INTERACTION PROFILE FOR: 1,1,1-TRICHLOROETHANE, 1,1-DICHLOROETHANE, TRICHLOROETHYLENE, AND TETRACHLOROETHYLENE

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PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program, initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found. The Food Quality Protection Act (FQPA) of 1996 requires that factors to be considered in establishing, modifying, or revoking tolerances for pesticide chemical residues shall include the available information concerning the cumulative effects of substances that have a common mechanism of toxicity, and combined exposure levels to the substance and other related substances. The FQPA requires that the Administrator of the Environmental Protection Agency (EPA) consult with the Secretary of the Department of Health and Human Services (which includes ATSDR) in implementing some of the provisions of the act.

To carry out these legislative mandates, ATSDR's Division of Toxicology (DT) has developed and coordinated a mixtures program that includes trend analysis to identify the mixtures most often found in environmental media, *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity. These efforts are interrelated. For example, the trend analysis suggests mixtures of concern for which assessments need to be conducted. If data are not available, further research is recommended. The data thus generated often contribute to the design, calibration or validation of the methodology. This pragmatic approach allows identification of pertinent issues and their resolution as well as enhancement of our understanding of the mechanisms of joint toxic action. All the information obtained is thus used to enhance existing or developing methods to assess the joint toxic action of environmental chemicals. Over a number of years, ATSDR scientists in collaboration with mixtures risk assessors and laboratory scientists have developed approaches for the assessment of the joint toxic action of chemical mixtures. As part of the mixtures program a series of documents, Interaction Profiles, are being developed for certain priority mixtures that are of special concern to ATSDR.

The purpose of an Interaction Profile is to evaluate data on the toxicology of the "whole" priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health. Joint toxic action includes additivity and interactions. A weight-of-evidence approach is commonly used in these documents to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur.

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PEER REVIEW

A peer review panel was assembled for this profile. The panel consisted of the following members:

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All reviewers were selected in conformity with the conditions for peer review specified in Sect 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

SUMMARY

1,1,1-Trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene frequently occur together in water samples collected from and in the vicinity of National Priorities List (NPL) hazardous waste sites and other sites assessed by the Agency for Toxic Substances and Disease Registry (ATSDR). These chemicals occur together more frequently than other volatile organic chemicals at the sites. In an unpublished survey of ATSDR Public Health Assessments for 210 NPL hazardous waste sites, this mixture of chemicals was found in groundwater samples from 95% of the sites, in soil samples from 23% of the sites, and in air samples from 12% of the sites. The purposes of this profile are (1) to evaluate data on the toxicology of mixtures of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene, (2) to evaluate data on the joint toxic actions (e.g., additive, less-than-additive, or greater-than-additive joint actions) of these chemicals in producing health hazards, and (3) to make recommendations for exposure-based assessments of the potential impact of joint toxic action of the mixture on public health.

There are no studies available that directly characterize health hazards and dose-response relationships for exposures to "whole" mixtures containing 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. Furthermore, physiologically based pharmacokinetic (PBPK) models have not been developed to predict dispositional and toxicological outcomes of joint action of mixtures of these four chemicals.

Exposure to the each of the individual chemicals can produce neurological impairment via parent chemical-induced physical and chemical changes in neuronal membranes and cause non-carcinogenic and carcinogenic responses (via reactive metabolites) in the liver and kidney of animals. No studies are available that directly examine joint toxic actions of binary or trinary mixtures of these chemicals on the nervous system, but additive joint action is plausible. Limited studies of joint toxic action of binary or trinary mixtures of these chemicals on the liver and kidney provide no evidence of greater-than-additive joint toxic actions. Additive joint action on the liver and kidney is plausible for binary combinations of each of the components, with the exception of limited evidence that tetrachloroethylene may inhibit the toxic action of trichloroethylene on the liver and kidney (Goldsworthy and Popp 1987; Seiji et al. 1989).

A component-based hazard index approach that assumes additive joint toxic action and uses ATSDR Minimal Risk Levels (MRLs) based on neurological impairment is recommended for exposure-based assessments of possible health hazards from exposure to mixtures of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. There is no evidence to indicate that greater-than-additive interactions would cause liver and kidney effects to occur at exposure levels lower than those influencing the nervous system.

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LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight of evidence
bw	body weight
CYP	cytochrome P-450
DCVC	S-(1,2-dichlorovinyl)-L-cysteine
DCVG	S-(1,2-dichlorovinyl)glutathione
EPA	Environmental Protection Agency
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
mg	milligram
mL	milliliter
mmol	millimole
MRL	Minimal Risk Level
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
PBPK	physiologically based pharmacokinetic
ppm	parts per million
RfC	Reference Concentration
RfD	Reference Dose
SDH	sorbitol dehydrogenase
U.S.	United States
WOE	weight of evidence
〉	greater than
≥	greater than or equal to
=	equal to
〈	less than
≤	less than or equal to

1. Introduction

The primary purpose of this Interaction Profile for 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene is to evaluate data on the toxicology of the "whole" mixture and the joint toxic action of the chemicals in the mixture in order to recommend approaches for assessing the potential hazard of this mixture to public health. To this end, the profile evaluates the whole mixture data (if available), focusing on the identification of health effects of concern, adequacy of the data as the basis for a mixture Minimal Risk Level (MRL), and adequacy and relevance of physiologically-based pharmacokinetic/pharmacodynamic models for the mixture. The profile also evaluates the evidence for joint toxic action—additivity and interactions—among the mixture components. A weight-of-evidence approach is commonly used in these profiles to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur. The profile provides environmental health scientists with ATSDR Division of Toxicology (DT) recommended approaches for the incorporation of the whole mixture data or the concerns for additivity and interactions into an assessment of the potential hazard of this mixture to public health. These approaches can then be used with specific exposure data from hazardous waste sites or other exposure scenarios.

An unpublished analysis of ATSDR Public Health Assessments of 1,608 National Priority List (NPL) hazardous waste sites indicates that the mixture of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene was found at 210 sites and was the most frequently occurring mixture of four volatile organic chemicals. This occurrence frequency was the basis for choosing the mixture as the subject of this profile. Contaminated media at sites with this mixture included groundwater (186/210 sites), soil (45/210 sites), and air (25/210 sites). Categories of activities associated with detection of this mixture in water samples included waste storage/treatment/disposal (35% of sites), manufacturing and industry (29%), waste recycling (9%), and "other" miscellaneous activities (18%). Other activity categories associated to a lesser degree with detection of the mixture in groundwater included "affected area/natural resource" (5% of sites), residential (2%), mining/extracting/processing (1%), and government (2%). The most frequent completed exposure pathway for volatile organic chemicals at these sites involved private well water. Completed exposure pathways involving municipal water or air contaminated with volatile organic chemicals were less frequent. Volatile organic chemicals were unimportant in most completed exposure pathways involving soil.

Each of the chemicals in the mixture of concern is volatile, has good hydrocarbon solvent properties, and does not persist in the body for long periods of time. They have been widely used in dry cleaning and textile-processing (tetrachloroethylene), vapor degreasing of fabricated metal parts (tetrachloroethylene, trichloroethylene, and 1,1,1-trichloroethane), or manufacturing of other chemical products such as vinyl chloride and high vacuum rubber (1,1-dichloroethane). Only one of the four chemicals, trichloroethylene, is extensively metabolized; the remaining three are predominately excreted unmetabolized in exhaled breath. The critical noncancer health effect in humans (i.e., the effect expected to occur at the lowest exposure levels) for each of these chemicals, regardless of exposure route or duration, is neurological impairment. Reflecting this expectation, neurological effects form the basis of ATSDR's inhalation and oral MRLs for these chemicals (ATSDR 1990, 1995, 1997a, 1997b).

Although some evidence of cancer, of varying weight, has been found in rodent studies for high doses of each of these chemicals, low level exposure of humans may not present high risks for cancer. The Environmental Protection Agency (EPA) (IRIS 2001) assigned 1,1,1-trichloroethane to Cancer Group D (Not Classifiable as to Human Carcinogenicity), 1,1-dichloroethane to Cancer Group C (Possible Human Carcinogen), and trichloroethylene and tetrachloroethylene to the boundary between Group C (Possible Human Carcinogen) and Group B2 (Probable Human Carcinogen). EPA lists no oral slope factors or inhalation unit risks for these chemicals on its Integrated Risk Information System (IRIS) (2001) database, but is currently evaluating several approaches to extrapolating from rodent tumor data to derive estimates of human cancer risks at environmentally relevant exposure levels of trichloroethylene and tetrachloroethylene. The National Toxicology Program (NTP 2001) list of chemicals reasonably anticipated to be human carcinogens includes trichloroethylene and tetrachloroethylene, but not 1,1-dichloroethane or 1,1,1-trichloroethane. IARC (2001) has not assigned a cancer classification for 1,1-dichloroethane, but assigned 1,1,1-trichloroethane to Cancer Group 3, not classifiable as to human carcinogenicity, and trichloroethylene and tetrachloroethylene to Cancer Group 2A, probably carcinogenic to humans.

2. Joint Toxic Action Data for the Mixture of Concern and Component Mixtures

2.1 Mixture of Concern

No data were located regarding health or pharmacokinetic endpoints in humans or animals exposed to mixtures containing all four of the chemicals: 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene.

No physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models were found for quaternary mixtures of these chemicals.

2.2 Component Mixtures

No PBPK/PD models were found for ternary or binary mixtures of these chemicals. The following subsections present evaluations of health effects and pharmacokinetic data and discussions of mechanistic information pertinent to the joint toxic action of combinations of the components.

2.2.1 1,1,1-Trichloroethane, Trichloroethylene, and Tetrachloroethylene

Stacey (1989) studied the joint action of 1,1,1-trichloroethane, trichloroethylene, and tetrachloroethylene on renal and hepatic endpoints in rats *in vivo* and in isolated rat hepatocytes *in vitro*. Groups of five to six male Sprague-Dawley rats were given doses of 1,1,1-trichloroethane (15 mmol/kg or 2,001 mg/kg), trichloroethylene (10 mmol/kg or 1,314 mg/kg), or tetrachloroethylene (15 mmol/kg or 2,487 mg/kg) alone by intraperitoneal injection. Preliminary experiments indicated that these doses were near (but below) thresholds for hepatotoxic effects. Similar groups were given these doses in a ternary mixture (15 mmol/kg 1,1,1-trichloroethane + 10 mmol/kg trichloroethylene + 15 mmol/kg tetrachloroethylene) or in binary mixtures (e.g., 15 mmol/kg 1,1,1-trichloroethane + 10 mmol/kg trichloroethylene). The control group received corn oil (0.6 mg/kg). Animals were sacrificed after 24 hours; livers were weighed and blood was collected for analysis of alanine aminotransferase (ALT), sorbitol dehydrogenase (SDH), and urea. Individually, 1,1,1-trichloroethane, trichloroethylene, and tetrachloroethylene did not produce any significant changes in these endpoints at the administered doses. Combined administration of all three agents produced a significant decrease in liver:body weight ratio and significant increases in blood levels

of ALT, SDH, and urea. Similar results were obtained with *in vivo* exposure to binary mixtures except that the magnitude of the changes was not as great as the changes produced by the ternary mixture.

In the *in vitro* experiments (Stacy 1989), freshly isolated rat hepatocytes were incubated for up to 3 hours in medium containing 1,1,1-trichloroethane (2 or 5 μL added to sealed 25 mL flasks), trichloroethylene (2 or 4 μL), or tetrachloroethylene (1 or 2 μL). These levels were chosen because they were below the threshold for induction of toxic effects based on preliminary experiments. Other hepatocytes were incubated with medium containing all three agents or binary mixtures at all possible combinations of the exposure levels used in the individual treatments (8 ternary combinations and 12 binary combinations). The media were sampled after 1, 2, and 3 hours of incubation and analyzed for several indices of toxicity (potassium ions, ALT, and lactate dehydrogenase) released from the hepatocytes. Incubation in the presence of 1,1,1-trichloroethane, trichloroethylene, or tetrachloroethylene alone caused no significant changes in the cytotoxicity indices compared with the control values. In contrast, leakage rates of potassium ions, ALT, and lactate dehydrogenase were significantly greater than control values for hepatocytes incubated for 3 hours with seven of the eight ternary combinations. The lowest level ternary combination (2 μL 1,1,1-trichloroethane + 2 μL trichloroethylene + 1 μL tetrachloroethylene) did not significantly change the cytotoxicity indices. Incubation for 3 hours to 5/12, 5/12, and 6/12 of the tested binary combinations significantly increased leakage rates for potassium ion, ALT, and lactate dehydrogenase, respectively, compared with control rates.

The results from the *in vivo* and *in vitro* studies consistently show that exposure to binary and ternary mixtures of the agents, at doses that were below individual thresholds, produced mild toxic hepatic or renal responses, and that the responses to the ternary mixtures were generally greater than responses to the binary mixtures. Although the individual doses were below individual threshold doses for hepatic or renal responses, the doses are much greater than any that might be expected to be associated with general population exposure to these compounds. For example, EPA (as cited in ATSDR 1997b) estimated that about 5% of the U.S. population using public drinking water is exposed to tetrachloroethylene levels above 0.5 ppb (0.014 μg/kg/day). Total tetrachloroethylene intakes by Canadians has been estimated at 1.2–2.7 μg/kg/day (ATSDR 1997b). In contrast, the dose of tetrachloroethylene given to rats in this study was >2 g/kg. Due to design limitations, the results of the study cannot discern whether the joint action of these agents at the high dose levels tested is additive, greater-than-additive, or less-than-additive. The study did not include dose levels of the individual agents that produced changes in the endpoints or, alternatively, include mixtures comprised of equal parts of the component agents at dose levels that additively equaled the applied individual-agent dose level. Without at least one effective dose level for

each agent, no indications of the individual dose-response relationships are given, and no conclusion can be drawn concerning their joint toxic action, except if the tested mixture includes equal doses of the components that add to the tested dose level of the individual agents. Unfortunately, Stacey's mixtures did not have the appropriate compositions to determine joint action of the agents as follows:

1 unit agent A alone; 1 unit agent B alone; ½ unit A + ½ unit B mixture, or

1 unit A alone; 1 unit B alone; 1 unit C alone; 1/3 unit A + 1/3 unit B + 1/3 unit C mixture.

