United States
Environmental Protection
Agency

Health Effects Support Document for 1,1,2,2-Tetrachloroethane

Health Effects Support Document for 1,1,2,2-Tetrachloroethane

U.S. Environmental Protection Agency
Office of Water (4304T)
Health and Ecological Criteria Division
Washington, DC 20460

www.epa.gov/safewater/ccl/pdf/1122tetrachloroethane.pdf

EPA Document Number EPA-822-R-08-007
January, 2008

FOREWORD

The Safe Drinking Water Act (SDWA), as amended in 1996, requires the Administrator of the U.S. Environmental Protection Agency (U.S. EPA) to establish a list of contaminants to aid the Agency in regulatory priority setting for the drinking water program. In addition, the SDWA requires EPA to make regulatory determinations for no fewer than five contaminants by August 2001 and every five years thereafter. The criteria used to determine whether or not to regulate a chemical on the Contaminant Candidate List (CCL) are the following:

The contaminant may have an adverse effect on the health of persons.

- The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern.

- In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The Agency's findings for all three criteria are used in making a determination to regulate a contaminant. The Agency may determine that there is no need for regulation when a contaminant fails to meet one of the criteria. The decision not to regulate is considered a final Agency action and is subject to judicial review.

This document provides the health effects basis for the regulatory determination for 1,1,2,2-tetrachloroethane. In arriving at the regulatory determination, data on toxicokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. In order to avoid wasteful duplication of effort, information from the following risk assessments by the U.S. EPA and other government agencies were used in the development of this document.

ATSDR (Agency for Toxic Substances and Disease Registry). 1996, 2006 (draft). Toxicological Profile for 1,1,2,2-Tetrachloroethane. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

Cal EPA (California Environmental Protection Agency). 2003. Public health goal for 1,1,2,2-tetrachloroethane in drinking water. Office of Environmental Health Hazard Assessment. Available from: <http://www.oehha.ca.gov/water/phg/pdf/Ph41122TCA92603.pdf>.

U.S. EPA. 1989c. United States Environmental Protection Agency. 1,1,2,2-Tetrachloroethane Drinking Water Health Advisory. Office of Water.

U.S. EPA (United States Environmental Protection Agency). 1986e. Integrated Risk Information System (IRIS): 1,1,2,2-tetrachloroethane (cancer assessment 1986). Available from: <http://www.epa.gov/iris/subst/0193.htm>.

World Health Organization. 1998. Concise International Chemical Assessment Document; 1,1,2,2-Tetrachloroethane. Geneva.

Information from the published risk assessments was supplemented with information from the primary references for key studies and recent studies of 1,1,2,2-tetrachloroethane identified by a literature search conducted in 2003 and updated in 2006 and 2008.

A Reference Dose (RfD) is provided as the assessment of long-term toxic effects other than carcinogenicity. RfD determination assumes that thresholds exist for certain toxic effects, such as cellular necrosis, significant body or organ weight changes, blood disorders, etc. It is expressed in terms of milligrams per kilogram per day (mg/kg/day). In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

The carcinogenicity assessment for 1,1,2,2-tetrachloroethane includes a formal hazard identification and an estimate of tumorigenic potency when available. Hazard identification is a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen via the oral route and of the conditions under which the carcinogenic effects may be expressed.

Development of these hazard identification and dose-response assessments for 1,1,2,2-tetrachloroethane has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986a), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996a), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a), *Guidelines for Carcinogen Assessment* (U.S. EPA, 2005a), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988), (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995a), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998b, 2000a), *Science Policy Council Handbook: Risk Characterization* (U.S. EPA, 2000b), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000d), and *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002a).

The chapter on occurrence and exposure to 1,1,2,2-tetrachloroethane through potable water was developed by the Office of Ground Water and Drinking Water (OGWDW). It is

based primarily on unregulated contaminant monitoring (UCM) data collected under the SDWA. The UCM data are supplemented with ambient water data, as well as data from the States, and published papers on occurrence in drinking water.

ACKNOWLEDGMENT

This document was prepared under the U.S. EPA Contract No. 68c-02-009, Work Assignment No. 3-54 with ICF Consulting, Inc. The Lead U.S. EPA Scientist is Joyce Morrissey Donohue, Ph.D., Health and Ecological Criteria Division, Office of Science and Technology, Office of Water.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 EXECUTIVE SUMMARY

1,1,2,2- Tetrachloroethane is one of a family of volatile, chlorinated, ethane and ethene compounds with a variety of commercial uses. 1,1,2,2-Tetrachloroethane is presently no longer manufactured in the United States. Some product continues to be released to the environment as a by-product in the synthesis of other chlorinated chemicals. Data from the Toxic Release Inventory (TRI) from show a total release of 5420 pounds in 2001 compared to a release of 17547 pounds in 1988. This change is indicative of the decline in production and use.

When considered in its totality, the data on the occurrence of 1,1,2,2-tetrachloroethane in public potable water systems indicate that a positive regulatory determination is not justified at this time. Although 1,1,2,2-tetrachloroethane is a likely carcinogen and has noncancer effects on several organ systems, it does not occur widely in drinking water systems, and continued decline of its commercial use and environmental release will further reduce the risk for source- and drinking water contamination. 1,1,2,2-Tetrachloroethane does not occur in potable water systems at levels of concern, and regulation would not provide a meaningful opportunity to reduce risk for the population.

1,1,2,2-Tetrachloroethane is fairly stable in the environment, especially in the upper atmosphere. Degradation by microbes is possible but appears to be slow. Prevalence in finished and ambient water is low and has declined in concert with the decrease in U.S. production and use. There are no data that demonstrate that it is present in the food supply, and there are no recent data from monitoring of ambient air samples.

Data on the occurrence of 1,1,2,2-tetrachloroethane in drinking water were obtained from the Unregulated Contaminant Monitoring program and represent two time periods: 1988 to 1992 (Round 1) and 1993 to 1997 (Round 2). Detection limits for the methods used by the states varied from 0.01 to 10 µg/L with a median value of 0.5 µg/L. Some under-reporting of the actual occurrence may have occurred as a result of the variability in the reporting limits. Results from Round 2 are likely to be more accurate than those from Round 1 because the upper bond for reporting decreased from 10 µg/L to 2.5 µg/L. Round 2 results are also more representative of current production and use conditions. In Round 2, 0.07% of 24,800 systems reported at least one detection of 1,1,2,2-tetrachloroethane at a level greater than the benchmark health reference level (HRL) of 0.4 µg/L. When extrapolated to a national level, an estimated 168,000 persons could have been exposed to 1,1,2,2-tetrachloroethane at levels greater than the HRL at some time during the reporting period.

Absorption of 1,1,2,2-tetrachloroethane by both the oral and inhalation routes is nearly complete. The major site of metabolism is the liver where it is dechlorinated, apparently by way of a cytochrome P450, and oxidized to dichloroacetic acid (DCA). There is some evidence for a free radical intermediate in this process. DCA is metabolized by cytosolic GST zeta, ultimately forming oxalate and carbon dioxide. Glycolate and glyoxalate are intermediates in this process and provide a route for some of the carbons from 1,1,2,2-tetrachloroethane to become incorporated in the synthesis of endogenously-formed intermediary metabolites like glycine and serine. There are several variants of GST zeta in the human population which leads to

differences in the amount of DCA that becomes metabolized. In addition, DCA is an inhibitor of GST zeta, leading to increased serum levels when exposure is continuous rather than episodic.

Numerous studies in humans and animals implicate the liver as the primary target organ and liver toxicity as the critical effect in dose-response analysis. 1,1,2,2-Tetrachloroethane also has effects on hematology, the kidney, testes, and nervous system. The human data are limited and often confounded by simultaneous exposure to other chemicals. Most human data apply to occupational exposures and lack quantification of exposure concentration and dose.

Animal data are available for the inhalation and oral routes in several species. A 2004 subchronic study by the National Toxicology Program (NTP) using F-344 rats and B6C3F1 mice provides the most comprehensive dose-response data on the noncancer effects of 1,1,2,2-tetrachloroethane and serves as the basis for the reference dose (RfD) of 10 µg/kg/day. The RfD was derived from a lower-bound limit on the dose (BMDL) associated with a one standard deviation increase in relative liver weight in F-344 rats (10.71 mg/kg/day) and supported by increased cytoplasmic vacuolization of hepatocytes in 7/10 males at the lowest tested dose plus increased levels of serum levels of liver enzymes that are biomarkers for liver toxicity at BMDLs of about 30 mg/kg/day. Rats were found to be more sensitive than mice to the noncancer effects of 1,1,2,2-tetrachloroethane. The uncertainty factor for the RfD calculation was 1000 (10 for intraspecies variability, 10 for interspecies variability, 3 for a duration adjustment from subchronic to chronic, and 3 for database uncertainties). The data for the inhalation route of exposure do not support the derivation of a reference concentration (RfC) at this time.

Range finding studies for developmental toxicity in rats and mice were conducted by NTP and demonstrate a lack of developmental effects except at doses that were maternally toxic and greater than the point of departure for the RfD calculation. The data on reproductive toxicity are more limited, consisting of a one-generation study of inhalation exposure to 13.3 mg/m^3 for 4 hours per day in 7 exposed male and 5 female rats. Although there were no effects on the number of pups, pup weights, pup mortality or malformations, there is a need for a more comprehensive study of reproductive toxicity using a range of doses, more animals per dose group and a broader suite of monitored endpoints. The observation of effects on the testes and decreases in sperm motility support the need for additional research on the reproductive effects of 1,1,2,2-tetrachloroethane.

The National Cancer Institute conducted studies of the tumorigenicity of 1,1,2,2-tetrachloroethane in Osborne-Mendel rats and B6C3F1 mice using gavage in corn oil as the exposure route. Liver tumors were identified in both species; the finding for mice was judged to be positive and that for rats, equivocal. These findings are consistent with those for DCA, its principal metabolite, which also causes liver tumors in both rats and mice after oral exposure with mice having the greater sensitivity.

Limited studies of the tumorigenic mode of action suggest that 1,1,2,2-tetrachloroethane acts as a promoter for tumor development and that it also has a weak initiation activity. Genotoxicity studies provide limited evidence for mutagenicity and stronger evidence for chromosomal effects. 1,1,2,2-Tetrachloroethane is *likely to be a human carcinogen* based on the

NCI cancer data and the data demonstrating its potential as both an initiator and promoter. There is a need for additional mode of action research on 1,1,2,2-tetrachloroethane and examination of the similarities and differences that exist between it and DCA. DCA is also a likely human carcinogen. IARC places 1,1,2,2-tetrachloroethane in Group 3 for inadequate human data and limited data from animal studies.

