue, muscle tissue, and fatty tissue of humans have been estimated at 12–16 hours, 30–40 hours, and 55 hours, respectively. In rats exposed to 10 ppm radiolabeled tetrachloroethylene, 68 and 3.6% of the absorbed radioactivity was exhaled as the parent material and carbon dioxide, respectively, over a 72-hour period; 24% of absorbed radioactivity was accounted for as nonvolatile urinary and fecal metabolites and 3–4% remained in the carcasses (Pegg et al. 1979). Metabolic saturation ensued with exposure to higher concentrations (600 ppm), as 88, 9, and 2% of the absorbed dose was accounted for by exhalation of parent chemical, urinary and fecal metabolites, and radioactivity remaining in the rat carcasses. The limited extent to which tetrachloro-

ethylene is metabolized in rats is not dramatically influenced by induction of CYP isozymes. For example, in rats pretreated with phenobarbital before intraperitoneal injection with 1,474 mg/kg trichloroethylene/kg or 1,632 mg/kg tetrachloroethylene, rates of appearance of trichloroethylene metabolites in urine during 2-hour periods for up to 10 hours after injection were approximately 200- to 1,000-fold higher than rates for tetrachloroethylene metabolites (Ikeda and Imamura 1973). In contrast to humans and rats, mice appear to metabolize tetrachloroethylene more rapidly and completely. Following inhalation exposure of mice to 10 ppm radiolabeled tetrachloroethylene, urinary metabolites accounted for more than 80% of the absorbed dose (Schumann et al. 1980).

Metabolism of tetrachloroethylene to trichloroacetic acid, the principal metabolite, involves initial saturable catalysis by CYP isozymes to produce a reactive epoxide intermediate (tetrachloroethylene oxide), that can potentially bind to cellular macromolecules or rearrange to trichloroacetyl chloride (ATSDR 1997b). Trichloroacetyl chloride is further oxidized to trichloroacetic acid. The liver is the predominant site of and CYP2B1/2 is an important isozyme in tetrachloroethylene metabolism. Pretreatment of rats with phenobarbital (an inducer of CYP2B1/2) or Aroclor 1254 (an inducer of CYP2B1/2and 1A1/2 isozymes) before oral administration of 1,244 mg tetrachloroethylene/kg body weight increased the rates of urinary excretion of tetrachloroethylene metabolites by about 5- to 7-fold (Moslen et al. 1977).

Other metabolic pathways for tetrachloroethylene include one that leads from tetrachloroethylene oxide to oxalic acid and formic acid formation via catalysis by epoxide hydrase, and another involving initial conjugation of tetrachloroethylene with glutathione via glutathione transferase (ATSDR 1997b). The glutathione conjugate can be transported to the kidney where it can be hydrolyzed by β-lyase, producing a reactive thiol compound that is thought to bind to cellular macromolecules and lead to renal cytotoxicity. Small amounts of trichloroethanol have also been detected in the urine of workers exposed to tetrachloroethylene, but it has been proposed that the trichloroethanol derives from metabolism of trichloroethylene contamination of tetrachloroethylene rather than metabolism of tetrachloroethylene (ATSDR 1997b). Evidence is available that mice have a greater hepatic capacity for total tetrachloroethylene metabolism than rats, which in turn have a higher capacity than do humans.

PBPK models have been developed to describe the disposition of tetrachloroethylene in mice, rats, and humans, and to predict doses of proposed carcinogenic metabolites in target organs for the purpose of assessing human cancer risks based on rodent exposure-response data (ATSDR 1997b). Further

development to link models for different chlorinated hydrocarbons that share metabolic pathways may be useful to predict dispositional and toxicological outcomes of possible interactions.

D.2 Health Effects

Studies of occupationally exposed humans as well as of humans under acute controlled conditions indicate that neurological effects are the most predominant and sensitive effects of tetrachloroethylene (ATSDR 1997b). Observed effects include neurological symptoms such as headache, dizziness, and drowsiness in subjects exposed to 100 ppm for 7 hours, increased latency of pattern reversal visual-evoked brain potentials and performance deficits in tests of vigilance and eye-hand coordination in subjects exposed to 50 ppm, 4 hours/day for 4 days, and increased incidence of subjectively reported symptoms, such as dizziness and forgetfulness, in workers repeatedly exposed to average concentrations of about 20 ppm (ATSDR 1997b). Studies of animals exposed *in utero* (via oral exposure of mothers) indicate that tetrachloroethylene can adversely influence the developing nervous system, but studies to examine possible associations between occupational exposure of humans to tetrachloroethylene and increased risks for birth defects in offspring or reproductive effects such as menstrual disorders and spontaneous abortions provide only suggestive evidence that these types of effects may occur in humans (ATSDR 1997b). Limitations of the human reproductive and developmental toxicity studies include confounding exposures to other chemicals, inability to adjust for confounding factors, and lack of exposure data for individuals in the studies.