Stacey (1989) concluded that the joint action of these chemicals "may best be described as additive," but acknowledged that "when the individual treatments have no effect, use of this term is not entirely appropriate." Stacey (1989) also proposed that the term "positive interaction has been generally used to indicate that the binary combinations demonstrate toxicity, while single chemicals do not and that ternary mixtures generally show toxicity greater than binary combinations." It should be noted, however, that this term, while consistent with the results, is not synonymous with the terms additive or greater-than-additive.

2.2.2 1,1,1-Trichloroethane and 1,1-Dichloroethane

No studies were located that examined health or pharmacokinetic endpoints after exposure to binary mixtures of 1,1,1-trichloroethane and 1,1-dichloroethane compared with exposure to the chemicals alone.

Acute exposures to high airborne concentrations of 1,1,1,-trichloroethane or 1,1-dichloroethane can produce central nervous system depression and anesthesia along with cardiac arrhythmias that may lead to ventricular fibrillation (see Appendices A and B, ATSDR 1990, 1995). 1,1,1-Trichloroethane-induced nervous system depression and cardiac arrhythmias are thought to be induced by the parent chemical and not by metabolites, and the cardiac arrhythmias are thought to involve parent-chemical sensitization of the heart to epinephrine-induced arrhythmias (ATSDR 1995). Although 1,1-dichloroethane has been studied less than 1,1,1-trichloroethane with respect to mechanisms of producing nervous system depression and cardiac arrhythmias (ATSDR 1990, 1995), it is likely to act by similar mechanisms to those of 1,1,1-trichloroethane, given that other small molecular weight halogenated hydrocarbons and other solvents produce similar effects, especially nervous system depression (ATSDR 1997b; Snyder and Andrews 1996). It is plausible that 1,1,1-trichloroethane and 1,1-dichloroethane may jointly act in an additive manner to depress the central nervous system and sensitize the heart to epinephrine, but no studies were located that were designed to test this hypothesis.

Unlike certain other chlorinated alkanes (such as carbon tetrachloride, chloroform, 1,1,2-trichloroethane, and 1,2-dichloroethane), 1,1,1-trichloroethane and 1,1-dichloroethane are not potent hepatotoxic, renotoxic, or carcinogenic agents, but some animal studies have found possible carcinogenic and noncarcinogenic effects in the liver and/or kidney following repeated high level exposure scenarios (ATSDR 1990, 1995). These effects are believed to be caused by reactive intermediates formed via cytochrome P-450 (CYP) catalysis. The low potencies of 1,1,1-trichloroethane and 1,1-dichloroethane to produce these effects have been associated with the limited degree to which they are metabolized.

The difference in hepatotoxic potency between 1,1,1-trichloroethane and its isomer, 1,1,2-trichloroethane, has been associated with differences in the degree to which the two isomers are metabolized, providing support for the general hypothesis that reactive products of metabolism (e.g., free radicals that are formed by reductive dechlorination catalyzed by CYP isozymes), and not parent chemicals, are responsible for the hepatotoxicity and carcinogenicity of chlorinated alkanes (Plaa 1986). In rats and mice dosed by gavage, urinary excretion of metabolites accounted for >70% of administered doses of the 1,1,2-isomer, whereas >85% of the 1,1,1-isomer was excreted unchanged in expired air (Mitoma et al. 1985).

The difference in hepatotoxic and carcinogenic potency between 1,1-dichloroethane and its isomer, 1,2-dichloroethane, appears to be associated with differences in metabolic disposition for the two isomers (McCall et al. 1983; Mitoma et al. 1985). 1,2-Dichloroethane can be conjugated to glutathione, leading to a reactive intermediate that is thought to be key to its relatively more toxic nature (McCall et al. 1983). The formation of reactive intermediates from conjugation of 1,1-dichloroethane with glutathione does not appear to occur. 1,1-Dichloroethane's low potency is also related to the limited degree to which it is metabolized. In mice given high doses (700 or 1,800 mg/kg), metabolism accounted for only 7 or 29% of the administered dose (Mitoma et al. 1985).

The mild hepatotoxic effects of 1,1,1-trichloroethane and 1,1-dichloroethane are believed to be caused by reactive metabolites formed by CYP catalysis. No studies were located that were designed to examine whether or not coexposure to 1,1,1-trichloroethane and 1,1-dichloroethane would influence each other's metabolic disposition. Competitive metabolic interactions (at CYP2B1/2or CYP2E1 active sites) between 1,1,1-trichloroethane and 1,1-dichloroethane are plausible. It does not appear likely, however, that metabolic inhibition at this site would lead to toxicologically significant shunting to alternative pathways (e.g., transformation of 1,1,1-trichloroethane to dechlorinated radical intermediates and acetylene; see Appendix A) given that neither chemical is extensively metabolized by the CYP oxidative pathway, which is the major pathway for each.

Results regarding the ability of 1,1,1-trichloroethane to induce it's own metabolic machinery or induce hepatic levels of CYP isozymes suggest that repeated inhalation or oral exposure to 1,1,1-trichloroethane is not likely to markedly alter CYP-mediated hepatic metabolism, especially at daily administered dose levels <500 mg/kg/day (see Appendix A). For example, in male rats exposed for up to 12 days to oral doses of 0, 0.1, 0.5, 5.0, or 10.0 g/kg/day 1,1,1-trichloroethane, only the two highest doses induced hepatic microsomal activities of CYP2E1 and CYP2B1/2 (Bruckner et al. 2000). Studies designed to examine whether induction of hepatic CYP isozymes would influence the toxicity of 1,1-dichloroethane were not located, although induction by phenobarbital has been demonstrated to increase rates of 1,1-dichloroethane metabolism in rat hepatic microsomes (McCall et al. 1983). It appears unlikely, however (given that 1,1,1-trichloroethane appears to be a weak inducer of CYP isozymes), that coexposure with 1,1,1-trichloroethane would lead to an increased capacity to transform 1,1-dichloroethane to putative toxic metabolites.

Studies designed to examine the ability of 1,1-dichloroethane to induce hepatic enzymes were not located. Even if it were known that 1,1-dichloroethane could induce hepatic CYP isozymes involved in 1,1,1-trichloroethane metabolism, enhancement of 1,1,1-trichloroethane metabolism to such a degree that hepatotoxicity or carcinogenicity would be enhanced is not expected. Downstream enzymes may prevent the elevation of hepatic concentrations of a proximate toxicant(s) and repair mechanisms may efficiently fix any damage to cellular macromolecules. Furthermore, results from studies in which rats have been pretreated with phenobarbital or ethanol to enhance hepatic metabolism of 1,1,1-trichloroethane have not shown consistent evidence that potentiation of 1,1,1-trichloroethane hepatotoxicity occurs (Carlson 1973; Cornish et al. 1973; see Appendix A).

In summary, it is plausible that 1,1,1-trichloroethane and 1,1-dichloroethane may act jointly in an additive manner to produce central nervous system depression and heart sensitization to epinephrine, but studies designed to test this hypothesis were not located. The mild hepatotoxic potency of both of these chemicals appears to be mediated by reactive metabolic intermediates, but it is unclear how or if these chemicals may influence each other's metabolism. In general, neither of these chemicals is extensively metabolized, and any mutual interference that they may have on each other's metabolism may have little influence on their toxicity. Additive joint toxic action to produce liver and kidney effects is plausible, but studies directly designed to test this hypothesis were not located.

2.2.3 1,1,1-Trichloroethane and Trichloroethylene

Acute exposures to high airborne concentrations or large oral doses of 1,1,1-trichloroethane or trichloroethylene can produce central nervous system depression and anesthesia, as well as cardiac arrhythmias that can lead to ventricular fibrillation (ATSDR 1995, 1997a). The nervous system depression by 1,1,1-trichloroethane is thought to be induced by the parent chemical (ATSDR 1995), whereas nervous system effects from trichloroethylene involve the parent chemical as well as the metabolite, trichloroethanol. 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. The cardiac arrhythmias are thought to involve parent-chemical sensitization of the heart to epinephrine-induced arrhythmias (ATSDR 1995, 1997a). It is plausible that 1,1,1-trichloroethane and trichloroethylene may jointly act in an additive manner to depress the central nervous system and sensitize the heart to epinephrine. However, no studies were located that were designed to test this hypothesis, and it is unknown whether or not they may influence each other's metabolism.

Another toxicity target that is shared by 1,1,1-trichloroethane and trichloroethylene is the liver. Animal experiments indicate that both are mild hepatotoxic agents whose tissue damaging activity may be due to reactive metabolic intermediates formed via CYP isozyme catalysis (ATSDR 1995, 1997a). No clear evidence for 1,1,1-trichloroethane carcinogenicity was found in animal cancer bioassays, including an adequate inhalation bioassay with rats and mice and two oral studies with design limitations (ATSDR 1995), whereas cancer of the liver and lung in B6C3F1 mice and cancer of the kidney and testes in rats have been observed in bioassays involving high level chronic exposure to trichloroethylene (ATSDR 1997a). Any carcinogenic action that these chemicals might exert is expected to be due to reactive metabolites (ATSDR 1995, 1997a; Bull 2000; Green 2000; Lash et al. 2000).

Animal studies indicate that the rate of 1,1,1-trichloroethane metabolism is much lower than that of trichloroethylene, even under conditions (e.g., repeated ethanol exposure) that induce hepatic CYP isozyme levels (Kaneko et al. 1994). In these studies, it was shown that ethanol pretreatment of rats increased the rate of metabolism of inhaled 1,1,1-trichloroethane to trichloroethanol and trichloroacetic acid, but most of the chemical still was expected to be eliminated (exhaled) unmetabolized (Kaneko et al. 1994). In contrast, ethanol pretreatment did not enhance trichloroethylene transformation to trichloroacetic acid or trichloroethanol after low-level trichloroethylene exposure (50–100 ppm), but did increase the rate of appearance of these metabolites in urine after exposure to high levels (500 or 1,000 ppm) of trichloro-

ethylene (Kaneko et al. 1994). Although Lee et al. (2000) recently reported that moderate to high (432 or 1,000 mg/kg), but not low (8 mg/kg), acute doses of trichloroethylene induced hepatic CYP2E1 activities in rats, results from studies of phenobarbital induction (Carlson 1973; Cornish et al. 1973) do not provide consistent evidence that CYP induction will lead to enhancement of 1,1,1-trichloroethane hepatotoxicity. Thus, trichloroethylene enhancement of 1,1,1-trichloroethane hepatoxicity is not expected, especially at administered trichloroethylene dose levels below 400 mg/kg when no CYP induction is expected.

Phenobarbital pretreatment and induction of hepatic CYP isozymes are associated with enhancement of acute high-level trichloroethylene hepatotoxicity in rodents (Allemand et al. 1978; Carlson 1973; Moslen et al. 1977; Nakajima et al. 1990), but no studies were located indicating that 1,1,1-trichloroethane pretreatment or coexposure with trichloroethylene would enhance trichloroethylene metabolism. 1,1,1-Trichloroethane modestly induced hepatic CYP 2B1/2 and 2E1 isozymes (involved in the bioactivation of trichloroethylene) only at near-lethal levels of exposure in rats (Bruckner et al. 2000; see Appendix A); thus 1,1,1-trichloroethane is not expected to enhance trichloroethylene hepatotoxicity via CYP induction at environmentally relevant exposure levels. Competitive metabolic interactions between these chemicals at catalytic sites of CYP isozymes does not appear to be likely either. 1,1,1-Trichloroethane is likely to be a poor competitor of trichloroethylene as suggested by observations that the extent of trichloroethylene metabolism is much greater than that of 1,1,1-trichloroethane. Furthermore, alteration of trichloroethylene metabolism at CYP catalytic sites is likely to be physiologically important only at high concentrations/exposure levels when substrate concentrations are in excess of enzyme catalytic sites. For example, CYP induction only altered trichloroethylene metabolic rates in rats exposed to high (500 or 1,000 ppm), but not low (50–100 ppm), trichloroethylene levels (Kaneko et al. 1994).

When adult male rats were exposed by inhalation to a mixture of 1,1,1-trichloroethane (500 ppm) and trichloroethylene (200 ppm) for 6 hours/day for 4 consecutive days and sacrificed 18 hours after cessation of the last exposure period, no trichloroethylene was detected in blood, brain tissue, lung tissue, or perirenal fat (Vainio et al. 1978). In contrast, 1,1,1-trichloroethane was detected in these tissues, presumably due to its slower rate of metabolism. These results are consistent with the hypothesis that, under these conditions, 1,1,1-trichloroethane did not inhibit metabolic disposition of trichloroethylene, but are not conclusive since the study did not include rats exposed to trichloroethylene alone.

The only located study that examined possible toxicological interactions between trichloroethylene and 1,1,1-trichloroethane is a report of *in vitro* and *in vivo* rat studies (Stacey 1989). Incubation of isolated rat

hepatocytes for up to 3 hours in medium containing trichloroethylene (2 or 4 μL added to sealed 25 mL flasks) or 1,1,1-trichloroethane (2 or 5 μL) did not cause statistically significant changes in intracellular potassium concentrations or leakage of ALT or lactate dehydrogenase, compared with hepatocytes incubated in control medium. Incubation in medium containing both trichloroethylene and 1,1,1-trichloroethane at all combinations of the exposure levels noted above did not significantly affect these indices of hepatocellular damage, except at the higher level of trichloroethylene when decreased intracellular potassium concentrations and increased leakage of ALT or lactate dehydrogenase were found compared with controls (Stacey 1989). These results are consistent with a combined effect of the two chemicals on membrane integrity at the higher mixed exposure level of trichloroethylene. Intraperitoneal injection of rats with 10 mmol/kg trichloroethylene (1,314 mg/kg) alone or 15 mmol/kg 1,1,1-trichloroethane (2,001 mg/kg) alone did not produce, 24 hours after injection, significant kidney (serum urea levels) or liver damage (serum ALT and SDH, and liver-to-body weight ratio) compared with controls injected with corn oil. These doses were expected to be just below individual threshold doses for liver and kidney effects. Combined exposure significantly increased serum ALT and SDH and significantly decreased mean liver:body weight ratio compared with controls. The results from this study clearly show that exposure to a mixture of trichloroethylene and 1,1,1-trichloroethane, at dose levels below the individual hepatotoxic thresholds for these chemicals, can produce liver damage. However, as discussed in more detail in Section 2.2.1, one cannot discern from the results whether the joint action of trichloroethylene and 1,1,1-trichloroethane is additive, greater-than-additive, or less-than-additive, due to study design limitations.