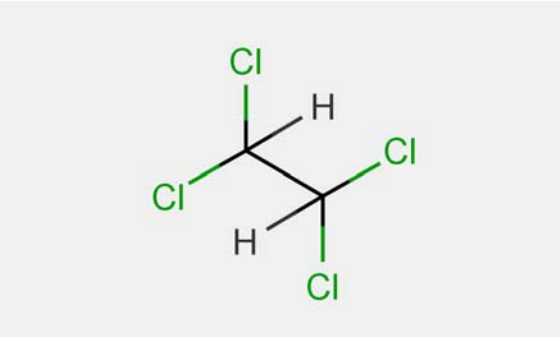
The Office of Water quantified the cancer risk for 1,1,2,2-tetrachloroethane using the multistage model of the Agency Benchmark Dose Software (version 3.1.2) following the 2005 cancer guidelines. The cancer slope factor is 8.5×10^{-2} $(mg/kg/day)^{-1}$; the concentration equivalent to a one-in-a-million risk is 0.4 µg/L, a value that serves as the HRL benchmark used in evaluating the occurrence data. This value differs from the 0.2 µg/L value calculated for the U.S. EPA Integrated Risk Information System (IRIS) under the 1986 cancer guidelines. Differences between the two cancer assessments are mostly a function of policy differences between the 1986 and 2005 guidelines.

There are several factors that could increase sensitivity to exposure to 1,1,2,2-tetrachloroethane. Continuous exposure to DCA from chlorinated water could increase the toxicity of 1,1,2,2-tetrachloroethane, if the DCA concentrations were sufficient to inhibit GST zeta activity and increase the production of free radical intermediates. Dietary deficiencies of antioxidant nutrients would increase the opportunity for liver damage through a free radical/lipid peroxidation mechanism, and preexisting damage to the liver or kidneys could increase the risks for target organ damage.

2.0 IDENTITY: CHEMICAL AND PHYSICAL PROPERTIES

At room temperature 1,1,2,2-tetrachloroethane is a heavy, pure, colorless to pale-yellow liquid with a sweetish, pungent, chloroform-like odor. It is a corrosive substance that will attack some forms of plastics, rubber, and coatings. 1,1,2,2-Tetrachloroethane is soluble in alcohol, ether, acetone, and benzene; it is miscible with methanol, ethanol, petroleum ether, carbon tetrachloride, chloroform, carbon disulfide, dimethylformamide, and some oils. Its solubility in water is about 2.87 g/L at 20°C. Technical grade 1,1,2,2-tetrachloroethane is 98% pure. 1,1,1,2-Tetrachloroethane is found as an impurity in technical grade 1,1,2,2-tetrachloroethane (HSDB, 2004).

Figure 2-1 Chemical Structure of 1,1,2,2-Tetrachloroethane



The chemical structure of 1,1,2,2-tetrachloroethane is shown above (Figure 2-1). Its physical and chemical properties are listed in Table 2-1, along with other reference information.

Table 2-1 Chemical and Physical Properties of 1,1,2,2-Tetrachloroethane

Property	Information
Chemical Abstracts Registry (CAS) No.	79-34-5
US EPA Pesticide Chemical Code	078601
Synonyms	Acetylene tetrachloride; sym-Tetrachloroethane; s-Tetrachloroethane
Registered Trade Name(s)	Bonoform; Cellon; Westron
Chemical Formula	$C_2H_2Cl_4$
Molecular Weight	167.85
Physical State	liquid
Boiling Point	146.1 - 146.5°C
Melting Point	-43.8°C
Density (at 20°C)	1.59 g/mL
Vapor Pressure:	
At 20°C	Not found
At 25°C	4.62 mm Hg
Partition Coefficients:	
Log K_{ow}	2.39
Log K_{oc}	1.68 - 2.38
Solubility in:	
Water	2.87 g/L (20°C) 2.86 g/L (25°C)
Other Solvents	Ethanol, Methanol, Ether, Acetone, Benzene, Petroleum, Carbon tetrachloride, Chloroform, Carbon disulfide, Dimethyl formamide, oils
Conversion Factors (at 25°C, 1 atm)	1 ppm= 6.98 mg/m^3 1 mg/m^3= 0.14 ppm

Sources: ATSDR (1996, 2006); HSDB (2004)

3.0 USES AND ENVIRONMENTAL FATE

This section summarizes information pertaining to the uses, manufacture, and environmental fate of 1,1,2,2-tetrachloroethane.

3.1 Production and Use

Prior to the 1980s, 1,1,2,2-tetrachloroethane was commonly used in the production of other chemicals, primarily trichloroethylene (TCE), tetrachloroethylene (PCE), and 1,2-dichloroethylene (Archer, 1979). It was also used as a metal degreaser, an extractant for oils and fats, and a component of paint removers, varnishes and lacquers, and photographic films (Hawley, 1981). More recently 1,1,2,2-tetrachloroethane use has declined, leading to an end to commercial production in the U.S. Some use of 1,1,2,2-tetrachloroethane in the production of chlorinated ethanes and ethenes has remained (ATSDR, 2006). Formerly it was used as a fumigant, insecticide, and weed killer but is not currently registered in the U.S. for such uses (U.S. EPA, 2004a).

Approximately 440 million pounds of 1,1,2,2-tetrachloroethane were produced in 1967 (Konietzko, 1984). Production fell to 34 million pounds in 1974, and production for commercial uses ceased in the U.S. by the late 1980s. 1,1,2,2-tetrachloroethane is no longer produced as a commercial product in the United States. The last production plant was Specialty Materials Division of Eagle-Picher Industries in Lenexa, Kansas (SRI, 1988). By the late 1980s, this facility was sold to the Vulcan Materials Company, and production was discontinued (Montgomery and Welkom, 1990; SRI, 1993). Imports are also thought to be minimal (ATSDR, 2006).

3.2 Environmental Release

Although 1,1,2,2-tetrachloroethane is no longer generated as a commercial product, it is still generated as an intermediate product and/or by-product in the manufacturing of other synthetic chemicals, including trichloroethylene, 1,1,2-trichloroethane, 1,2-dichloroethene, tetrachloroethylene, vinyl chloride, ethylene dichloride, and 1,1,1-trichloroethane. It can occur as a trace contaminant in these and other manufactured chemicals, and in the waste stream of facilities that produce them. ATSDR (2006) lists 95 facilities that produce 1,1,2,2-tetrachloroethane as a by-product or use it as an intermediate product; the list is likely not exhaustive.

1,1,2,2-Tetrachloroethane is listed as a Toxic Release Inventory (TRI) chemical. The EPA established the TRI in 1987 in response to Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA). EPCRA requires the U.S. EPA and the states to collect annual information on toxic chemical releases and transfers from industrial facilities and to make this information available to the public through TRI. TRI details not only the types and quantities of toxic chemicals released to the air, water, and land by facilities, but also provides information on the quantities of chemicals sent to other facilities for further processing. The scope of TRI was expanded in 1990 by the Pollution Prevention Act requiring additional

information to be reported on waste management and source reduction activities. The purpose of TRI is to educate the public on releases and transfer so that they can make informed decisions on the consequences of those actions. The increased transparency has also forced industries to pay closer attention to their use of toxic chemicals, resulting in internally-motivated reductions in use (U.S. EPA, 2003a).

Facilities are required to report releases or transfers of chemicals if they manufacture, process, or otherwise use more than established threshold quantities of these chemicals (currently 25,000 pounds for manufacture and process and 10,000 pounds for use). Both the number and type of facilities required to report has increased over time so that in 2002 over 24,000 industrial and federal facilities submitted in excess of 93,000 reports on toxic releases (U.S. EPA, 2002b). In 2000, special thresholds were added for persistent bioaccumulative toxic chemicals, for example dioxin and dioxin-like compounds. Today, TRI reports on releases of nearly 670 chemicals (U.S. EPA, 2002b).

Although TRI can provide a general idea of release trends, it is far from exhaustive and has significant limitations. For example, small facilities (those with fewer than 10 full-time employees, and those that do not exceed manufacture and use limits) are not required to report releases. In addition, the reporting threshold for the manufacturing and processing of TRI chemicals changed between 1987 and 1989, dropping from 75,000 pounds per year in 1987 to 50,000 in 1988 to the current 25,000 in 1989; this creates the potential for misleading data trends over time (U.S. EPA, 1996b). Finally, TRI data are meant to reflect releases and should not be used to estimate general public exposure to a chemical (U.S. EPA, 2002b).

TRI data for 1,1,2,2-tetrachloroethane (see Table 3-1) are reported for the years 1988 to 2001 (U.S. EPA, 2004b). Air emissions constitute most of the on-site releases. Reported air releases peaked in 1991 and then generally declined. Surface water discharges ranged in the thousands of pounds until the mid-1990s, and then dropped off significantly. There is no detectable pattern in on-site underground injections or releases to land. Reported off-site releases were most significant in the first year of reporting, and then generally declined, with an aberrant peak in 1998 and a rising trend in the last few recorded years.

The TRI data for 1,1,2,2-tetrachloroethane were reported from nineteen states (AK, CT, CO, FL, KS, KY, LA, MI, MO, NC, NE, NJ, NY, OH, PA, SC, TN, TX, and VA), but no more than 11 states reported in a given year. Louisiana and Texas were the only states to report every year. Louisiana consistently discharged the most pounds per year to the environment, but that state's reported releases dropped off considerably from 112,445 lbs. in 1988 to 2,367 lbs. in 2001 (U.S. EPA, 2004b).

Table 3-1 Environmental Releases of 1,1,2,2-Tetrachloroethane in the U.S., 1988-2001 (pounds)

Year	On-Site Releases				Off-Site Releases	Total On- & Off-Site Releases
	Air Emissions	Surface Water Discharges	Underground Injection*	Releases to Land		
2001	3,462	56	0	961	941	5,420
2000	4,461	13	5	0	631	5,110
1999	5,202	1	0	15	30	5,248
1998	7,299	269	5	0	6,503	14,076
1997	13,614	0	0	0	511	14,125
1996	15,488	130	0	0	7	15,625
1995	8,275	2,222	0	0	7	10,504
1994	12,484	1,517	26	0	52	14,079
1993	28,203	2,930	0	1	80	31,214
1992	48,899	5,164	0	0	273	54,336
1991	64,251	2,113	0	0	262	66,626
1990	44,796	3,529	80	495	771	49,671
1989	35,611	5,429	283	18	15,209	56,550
1988	43,865	1,903	0	29	128,750	174,547

Source: U.S. EPA, 2004b

3.3 Environmental Fate

1,1,2,2-Tetrachloroethane may be found primarily in the troposphere, where it is not expected to react readily with photochemically produced hydroxyl radicals. It can be expected to diffuse slowly into the stratosphere where it will degrade rapidly by photodissociation. Half-life estimations have been derived using structure-activity models. In one case, Singh, et al. (1981) suggested a half-life of >2 years in the troposphere. Another estimate, however, assumed first order kinetics and suggested a half-life of approximately 53 days (Atkinson, 1987). The half-life in the troposphere is sufficiently long to suggest that 1,1,2,2-tetrachloroethane will distribute throughout the atmosphere.