Based on analogy to other low molecular weight halogenated hydrocarbons, cardiac arrhythmias (associated with sensitization of the heart to epinephrine) from acute high level exposures to tetrachloro-ethylene may be expected to occur in humans. However, ATSDR (1997b) reviewed only one case of cardiac arrhythmia in a dry cleaning worker exposed to tetrachloroethylene, and a study of beagle dogs exposed to 5,000 or 10,000 ppm tetrachloroethylene found no evidence of heart sensitization to epinephrine.

Associations have also been made between human exposure to tetrachloroethylene and subtle renal effects in tetrachloroethylene-exposed workers (e.g., increased levels of enzymes or other proteins in urine) or liver effects in cases of people acutely exposed to high levels (e.g., enlarged liver or elevated serum ALT activity) (ATSDR 1997b). Renal effects have been observed in rats and mice chronically exposed to inhaled or ingested tetrachloroethylene. Rats and mice of both sexes exposed for 2 years to tetrachloroethylene air concentrations $\geq$200 and 100 ppm, respectively, showed dose-related renal tubular

cell karyomegaly (nuclear enlargement) (NTP 1986). Nephropathy was observed in rats and mice exposed to gavage doses ≥471 and 386 mg/kg/day, respectively (NCI 1977). Kidney cancer responses observed in male rats following inhalation exposure to tetrachloroethylene (NTP 1986) have been proposed to involve accumulation of α-2μ-globulin, a process not relevant to humans (ATSDR 1997b).

Liver effects also have been observed in rats and mice repeatedly exposed to inhaled or ingested tetrachloroethylene, but mice appear more sensitive than rats (ATSDR 1997b). For example, hepatocellular degeneration and necrosis was found in male mice exposed for 2 years to air concentrations ≥100 ppm, and increased liver tumors developed in both sexes of mice under these conditions (NTP 1986). In contrast, rats exposed for 2 years to concentrations up to 400 ppm showed no increased incidence of non-neoplastic or neoplastic hepatic lesions (NTP 1986). In shorter-term experiments, mice exposed for 14–28 days to 200 or 400 ppm in air showed hepatocellular vacuolization and proliferation of peroxisomes, whereas rats under these conditions showed no proliferation of hepatic peroxisomes and less severe hepatocellular changes (i.e., hypertrophy) (Odum et al. 1988).

D.3 Mechanisms of Action

Nervous system depression appear to be the most sensitive effects in humans from exposure to tetrachloroethylene, regardless of exposure route, and are thought to be caused predominately by the parent material (ATSDR 1997b). Hypothetical mechanisms of action include tetrachloroethylene-induced changes in the fatty acid pattern of neuronal membranes or the direct effect of incorporation of tetrachloroethylene in the membranes leading to an alteration in membrane structure and function. Possible contributions from metabolites cannot be conclusively ruled out, but appear unlikely given the slow rates at which tetrachloroethylene is expected to be metabolized in humans. Trichloroethanol, a metabolite of trichloroethylene that is a potent neurotoxic agent, does not appear to be a metabolite of tetrachloroethylene (ATSDR 1997b).

Liver and kidney effects observed in animals exposed to tetrachloroethylene have been proposed to be caused by reactive metabolic intermediates: a proposed reactive epoxide product of CYP catalysis in the liver; reactive oxygen species from proliferation of peroxisomes by trichloroacetic acid, the principal metabolite of tetrachloroethylene; and a reactive thiol product produced by hydrolysis of glutathione conjugates via β-lyase catalysis in the kidney (ATSDR 1997b). The latter reaction has been proposed to gain importance at high exposure concentrations when rates of elimination of the parent chemical in exhaled breath are maximized and CYP catalysis is saturated. The initial liver reaction leading to the

thiol product, glutathione conjugation, competes for tetrachloroethylene as a substrate. The relevance of the observed rat kidney effects to humans has been questioned because glutathione conjugation activity was not detected in human liver preparations, β-lyase activities were low in human kidney preparations, and some of the kidney effects appear to be due to accumulation of α-2μ-globulin, a protein that is produced in male rats but not in female rats or humans of either sex (ATSDR 1997b). Evidence that metabolites may be involved in tetrachloroethylene hepatotoxicity includes the observation that pretreatment of rats with Aroclor 1254 before oral administration of 7.5 mmol tetrachloroethylene/kg (1,244 mg/kg) increased rates of urinary excretion of tetrachloroethylene metabolites and increased levels of serum AST compared with levels in nonpretreated rats (Moslen et al. 1977). The relevance of tetrachloroethylene-induced rodent liver effects to humans has been questioned based on evidence that humans produce little trichloroacetic acid from tetrachloroethylene (i.e., rates of total tetrachloroethylene metabolism in humans are low compared to rates in mice), mice and rats respond to trichloroacetic acid by induction of hepatocellular peroxisomes (that produce tissue damaging substances), and humans are relatively insensitive to the induction of hepatocellular peroxisomes (ATSDR 1997b; Lake 1995).