In summary, it is plausible that 1,1,1-trichloroethane and trichloroethylene may jointly act in an additive manner to produce cardiac sensitization and toxic effects in the nervous system (CNS depression), the liver, and the kidney, but evidence in support of this hypothesis is weak due to the limited and ambiguous joint toxic action data on liver and kidney endpoints (Stacey 1989), a lack of joint action data on cardiac sensitization and nervous system endpoints, and a lack of data regarding how these chemicals may enhance or inhibit each other’s metabolism and general disposition in the body.

Table 1. Summary of Available Data on the Influence of 1,1,1-Trichloroethane on Toxicity/Carcinogenicity of Trichloroethylene and the Influence of Trichloroethylene on Toxicity/Carcinogenicity after 1,1,1-Trichloroethane after Simultaneous Exposure

Duration	Endpoint	Results			Conclusions	References
		Greater than additive	Additive/no effect	Less than additive		
Intraperitoneal Exposure (mg/kg/day)[a]						
1,1,1-Trichloroethane Influence on Toxicity/Carcinogenicity of Trichloroethylene						
acute	serum ALT and SDH, liver-to-BW ratio		2,001 + 1,314 (r)[b]		Endpoints were increased with mixed exposure, but not by single components alone. Joint action is ambiguous due to study design limitation.	Stacey 1989
Trichloroethylene Influence on Toxicity/Carcinogenicity of 1,1,1-Trichloroethane						
acute	serum ALT and SDH, liver-to-BW ratio		1,314 + 2,001 (r)[b]		Endpoints were increased with mixed exposure, but not by single components alone. Joint action is ambiguous due to study design limitation.	Stacey 1989

[a] First dose listed is for the chemical influencing the other chemical's toxicity/carcinogenicity.
[b] Species code: r = rat

ALT = alanine aminotransferase; BW = body weight; SDH = sorbitol dehydrogenase

2.2.4 1,1,1-Trichloroethane and Tetrachloroethylene

1,1,1-Trichloroethane and tetrachloroethylene are both metabolized initially by CYP isozymes, with glutathione conjugation as a minor pathway for tetrachloroethylene (ATSDR 1995, 1997b). Exhalation of nonmetabolized (parent) chemical is expected to be the principal route of excretion for both chemicals in humans due to the low rates of metabolism and high volatility. Central nervous system depression, common to both, is thought to be produced by interaction of the parent chemicals with neuronal membrane components (ATSDR 1995, 1997b). Metabolites of these chemicals are thought to be responsible for the liver and kidney effects observed in studies of rodents exposed to either 1,1,1-trichloroethane or tetrachloroethylene, but the potential for either chemical to cause liver or kidney effects in humans is generally thought to be low due to limited human capacity to metabolize them.

Studies designed to examine possible metabolic interactions between 1,1,1-trichloroethane and tetrachloroethylene are restricted to a study of urinary metabolites in rats exposed by inhalation for 8 hours to about 350 ppm 1,1,1-trichloroethane, 100 ppm tetrachloroethylene, or a mixture of both at these concentrations (Koizumi et al.1982). The mean rate of urinary excretion of trichloroethanol during exposure to the mixture (75 μg/kg/hour ±40) was significantly less than the mean rate during exposure to 1,1,1-trichloroethane alone (179 μg/kg/hour ±39). Trichloroethanol was not detected in the urine during or after exposure to tetrachloroethylene alone. The results suggest that tetrachloroethylene inhibited the metabolism of 1,1,1-trichloroethane. In general however, neither of these chemicals is extensively metabolized; any alterations that they may have on each other's metabolism should have little influence on their toxicity. Pretreatment of rats with CYP inducers, including ethanol (Cornish and Adefuin 1966; Klaassen and Plaa 1966), phenobarbital (Cornish et al. 1973; Moslen et al. 1977), or Aroclor 1254 (Moslen et al. 1977) has not consistently potentiated acute high level tetrachloroethylene hepatotoxicity. Likewise, results from similar studies with 1,1,1-trichloroethane do not provide consistent evidence of potentiation of acute hepatotoxicity from CYP induction (Carlson 1973; Cornish et al. 1973).

Results from studies of hepatic and renal endpoints in rats exposed by intraperitoneal injection and in isolated rat hepatocytes *in vitro* (Stacey 1989) are consistent with the hypothesis that 1,1,1-trichloroethane and tetrachloroethylene may jointly act in a positive manner, but cannot exclude the possibility of greater-than-additive or less-than-additive interactions due to study design limitations as discussed in Section 2.2.1. Incubation of isolated rat hepatocytes for up to 3 hours in medium containing tetrachloroethylene (1 or 2 μL added to sealed 25 mL flasks) or 1,1,1-trichloroethane (2 or 5 μL) did not cause statistically significant changes in intracellular potassium concentrations or leakage of ALT or lactate

dehydrogenase, compared with hepatocytes incubated in control medium. Incubation in medium containing both tetrachloroethylene and 1,1,1-trichloroethane at combinations of the exposure levels noted above did not significantly affect these indices of hepatocellular damage, except at the higher level of tetrachloroethylene when decreased intracellular potassium concentrations and increased leakage of ALT or lactate dehydrogenase were found (Stacey 1989). These results are consistent with a joint toxic effect on membrane integrity at the higher mixed exposure level of tetrachloroethylene. Intraperitoneal injection of rats with near-threshold doses of 15 mmol/kg tetrachloroethylene (2,487 mg/kg) or 15 mmol/kg 1,1,1-trichloroethane (2,001 mg/kg) alone did not significantly change, 24 hours after injection, measures of liver (serum ALT and SDH, and liver-to-body weight ratio) or kidney damage (serum urea levels) compared with controls injected with corn oil. However, coadministration of 15 mmol/kg tetrachloroethylene + 15 mmol/kg 1,1,1-trichloroethane caused statistically significant increases (compared with controls or either chemical alone) in serum ALT and SDH, a nonsignificant increase in serum urea, and a nonsignificant decrease in liver:body weight ratio. These results clearly show that a mixture of subthreshold doses of tetrachloroethylene and 1,1,1-trichloroethane can produce liver and/or kidney damage, but cannot clearly discern the mode of joint action due to study design limitations.

In summary, it is plausible that 1,1,1-trichloroethane and tetrachloroethylene may jointly act in an additive manner to produce cardiac sensitization and effects in the nervous system, the liver, and the kidney, but evidence in support of this hypothesis is weak due to the limited and ambiguous interaction data on liver and kidney endpoints (Stacey 1989), a lack of data regarding how these chemicals may enhance or inhibit each other's metabolism and general disposition in the body, and a lack of interaction data on cardiac sensitization and nervous system endpoints. There are data to suggest that tetrachloroethylene may suppress 1,1,1-trichloroethane metabolism in rats (Koizumi et al. 1982), but the limited degree to which 1,1,1-trichloroethane is metabolized suggests that this should have little effect on its toxicity.

Table 2. Summary of Available Data on the Influence of 1,1,1-Trichloroethane on Toxicity/Carcinogenicity of Tetrachloroethylene and the Influence of Tetrachloroethylene on Toxicity/Carcinogenicity of 1,1,1-Trichloroethane after Simultaneous Exposure

Duration	Endpoint	Results			Conclusions	References
		Greater than additive	Additive/no effect	Less than additive		
Intraperitoneal Exposure (mg/kg/day)[a]						
1,1,1-Trichloroethane Influence on Toxicity/Carcinogenicity of Tetrachloroethylene						
acute	serum ALT and SDH, liver-to-BW ratio		2,001 + 2,487 (r)[b]		Endpoints were changed with mixed exposure, but not by single components alone. Joint action is ambiguous due to study design limitation.	Stacey 1989
Tetrachloroethylene Influence on Toxicity/Carcinogenicity of 1,1,1-Trichloroethane						
acute	serum ALT and SDH, liver-to-BW ratio		2,487 + 2,001 (r)[b]		Endpoints were changed with mixed exposure, but not by single components alone. Joint action is ambiguous due to study design limitation.	Stacey 1989

[a] First dose listed is for the chemical influencing the other chemical's toxicity/carcinogenicity.
[b] Species code: r = rat

ALT = alanine aminotransferase; BW = body weight; SDH = sorbitol dehydrogenase

2.2.5 1,1-Dichloroethane and Trichloroethylene

No studies were located that examined health or pharmacokinetic endpoints after exposure to binary mixtures of 1,1-dichloroethane and trichloroethylene compared with exposure to the chemicals alone.

The initial steps in the metabolism of 1,1-dichloroethane and trichloroethylene involve oxidation catalyzed by CYP isozymes (ATSDR 1990, 1997a). The capacity of rodent hepatic liver microsomes to metabolize these chemicals has been demonstrated to be induced by phenobarbital and chronic ethanol pretreatment (Colacci et al. 1985; Cornish and Adefuin 1966; McCall et al. 1983; Nakajima et al. 1990, 1993; Sato et al. 1980, 1981), indicating that similar CYP isozymes are involved in metabolism of each (ATSDR 1990, 1997a). Competitive metabolic interactions at CYP catalytic sites between these chemicals are possible, but not likely. Although studies designed to test this hypothesis were not located, 1,1-dichloroethane is much more slowly metabolized than trichloroethylene (see below) and is, thus, unlikely to be an effective competitive inhibitor of trichloroethylene at CYP catalytic sites. Also, as discussed in Section 2.2.3, alteration of trichloroethylene metabolism at CYP catalytic sites is likely to be physiologically important only at high exposure levels (Kaneko et al. 1994). Given the limited extent to which 1,1-dichloroethane is metabolized, any influence that trichloroethylene may exert on 1,1-dichloroethane metabolism should have minimal influence on toxicity.

Like other solvents, both parent chemicals appear to sensitize the heart to epinephrine and to act on neuronal membranes producing reversible nervous system depression (ATSDR 1990, 1997a). Trichloroethanol, a metabolite of trichloroethylene, is thought to act similarly on neuronal membranes. It is plausible that both parent chemicals may act jointly in an additive manner to produce central nervous system depression and heart sensitization to epinephrine, but studies designed to test this hypothesis were not located.

In experiments with animals, trichloroethylene exposure has produced carcinogenic and noncarcinogenic responses in the liver and kidney that are thought to be caused by reactive metabolites (ATSDR 1997a). Studies designed to examine if coexposure to 1,1-dichloroethane would interfere with trichloroethylene metabolism and trichloroethylene induction of liver and kidney effects were not located. 1,1-Dichloroethane has a low potential for producing liver and kidney damage, as evidenced by the observation that 78-week oral exposure to 1,1-dichloroethane doses as high as 950 mg/kg/day in rats and 3,331 mg/kg/day in mice did not induce histological changes in liver or kidney tissue (ATSDR 1990; NCI 1977). 1,1-Dichloroethane's low hepatic and renal toxicities are associated with the limited extent to which it is

metabolized and the absence of formation of a reactive metabolite via conjugation with glutathione (such as that which is formed from 1,2-dichloroethane, the more toxic dichloroethane isomer) (McCall et al. 1983; Mitoma et al. 1985). For example, 48 hours after administration of high oral doses of 1,1-dichloroethane 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). In contrast, metabolism accounted for about 30 and 82% of doses of trichloroethylene administered orally to rats (1,300 mg/kg) and mice (2,000 mg/kg) (Mitoma et al. 1985). Due to the limited extent to which it is metabolized, 1,1-dichloroethane is not likely to be an effective competitor of trichloroethylene metabolism and may not interfere with the toxic action of trichloroethylene. However, studies directly designed to test this hypothesis were not located.

In summary, despite limited mechanistic understanding of the toxic actions of 1,1-dichloroethane and trichloroethylene, it is plausible that they may act jointly in an additive manner to produce cardiac sensitization and effects on the nervous system, the liver, and the kidney, but studies directly designed to test hypotheses associated with this contention were not located.

2.2.6 1,1-Dichloroethane and Tetrachloroethylene

Studies that examined health or pharmacokinetic endpoints after exposure to binary mixtures of 1,1-dichloroethane and tetrachloroethylene compared with exposure to the chemicals alone were not located.

Like other solvents, both parent chemicals sensitize the heart to epinephrine and act on neuronal membranes producing reversible nervous system depression (ATSDR 1990, 1997b). It is plausible that 1,1-dichloroethane and tetrachloroethylene may act jointly in an additive manner to produce central nervous system depression and heart sensitization to epinephrine, but studies designed to test this hypothesis were not located.

Any carcinogenic or noncarcinogenic effects that these chemicals may exert on tissues outside of the nervous system (such as the liver and kidney) are expected to occur with repeated exposure to high doses (based on results from animal studies) and to be caused by reactive metabolites (ATSDR 1990, 1997b). The extent to which either is metabolized, however, is limited. For example, within 48 hours of administration of high oral doses, metabolism of 1,1-dichloroethane accounted for only about 7 and 29% of administered doses in rats (700 mg/kg) and mice (1,800 mg/kg), and metabolism of tetrachloroethylene accounted for only 5 and 22% of administered doses in rats (1,000 mg/kg) and mice (899 mg/kg)

(Mitoma et al. 1985). The initial steps in the metabolism of 1,1-dichloroethane and tetrachloroethylene involve oxidation catalyzed by CYP isozymes, indicating the potential for competitive metabolic interactions (ATSDR 1990, 1997b). However, neither of these chemicals is extensively metabolized, and any mutual interference that they may have on each other's metabolism may have little influence on their toxicity. Studies designed to examine possible metabolic interactions, however, were not located.