1,1,2,2-Tetrachloroethane that reaches the stratosphere via diffusion will photodegrade rapidly due to the shorter wavelengths of ultraviolet radiation. Chlorine radicals are produced. The chlorine radicals may react with ozone, and perhaps deplete the stratospheric ozone layer. Based on an estimated half-time and a tropospheric-to-stratospheric turnover time of 30 years (U.S. EPA, 1979), it has been predicted that less than 1% of tropospheric 1,1,2,2-tetrachloroethane would eventually reach the stratosphere. The ozone depletion potential for 1,1,2,2-tetrachloroethane is 0.001 relative to CFC-11 (trichlorofluoromethane), based on the method developed by Nimitz and Skaggs (1992).

Due to the moderate vapor pressure of 5.95 mm Hg at 25°C, some 1,1,2,2-tetrachloroethane in surface water is expected to volatilize to ambient air. The volatilization half-life of 1,1,2,2-tetrachloroethane is estimated to be 6.3 hours (Thomas, 1982). This is based on a calculated Henry's law constant of 4.7×10^{-4} atm-m^3/mol (Mackay and Shiu, 1981), and a model river 1 m deep, flowing at 1 m/s, with a wind velocity of 3 m/sec. First-order decay kinetics is assumed.

In wastewater treatment plants, aeration towers are used to remove 1,1,2,2-tetrachloroethane. The contaminated water is cascaded over trickling towers, and streams of air to create aerosolized droplets that accelerate the volatilization processes. In stripping, as opposed to ordinary volatilization, the liquid and gas phases are dispersed. Stripping was able to remove 96% of the 1,1,2,2-tetrachloroethane in tests performed with activated sludge reactors (Kincannon et al., 1983). The half-life for 1,1,2,2-tetrachloroethane removal by air stripping was 0.3 hour.

Chlorinated hydrocarbons are degraded through one or more of three possible degradation pathways all of which accomplish reductive dechlorination: hydrogenolysis, dichloroelimination, and dehydrochlorination (O'Loughlin et al., 1999). Hydrogenolysis is the sequential replacement of chlorine atoms by hydrogen atoms (i.e., 1,1,2,2-tetrachloroethane → 1,1,2-trichloroethane). This is usually driven by microbial activity. Dichloroelimination is an abiotic reaction where there is a simultaneous release of two chlorine atoms and a hydrogen, which forms an alkene (i.e., 1,1,2,2-tetrachloroethane → *cis/trans* 1,2-dichloroethene). Dehydrochlorination is an abiotic elimination reaction (i.e., 1,1,2,2-tetrachloroethane → trichloroethene). Studies have shown that the biotic reactions found in natural systems can effectively degrade 1,1,2,2-tetrachloroethane levels to below detection limits (Lorah et al., 2003).

In some studies, 1,1,2,2-tetrachloroethane was reported to undergo a base-catalyzed hydrolysis in water (25°C and pH=7.0). Its calculated half-life is 102 days when assuming a second order rate reaction (Cooper et al., 1987). Solutions of lower ionic strength, which are more typical of groundwater, had half-lives of 573 days for 1,1,2,2-tetrachloroethane removal at pH=6.05 and 36 days at pH=7.01 (Haag and Mill, 1988). In a sterile, anaerobic solution of pH 7.0, after 28 days, 25% of the chemical had degraded (Klecka and Gonsior, 1983). 1,1,2,2-Tetrachloroethane underwent hydrolysis in pore-water extracted from sediments (low-carbon sandy material) with a half-life of 29.1 days at pH values between 7.0 and 7.5 (Haag and Mill, 1988). In an anoxic sediment-water system (pH unreported) the half-life of 1,1,2,2-tetrachloroethane with both chemical hydrolysis and biotic degradation was 6.6 days (Jafvert and Wolfe, 1987).

In early studies, aerobic biodegradability tests results were conflicting. A study with 5 and 10 parts per million (ppm) 1,1,2,2-tetrachloroethane incubated with sewage seed for 7 days, followed by 3 successive 7-day subcultures, found no significant degradation (Tabak et al., 1981). Other investigators (Mudder and Musterman, 1982) found that in an unacclimated biodegradability test when the initial concentration of 1,1,2,2-tetrachloroethane was 4.4 ppm, it degraded by 41% in 24 days. There was no degradation over 5 days at an initial 1,1,2,2-tetrachloroethane concentration of 0.85 ppm using acclimated microbes. A river die-away test yielded 19% loss after 5 days using an acclimated system with an initial concentration of 17.3 ppm. None of the other chlorinated ethanes and ethenes in the study were found to be biodegradable. Many researchers attribute most 1,1,2,2-tetrachloroethane loss associated with sewage treatment to air-stripping processes and not biodegradation (Kincannon et al., 1983).

Current studies conducted by the Air Force investigated the redox chemistry of humic substances under anoxic conditions. Humic materials have electron-donating and terminal electron-accepting properties which in the presence on nickel ions can accelerate redox reactions (O'Loughlin et al., 2003). 1,1,2,2-Tetrachloroethane undergoes a β-elimination or dichloroelimination to *cis/trans*-1,2-dichloroethene under anoxic conditions with humic acid and nickel. The half-life for this reaction was 61 minutes; with titanium and nickel, the half-life was 4 hours and with nickel alone the half-life was 23 hours, demonstrating the high redox potential of humic acid.

1,1,2,2-Tetrachloroethane is expected to volatilize from moist soil surfaces because of its vapor pressure, Henry's Law constant, low adsorption to soil, and a log K_{OC} of 1.66 (Chiou et al., 1979) or 2.38 (Valsaraj et al., 1999). The K_{OC} of 1,1,2,2-tetrachloroethane is 46 in a silt loam soil (Chiou et al., 1979). These chemical factors suggest that 1,1,2,2-tetrachloroethane will not adsorb appreciably to soil, suspended solids, or sediment.

A measured aqueous hydrolysis rate constant, K_b (also referred to as the ionization constant of a base), of $2.3x10^7$ L/moles-yr, corresponds to a half-life of 1.1 days at pH 9 (Kolling et al., 1987). Samples were incubated for six weeks under anaerobic conditions after inoculation with a microorganism culture, consisting of primarily of anaerobic microorganisms that were obtained from an anaerobic digester of a municipal wastewater treatment facility. The products formed were: 1,1,2-trichloroethane, trichloroethene, *cis*-1,2-dichloroethene, *trans*-1,2-dichloroethene, 1,1-dichloroethene, and vinyl chloride (Hallen et al., 1986).

Bioconcentration is not expected to occur with 1,1,2,2-tetrachloroethane, because only bioconcentration factors (BCF) of values greater than 500-1000 are considered significant. The BCF in bluegill sunfish was found to be 8 after 16 days (Barrows et al., 1980). A bioconcentration factor of 2.0 is predicted for fathead minnows (ASTER, 1995). These BCF values are in agreement with those estimated by regression analysis using K_{ow}. The estimated values are between 21 and 36 (Veith et al., 1980).

3.4 Summary

1,1,2,2-Tetrachloroethane once was used to produce various chlorinated chemicals; however, its production for this purpose has declined. Other uses included cleaning/degreasing solvent for metals, paint remover, varnishes and lacquers, photographic film, and fats /oils extractant. It now is found primarily as an intermediate during the manufacture of some chlorinated chemicals and is no longer produced commercially in the United States. The TRI data on releases to the environment confirm the decline in production and use during the past decade.

1,1,2,2-Tetrachloroethane is found in the troposphere where it is stable. At higher atmospheric levels, it can be photodegraded releasing chlorine radicals. Its half-life in the tropospheric atmosphere has been estimated to be between 53 days to >2 years. The chlorine radicals that are formed by photodegradation may react with ozone leading to its depletion.

Due to its moderate vapor pressure, 1,1,2,2-tetrachloroethane in surface water is expected to volatilize to the atmosphere. The volatilization half-life is estimated to be about 6.3 hours.

1,1,2,2-Tetrachloroethane can hydrolyze in water (25°C, pH=7.0). Its half-life in water is pH-dependent. In experimental studies with solutions that had ionic strengths similar to groundwater, 1,1,2,2-tetrachloroethane's half-life was between 36 and 573 days at pH levels between 6.05 and 7.01. When incubated under anaerobic conditions in the presence of a culture of primarily anaerobic microorganisms, the products formed included 1,1,2-trichloroethane, trichloroethene, *cis*-1,2-dichloroethene, *trans*-1,2-dichloroethene, 1,1-dichloroethene, and vinyl chloride. Aerobic biodegradability test results are conflicting, and range from none to 41% degradation with various concentrations of 1,1,2,2-tetrachloroethane, and the presence or absence of acclimated microbes. Most 1,1,2,2-tetrachloroethane loss associated with sewage treatment is attributable to air-stripping processes and not biodegradation.

1,1,2,2-Tetrachloroethane is not expected to bioconcentrate in fish and, subsequently, to higher life forms. BCFs, when estimated, range between 2 and 36; when measured in bluegill sunfish, the BCF was 8.

4.0 EXPOSURE FROM DRINKING WATER

4.1 Introduction

EPA used data from several sources to evaluate the potential for occurrence of 1,1,2,2-tetrachloroethane in Public Water Systems (PWSs). The primary source of drinking water occurrence data for 1,1,2,2-tetrachloroethane was the Unregulated Contaminant Monitoring (UCM) program. The Agency also evaluated ambient water quality data from the United States Geological Survey (USGS).

4.2 Ambient Occurrence

4.2.1 Data Sources and Methods

USGS instituted the National Water Quality Assessment (NAWQA) program in 1991 to examine ambient water quality status and trends in the United States. NAWQA is designed to apply nationally consistent methods to provide a consistent basis for comparisons among study basins across the country and over time. These occurrence assessments serve to facilitate interpretation of natural and anthropogenic factors affecting national water quality. For more detailed information on the NAWQA program design and implementation, please refer to Leahy and Thompson (1994) and Hamilton and colleagues (2004).

Study Unit Monitoring

The NAWQA program conducts monitoring and water quality assessments in significant watersheds and aquifers referred to as "study units." NAWQA's sampling approach is not "statistically" designed (i.e., it does not involve random sampling), but it provides a representative view of the nation's waters in its coverage and scope. Together, the 51 study units monitored between 1991 and 2001 include the aquifers and watersheds that supply more than 60% of the nation's drinking water and water used for agriculture and industry (NRC, 2002). NAWQA monitors the occurrence of chemicals such as pesticides, nutrients, volatile organic compounds (VOCs), trace elements, and radionuclides, and the condition of aquatic habitats and fish, insects, and algal communities (Hamilton et al., 2004).