D.4 Health Guidelines

ATSDR (1997b) derived an acute inhalation MRL of 0.2 ppm for tetrachloroethylene based on a NOAEL of 10 ppm and a LOAEL of 50 ppm for neurological effects (e.g., performance deficits in tests of vigilance and eye-hand coordination) in volunteers exposed 4 hours/day for 4 days (Altmann et al. 1992), and an uncertainty factor of 10 for human variability.

ATSDR (1997b) derived a chronic-duration inhalation MRL of 0.04 ppm for tetrachloroethylene based on a LOAEL of 15 ppm for significantly prolonged reaction times in women who worked in dry cleaning shops for an average period of 10 years (Ferroni et al. 1992) and an uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability). Signs of mild kidney damage (increased urinary levels of lysozyme and β-glucuronidase) were found in another study of workers exposed to an average concentration of 10 ppm for an average of 14 years (Franchini et al. 1983). ATSDR (1997b) considered nervous system effects to be a more appropriate basis for the MRL and noted that the significance and adversity of the mild kidney effects were not clear.

ATSDR (1997b) did not derive an intermediate-duration inhalation MRL for tetrachloroethylene due to the lack of studies of neurological endpoints in humans exposed for intermediate durations. It was noted that liver enlargement was observed in mice exposed to 9 ppm, 24 hours/day for 30 days, but data in

humans were considered more appropriate for MRL derivation because mice metabolize more tetrachloroethylene to trichloroacetic acid than humans and the peroxisomal proliferation response is greater in mice than humans.

ATSDR (1997b) derived an acute oral MRL of 0.05 mg/kg/day for tetrachloroethylene based on a LOAEL of 5 mg/kg/day for hyperactivity at 60 days of age in mice exposed to gavage doses for 7 days beginning at 10 days of age (Fredriksson et al. 1993) and an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolating from animals to humans, and 10 for human variability).

ATSDR (1997b) did not derive intermediate- or chronic-duration oral MRLs for tetrachloroethylene due to the lack of suitable data. It was noted that intermediate-duration oral studies have observed liver effects in rats and mice and kidney effects in male rats, but these effects were not considered appropriate for MRL derivation due to apparent differences between humans and rodents in metabolism of tetrachloroethylene and in peroxisomal proliferation response, and indications that the kidney effects in male rats may be associated with accumulation of α-2μ-globulin, a male rat-specific protein (ATSDR 1997b).

EPA's IRIS database (IRIS 2001) lists an RfD of 0.01 mg/kg/day for tetrachloroethylene based on a NOAEL of 20 mg/kg/day for hepatotoxic effects in mice exposed by gavage for 6 weeks (Buben and O'Flaherty 1985) and an uncertainty factor of 1,000 (10 for extrapolating from animals to humans, 10 for human variability, and 10 for extrapolating from subchronic exposure duration to chronic duration).

EPA's IRIS database (IRIS 2001) does not list an RfC or a carcinogenicity assessment for tetrachloroethylene. As reviewed by ATSDR (1997b), the EPA Science Advisory Board in 1987 offered the opinion that the weight of evidence for tetrachloroethylene carcinogenicity was on a Group B2/C continuum (i.e., on the border between Group B2 and Group C). In 1991, another statement of this opinion was issued by the Science Advisory Board Executive Committee noting that tetrachloroethylene "should be considered to be an animal carcinogen, based on three endpoints in two species: liver tumors in male and female mice, kidney tumors in male rats, and, possibly, mononuclear cell leukemia in male and female rats" and that they did "not consider the evidence strong enough to classify this chemical as a probable human carcinogen." EPA has yet to present a more recent position on the weight-of-evidence classification for trichloroethylene carcinogenicity, but is expected to present, in 2001, an updated carcinogenicity assessment for tetrachloroethylene based on its 1996 Proposed Guidelines for Carcinogen Risk Assessment. NTP (2001) lists tetrachloroethylene as reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals. IARC (1995) concluded that

tetrachloroethylene is probably carcinogenic to humans (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals. IARC (1995) made the following notes to accompany its conclusions:

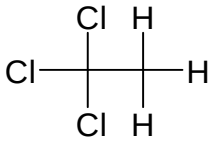
"(i) Although tetrachloroethylene is known to induce peroxisome proliferation in mouse liver, a poor quantitative correlation was seen between peroxisome proliferations and tumor formation in the liver after administration of tetrachloroethylene by inhalation. The spectrum of mutations in proto-oncogenes in liver tumors from mice treated with tetrachloroethylene is different from that in liver tumors from mice treated with trichloroethylene.

(i) The compound induced leukemia in rats.

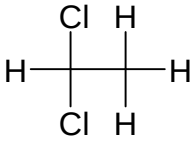
(ii) Several epidemiological studies showed elevated risks for oesophageal cancer, non-Hodgkin's lymphoma, and cervical cancer."

Appendix E: Chemical Structures of Mixture Components

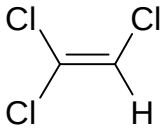
1,1,1-Tetrachloroethane



1,1-Dichloroethane



Trichloroethylene



Tetrachloroethylene