In summary, despite limited mechanistic understanding of the toxic actions of 1,1-dichloroethane and tetrachloroethylene, it is plausible that they may act jointly in an additive manner to produce cardiac sensitization and effects on the nervous system, the liver, and the kidney, but studies designed to test hypotheses associated with this contention were not located.

2.2.7 Trichloroethylene and Tetrachloroethylene

High levels of exposure to either trichloroethylene or tetrachloroethylene can produce reversible central nervous system depression due to parent chemical or metabolite (i.e., trichloroethanol) actions on neuronal membranes (ATSDR 1997a, 1997b). There is no conclusive evidence of liver damage, kidney damage, or cancer in humans exposed to either of these chemicals, but liver damage, kidney damage, and cancer have been demonstrated in bioassays of animals exposed to levels of trichloroethylene or tetrachloroethylene that are higher than those expected to be experienced by humans exposed in the workplace or in the general environment (ATSDR 1997a, 1997b). Although the mechanisms of liver damage, kidney damage, or cancer induction by these chemicals are incompletely understood, it is expected that metabolites, rather than parent chemicals, are responsible (ATSDR 1997a, 1997b; Green et al. 1990; Reitz et al. 1996). Metabolic pathways for the two chemicals, while not identical, share an initial epoxidation of the ethylene group catalyzed by CYP isozymes and a minor glutathione conjugation pathway, but trichloroethylene is metabolized to a greater extent than tetrachloroethylene (ATSDR 1997a, 1997b). For example, in rats pretreated with phenobarbital before intraperitoneal administration of 1,474 mg trichloroethylene/kg or 1,632 mg tetrachloroethylene/kg, 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). The principal mode of elimination of tetrachloroethylene from the body is exhalation of the parent chemical, whereas elimination of urinary metabolites is the more important route of elimination for trichloroethylene (ATSDR 1997a, 1997b). Due to overlap in CYP-mediated metabolic pathways for trichloroethylene and tetrachloroethylene, it is plausible that they may interfere with each other's metabolism. It is likely that such an interaction would have greater toxicologic significance for trichloroethylene (which is

extensively metabolized) than for tetrachloroethylene (which is poorly metabolized), and that it would occur only at high concentrations saturating CYP catalytic sites.

Seiji et al. (1989) reported that workers exposed to both trichloroethylene and tetrachloroethylene had lower levels of metabolites (total trichloro compounds) in the urine than workers exposed only to trichloroethylene at approximately the same level as in the mixed exposure. Geometric means of workplace air concentrations (determined from personal air samples) were 9.4 ppm trichloroethylene and 16.6 ppm tetrachloroethylene for the workers exposed to the mixture and 7.7 ppm trichloroethylene for workers exposed to trichloroethylene alone. In contrast, urinary levels of total trichloro compounds in workers exposed to tetrachloroethylene alone (at a geometric mean air concentration of 10.8 ppm) were much lower than levels in workers exposed to trichloroethylene alone or workers exposed to the mixture. The slope of a linear regression equation relating total trichloro compounds in urine (corrected for creatinine) to trichloroethylene air concentrations for workers exposed to trichloroethylene alone was 3.9-fold greater than the slope for a similar regression for workers exposed to the mixture. The slope of a regression relating total trichloro compounds in urine to tetrachloroethylene air concentrations for workers exposed to tetrachloroethylene alone was 5% of the slope of the regression relating trichloroethylene air concentrations to urinary total trichloro compounds in workers exposed to trichloroethylene alone. The data suggest that inhaled trichloroethylene is metabolized to a much greater extent than inhaled tetrachloroethylene, and that coexposure to tetrachloroethylene at fairly low exposure levels inhibits the metabolism of trichloroethylene in humans.

Stacey (1989) studied the joint action of trichloroethylene and tetrachloroethylene on renal and hepatic endpoints in rats *in vivo* and in isolated rat hepatocytes *in vitro*. Groups of five to six Sprague Dawley rats were given near-threshold doses of trichloroethylene (10 mmol/kg or 1,314 mg/kg) and tetrachloroethylene (15 mmol/kg or 2,487 mg/kg) alone and in combination, by intraperitoneal injection. The control group received corn oil (0.6 mg/kg). Animals were sacrificed after 24 hours; livers were weighed and blood was collected for analysis of ALT, SDH, and urea. Neither trichloroethylene nor tetrachloroethylene produced any effects individually at the doses administered. Combined administration produced a significant decrease in liver:body weight ratio, significant increases in ALT and SDH, and a nonsignificant increase in blood urea. The *in vitro* studies in isolated rat hepatocytes yielded similar results. Using doses at which the single chemicals did not produce effects (2 or 4 μL trichloroethylene, 1 or 2 μL tetrachloroethylene), mixtures containing either dose of trichloroethylene and tetrachloroethylene at the higher dose produced toxicity (leakage of potassium ions, ALT, and lactate dehydrogenase). These results clearly show that a mixture of subthreshold doses of tetrachloroethylene

and trichloroethylene can produce liver and/or kidney damage, but they cannot clearly discern the mode of joint action due to study design limitations as discussed in Section 2.2.1.

Goldsworthy and Popp (1987) investigated the joint effect of trichloroethylene and tetrachloroethylene on peroxisome proliferation in the livers and kidneys of rats and mice. Male Fischer 344 rats and B6C3F1 mice were given trichloroethylene alone (1,000 mg/kg/day), tetrachloroethylene alone (1,000 mg/kg/day) or both chemicals together (1,000 mg/kg/day trichloroethylene + 1,000 mg/kg/day tetrachloroethylene, one right after the other) by gavage in corn oil on 10 consecutive days. A corn oil control group was also included. At sacrifice, liver and kidney samples were collected and analyzed for cyanide-insensitive palmitoyl CoA oxidase activity as a marker for peroxisome proliferation. The individual chemicals produced statistically significantly increased palmitoyl CoA oxidase activity in rat and mouse liver and kidney compared with controls (except for tetrachloroethylene alone in rat kidney). In animals exposed to trichloroethylene alone, palmitoyl CoA oxidase activity values (expressed as a percentage of control values) were 239 and 261% for rat liver and kidney, respectively, and 625 and 360% for mouse liver and kidney, respectively. In animals exposed to tetrachloroethylene alone, values were 167 and 87% for rat liver and kidney, respectively, and 428 and 232% for mouse liver and kidney, respectively. In animals exposed to the mixture, values were 263 and 319% for rat liver and kidney, respectively, and 460 and 232% for mouse liver and kidney, respectively. In each case except rat kidney values, the response of the peroxisome proliferation marker to the mixture was less than the sum of the responses to the individual chemicals. Goldsworthy and Popp (1987) concluded that joint administration of these two chemicals did not produce additive or synergistic effects and did not differ from administration of the chemicals individually; however the results seem to be more consistent with a less-than-additive joint action of tetrachloroethylene and trichloroethylene on peroxisomal proliferation at the dose levels tested. Trichloroacetic acid, a metabolite of both chemicals via initial catalysis by CYP isozymes, is expected to be the responsible agent for producing the observed increase in peroxisomal enzyme activity. It is plausible that tetrachloroethylene may competitively or non-competitively inhibit the binding of trichloroethylene to the active sites of CYP isozymes, and slow the overall rate of formation of trichloroacetic acid.

Jonker et al. (1996) tested the hypothesis of dose addition with regard to renal effects produced by gavage of rats for 32 days with ternary or quaternary mixtures including trichloroethylene, tetrachloroethylene, and two other chemicals also thought to produce renal effects by a mechanism involving conjugation with glutathione and β-lyase hydrolysis (hexachloro-1,3-butadiene and 1,1,2-trichloro3,3,3-trifluoropropene). Relative kidney weight in rats was increased to a similar extent by the four chemicals at their renal

LOAEL values, by a mixture of the four chemicals together at 1/4 of their renal LOAEL values (one toxicity unit: 600 mg/kg/day tetrachloroethylene, 500 mg/kg/day trichloroethylene) and by ternary mixtures of the chemicals at 1/3 of their renal LOAEL values (one toxicity unit: 800 mg/kg/day tetrachloroethylene, 667 mg/kg/day trichloroethylene). This result is consistent with the renal toxicity of the mixture being determined by dose additivity. Other endpoints indicative of renal toxicity (histopathology and numerous urinanalytic variables such as glucose, total protein, and alkaline phosphatase) were not affected by exposure to the ternary (at 1/3 LOAEL values) or quaternary (at 1/4 LOAEL values) mixtures. Because the individual chemicals differentially affected these endpoints at the renal LOAEL values (e.g., tetrachloroethylene and trichloroethylene produced renal multifocal vacuolation, but the other two chemicals did not), the results were unsuitable for assessing the mode of joint action on these endpoints. Rats exposed to quaternary mixtures with components at ½ LOAEL values (two toxicity units) displayed clear renal toxicity in many endpoints including increased renal weight, decreasing urinary concentration ability, increased urinary excretion of protein, glucose, and various enzymes, and renal multifocal vacuolation. However, the lack of data for exposures to single chemical doses at two toxicity units in this study precluded further assessment of the additivity hypothesis. In general, this study provides evidence that trichloroethylene and tetrachloroethylene, along with two other similarly acting nephrotoxicants, jointly act in an additive manner in affecting kidney weight.

In summary, a study of urinary metabolites in workers exposed to tetrachloroethylene alone, trichloroethylene alone, or a mixture of tetrachloroethylene and trichloroethylene provides *in vivo* evidence that tetrachloroethylene inhibits the metabolism of trichloroethylene in humans (Seiji et al. 1989). This observation is consistent with results of a rat study indicating that tetrachloroethylene and trichloroethylene jointly act in a less-than-additive manner in inducing hepatic and renal peroxisomal proliferation, a response to trichloroacetic acid, a major metabolite of both chemicals (Goldsworthy and Popp 1987). The results in rats may be partly explained by tetrachloroethylene competitively or non-competitively inhibiting the binding of trichloroethylene to active sites of CYP enzymes and slowing the overall rate of appearance of trichloroacetic acid (compared with the rate with trichloroethylene exposure alone) due to its slower rate of conversion to trichloroacetic acid. The less-than-additive interaction in rats was observed at high exposure levels relative to environmental levels. If the observed interaction is competitive, it is unlikely to occur at lower exposure levels, when substrate concentrations are not in excess of hepatic CYP enzyme levels. In PBPK model simulations of competitive metabolic interactions between trichloroethylene and vinyl chloride, less-than-additive interaction occurred only at concentrations of substrates in excess of hepatic enzyme levels (Barton et al. 1995). In contrast, evidence of tetrachloroethylene inhibition of trichloroethylene metabolism has been reported in workers exposed to

both chemicals at low (<20 ppm) exposure levels (Seiji et al. 1989). A possible explanation of this finding is that tetrachloroethylene may inhibit trichloroethylene metabolism by a non-competitive mechanism that operates at low and high exposure levels.

Other rat studies of possible interactions between tetrachloroethylene and trichloroethylene in affecting liver or kidney endpoints include one indicating that the chemicals, along with two other chemicals that are also thought to produce renal effects by a mechanism involving conjugation with glutathione and β-lyase hydrolysis, additively act to increase kidney weight (Jonker et al. 1996), and another, of inadequate design to determine joint toxic action, that showed that a mixture of subthreshold doses of tetrachloroethylene and trichloroethylene could produce adverse effects on liver and kidney endpoints (Stacey 1989). Overall, the available weight-of-evidence suggests that coexposure of humans to tetrachloroethylene and trichloroethylene may inhibit the metabolism of trichloroethylene and thereby may inhibit carcinogenic and noncarcinogenic responses in the liver and kidney to trichloroethylene metabolites. However, the significance of this metabolic interaction to the nervous system effects (central nervous system depression) from trichloroethylene is not obvious since these effects have been attributed to both the parent chemical and a metabolite of trichloroethylene, (i.e., trichloroethanol). It is plausible that both parent chemicals and trichloroethanol may jointly act in an additive manner to produce nervous system effects, but studies designed to test this hypothesis were not located. The available data provide no direct evidence that trichloroethylene influences the metabolism of tetrachloroethylene (or its liver or kidney toxicity), but the limited capacity for tetrachloroethylene metabolism suggests that any influence of trichloroethylene on tetrachloroethylene metabolism should be of little toxicological significance.