Monitoring of study units occurs in stages. Between 1991 and 2001, approximately one-third of the study units at a time were studied intensively for a period of three to five years, alternating with a period of less intensive research and monitoring that lasted between five and seven years. Thus, all participating study units rotated through intensive assessment in a ten-year cycle (Leahy and Thompson, 1994). The first ten-year cycle was called "Cycle 1." Summary reports are available for the 51 study units that underwent intensive monitoring in Cycle 1 (USGS, 2001). Cycle 2 monitoring is scheduled to proceed in 42 study units from 2002 to 2012 (Hamilton et al., 2004).

VOC National Synthesis

Through a series of National Synthesis efforts, the USGS NAWQA program is preparing comprehensive analyses of data on topics of particular concern. These data are aggregated from the individual study units and other sources to provide a national overview.

The VOC National Synthesis began in 1994. The most comprehensive VOC National Synthesis reports to date are one random survey and one focused survey funded by the American Water Works Association Research Foundation (AwwaRF) and carried out by USGS in collaboration with the Metropolitan Water District of Southern California and the Oregon Health & Science University. The random survey (Grady, 2003) targeted surface and ground waters used as source water by community water systems (CWSs). Samples were taken from the source waters of 954 CWSs in 1999 and 2000. The random survey was designed to be nationally representative of CWS source water. In the focused survey (Delzer and Ivahnenko, 2003), 134 CWS source waters were monitored for VOCs between 1999 and 2001. These surface and ground waters were chosen because they were suspected or known to contain methyl tertiary-butyl ether (MTBE). The focused survey was designed to provide insight into temporal variability and anthropogenic factors associated with VOC occurrence. Details of the monitoring plan for these two studies are provided by Ivahnenko and colleagues (2001).

Additional products of the VOC National Synthesis include a compilation of historical VOC monitoring data from multiple studies (Squillace et al., 1999). The data, collected from 2948 wells between 1985 and 1995 by local, state, and federal agencies, were reviewed to ensure they met data quality criteria. Most of the data were from early study unit monitoring. The samples represent both urban and rural areas, and both drinking water and non-drinking water wells. A full analysis of 10 years of study unit monitoring data has not yet been performed by the VOC National Synthesis.

4.2.2 Results

Random and Focused VOC Surveys

The national random survey and focused survey both found no detections of 1,1,2,2-tetrachloroethane at the reporting level of 0.2 µg/L (Grady, 2003; Delzer and Ivahnenko, 2003). In addition, the focused survey provided results for 1,1,2,2-tetrachloroethane below the reporting level. At levels as low as the method detection limit (0.26 µg/L), no detections of 1,1,2,2-tetrachloroethane were found (Delzer and Ivahnenko, 2003).

Compilation of Historical VOC Monitoring Data

Multiple investigators collected 1,1,2,2-tetrachloroethane samples from 204 urban wells and 1267 rural wells. At a reporting level of 0.2 µg/L, there were no detections of 1,1,2,2-tetrachloroethane (Squillace et al., 1999).

4.3 Drinking Water Occurrences

4.3.1 Data Sources and Methods

In 1987, EPA initiated the UCM program to fulfill a 1986 SDWA Amendment that required monitoring of specified unregulated contaminants to gather information on their occurrence in drinking water for future regulatory decision-making purposes. EPA implemented the UCM program in two phases or rounds. The first round of UCM monitoring generally extended from 1988 to 1992 and is referred to as UCM Round 1 monitoring. The second round of UCM monitoring generally extended from 1993 to 1997 and is referred to as UCM Round 2 monitoring.

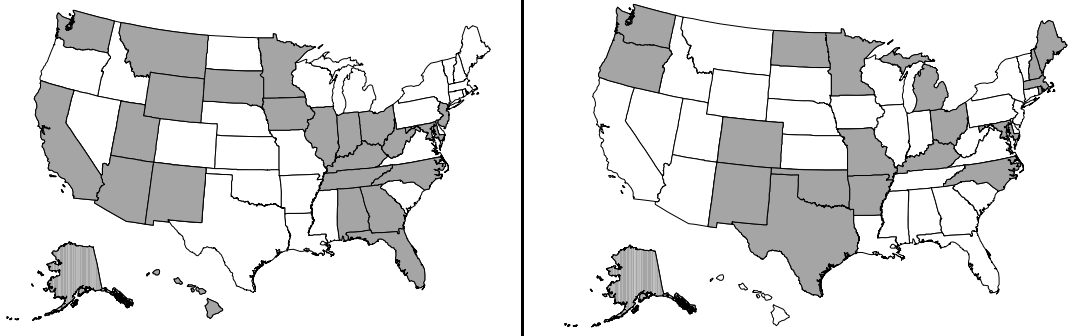
UCM Round 1 monitored for 34 volatile organic compounds (VOCs), including 1,1,2,2-tetrachloroethane (52 FR 25720, July 8, 1987). UCM Round 2 monitored for the same 34 VOCs, plus 13 synthetic organic compounds (SOCs) and sulfate (57 FR 31776, July 17, 1992). The UCM Round 1 database contains contaminant occurrence data from 38 States, Washington, DC, and the U.S. Virgin Islands. The UCM Round 2 database contains data from 34 States and several Tribes. Due to incomplete State data sets, national occurrence estimates based on raw (unedited) UCM Round 1 or Round 2 data could be skewed to low-occurrence or high-occurrence settings (e.g., some States only reported detections). To address potential biases in the data[1], EPA developed national cross-sections from the UCM Round 1 and Round 2 State data using an approach similar to that used for EPA's 1999 Chemical Monitoring Reform (CMR), the first Six Year Review, and the first CCL Regulatory Determinations. This national cross-section approach was developed to support occurrence analyses and was supported by scientific peer reviewers and stakeholders. Because UCM Round 1 and Round 2 data represent different time periods and include occurrence data from different States, EPA developed separate national cross-sections for each data set.

The UCM Round 1 national cross-section consists of data from 24 States, with approximately 3.3 million total analytical data points from approximately 22,000 unique PWSs. The UCM Round 2 national cross-section consists of data from 20 States, with approximately 3.7 million analytical data points from slightly more than 27,000 unique PWSs. The two national cross-sections represent significantly large samples of national occurrence data. Within each cross-section, the number of systems and analytical records for each contaminant varies. EPA constructed the national cross-sections in a way that provides a balance and range of States with varying pollution potential indicators, a wide range of the geologic and hydrologic conditions, and a very large sample of monitoring data points. While EPA recognizes that some limitations exist, the Agency believes that the national cross-sections provide a reasonable estimate of the overall distribution and the central tendency of contaminant occurrence. See Figure 4-1 for a listing of States in each national cross-section. Further details on the UCM program and the construction of cross-sections can be found in other documents (U.S. EPA, 2000e).

[1] The potential biases in the raw UCM data are due to lack of representativeness (since not all States provided UCM data) and incompleteness (since some States that provided data had incomplete data sets).

Figure 4-1 Cross-section States for Round 1 (24 States) and Round 2 (20 States)

Round 1		Round 2	
Alabama	Minnesota*	Alaska*	New Hampshire
Alaska*	Montana	Arkansas	New Mexico*
Arizona	New Jersey	Colorado	North Carolina*
California	New Mexico*	Kentucky*	North Dakota
Florida	North Carolina*	Maine	Ohio*
Georgia	Ohio*	Maryland*	Oklahoma
Hawaii	South Dakota	Massachusetts	Oregon
Illinois	Tennessee	Michigan	Rhode Island
Indiana	Utah	Minnesota*	Texas
Iowa	Washington*	Missouri	Washington*
Kentucky*	West Virginia		
Maryland*	Wyoming		



** Cross-section state in both Round 1 and Round 2*

4.3.2 Derivation of the Health Reference Value

To evaluate the systems and populations exposed to 1,1,2,2-tetrachloroethane through PWSs, the monitoring data were analyzed against the Minimum Reporting Level (MRL) and a benchmark value for health that is termed the Health Reference Level (HRL). Two different approaches were used to derive the HRL, one for chemicals that cause cancer and exhibit a linear response to dose and the other applies to noncarcinogens and carcinogens evaluated using a non-linear approach.

For those contaminants considered to be likely or probable human carcinogens, EPA evaluated data on the mode of action of the chemical to determine the method of low dose extrapolation. When the mode of action analysis indicated that a linear low dose extrapolation was needed or when data on the mode of action were lacking, a default low dose linear extrapolation was used to calculate the risk-specific dose equivalent to a one cancer in a million

(10^{-6}) risk. The risk-specific dose was combined with adult body weight and drinking water consumption data to estimate the drinking water concentration equivalent to a one-in-a-million (10^{-6}) cancer risk and this value was used as the HRL for likely or probable carcinogens.

For those chemicals not considered to be carcinogenic to humans, EPA generally calculates a reference dose (RfD). An RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD can be derived from either a "no observed adverse effect level" (NOAEL), a "lowest observed adverse effect level" (LOAEL), or a benchmark dose, with uncertainty factors applied to reflect limitations of the data used. EPA derived the HRLs for noncarcinogens using the RfD approach as follows:

HRL = [(RfD x BW)/DWI] x RSC

Where:

RfD = Reference Dose
BW = Body Weight for an adult, assumed to be 70 kilograms (kg)
DWI = Drinking Water Intake, assumed to be 2 L/day (90th percentile)
RSC = Relative Source Contribution, or the level of exposure believed to result from drinking water when compared to other sources (e.g., food, ambient air). In all cases a 20 percent RSC is used for HRL derivation because it is the lowest and most conservative RSC used in the derivation of an MCLG for drinking water.

In the case of 1,1,2,2-tetrachloroethane, the HRL is based on the concentration in drinking water equivalent to a one-in-a million risk (10^{-6}) of cancer above back ground calculated as follows:

Concentration at 10^{-6} Risk = (Risk x Body Weight)/(Slope Factor x Drinking Water Intake)

= (0.000001 x 70 kg)/(0.085 $(mg/kg/day)^{-1}$ x 2 L/day)

= 4.12 x 10^{-4} mg/L (0.4 µg/L rounded to one significant figure)

The cancer assessment for 1,1,2,2-tetrachloroethane is found in section 8.2 of this document.

4.3.3 Results

Tables 4-1 and 4-2 show the results from the Round 1 and Round 2 cross-sections. Results from all states, including those with incomplete and less reliable data, are also presented for the sake of comparison. Results are analyzed at the level of simple detections (at or above the minimum reporting level, or ≥MRL), exceedances of the health reference level (>HRL or >0.4 µg/L), and exceedances of one half the value of the HRL (>½HRL or >0.2 µg/L). MRLs for

1,1,2,2-tetrachloroethane were not uniform. They varied from 0.01 µg/L to 10 µg/L in the first round, and from 0.01 µg/L to 2.5 µg/L in the second round. The modal (most common) MRL in both rounds was 0.5 µg/L. Because the MRL was often higher than the HRL and ½HRL, it is likely that the sampling failed to capture some HRL and ½HRL exceedances at the participating systems, and that the HRL and ½HRL analyses underestimate actual 1,1,2,2-tetrachloroethane occurrence.

In Round 1 cross-section states, 1,1,2,2-tetrachloroethane was detected at approximately 0.45% of PWSs, affecting 1.86% of the population served, equivalent to approximately 4.0 million people nationally. Exceedances of one-half the value of the HRL were found at 0.22% of PWSs, affecting 1.69% of the population served, equivalent to approximately 3.6 million people nationally. HRL exceedances were found at 0.20% of PWSs, affecting 1.63% of the population served, equivalent to approximately 3.5 million people nationally.

When all Round 1 results are included in the analysis, including results from states with incomplete or less reliable data, 1,1,2,2-tetrachloroethane detection frequencies appear to be slightly higher than the cross-section data indicate. Detections affect 0.48% of PWSs and 2.16% of the population served; exceedances of the ½HRL benchmark affect 0.26% of PWSs and 1.99% of the population served; and HRL exceedances affect 0.24% of PWSs and 1.90% of the population served.

In Round 2 cross-section states, 1,1,2,2-tetrachloroethane was detected at 0.08% of PWSs, affecting 2.61% of the population served, equivalent to approximately 5.6 million people nationally. The ½HRL benchmark was exceeded in 0.07% of PWSs (18 of 24,800), affecting 0.51% of the population served, equivalent to approximately 1.1 million people nationally. The HRL benchmark was exceeded in 0.07% of PWSs (17 of 24,800 - one fewer than the ½HRL benchmark), affecting 0.08% of the population served, equivalent to approximately 0.2 million people nationally. Round 2 generally shows lower occurrence of 1,1,2,2-tetrachloroethane than Round 1. One apparently contradictory indicator, the strikingly high proportion of the population served by PWSs with detections in Round 2, is due to the unusually large size of one of the relatively few contaminated surface water systems.

Including Round 2 results from all reporting states in the analysis does not substanially change the picture of 1,1,2,2-tetrachloroethane occurrence. Detections affect 0.08% of PWSs and 2.23% of the population served; ½HRL exceedances affect 0.07% of PWSs and 0.44% of the population served; and HRL exceedances affect 0.06% of PWSs and 0.08% of the population served.

Table 4-1 Summary UCM Occurrence Statistics for 1,1,2,2-Tetrachloroethane (Round 1)

Frequency Factors	24 State Cross-Section[1]		All Reporting States[2]		National System & Population Numbers[3]	
Total Number of Samples	67,688		70,784		--	
Percent of Samples with Detections	0.16%		0.16%		--	
99th Percentile Concentration (all samples)	< MRL		< MRL		--	
Health Reference Level (HRL)	0.4 µg/L		0.4 µg/L		--	
Minimum Reporting Level (MRL) - Range - (modal value)[4]	0.01 - 10 µg/L (0.5 µg/L)		0.01 - 10 µg/L (0.5 µg/L)		--	
Maximum Concentration of Detections	200 µg/L		200 µg/L		--	
99th Percentile Concentration of Detections	112 µg/L		112 µg/L		--	
Median Concentration of Detections	0.5 µg/L		0.5 µg/L		--	
Total Number of PWSs Number of GW PWSs Number of SW PWSs	20,407 18,693 1,867		20,899 19,054 2,019		65,030 59,440 5,590	
Total Population Population of GW PWSs Population of SW PWSs	94,710,065 55,763,644 43,763,942		98,334,686 57,663,608 45,776,159		213,008,182 85,681,696 127,326,486	
Occurrence by System	**Number**	**Percentage**	**Number**	**Percentage**	**National Extrapolation[5]**	
					Cross-Section	**All States**
PWSs with detections (≥ MRL) Range across States GW PWSs with detections SW PWSs with detections	91 0 - 39 72 19	0.45% 0 - 11.64% 0.39% 1.02%	101 0 - 39 80 21	0.48% 0 - 100% 0.42% 1.04%	290 N/A 229 57	314 N/A 250 58
PWSs > 1/2 HRL Range across States GW PWSs > 1/2 HRL SW PWSs > 1/2 HRL	44 0 - 11 33 11	0.22% 0 - 2.76% 0.18% 0.59%	54 0 - 11 41 13	0.26% 0 - 100% 0.22% 0.64%	140 N/A 105 33	168 N/A 128 36
PWSs > HRL Range across States GW PWSs > HRL SW PWSs > HRL	41 0 - 11 32 9	0.20% 0 - 2.76% 0.17% 0.48%	50 0 - 11 39 11	0.24% 0 - 100% 0.20% 0.54%	131 N/A 102 27	156 N/A 122 30
Occurrence by Population Served						
Population served by PWSs with detections Range across States Pop. Served by GW PWSs with detections Pop. Served by SW PWSs with detections	1,762,198 0 - 616,019 1,017,630 744,568	1.86% 0 - 25.48% 1.82% 1.70%	2,119,844 0 - 616,019 1,365,976 753,868	2.16% 0 - 100% 2.37% 1.65%	3,963,000 N/A 1,564,000 2,166,000	4,592,000 N/A 2,030,000 2,097,000
Population served by PWSs > 1/2 HRL Range across States Pop. Served by GW PWSs > 1/2 HRL Pop. Served by SW PWSs > 1/2 HRL	1,597,140 0 - 616,019 864,770 732,370	1.69% 0 - 25.48% 1.55% 1.67%	1,954,786 0 - 616,019 1,213,116 741,670	1.99% 0 - 100% 2.10% 1.62%	3,592,000 N/A 1,329,000 2,131,000	4,234,000 N/A 1,803,000 2,063,000
Population served by PWSs > HRL Range across States Pop. Served by GW PWSs > HRL Pop. Served by SW PWSs > HRL	1,543,647 0 - 616,019 851,641 692,006	1.63% 0 - 25.48% 1.53% 1.58%	1,868,493 0 - 616,019 1,167,187 701,306	1.90% 0 - 100% 2.02% 1.53%	3,472,000 N/A 1,309,000 2,013,000	4,047,000 N/A 1,734,000 1,951,000

1. Summary Results based on 24-State Cross-Section, UCM Round 1 data.
2. Summary Results based on All Reporting States, UCM Round 1 data.
3. Total PWS and population numbers are from EPA March 2000 Water Industry Baseline Handbook, 2nd Edition.
4. Because several different analytical methods were used, MRLs were not uniform. The modal value is the most common MRL.
5. National extrapolations are generated by multiplying the system/population percentages and the national Baseline Handbook system/population numbers.

Abbreviations:
PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; N/A = Not Applicable; Total Number of Samples= total number of samples on record for the contaminant; 99th Percentile Concentration = the concentration in the 99th percentile sample (out of either all samples or just samples with detections); Median Concentration of Detections = the concentration in the median sample (out of samples with detections); Total Number of PWSs = the total number of PWSs for which sampling results are available; Total Population Served = the total population served by PWSs for which sampling results are available; Percentages of PWSs with Detections, PWSs >½HRL, and PWSs >HRL = percentages of PWS with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark; Percentages of Population Served by PWSs with Detections, by PWSs >½HRL, and by PWSs >HRL = percentages of the population served by PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark.

Notes:
-Only results at or above the MRL were reported as detections. Concentrations below the MRL are considered non-detects.
-Because some systems were counted as both ground water and surface water systems and others could not be classified, GW and SW figures might not add up to totals.
-Due to differences between the ratios of GW and SW systems with monitoring results and the national ratio, extrapolated GW and SW figures might not add up to extrapolated totals..

Table 4-2 Summary UCM Occurrence Statistics for 1,1,2,2-Tetrachloroethane (Round 2)

Frequency Factors	20 State Cross-Section[1]		All Reporting States[2]		National System & Population Numbers[3]	
Total Number of Samples	98,911		112,480		--	
Percent of Samples with Detections	0.02%		0.03%		--	
99th Percentile Concentration (all samples)	< MRL		< MRL		--	
Health Reference Level (HRL)	0.4 µg/L		0.4 µg/L		--	
Minimum Reporting Level (MRL) - Range - (modal value)[4]	0.1 - 2.5 µg/L (0.5 µg/L)		0.1 - 2.5 µg/L (0.5 µg/L)		--	
Maximum Concentration of Detections	2 µg/L		3.9 µg/L		--	
99th Percentile Concentration of Detections	2 µg/L		3.9 µg/L		--	
Median Concentration of Detections	0.5 µg/L		0.5 µg/L		--	
Total Number of PWSs Number of GW PWSs Number of SW PWSs	24,800 22,106 2,694		28,209 25,152 3,057		65,030 59,440 5,590	
Total Population Population of GW PWSs Population of SW PWSs	71,294,263 25,978,359 45,315,904		84,692,367 31,069,576 53,622,791		213,008,182 85,681,696 127,326,486	
Occurrence by System	**Number**	**Percentage**	**Number**	**Percentage**	**National Extrapolation[5]**	
					Cross-Section	**All States**
PWSs with detections (≥ MRL) Range across States GW PWSs with detections SW PWSs with detections	19 0 - 9 11 8	0.08% 0 - 0.5% 0.05% 0.30%	22 0 - 9 13 9	0.08% 0 - 3.49% 0.05% 0.29%	50 N/A 30 17	51 N/A 31 16
PWSs > 1/2 HRL Range across States GW PWSs > 1/2 HRL SW PWSs > 1/2 HRL	18 0 - 9 11 7	0.07% 0 - 0.50% 0.05% 0.26%	19 0 - 9 12 7	0.07% 0 - 1.16% 0.05% 0.23%	47 N/A 30 15	41 N/A 28 13
PWSs > HRL Range across States GW PWSs > HRL SW PWSs > HRL	17 0 - 9 11 6	0.07% 0 - 0.50% 0.05% 0.22%	18 0 - 9 12 6	0.06% 0 - 1.16% 0.05% 0.20%	45 N/A 30 12	41 N/A 28 11
Occurrence by Population Served						
Population served by PWSs with detections Range across States Pop. Served by GW PWSs with detections Pop. Served by SW PWSs with detections	1,862,105 0 - 1,500,000 24,115 1,837,990	2.61% 0 - 29.92% 0.09% 4.06%	1,892,850 0 - 1,500,000 51,543 1,841,307	2.23% 0 - 29.92% 0.17% 3.43%	5,563,000 N/A 80,000 5,164,000	4,761,000 N/A 142,000 4,372,000
Population served by PWSs > 1/2 HRL Range across States Pop. Served by GW PWSs > 1/2 HRL Pop. Served by SW PWSs > 1/2 HRL	362,105 0 - 306,000 24,115 337,990	0.51% 0 - 7.12% 0.09% 0.75%	371,980 0 - 306,000 33,990 337,990	0.44% 0 - 7.12% 0.11% 0.63%	1,082,000 N/A 80,000 950,000	936,000 N/A 94,000 803,000
Population served by PWSs > HRL Range across States Pop. Served by GW PWSs > HRL Pop. Served by SW PWSs > HRL	56,105 0 - 26,550 24,115 31,990	0.08% 0 - 0.54% 0.09% 0.07%	65,980 0 - 26,550 33,990 31,990	0.08% 0 - 0.54% 0.11% 0.06%	168,000 N/A 80,000 90,000	166,000 N/A 94,000 76,000

1. Summary Results based on 20-State Cross-Section, UCM Round 2 data.
2. Summary Results based on All Reporting States, UCM Round 2 data.
3. Total PWS and population numbers are from EPA March 2000 Water Industry Baseline Handbook, 2nd Edition.
4. Because several different analytical methods were used, MRLs were not uniform. The modal value is the most common MRL.
5. National extrapolations are generated by multiplying the system/population percentages and the national Baseline Handbook system/population numbers.