Table 3. Summary of Available Data on the Influence of Trichloroethylene on Toxicity/Carcinogenicity of Tetrachloroethylene and the Influence of Tetrachloroethylene on Toxicity/Carcinogenicity of Trichloroethylene after Simultaneous Exposure

Duration	Endpoint	Results			Conclusions	References
		Greater than additive	Additive/no effect	Less than additive		
Trichloroethylene Influence on Toxicity/Carcinogenicity of Tetrachloroethylene						
Inhalation Exposure (ppm)[a]						
Repeated Exposure	urinary excretion of metabolites		9.4 + 16.6 (h)[b]		No indication of trichloroethylene influence on tetrachloroethylene metabolism	Seiji et al. 1989
Oral Exposure (mg/kg/day)[a]						
Repeated Exposure	liver and kidney palmitoyl CoA oxidase activity			1,000 + 1,000 (r)[b] 1,000 + 1,000 (m)[b]	Less-than-additive joint action. May be due to tetrachloroethylene inhibition of trichloroethylene metabolism via CYP isozymes	Goldsworthy and Popp 1987
Repeated Exposure	kidney-to-body weight ratio		500 + 600 (r)[b]		Additive joint action with two other chemicals	Jonker et al. 1996
Intraperitoneal Exposure (mg/kg/day)[a]						
acute	serum ALT and SDH, liver-to-BW ratio		1,314 + 2,487 (r)[b]		Joint action is indeterminate due to study design limitation	Stacey 1989

Table 3. Summary of Available Data on the Influence of Trichloroethylene on Toxicity/Carcinogenicity of Tetrachloroethylene and the Influence of Tetrachloroethylene on Toxicity/Carcinogenicity of Trichloroethylene after Simultaneous Exposure *(continued)*

Duration	Endpoint	Results			Conclusions	References
		Greater than additive	Additive/no effect	Less than additive		
Tetrachloroethylene Influence on Toxicity/Carcinogenicity of Trichloroethylene						
Inhalation Exposure (ppm)[a]						
Repeated Exposure	urinary excretion of metabolites			16.6 + 9.4 (h)[b]	Less than additive metabolic interaction	Seiji et al. 1989
Oral Exposure (mg/kg/day)[a]						
Repeated Exposure	liver and kidney palmitoyl CoA oxidase activity			1,000 + 1,000 (r)[b] 1,000 + 1,000 (m)[b]	Less-than-additive joint action. May be due to tetrachloroethylene inhibition of trichloro-ethylene metabolism via CYP isozymes	Goldsworthy and Popp 1987
Repeated Exposure	kidney-to-body weight ratio		600 + 500 (r)[b]		Additive joint action with two other chemicals	Jonker et al. 1996
Intraperitoneal Exposure (mg/kg/day)[a]						
acute	serum ALT and SDH, liver-to-BW ratio		2,487 + 1,314 (r)[b]		Joint action is indeterminate due to study design limitation.	Stacey 1989

[a] First dose listed is for the chemical influencing the other chemical's toxicity/carcinogenicity.
[b] Species code: h = human; m = mouse; r = rat

ALT = alanine aminotransferase; BW = body weight; SDH = sorbitol dehydrogenase

2.3 Relevance of the Joint Toxic Action Data and Approaches to Public Health

1,1,1-Trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene are frequently encountered together at hazardous waste sites. Acute or repeated inhalation exposure to any of these chemicals starting at concentrations as low as 20–100 ppm is expected to produce neurological impairment resulting from the parent chemicals (and a metabolite in the case of trichloroethylene) acting on components of neuronal membranes (see Appendices A, B, C, and D). Animal studies also provide evidence, of varying weights for the four chemicals, that repeated inhalation exposure at high exposure levels (>100–500 ppm) can damage liver and kidney tissue and produce cancer due to the formation of reactive metabolites (see Appendices A, B, C, and D). Table 4 shows that neurological impairment forms the basis for ATSDR's inhalation MRLs for these chemicals. Acute oral exposure to trichloroethylene or tetrachloroethylene during pregnancy is also thought to present a hazard to the neurological development of offspring, and these effects form the basis of the oral MRLs for these chemicals (see Table 4). It should be noted, however, that significant data gaps exist with regard to deriving MRLs for the four chemicals. For example, no MRLs of any kind have been derived for 1,1-dichloroethane due to inadequate data.

There is only limited weight of evidence that inhalation or oral exposures to these chemicals may present significant cancer risks to humans. Reflecting this limited weight, EPA (IRIS 2001) assigned cancer classifications of Group D (Not Classifiable as to Human Carcinogenicity) to 1,1,1-trichloroethane, Group C (Possible Human Carcinogen) to 1,1-dichloroethane, and an intermediate B2/C (Probable/Possible Human Carcinogen) to trichloroethylene and tetrachloroethylene, and lists no oral slope factor or inhalation unit risk for these chemicals on the IRIS (2001) database. Part of the uncertainty concerning the possible carcinogenicity of these chemicals in humans arises from evidence that reactive metabolites are responsible for observed carcinogenic responses in rodents and that responsive species more readily metabolize these chemicals than humans.

In the absence of pertinent data on neurological responses to mixtures of all four chemicals and PBPK models that predict the direction and magnitude of interactions among the four chemicals, health hazards from inhalation or oral exposure to mixtures of these chemicals may best be assessed by a components-based approach such as the Hazard Index approach (ATSDR 2001a). Such an approach requires judgements concerning the presence or absence of interactions affecting the response of the shared apparent critical target organ, the nervous system, and other shared targets, the liver and kidney.

Table 4. Health Effects Forming the Basis of ATSDR Inhalation and Oral MRLs for Chemicals of Concern
(Source: ATSDR 1990, 1995, 1997a, 1997b)

Chemical	Inhalation MRLs			Oral MRLs		
	Acute	Intermediate	Chronic	Acute	Intermediate	Chronic
1,1,1-Trichloro-ethane	neuro-behavioral changes in humans	brain chemistry changes in gerbils	ND	ND	ND	ND
1,1-Dichloro-ethane	ND	ND	ND	ND	ND	ND
Trichloro-ethylene	neuro-behavioral changes in humans	neuro-behavioral changes in rats	ND	neuro-behavioral changes in rat offspring	ND	ND
Tetra-chloroethylene	neuro-behavioral changes in humans	ND	neuro-behavioral changes in humans	neuro-behavioral changes in mouse offspring	ND	ND

ND = None derived due to inadequate data

No studies were located that examined neurological endpoints and described dose-response relationships in humans or animals following exposure to mixtures of all four of these chemicals, but mechanistic data and interactions data have been evaluated in Section 2.2 to determine how pairs of these chemicals may jointly act in producing nervous system, liver, and kidney effects. To characterize the overall potential for interactions among 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloro-ethylene, four binary weight-of-evidence determinations (BINWOEs) were derived for each of the six pairs of chemicals (two for the effects of chemical A on the nervous system effects of chemical B and the liver and kidney toxicity of B, and the other two for the effects of B on the toxicities of A) using the classification scheme described by ATSDR (2001b) and shown in Figure 1. The BINWOEs are described in the text of Tables 5 to 16. Tables 17 and 18 summarize the BINWOE determinations for noncancer effects on the nervous system (the apparent shared critical toxicity target of all four chemicals) and noncancer and cancer effects on the liver and kidney (shared cancer targets of several of the chemicals in animals), respectively.

No studies were located that directly examined joint action of the chemicals on the nervous system, but mechanistic understanding indicates that each of the chemicals is expected to produce nervous system effects by reversible actions of parent chemicals (and the trichloroethylene metabolite, trichloroethanol) on neuronal membrane components. Nervous system depression from lipophilic solvents such as the chemicals of concern for this document is thought to involve reversible intercalation 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 (Balster 1998; Cruz et al. 1998; Engelke et al. 1996; Franks and Lieb 1985, 1987; Mihic et al. 1994; von Euler 1994). Based on the plausibility that the chemicals may act jointly in an additive manner via the same mechanisms of action in affecting neuronal membranes, each of the BINWOEs for nervous system effects determined an additive joint action with data quality factors of "II" for mechanistic understanding to reflect moderate mechanistic understanding and "C" for toxicologic significance to reflect lack of studies designed to test the hypothesis of joint additive actions on the nervous system (see Table 17).

BINWOE determinations were made for noncancer and cancer effects in the liver and kidney and are discussed in Tables 5 to 16. Based on results from animal studies, each of the chemicals is expected to produce noncancer and cancer effects in the liver and/or kidney via reactive metabolites formed under high exposure chronic conditions. BINWOE determinations for liver and kidney endpoints were made in anticipation of public health concerns that there might be greater-than-additive interactions that might cause liver and kidney effects to occur. The analysis of the available data, however, provides no indication that this type of interaction might occur. Additive joint action was determined in 11 of the 12 BINWOEs (see Table 18) based on plausibility from mechanistic understanding and/or limited evidence from rat studies examining joint action on liver or kidney endpoints (e.g., Stacey 1989). The twelfth BINWOE, for the effect of tetrachloroethylene on trichloroethylene (Table 16), was determined as a less-than-additive joint action (i.e., tetrachloroethylene may antagonize trichloroethylene-induced liver and kidney effects by inhibiting the formation of trichloroacetic acid from trichloroethylene) based on *in vivo* evidence that tetrachloroethylene inhibits the metabolism of trichloroethylene in humans under occupational exposure conditions (Seiji et al. 1989), and tetrachloroethylene and trichloroethylene acted in a less-than-additive manner in causing hepatic and renal peroxisomal proliferation in orally exposed rats (Goldsworthy and Popp 1987).

The use of a Target Toxicity Dose approach does not appear to be warranted because neurological effects are the basis for all of ATSDR's MRLs for these chemicals regardless of exposure duration or route, and there is no evidence for greater-than-additive interactions in the liver and kidney, which also are shared targets of the chemicals.

Figure 1. Binary Weight-of-Evidence Scheme for the Assessment of Chemical Interactions*

Classification		Factor
Direction of Interaction		**Direction**
=	Additive	0
>	Greater than additive	+1
<	Less than additive	–1
?	Indeterminate	0
Quality of the Data		**Weighting**
Mechanistic Understanding		
I.	Direct and Unambiguous Mechanistic Data: The mechanism(s) by which the interactions could occur has been well characterized and leads to an unambiguous interpretation of the direction of the interaction.	1.0
II.	Mechanistic Data on Related Compounds: The mechanism(s) by which the interactions could occur is not been well characterized for the chemicals of concern but structure-activity relationships, either quantitative or informal, can be used to infer the likely mechanisms(s) and the direction of the interaction.	0.71
III.	Inadequate or Ambiguous Mechanistic Data: The mechanism(s) by which the interactions could occur has not been well characterized or information on the mechanism(s) does not clearly indicate the direction that the interaction will have.	0.32
Toxicological Significance		
A.	The toxicological significance of the interaction has been directly demonstrated.	1.0
B.	The toxicological significance of the interaction can be inferred or has been demonstrated for related chemicals.	0.71
C.	The toxicological significance of the interaction is unclear.	0.32
Modifiers		
1.	Anticipated exposure duration and sequence.	1.0
2.	Different exposure duration or sequence.	0.79
a.	*In vivo* data	1.0
b.	*In vitro* data	0.79
i.	Anticipated route of exposure	1.0
ii.	Different route of exposure	0.79

Weighting Factor = Product of Weighting Scores: Maximum = 1.0, Minimum = 0.05

BINWOE = Direction Factor x Weighting Factor: Ranges from –1 through 0 to +1

* Source: ATSDR 2001a

Table 5. Effect of **1,1,1-Trichloroethane** on **1,1-Dichloroethane**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIC
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - It is plausible that 1,1,1-trichloroethane and 1,1-dichloroethane may jointly act in an additive manner to depress the central nervous system and sensitize the heart to epinephrine, but studies designed to test this hypothesis were not located. Although reactive metabolites of both chemicals are expected to produce liver and kidney effects, neither chemical is extensively metabolized, nor hepatotoxic except at high exposure levels. Additive joint action to produce effects on the liver or kidney is plausible.

Mechanistic Understanding - Like other solvents, the parent chemicals depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices A and B; ATSDR 1990, 1995). They may act jointly in an additive manner to produce central nervous system depression and heart sensitization to epinephrine, but studies designed to test this hypothesis were not located.

Mild liver or kidney effects observed in rodents from either of these chemicals are believed to be caused by reactive metabolic intermediates formed via CYP 2B1/2 or 2E1 catalysis (see Appendices A and B). These chemicals are of low potency because they are poorly metabolized (Kaneko et al. 1994; McCall et al. 1983; Mitoma et al. 1985; Nolan et al. 1984). Any influence (e.g., inhibition at CYP active sites or induction of Phase I or Phase II enzymes) that they may have on each other's metabolism should have little influence on their toxicity, since they are poorly metabolized, downstream enzymes may prevent elevation of intracellular concentrations of putative toxic metabolites, and repair mechanisms may efficiently fix any damage to cellular macromolecules. Studies directly designed to examine how they may influence each other's metabolism or toxicity, however, were not located.

Mechanistic understanding was assigned a moderate data quality factor, II, to reflect lack of data regarding joint action on nervous system, liver, and kidney endpoints.

Toxicological Significance - No interaction data for 1,1,1-trichloroethane and 1,1-dichloroethane were located for any toxicological endpoints; thus, the lowest possible toxicologic significance data quality factor, C, was assigned to both BINWOE determinations.

Additional Uncertainties - Competitive metabolic interactions may exist between these chemicals at CYP isozyme catalytic sites under high exposure conditions when CYP catalytic sites are saturated. Pretreatment of rats with phenobarbital or ethanol increased rates of 1,1-dichloroethane metabolism in liver microsomes (McCall et al. 1983; Sato et al. 1980), but the possible influence of CYP induction on 1,1-dichloroethane is unexamined. Furthermore, 1,1,1-trichloroethane did not induce hepatic CYP2E1 or 2B1/2 in rats until doses approached lethal levels above 500 mg/kg (Bruckner et al. 2000). The limited degree to which 1,1-dichloroethane is metabolized suggests that any interactions should have little influence on toxicity.

Table 6. Effect of **1,1-Dichloroethane** on **1,1,1-Trichloroethane**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIC
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - It is plausible that 1,1,1-trichloroethane and 1,1-dichloroethane may jointly act in an additive manner to depress the central nervous system and sensitize the heart to epinephrine, but studies designed to test this hypothesis were not located. Although reactive metabolites of both chemicals are expected to produce liver and kidney effects, neither chemical is extensively metabolized, nor hepatotoxic except at high exposure levels. Additive joint action to produce effects on the liver or kidney is plausible.

Mechanistic Understanding - Like other solvents, the parent chemicals depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices A and B; ATSDR 1990, 1995). They may act jointly in an additive manner to produce central nervous system depression and heart sensitization to epinephrine, but studies designed to test this hypothesis were not located.