Abbreviations:
PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; N/A = Not Applicable; Total Number of Samples= total number of samples on record for the contaminant; 99th Percentile Concentration = the concentration in the 99th percentile sample (out of either all samples or just samples with detections); Median Concentration of Detections = the concentration in the median sample (out of samples with detections); Total Number of PWSs = the total number of PWSs for which sampling results are available; Total Population Served = the total population served by PWSs for which sampling results are available; Percentages of PWSs with Detections, PWSs >½HRL, and PWSs >HRL = percentages of PWS with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark; Percentages of Population Served by PWSs with Detections, by PWSs >½HRL, and by PWSs >HRL = percentages of the population served by PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark.

Notes:
-Only results at or above the MRL were reported as detections. Concentrations below the MRL are considered non-detects.
-Due to differences between the ratios of GW and SW systems with monitoring results and the national ratio, extrapolated GW and SW figures might not add up to extrapolated totals.

Regional Patterns

Each of the following maps focuses on a somewhat different aspect of the geographical distribution of 1,1,2,2-tetrachloroethane occurrence. Figure 4-2 identifies all states with at least one PWS with a detection of 1,1,2,2-tetrachloroethane in Round 1 or Round 2. All states are included in this analysis, including both cross-section states with reliable data and non-cross-section states with less reliable data, in order to provide the broadest assessment of possible 1,1,2,2-tetrachloroethane occurrence. Figure 4-3 presents the same information (identifying states with detections, regardless of whether they were included in the cross-sections) separately for Round 1 (1988-1992) and Round 2 (1993-1999), to reveal temporal trends.

Figure 4-4 illustrates the geographic distribution of states with different detection frequencies (percentage of PWSs with at least one detection), and Figure 4-5 illustrates the geographic distribution of different HRL exceedance frequencies (percentage of PWSs with at least one HRL exceedance). Only cross-section states, which have the most complete and reliable occurrence data, are included in these two analyses. In each figure, Round 1 data are presented in the upper map and Round 2 data are presented in the lower map to reveal temporal trends.

In each map, two color categories represent states with no data. Those in white do not belong to the relevant Round or cross-section, and those in the lightest category of shading were included in the Round or cross-section but have no data for 1,1,2,2-tetrachloroethane. The darker shades are used to differentiate occurrence findings in states with 1,1,2,2-tetrachloroethane data.

The number of Northeastern, Mid-Atlantic, Great Lakes, and Southwestern states, reporting at least one detection, especially in Round 1, suggests a possible regional pattern to the environmental release. However, states with detections are distributed from the east to the west coast, and from the Canadian to the Mexican borders. Even the states with the highest proportion of PWSs with detections are generally distributed across the United States.

Figure 4-2 Geographic Distribution of 1,1,2,2-Tetrachloroethane Detections in Both Cross-Section and Non-Cross-Section States (Combined UCM Rounds 1 and 2)

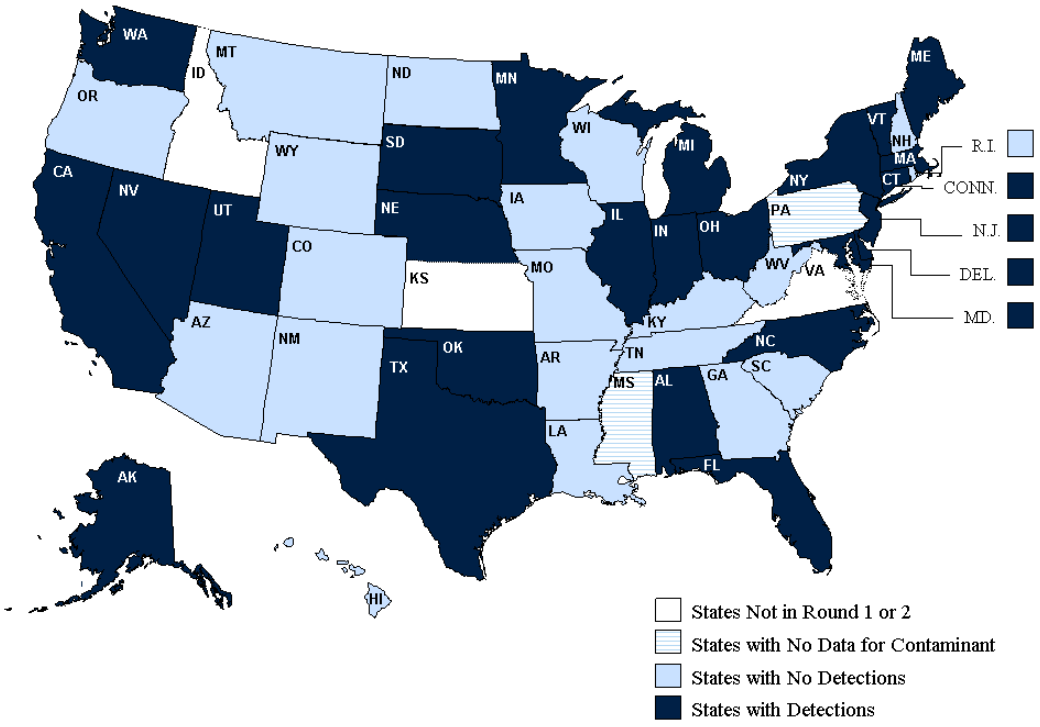
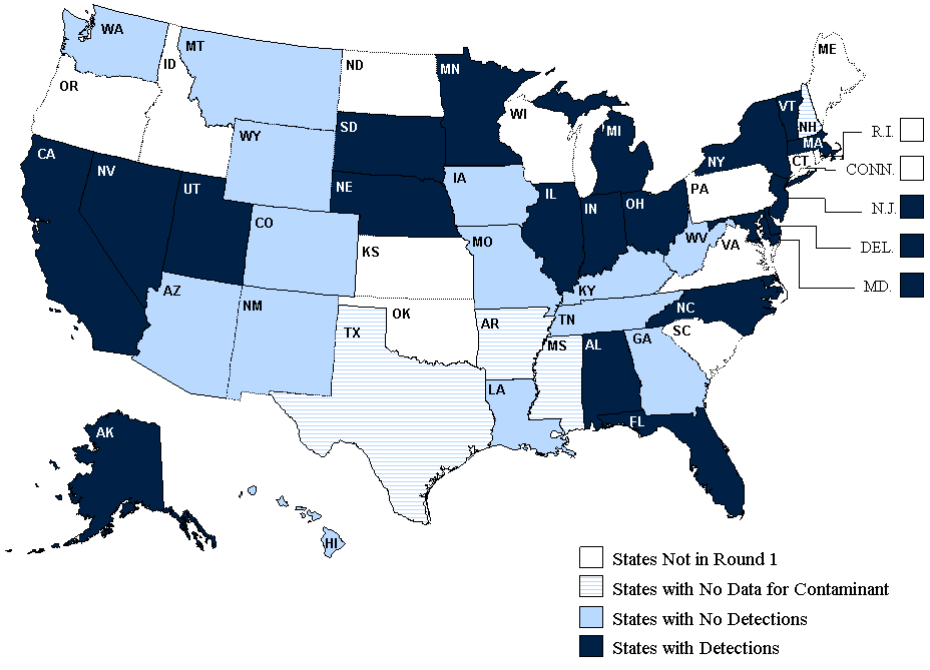


Figure 4-3 Geographic Distribution of 1,1,2,2-Tetrachloroethane Detections in Both Cross-Section and Non-Cross-Section States (Above: UCM Round 1; Below: UCM Round 2)



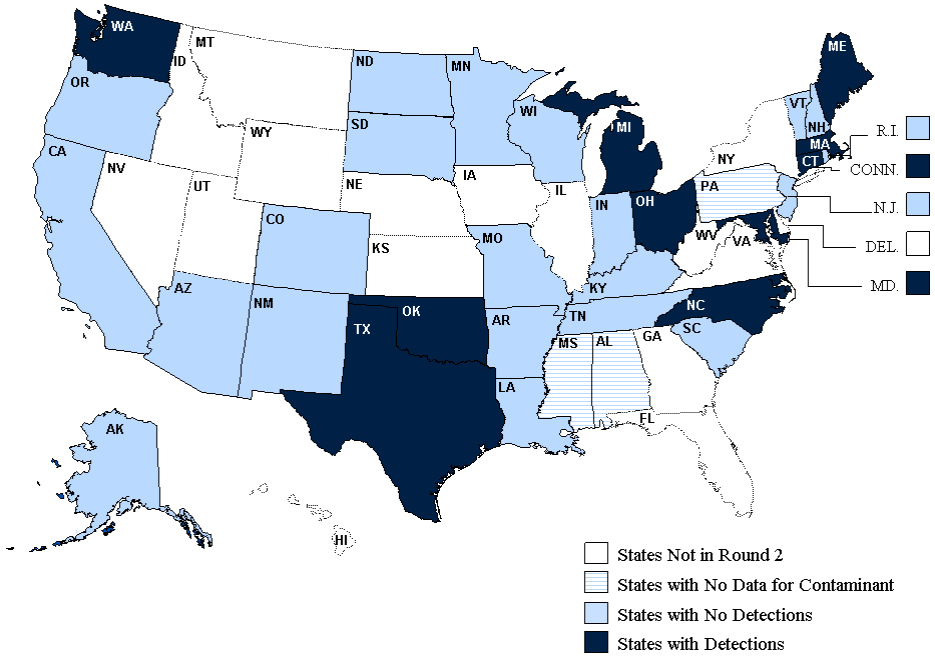


Figure 4-4 Geographic Distribution of 1,1,2,2-Tetrachloroethane Detection Frequencies in Cross-Section States (Above: UCM Round 1; Below: UCM Round 2)

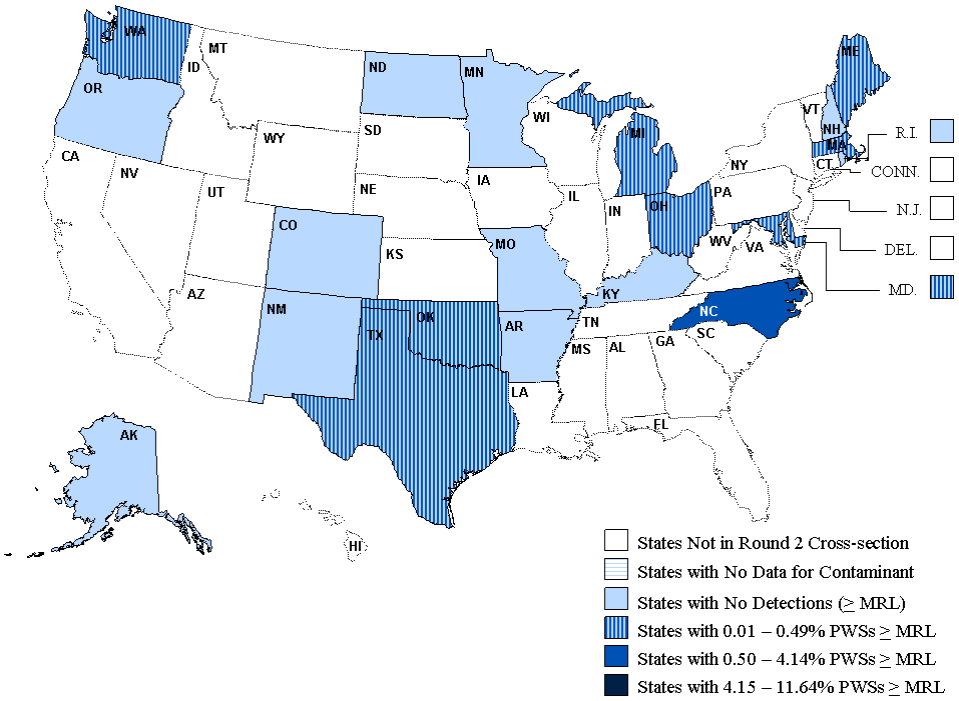
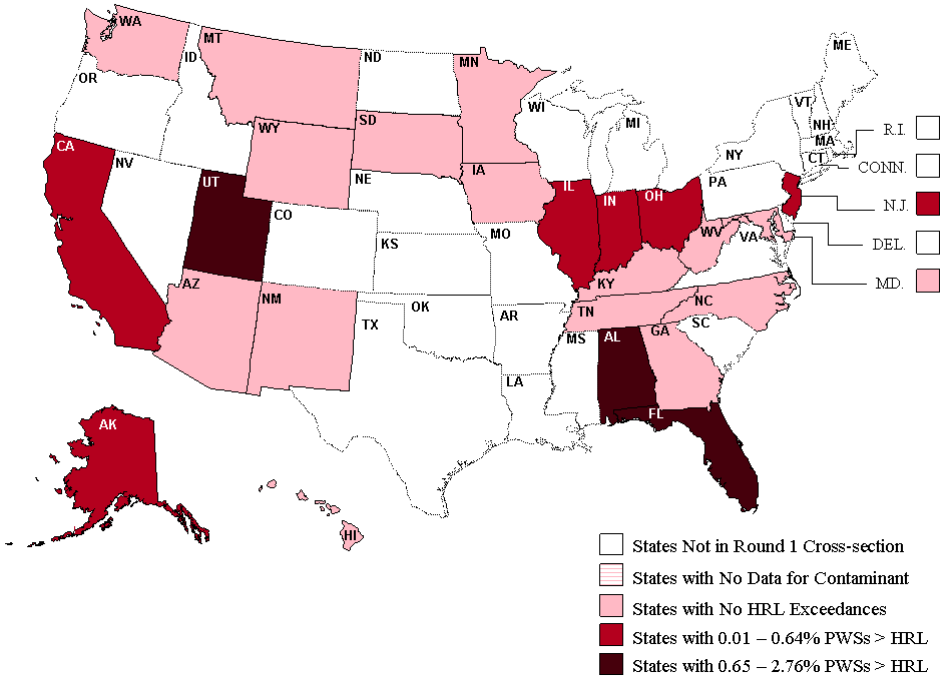
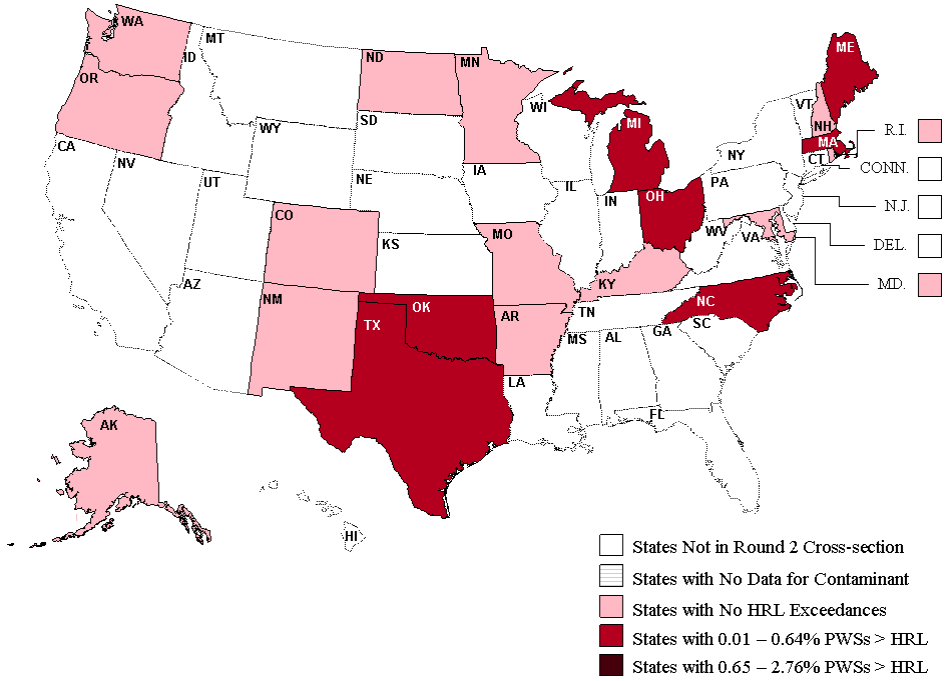


Figure 4-5 Geographic Distribution of 1,1,2,2-Tetrachloroethane HRL Exceedance Frequencies in Cross-Section States (Above: UCM Round 1; Below: UCM Round 2)

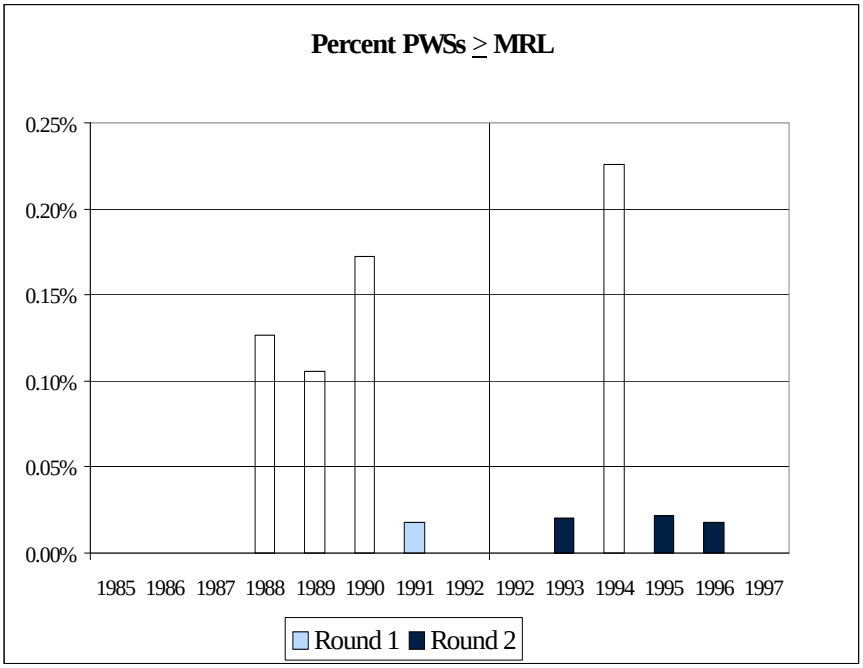


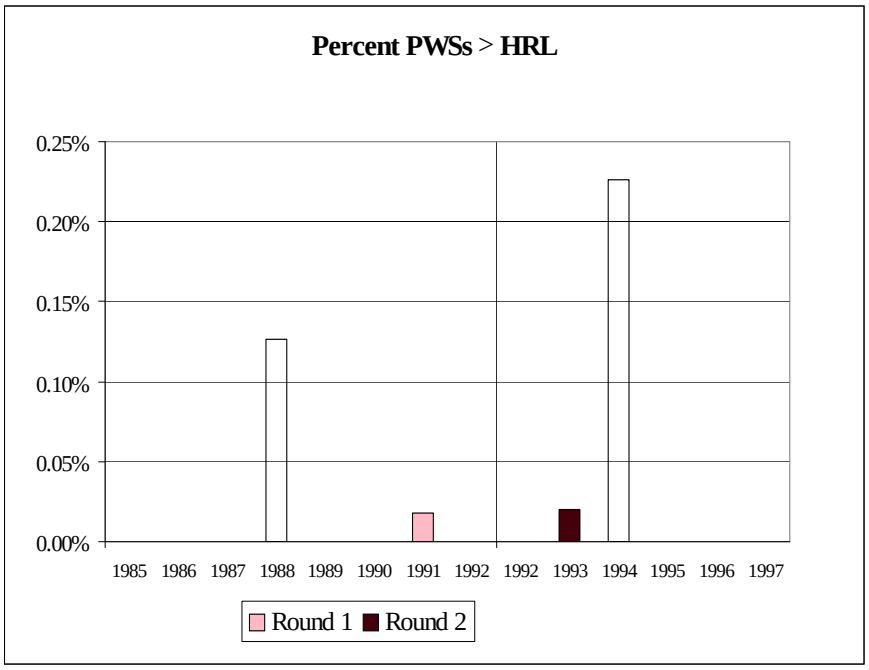


Temporal Patterns

Eight states (Alaska, Kentucky, Maryland, Minnesota, New Mexico, North Carolina, Ohio, and Washington) contributed 1,1,2,2-tetrachloroethane data to both the Round 1 and Round 2 cross-sections. While these states are not necessarily nationally representative, they enable a preliminary assessment of temporal trends in 1,1,2,2-tetrachloroethane occurrence. Figures 4-6 and 4-7 suggest that detections in those states were most common in 1988-1990, and again in 1994. HRL exceedances were also most common in 1988 and 1994. Only three of the eight states had detections in both Rounds, and only one state (Ohio) had HRL exceedances in both Rounds.