Mild liver or kidney effects observed in rodents from either of these chemicals are believed to be caused by reactive metabolic intermediates formed via CYP 2B1/2 or 2E1 catalysis (see Appendices A and B). These chemicals are of low potency because they are poorly metabolized (Kaneko et al. 1994; McCall et al. 1983; Mitoma et al. 1985; Nolan et al. 1984). Any influence (e.g., inhibition at CYP active sites or induction of Phase I or Phase II enzymes) that they may have on each other's metabolism should have little influence on their toxicity, since they are poorly metabolized, downstream enzymes may prevent elevation of intracellular concentrations of putative toxic metabolites, and repair mechanisms may efficiently fix any damage to cellular macromolecules. Studies directly designed to examine how they may influence each other's metabolism or toxicity, however, were not located.

Mechanistic understanding was assigned a moderate data quality factor, II, to reflect lack of data regarding joint action on nervous system, liver, and kidney endpoints.

Toxicological Significance - No interaction data for 1,1-dichloroethane and 1,1,1-trichloroethane were located; thus, the lowest possible toxicologic significance data quality factor, C, was assigned to both BINWOE determinations.

Additional Uncertainties - Competitive metabolic interactions may exist between these chemicals at CYP isozyme catalytic sites under high exposure conditions when CYP catalytic sites are saturated. Pretreatment of rats with phenobarbital or ethanol to increase rates of 1,1,1-trichloroethane metabolism in liver microsomes has not shown a consistent potentiation of hepatotoxicity (Carlson 1973; Cornish et al 1973). Rates of 1,1,1-trichloroethane metabolism in rats, even under induced conditions (ethanol pretreatment), are much lower than rates for highly metabolized chlorinated hydrocarbons such as trichloroethylene (Kaneko et al. 1994). The limited degree to which 1,1,1-trichloroethane is metabolized suggests that any interactions should have little influence on toxicity.

Table 7. Effect of **1,1,1-Trichloroethane** on **Trichloroethylene**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIB
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - There are limited data to suggest that these chemicals may jointly act in an additive manner to produce effects on the central nervous system, the liver, and the kidney.

Mechanistic Understanding - Like other solvents, the parent chemicals (and a trichloroethylene metabolite, trichloroethanol) depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices A and C, ATSDR 1995, 1997a). They may act jointly in an additive manner to produce these effects, but studies designed to test this hypothesis were not located.

Noncancer or cancer effects in the liver and kidney from trichloroethylene or 1,1,1-trichloroethane are thought to be caused by reactive metabolites, produced via CYP catalysis (see Appendices A and C). CYP2E1 is the predominant isozyme involved in Phase I metabolism of both chemicals, but trichloroethylene is metabolized to a much greater extent than 1,1,1-trichloroethane (Kaneko et al. 1994; Lash et al. 2000). Although phenobarbital induction of CYP has been associated with enhancement of acute high level trichloroethylene hepatotoxicity (Allemand et al. 1978; Carlson 1974; Moslen et al. 1977; Nakajima et al. 1990), 1,1,1-trichloroethane is not expected to influence Phase I trichloroethylene metabolism or toxicity, especially at environmentally relevant exposure levels (see Additional Uncertainties section below). In rats exposed by inhalation to a mixture of 500 ppm 1,1,1-trichloroethane and 200 ppm trichloroethylene, trichloroethylene metabolism did not appear to be impaired (Vainio et al. 1978). This study, however, did not include a trichloroethylene-alone exposure group. Limited data from rat studies indicate that they may jointly act on the liver and kidney (see Section 2.2.3; Stacey 1989). Mechanistic understanding was assigned a moderate data quality factor of II to reflect the lack of data regarding joint action on the nervous system and data availability regarding joint action on the liver and kidney.

Toxicological Significance - There is limited evidence from rat *in vitro* and *in vivo* studies (Stacey 1989) that reactive metabolites of these chemicals may jointly act in an additive manner to produce liver and kidney damage, but the study design could not definitively rule out greater-than-additive or less-than-additive interactions (see Section 2.2.3). To reflect the availability of these data (even though they are ambiguous), a medium data quality factor, B, was assigned. To reflect the lack of data on joint action on the nervous system, the lowest possible data quality factor, C, was assigned.

Additional Uncertainties - The effects of trichloroethylene on the central nervous system may involve not only the parent chemical, but also metabolites such as trichloroethanol. Competitive metabolic interaction between these chemicals are possible under conditions saturating CYP catalytic sites, but 1,1,1-trichloroethane is likely to be a poor competitor of trichloroethylene given that it is much more slowly metabolized than trichloroethylene. Furthermore, alteration of trichloroethylene metabolism at CYP catalytic sites is likely to be physiologically important only at high exposure levels when substrate concentrations are in excess of catalytic sites. For example, CYP induction by ethanol only altered trichloroethylene metabolic rates in rats exposed to high (500–1,000 ppm), but not low (50–100 ppm), trichloroethylene levels (Kaneko et al. 1994). 1,1,1-Trichloroethane modestly and transiently induced hepatic CYP 2B1/2 and CYP2E1 in rats only at lethal dose levels (5 or 10 g/kg; Bruckner et al. 2000).

Table 8. Effect of **Trichloroethylene** on **1,1,1-Trichloroethane**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIB
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - There are limited data to suggest that these chemicals may jointly act in an additive manner to produce effects on the central nervous system, the liver, and the kidney.

Mechanistic Understanding - Like other solvents, the parent chemicals (and a trichloroethylene metabolite, trichloroethanol) depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias. They may act jointly in an additive manner to produce these effects, but studies designed to test this hypothesis were not located.

Noncancer or cancer effects in the liver or kidney from trichloroethylene or 1,1,1-trichloroethane are thought to be caused by reactive metabolites via CYP catalysis (see Appendices A and C). CYP2E1 is the predominant isozyme involved in Phase I metabolism of both chemicals, but trichloroethylene is metabolized to a much greater extent than 1,1,1-trichloroethane (Kaneko et al. 1994; Lash et al. 2000). 1,1,1-Trichloroethane is not a potent toxicant to the liver or kidney because it is poorly metabolized. Trichloroethylene enhancement of 1,1,1-trichloroethane metabolism or hepatotoxicity is not expected. Only high doses of trichloroethylene (>400 mg/kg), not low doses (8 mg/kg), induced hepatic CYP2E1 in rats (Lee et al. 2000), and phenobarbital or ethanol induction to enhance hepatic 1,1,1-trichloroethane metabolism in rats has not produced consistent evidence of potentiation of 1,1,1-trichloroethane hepatotoxicity (Carlson et al. 1973; Cornish et al. 1973). Limited data from rat studies indicate that the two chemicals may jointly act on the liver and kidney (Stacey 1989; see Section 2.2.3). Mechanistic understanding was assigned a data quality factor of II to reflect the lack of data regarding joint action on the nervous system and data availability regarding joint action on the liver and kidney.

Toxicological Significance - There is limited evidence from rat *in vitro* and *in vivo* studies (Stacey 1989) that reactive metabolites of these chemicals may jointly act in an additive manner to produce liver and kidney damage, but the study design could not definitively rule out greater-than-additive or less-than-additive interactions (see Section 2.2.3). To reflect the availability of these data (even though they are ambiguous), a medium data quality factor, B, was assigned. To reflect the lack of data on joint action on the nervous system, the lowest possible data quality factor, C, was assigned.

Additional Uncertainties - In general, 1,1,1-trichloroethane is poorly metabolized, but metabolism can be influenced by induction of CYP isozymes. For example, CYP induction by ethanol increased metabolism of inhaled 1,1,1-trichloroethane in rats, but most of the chemical was still eliminated unmetabolized (Kaneko et al. 1994). Thus, any possible interference or enhancement that trichloroethylene may have on 1,1,1-trichloroethane metabolism should have little influence on 1,1,1-trichloroethane toxicity. Furthermore, the balance of Phase I and II metabolism should determine whether or not toxicity is expressed. Capabilities of downstream enzymes may be sufficient to prevent increased concentrations of putative toxic intermediate metabolites of 1,1,1-trichloroethane, even under conditions of Phase I induction.

Table 9. Effect of **Tetrachloroethylene** on **1,1,1-Trichloroethane**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIB
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - There are limited data to suggest that these chemicals may jointly act in an additive manner to produce effects on the central nervous system, liver, and kidney.

Mechanistic Understanding - Like other solvents, the parent chemicals depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices A and D; ATSDR 1995, 1997b). They may act jointly in an additive manner to produce these effects, but studies designed to test this hypothesis were not located.

Liver and kidney effects from these chemicals are expected to involve reactive intermediates formed via CYP catalysis (CYP 2E1 and 2B1/2) in the liver or hydrolysis by β-lyase of a glutathione conjugate in the kidney, but neither chemical is a potent toxicant in these tissues because they are poorly metabolized (see Appendices A and D). Tetrachloroethylene inhibited the rates of urinary excretion of a 1,1,1-trichloroethane metabolite, trichloroethanol, in rats exposed by inhalation to a mixture of 350 ppm 1,1,1-trichloroethane and 100 ppm tetrachloroethylene (Koizumi et al. 1982). The limited degree to which 1,1,1-trichloroethane is metabolized indicates that any influence that tetrachloroethylene may have on 1,1,1-trichloroethane metabolism should have little influence on toxicity, because downstream enzymes may prevent elevation of intracellular concentrations of putative toxicants and repair mechanisms may fix any damage to cellular macromolecules. Limited data from rat studies indicate that they may jointly act on the liver and kidney (see Section 2.2.4; Stacey 1989). Mechanistic understanding was assigned a data quality factor of II to reflect the lack of data regarding joint action on the nervous system and data availability regarding joint action on the liver and kidney (see below).

Toxicological Significance - Due to the lack of data on joint action on the nervous system, the lowest possible data quality factor, C, was assigned. Limited evidence from rat *in vitro* and *in vivo* studies (Stacey 1989) suggests that reactive metabolites of these chemicals may jointly act in an additive manner to produce liver damage, but the study design could not definitively rule out greater-than-additive or less-than-additive interactions (see Section 2.2.4.) To reflect the availability of these data (even though they are ambiguous), a moderate data quality factor, B, was assigned.

Additional Uncertainties - No information was located to indicate whether tetrachloroethylene may enhance the metabolism of 1,1,1-trichloroethane. CYP induction by ethanol has not produced consistent potentiation of acute high-level 1,1,1-trichloroethane hepatotoxicity (Carlson 1973; Cornish et al. 1973). Competitive interactions at CYP isozymes are possible, especially at high concentrations saturating catalytic sites. However, any interference or enhancement of 1,1,1-trichloroethane metabolism should have little influence on toxicity in the liver or kidney.

Table 10. Effect of **1,1,1-Trichloroethane** on **Tetrachloroethylene**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIB
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - There are limited data to suggest that these chemicals may jointly act in an additive manner to produce effects on the central nervous system, liver, and kidney.

Mechanistic Understanding - Like other solvents, the parent chemicals depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices A and D; ATSDR 1995, 1997b). They may act jointly in an additive manner to produce these effects, but studies designed to test this hypothesis were not located.

Liver and kidney effects from these chemicals are believed to involve reactive intermediates formed via CYP catalysis (CYP 2E1 and/or 2B1/2) in the liver or hydrolysis by β-lyase of a glutathione conjugate in the kidney, but neither chemical is a potent toxicant in these tissues because they are poorly metabolized (see Appendices A and D; ATSDR 1995; 1997b). The limited degree to which either of these chemicals is metabolized indicates that any influence that they may have on each other's metabolism should have little influence on their toxicity, because downstream enzymes may prevent elevation of intracellular concentrations of putative toxicants and repair mechanisms may fix any damage to cellular macromolecules. Limited data from rat studies indicate that they may jointly act on the liver and kidney (see Section 2.2.4; Stacey 1989). Mechanistic understanding was assigned a data quality factor of II to reflect the lack of data regarding joint action on the nervous system and data availability regarding joint action on the liver and kidney (see below).

Toxicological Significance - Due to the lack of data on joint action on the nervous system, the lowest possible data quality factor, C, was assigned. Limited evidence from rat *in vitro* and *in vivo* studies (Stacey 1989) suggests that reactive metabolites of these chemicals may jointly act in an additive manner to produce liver damage, but the study design could not definitively rule out greater-than-additive or less-than-additive interactions (see Section 2.2.4.) To reflect the availability of these data (even though they are ambiguous), a moderate data quality factor, B, was assigned.

Additional Uncertainties - 1,1,1-Trichloroethane modestly and transiently induced hepatic CYP2E1 and 2B1/2 levels in rats at exposure levels >500 mg/kg (Bruckner et al. 2000). CYP induction by ethanol, phenobarbital, or PCBs has not produced consistent potentiation of acute high-level tetrachloroethylene hepatotoxicity (Cornish and Adefuin 1966; Cornish et al. 1973; Klaassen and Plaa 1966; Moslen et al. 1977). Competitive interactions between 1,1,1-trichloroethane and tetrachloroethylene at CYP isozymes are possible, especially at high concentrations saturating catalytic sites. However, any possible interference or enhancement that 1,1,1-trichloroethane may have on tetrachloroethylene metabolism should have little influence on toxicity, because tetrachloroethylene is poorly metabolized.

Table 11. Effect of **1,1-Dichloroethane** on **Trichloroethylene**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIC
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - It is plausible that 1,1-dichloroethane and trichloroethylene may jointly act in an additive manner to produce central nervous system effects, liver effects, and kidney effects, but studies designed to test this hypothesis were not located.

Mechanistic Understanding - Like other solvents, the parent chemicals (and tetrachloroethanol, a metabolite of trichloroethylene) depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices B and C; ATSDR 1990, 1997a). They may act jointly in an additive manner to produce these effects, but studies designed to test this hypothesis were not located.

Development of liver and kidney damage and cancer effects in animals from trichloroethylene are believed to involve reactive intermediates produced via CYP catalysis in the liver or β-lyase hydrolysis of a glutathione conjugate (of trichloroethylene) in the kidney (see Appendix C). Phenobarbital induction of CYP has been associated with enhancement of acute high level trichloroethylene hepatotoxicity (Allemand et al. 1978; Carlson 1974; Moslen et al. 1977), but 1,1-dichloroethane is not expected to influence Phase I trichloroethylene metabolism or hepatotoxicity (see Additional Uncertainties section below). Studies designed to examine if coexposure to 1,1-dichloroethane would influence trichloroethylene metabolism or toxicity were not located, but joint additive action on the liver or kidney is plausible.

Mechanistic understanding was assigned a moderate data quality factor, II, to reflect lack of data regarding joint action on nervous system, liver, and kidney endpoints.

Toxicological Significance - Due to the lack of data on joint action on the nervous system, liver, and kidney, the lowest possible data quality factor, C, was assigned for each BINWOE.

Additional Uncertainties - Competitive metabolic interactions between 1,1-dichloroethane and trichloroethylene at CYP-catalyzed reactions are possible under high exposure conditions saturating CYP catalytic sites. However, 1,1-dichloroethane should be a poor competitor of trichloroethylene because it is much more slowly metabolized than trichloroethylene (see Appendices A and C). No data are available to indicate whether 1,1-dichloroethane may enhance trichloroethylene metabolism, but demonstration of metabolic enhancement alone is an insufficient condition for predicting greater-than-additive interaction due to possibilities of detoxification by downstream enzymes and/or repair of damaged cellular macromolecules. Furthermore, any possible alteration (inhibition or enhancement) of trichloroethylene metabolism by 1,1-dichloroethane is likely to be physiologically important only at high exposure levels when trichloroethylene concentrations are in excess of CYP catalytic sites (Kaneko et al. 1994).

Table 12. Effect of **Trichloroethylene** on **1,1-Dichloroethane**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIC
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - It is plausible that trichloroethylene and 1,1-dichloroethane may jointly act in an additive manner to produce central nervous system effects, liver effects, and kidney effects, but studies designed to test this hypothesis were not located.

Mechanistic Understanding - Like other solvents, the parent chemicals (and trichloroethanol, a metabolite of trichloroethylene) depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices B and C; ATSDR 1990, 1997a) The chemicals may act jointly in an additive manner to cause these effects, but studies designed to test this hypothesis were not located.

Development of liver or kidney effects in rodents from these chemicals are believed to involve reactive metabolic intermediates formed via CYP catalysis in the liver or β-lyase hydrolysis of a glutathione conjugate (of trichloroethylene) in the kidney (see Appendices B and C). 1,1-Dichloroethane is of low potency because it is poorly metabolized *in vivo* (Mitoma et al., 1985) and may not be conjugated to glutathione to the same degree as its more toxic isomer, 1,2-dichloroethane (McCall et al., 1983). Any influence (e.g., inhibition at CYP active sites or induction of Phase I or Phase II enzymes) that trichloroethylene may have on 1,1-dichloroethane metabolism should have little influence on its toxicity, due to this low rate of metabolism, downstream metabolism that may prevent elevation of concentrations of potentially toxic intermediates, and repair mechanisms that may fix damaged cellular macromolecules. Studies directly designed to examine how trichloroethylene and 1,1-dichloroethane may influence each other's metabolism or toxicity, however, were not located.

Mechanistic understanding was assigned a moderate data quality factor, II, to reflect lack of data regarding joint action on nervous system, liver, and kidney endpoints.

Toxicological Significance - Due to the lack of data on joint action on the nervous system, liver, and kidney, the lowest possible data quality factor, C, was assigned for each BINWOE.

Additional Uncertainties - Due to overlap in metabolic reactions catalyzed by CYP isozymes, competitive metabolic interactions between 1,1-dichloroethane and trichloroethylene are possible under high exposure conditions saturating CYP catalytic sites. Pretreatment of rats with phenobarbital increased rates of CYP-mediated metabolism of 1,1-dichloroethane in liver microsomes (McCall et al. 1983), but the influence of CYP induction on 1,1-dichloroethane toxicity is unexamined. 1,1,1-Trichloroethylene induced hepatic levels of CYP2E1 in rats only at high doses (>400 mg/kg) and not at low doses (8 mg/kg) (Lee et al., 2000). The limited degree to which 1,1-dichloroethane is metabolized suggests that any influence that trichloroethylene may exert on 1,1-dichloroethane metabolism should have minimal influence on toxicity.

Table 13. Effect of **1,1-Dichloroethane** on **Tetrachloroethylene**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIC
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - It is plausible that tetrachloroethylene and 1,1-dichloroethane may jointly act in an additive manner to produce central nervous system effects, liver effects, and kidney effects, but studies designed to test this hypothesis were not located.

Mechanistic Understanding - Like other solvents, the parent chemicals depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices B and D; ATSDR 1990, 1997b) . They may act jointly in an additive manner to produce these effects, but studies designed to test this hypothesis were not located.

Liver or kidney effects observed in rodents repeatedly exposed to high levels of either of these chemicals are believed to be caused by reactive metabolic intermediates formed via CYP 2B1/2 or 2E1 catalysis or β-lyase hydrolysis of a glutathione conjugate (see Appendices B and D). These chemicals are of low potency because they are poorly metabolized (Mitoma et al., 1985; Monster et al. 1979; Pegg et al. 1979). Any influence (e.g., inhibition at CYP active sites or induction of Phase I or Phase II enzymes) that they may have on each other's metabolism should have little influence on their toxicity, because they are poorly metabolized, downstream enzymes may prevent elevation of intracellular concentrations of metabolic toxicants, and repair mechanisms may efficiently fix any damage to cellular macromolecules. Studies directly designed to examine how they may influence each other's metabolism or toxicity, however, were not located.

Mechanistic understanding was assigned a moderate data quality factor, II, to reflect lack of data regarding joint action on nervous system, liver, and kidney endpoints.

Toxicological Significance - Due to the lack of data on joint action on the nervous system, liver, and kidney, the lowest possible data quality factor, C, was assigned for each BINWOE.

Additional Uncertainties - Due to overlap in metabolic reactions catalyzed by CYP isozymes, competitive interactions between 1,1-dichloroethane and tetrachloroethylene are possible under high exposure conditions saturating CYP catalytic sites. CYP induction by ethanol, phenobarbital, or Aroclor 1254 has not produced consistent potentiation of acute high-level tetrachloroethylene hepatotoxicity (Cornish and Adefuin 1966; Cornish et al. 1973; Klaassen and Plaa 1966; Moslen et al. 1977). However, both chemicals are poorly metabolized, and any possible interference or enhancement that they may have on each other's metabolism should have little influence on their toxicity.

Table 14. Effect of **Tetrachloroethylene** on **1,1-Dichloroethane**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIC
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - It is plausible that tetrachloroethylene and 1,1-dichloroethane may jointly act in an additive manner to produce central nervous system effects, liver effects, and kidney effects, but studies designed to test this hypothesis were not located.

Mechanistic Understanding - Like other solvents, the parent chemicals depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias. The chemicals may act jointly in an additive manner to cause these effects, but studies designed to test this hypothesis were not located.

Liver or kidney effects observed in rodents repeatedly exposed to high levels of either of these chemicals are believed to be caused by reactive metabolic intermediates formed via CYP 2B1/2 or 2E1 catalysis or β-lyase hydrolysis of a glutathione conjugate (see Appendices B and D; ATSDR 1990, 1997b). These chemicals are of low potency because they are poorly metabolized (Mitoma et al., 1985; Monster et al. 1979; Pegg et al. 1979). Any influence (e.g., inhibition at CYP active sites or induction of Phase I or Phase II enzymes) that they may have on each other's metabolism should have little influence on their toxicity, because they are poorly metabolized, downstream enzymes may prevent elevation of intracellular concentrations of putative toxicants, and repair mechanisms may efficiently fix any damage to cellular macromolecules. Studies directly designed to examine how they may influence each other's metabolism or toxicity, however, were not located.

Mechanistic understanding was assigned a moderate data quality factor, II, to reflect lack of data regarding joint action on nervous system, liver, and kidney endpoints.

Toxicological Significance - Due to the lack of data on joint action on the nervous system, liver, and kidney, the lowest possible data quality factor, C, was assigned for each BINWOE.

Additional Uncertainties - Due to overlap in metabolic reactions catalyzed by CYP isozymes, competitive metabolic interactions between 1,1-dichloroethane and tetrachloroethylene are possible under high exposure conditions saturating CYP catalytic sites. Pretreatment of rats with phenobarbital or ethanol increased rates of 1,1-dichloroethane metabolism in liver microsomes (McCall et al. 1983; Sato et al. 1980), but the influence of CYP induction on acute or chronic 1,1-dichloroethane toxicity is unexamined. Both chemicals are poorly metabolized and any possible interference or enhancement that they may have on each other's metabolism should have little influence on their toxicity.

Table 15. Effect of **Trichloroethylene** on **Tetrachloroethylene**
BINWOE: =IIC
(for nervous system effects)
BINWOE: =IIB
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - It is plausible that the parent chemicals and trichloroethanol (a metabolite of trichloroethylene) may additively act to produce nervous system effects, but studies designed to test this hypothesis were not located. It is plausible that trichloroethylene may have little influence on tetrachloroethylene metabolism, and that tetrachloroethylene and trichloroethylene metabolites would additively act to produce liver and kidney effects.

Mechanistic Understanding - Like other solvents, the parent chemicals (and the trichloroethylene metabolite, trichloroethanol) depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices C and D; ATSDR 1997a, 1997b).

Liver or kidney effects in rodents exposed to high levels of tetrachloroethylene are believed to involve reactive metabolic intermediates (see Appendices C and D). Tetrachloroethylene is not a potent liver or kidney toxicant because it is poorly metabolized (Monster et al. 1979; Pegg et al. 1979). Any influence that trichloroethylene may have on tetrachloroethylene metabolism should have little influence on tetrachloroethylene toxicity due to detoxification from downstream metabolism and/or repair of damaged cellular macromolecules. Results from a rat and mouse study suggest that trichloroethylene and tetrachloroethylene act in a less-than-additive manner to cause hepatic and renal peroxisomal proliferation (Goldsworthy and Popp 1987; see Section 2.2.7). This observation may be explained by non-competitive inhibition of CYP isozymes leading to slower rates of trichloroacetic acid formation from trichloroethylene. Other rat studies (see Section 2.2.7) show that the chemicals act additively to increase kidney weight (Jonker et al. 1996), and mixtures of subthreshold doses can produce increased serum ALT (Stacey 1989). The latter observation could be consistent with additive joint action on the liver, but the study design could not definitively rule out greater-than-additive or less-than-additive joint action (Stacey 1989).

Mechanistic understanding was assigned a moderate quality factor (II) to reflect lack of data regarding joint actions on the nervous system, and uncertainties regarding joint actions on the liver and kidney.

Toxicological Significance - Studies designed to examine the joint toxic action of these chemicals on nervous system endpoints were not located. Thus, the lowest possible toxicologic significance data quality factor, C, was assigned for nervous system effects. For liver and kidney effects, a moderate data quality factor, B, was assigned because there are studies on the joint toxic action of these chemicals on liver and kidney endpoints in rats, but results are not consistent across endpoints (see above and Section 2.2.7).

Additional Uncertainties - Competitive metabolic interactions at CYP catalytic sites are possible, especially at high exposure levels when sites are saturated. CYP induction by ethanol, phenobarbital, or Aroclor 1254 has not produced consistent potentiation of acute high-level tetrachloroethylene hepatotoxicity (Cornish and Adefuin 1966; Cornish et al. 1973; Klaassen and Plaa 1966; Moslen et al. 1977). Any influence that trichloroethylene may have on tetrachloroethylene metabolism (enhancement or inhibition) should have little influence on toxicity, because tetrachloroethylene is poorly metabolized.

Table 16. Effect of **Tetrachloroethylene** on **Trichloroethylene**
BINWOE: =IIC
(for nervous system effects)
BINWOE: <IIB (-1 x 0.71 x 0.71= -0.50)
(for cancer and noncancer liver or kidney effects)

Direction of Interaction - It is plausible that the parent chemicals and trichloroethanol may jointly act in an additive manner to interact with nervous system membranes. There is evidence that tetrachloroethylene inhibits the metabolism of trichloroethylene in humans (Seiji et al. 1989) and evidence of less-than-additive joint action on hepatic and renal peroxisomal proliferation in rats and mice (Goldsworthy and Popp 1987). It is plausible that the interaction may antagonize liver and kidney effects from trichloroethylene metabolites.

Mechanistic Understanding - Like other solvents, the parent chemicals (and the trichloroethylene metabolite, trichloroethanol) depress nervous system functions by reversibly acting on neuronal membranes and sensitize the heart to epinephrine-induced arrhythmias (see Appendices C and D; ATSDR 1997a, 1997b). Mechanistic understanding was assigned a moderate quality factor (II) to reflect the lack of direct data on the joint action of these chemicals on the nervous system.

Liver or kidney effects in rodents exposed to high levels of these chemicals are believed to involve reactive metabolic intermediates (see Appendices C and D). Studies of urinary metabolites in workers exposed to trichloroethylene alone, tetrachloroethylene alone, or mixtures of trichloroethylene and tetrachloroethylene indicate that tetrachloroethylene inhibits the metabolism of trichloroethylene at low exposure levels (<20 ppm) (Seiji et al. 1989). Results from a rat and mouse study suggest that trichloroethylene and tetrachloroethylene act in a less-than-additive manner to cause hepatic and renal peroxisomal proliferation (Goldsworthy and Popp 1987). This observation may be explained by non-competitive inhibition of CYP isozymes leading to slower rates of trichloroacetic acid formation. Other rat studies show that the chemicals act additively to increase kidney weight (Jonker et al. 1996), and mixtures of subthreshold doses can produce increased serum ALT in rats (Stacey 1989; see Section 2.2.7). A moderate quality factor (II) was selected to reflect ambiguities (i.e., inconsistency of the database) regarding the projection of less-than-additive joint action on the liver and kidney.

Toxicological Significance - Studies designed to examine the joint toxic action of these chemicals on nervous system endpoints were not located. Thus, the lowest possible toxicologic significance data quality factor, C, was applied for nervous system effects. For liver and kidney effects, a moderate data quality factor, B, was selected. There is evidence for tetrachloroethylene inhibition of trichloroethylene metabolism in humans (Seiji et al. 1989), but evidence for less-than-additive joint action on liver and kidney endpoints in rats is not consistent across endpoints (see above and Section 2.2.7).

Additional Uncertainties - Data for humans exposed to low levels of these chemicals indicate that tetrachloroethylene inhibits trichloroethylene metabolism (Seiji et al. 1989). PBPK simulations of trichloroethylene and vinyl chloride indicate that competitive metabolic interactions between halogenated hydrocarbons only occur at high concentrations (Barton et al. 1995). Thus, tetrachloroethylene may inhibit trichloroethylene metabolism by a non-competitive mechanism. The design of the study observing joint action to increase serum ALT in rats (Stacey 1989) could not discern additive from greater-than-additive or less-than-additive joint action.

Table 17. Matrix of BINWOE Determinations for Nervous System Effects from Simultaneous Exposure to Chemicals of Concern

		ON TOXICITY OF			
		1,1,1-Trichloro-ethane	1,1-Dichloroethane	Trichloro-ethylene	Tetrachloro-ethylene
EFFECT OF	1,1,1-Trichloroethane		=IIC (0)	=IIC (0)	=IIC (0)
	1,1-Dichloroethane	=IIC (0)		=IIC (0)	=IIC (0)
	Trichloroethylene	=IIC (0)	=IIC (0)		=IIC (0)
	Tetrachloroethylene	=IIC (0)	=IIC (0)	=IIC (0)	

Condensed from ATSDR 2001a
(Numerical weight values are indicated in parentheses below)

INTERACTIONS: = additive (0); > greater than additive (+1); < less than additive (-1); ? indeterminate (0)

MECHANISTIC UNDERSTANDING:
I: direct & unambiguous mechanistic data to support direction of interaction (1.0);
II: mechanistic data on related compounds to infer mechanism(s) & likely direction (0.71);
III: mechanistic data does not clearly indicate direction of interaction (0.32).
TOXICOLOGIC SIGNIFICANCE:
A. toxicologic significance has been directly demonstrated (1.0);
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals (0.71);
C: toxicologic significance of interaction is unclear (0.32).
MODIFYING FACTORS:
1: anticipated exposure duration and sequence (1.0)
2: different exposure duration or sequence (0.79)
a: *in vivo* data (1.0)
b: *in vitro* data (0.79)
i: anticipated route of exposure (1.0)
ii different route of exposure (0.79)

Table 18. Matrix of BINWOE Determinations for Liver and Kidney Effects from Simultaneous Exposure to Chemicals of Concern

		ON TOXICITY OF			
		1,1,1-Trichloroethane	1,1-Dichloroethane	Trichloro-ethylene	Tetrachloro-ethylene
EFFECT OF	1,1,1-Trichloroethane		=IIC (0)	=IIB (0)	=IIB (0)
	1,1-Dichloroethane	=IIC (0)		=IIC (0)	=IIC (0)
	Trichloroethylene	=IIB (0)	=IIC (0)		=IIB (0)
	Tetrachloroethylene	=IIB (0)	=IIC (0)	<IIB (-0.50)	

Condensed from ATSDR 2001a
(Numerical weight values are indicated in parentheses below)

INTERACTIONS: = additive (0); > greater than additive (+1); < less than additive (-1); ? indeterminate (0)

MECHANISTIC UNDERSTANDING:
I: direct & unambiguous mechanistic data to support direction of interaction (1.0);
II: mechanistic data on related compounds to infer mechanism(s) & likely direction (0.71);
III: mechanistic data does not clearly indicate direction of interaction (0.32).
TOXICOLOGIC SIGNIFICANCE:
A. toxicologic significance has been directly demonstrated (1.0);
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals (0.71);
C: toxicologic significance of interaction is unclear (0.32).
MODIFYING FACTORS:
1: anticipated exposure duration and sequence (1.0)
2: different exposure duration or sequence (0.79)
a: *in vivo* data (1.0)
b: *in vitro* data (0.79)
i: anticipated route of exposure (1.0)
ii different route of exposure (0.79)

3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture

1,1,1-Trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene frequently occur together in water samples, and in air samples to a less frequent extent, collected from hazardous waste sites. As discussed in Chapter 2 and the Appendices, each of the chemicals can produce neurological impairment via parent compound-induced physical and chemical changes in neuronal membranes and cause noncarcinogenic and carcinogenic responses (via reactive metabolites) in the liver and kidneys of animals. Each of the chemicals is volatile and has good solvent properties. Confidence is high that all of these chemicals are rapidly eliminated from the body based on human and animal toxicokinetic studies for three of the chemicals (1,1,1-trichloroethane, trichloroethylene, and tetrachloroethylene) and animal studies for the fourth (1,1-dichloroethane) (Appendices A, B, C, and D). There are data to indicate that some accumulation in fat can occur due to the lipophilicity of the compounds, but elimination half-lives from fat (the tissue type with the longest elimination half-lives) have been estimated on the order of hours (e.g., Monster et al. 1976, 1979), compared with much longer half-lives for biopersistent compounds such as polychlorinated biphenyls. Only one of the four, trichloroethylene, is extensively metabolized; the remaining three are predominately excreted unmetabolized in exhaled breath.

Neurological impairment forms the basis for each of ATSDR's MRLs for these chemicals, regardless of exposure route or duration (Table 4). Although some evidence of cancer, of varying weight, has been found in animal studies for each of these chemicals, low level exposure of humans may not present high risks for cancer. EPA (IRIS 2001) assigned 1,1,1-trichloroethane to Cancer Group D (Not Classifiable as to Human Carcinogenicity), 1,1-dichloroethane to Cancer Group C (Possible Human Carcinogen), and trichloroethylene and tetrachloroethylene to the boundary between Group C (Possible Human Carcinogen) and Group B2 (Probable Human Carcinogen). EPA lists no oral slope factors or inhalation unit risks for these chemicals on its IRIS (2001) database. The National Toxicology Program (NTP 2001) list of chemicals reasonably anticipated to be human carcinogens includes trichloroethylene and tetrachloroethylene, but not 1,1-dichloroethane or 1,1,1-trichloroethane. IARC (2001) has not assigned a cancer classification for 1,1-dichloroethane, but assigned 1,1,1-trichloroethane to Cancer Group 3, not classifiable as to human carcinogenicity, and trichloroethylene and tetrachloroethylene to Cancer Group 2A, probably carcinogenic to humans.

To conduct exposure-based assessments of possible health hazards from exposures to mixtures of these chemicals, a component-based Hazard Index approach is recommended, because there are no direct data

available to characterize health hazards (and dose-response relationships) from exposure to the mixture. Furthermore, PBPK models have not yet been developed that would predict appropriate target doses of the components from exposure to the mixture; such models would be useful in assessing health hazards from exposure to the mixture. As discussed by ATSDR (1992, 2001a), exposure-based health assessments are used, in conjunction with evaluation of community-specific health outcome data, consideration of community health concerns, and biomedical judgement, to assess the degree of public health hazard presented by mixtures of hazardous substances released into the environment.

To calculate hazard indices for each exposure scenario of concern, hazard quotients (i.e., the ratio of an exposure estimate to the appropriate MRL; see Appendices for MRLs) should first be calculated for each of the components (see Figure 2 in *Guidance Manual for the Assessment of the Joint Toxic Action of Chemical Mixtures*, ATSDR 2001a). If two or more of the individual components have hazard quotients equaling or exceeding ratios of 0.1, then the assessment should proceed. If only one or if none of the components have a hazard quotient that equals or exceeds 0.1, then no further assessment of the joint toxic action is needed because additivity and/or interactions are unlikely to result in significant health hazard. As exposure levels approach threshold levels for toxic effects, a hazard index approach is likely to give a more accurate assessment of health hazards than an approach that only examines hazard quotients for individual components in a mixture, as evidenced by results showing that liver endpoints were adversely affected by exposure to binary or ternary mixtures of trichloroethylene, tetrachloro-ethylene, and 1,1,1-trichloroethane at dose levels of the components that were near, but below, threshold levels for the individual (Stacey 1989). Under conditions for proceeding with the hazard index approach, the hazard quotients are summed to derive the hazard index as follows:

$$HI = \frac{E_{TCA}}{MRL_{TCA}} + \frac{E_{DCA}}{MRL_{DCA}} + \frac{E_{TCE}}{MRL_{TCE}} + \frac{E_{PERC}}{MRL_{PERC}}$$

where *HI* is the hazard index (a different hazard index is derived for each duration of exposure—acute, intermediate, and chronic—and each exposure route of concern), *E* represents the exposure estimates for the individual components, MRL represents the appropriate minimal risk levels for the components, and TCA, DCA, TCE, and PERC represent 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. Because there are no ATSDR MRLs (or EPA RfDs or RfCs) for 1,1-dichloroethane for any exposure duration or route, hazard quotients for this chemical cannot be calculated. Because all of the MRLs for these chemicals are based on neurological impairment as the critical effect, the calculated hazard indices will provide indicators of the hazard for neurological impairment. Preliminary evidence

that the exposure to the mixture may constitute a hazard for neurological impairment is provided when the hazard index for a particular exposure scenario exceeds one. In practice, concern for the possibility of a health hazard increases with increasing value of the hazard index above 1.

The addition of hazard quotients for a particular exposure scenario assumes that the mixture components additively act on a common toxicity target by a common mechanism or mode of action, and that less-than-additive (e.g., antagonistic interactions) or greater-than-additive (e.g., synergism or potentiation) interactions do not occur among the components of the mixture. A primary objective of this profile was to assess available information on modes of joint toxic actions of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. As discussed in Section 2.3, a weight-of-evidence approach was used to evaluate the possible influence of interactions in the overall toxicity of the mixture. Twelve BINWOE determinations were made for the mode of joint action on the nervous system by the six pairs of the chemicals. As shown in Table 17, each of the BINWOEs for nervous system effects determined an additive joint action with data quality factors of "II" to reflect moderate mechanistic understanding supporting the plausibility of joint additive action (without interactions) and "C" to reflect the lack of direct toxicological data to test the hypothesis of joint additive action on the nervous system. The BINWOE determinations are taken to be applicable to all routes and durations of exposure because neurological effects are the basis for all of ATSDR's MRLs for these chemicals, regardless of exposure route or duration. In summary, it is plausible that 1,1,1-trichloroethane, 1,1,-dichloroethane, trichloroethylene, and tetrachloroethylene jointly act in an additive manner to impair nervous system function based on mechanistic understanding that the parent chemicals and a metabolite (trichloroethanol), like other lipophilic solvents, produce reversible chemical and physical changes in neuronal membranes that impair their functions. No evidence was found to indicate that the components may jointly act on the nervous system in a less-than-additive or greater-than-additive mode, but studies directly designed to examine the mode of joint toxic action of these chemicals on the nervous system were not located.

BINWOE determinations were made for the joint toxic actions of binary combinations of the mixture components on the liver and kidney, in anticipation of public health concerns that there may be greater-than-additive interactions that might cause liver and kidney effects to occur. Additive joint action was selected as plausible in 11 of 12 BINWOE considerations (see Tables 5–16 and Table 18) based on plausibility from mechanistic understanding and/or limited evidence from rat studies of joint action of binary mixtures on liver and kidney endpoints. The effect of tetrachloroethylene on trichloroethylene's hepato and renal toxicity (the twelfth BINWOE) was projected to occur by a less-than-additive joint action based on *in vivo* evidence that tetrachloroethylene inhibits the metabolism of trichloroethylene in

humans under occupational exposure conditions (Seiji et al. 1989), and evidence that trichloroethylene and tetrachloroethylene act in a less-than-additive manner to cause hepatic and renal peroxisomal proliferation (Goldsworthy and Popp 1987). In summary, the available data provide no evidence of greater-than-additive interactions among 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, or tetrachloroethylene that might cause liver and kidney effects to occur.

4. Conclusions

There are no studies available that directly characterize health hazards and dose-response relationships for exposures to mixtures of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. Each of the chemicals can produce neurological impairment via parent compound-induced physical and chemical changes in neuronal membranes and cause non-carcinogenic and carcinogenic responses (via reactive metabolites) in the liver and kidneys of animals. No studies were located that directly examined joint toxic actions of these chemicals on the nervous system, but additive joint toxic action is plausible. Limited studies of joint toxic action of ternary and binary mixtures of these chemicals on the liver and kidney provide no evidence of greater-than-additive joint toxic actions. Additive joint toxic action on the liver and kidney is plausible for binary combinations of each of the components, with the exception of limited evidence that tetrachloroethylene may inhibit the toxic action of trichloroethylene on the liver and kidney (Goldsworthy and Popp 1987; Seiji et al. 1989). A component-based hazard index approach that assumes additive joint toxic action and uses ATSDR MRLs based on neurological impairment is recommended for exposure-based assessments of possible health hazards from exposure to mixtures of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. There is no evidence to indicate that greater-than-additive interactions would cause liver and kidney effects to occur at exposure levels lower than those influencing the nervous system.

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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:

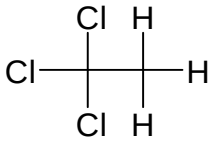
"(i) Although tetrachloroethylene is known to induce peroxisome proliferation in mouse liver, a poor quantitative correlation was seen between peroxisome proliferations and tumor formation in the liver after administration of tetrachloroethylene by inhalation. The spectrum of mutations in proto-oncogenes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

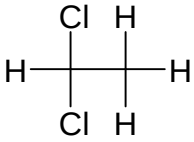
(ii) Several epidemiological studies showed elevated risks for oesophageal cancer, non-Hodgkin's lymphoma, and cervical cancer."

Appendix E: Chemical Structures of Mixture Components

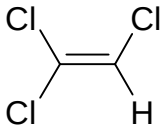
1,1,1-Tetrachloroethane



1,1-Dichloroethane



Trichloroethylene



Tetrachloroethylene