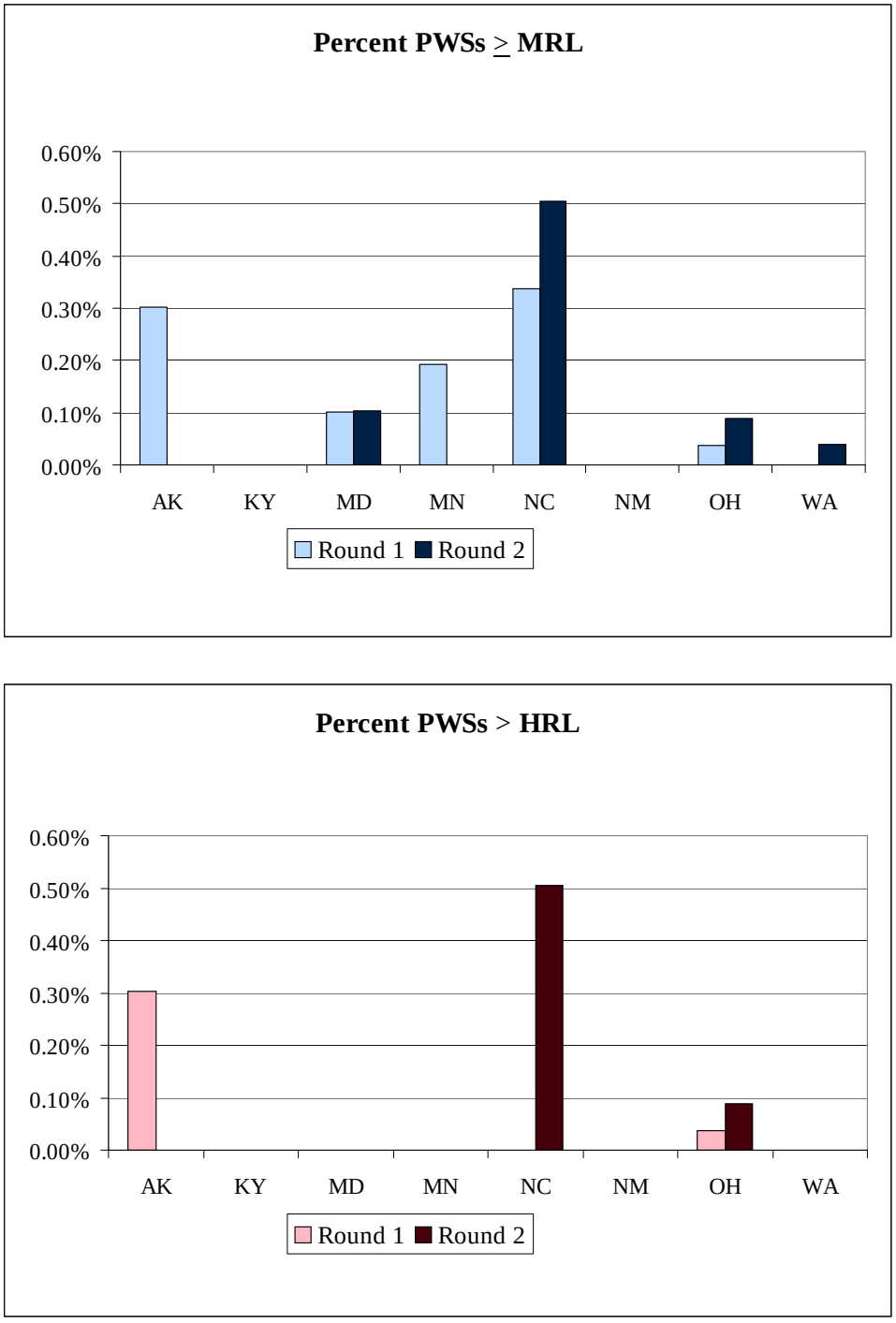
Figure 4-6 Annual Frequency of 1,1,2,2-Tetrachloroethane Detections (above) and HRL Exceedances (below), 1985-1997, in Select Cross-Section States





Notes: Data are from AK, KY, MD, MN, NC, NM, OH, and WA. (These eight states are the only states in both the Round 1 cross-section and the Round 2 cross-section.) Both Round 1 and Round 2 have data for 1992; 1992 results from each Round are presented separately. The HRL for 1,1,2,2-tetrachloroethane is 0.4 µg/L.

Figure 4-7 Distribution of 1,1,2,2-Tetrachloroethane Detections (above) and HRL Exceedances (below) Among Select Cross-Section States



Notes: These eight states are the only states in both the Round 1 cross-section and the Round 2 cross-section. The HRL for 1,1,2,2-tetrachloroethane is 0.4 µg/L.

4.4 Summary

The available data for the occurrence of 1,1,2,2-tetrachloroethane in drinking water are consistent with the decrease in production and use within the United States over the past three decades. Between Round 1 (1987-1992) and Round 2 (1992-1997) of drinking water monitoring, the 99th percentile concentration for detections for all reporting states declined from 112 µg/L to 2 µg/L and the percent of systems with detections declined from 0.45% to 0.08%. The Round 2 monitoring is likely to be more reflective of current conditions based on the release data presented in Chapter 3 and the lower upper limit on the method detection capabilities. During Round 2, 2.61% of the population of the cross-section states was exposed to 1,1,2,2-tetrachloroethane at least once during the monitoring period. The exposed population served by surface water systems was far larger than that served by ground water systems (4.06% vs. 0.09%, respectively, for the cross-section states. When looking at the systems with detections in Round 2 monitoring, the numbers also decline compared to Round 1 although the total population exposed increased. The increase in the exposed population can be explained by one particularly large surface water system, serving 1.5 million people, that had a detection above the MRL but below the ½ the HRL and HRL benchmarks in Round 2.

The decline in the percent of PWSs with concentrations higher than the ½HRL and HRL benchmarks between Rounds 1 and 2 suggests a decline in environmental levels of 1,1,2,2-tetrachloroethane that correlates with the decline in releases over the same period (see Chapter 3). However, these values may underestimate actual exposure because not all systems were able to detect 1,1,2,2-tetrachloroethane at concentrations as low as the HRL or ½HRL. Round 2 results are more certain than those from Round 1 since the upper bound of the range of MRLs decreased from 10 µg/L to 2.5 µg/L. The cross-section states with reported exceedances of the HRL in Round 2 were Maine, Massachusetts, Michigan, North Carolina, Ohio, Oklahoma, and Texas. States with detections are distributed from the east to the west coast, and from the Canadian to the Mexican borders. No national patterns are evident from ½HRL and HRL exceedances.

5.0 EXPOSURE FROM MEDIA OTHER THAN WATER

5.1 Exposure from Food

There was no information found in the literature reviewed concerning the exposure of 1,1,2,2-tetrachloroethane from food. It is not included in the Food and Drug Administration (FDA) database on direct and indirect additives approved for use in the United States (U.S. FDA, 2004).

5.1.1 Concentration in Non-Fish Food Items

There was no information found in the literature reviewed concerning the concentration of 1,1,2,2-tetrachloroethane in non-fish food items.

5.1.2 Concentrations in Fish and Shellfish

There is a lack of information concerning the occurrence of 1,1,2,2-tetrachloroethane in fish. In 1996, 1,1,2,2-tetrachloroethane was detected in tissue samples from fish at a National Priority List (NPL) site in the Ashtabula River watershed, Ohio. An advisory was in effect for all species of fish on the lower Ashtabula River as determined from the EPA's Fish Consumption Advisory Database (U.S. EPA, 1995b).

5.1.3 Intake of 1,1,2,2-Tetrachloroethane from Food

There was no information found in the literature reviewed concerning the intake of 1,1,2,2-tetrachloroethane from food. Any exposure would be due to accidental contamination and would likely be episodic and rare. The related compounds, tetrachloroethene and 1,1,1,2-tetrachloroethane, were present in food samples collected and analyzed for volatile organic compounds (VOCs) during the FDA Total Diet Study Program (Fleming-Jones and Smith, 2003; U.S. FDA, 2003). Although tetrachloroethene was present at low levels in a wide variety of foods, very few of the foods collected had any detectable concentrations of 1,1,1,2-tetrachloroethane. No detection of 1,1,2,2-tetrachloroethane was reported.

5.2 Exposure from Air

1,1,2,2-Tetrachloroethane can be released into the air during the process of manufacturing trichloroethylene or during its uses as a solvent, degreaser, intermediate, or cleaning solvent (Verschueren, 1983). 1,1,2,2-Tetrachloroethane may be emitted from hazardous landfills (Harkov et al., 1987). It was one of the ten most prevalent chlorinated chemicals found in solvent wastes that were incinerated each year prior to 1980 (Travis et al., 1986).

5.2.1 Concentration of 1,1,2,2-Tetrachloroethane in Air

Much of the data on the concentrations of 1,1,2,2-tetrachloroethane present in ambient and indoor air come from sampling programs conducted in the 1980s or earlier. 1,1,2,2-Tetrachloroethane production in this country, and its use by the chemical industry, has declined since the late 1980s (see Table 3-1). The decline in production and use should be considered in evaluating the monitoring data discussed below.

Concentrations of 1,1,2,2-tetrachloroethane were detected in the troposphere at levels that ranged between 0.1 to 0.4 parts per trillion (ppt) (Class and Ballschmiter, 1986). Data collected in the late 1970s to early 1980s at 853 urban/suburban sites in the United States, revealed a median concentration of 1,1,2,2-tetrachloroethane of 5.4 ppt, with values ranging from less than detection limits to a maximum of 4800 ppt. Two rural areas sampled did not have detectable levels of 1,1,2,2-tetrachloroethane (Brodzinsky and Singh, 1982). Shah and Heyerdahl (1988) supplemented this database by monitoring an additional 158 sites. The total number of monitoring sites between the two studies was 1011. The overall median levels of 1,1,2,2-tetrachloroethane were at or below the lower detection limit; 75% of the samples showed concentrations less than or equal to 8ppt. About 25% of the samples collected from 25 sites in Minnesota between 1991 and 1998 had detections of 1,1,2,2-tetrachloroethane. The mean, median and maximum concentrations were 0.84, 4.2 and 962 ppt respectively. All samples collected from 13 sites in Louisiana. New Jersey, Texas and Vermont by Mohamed et al. (2002) had concentrations of 1,1,2,2-tetrachloroethane less than 1 ppb.

Air samples from several New Jersey cities were analyzed in the summer of 1981. Levels of 1,1,2,2-tetrachloroethane were detected in 9 of 38 samples from Newark; 1 of 37 samples from Elizabeth; and 4 of 35 samples from Camden (Harkov et al., 1983). Additionally, it was detected in 4 out of 105 samples from the same 3 cities in the winter of 1982 (Harkov et al., 1987). Mean concentrations of 1,1,2,2-tetrachloroethane in major U.S. cities listed in other reports ranged from trace levels below detection limits to 57 parts per billion (ppb) (Harkov et al., 1981, 1983; Lioy et al., 1985; Singh et al., 1981, 1982).

Indoor levels of 1,1,2,2-tetrachloroethane were detected in air samples from eight homes in Knoxville, Tennessee during the winter (Gupta et al., 1984). The mean concentration was 13.0 $\mu g/m^3$ (1.8 ppb) in 10/16 samples (detection limits were not reported). The source was not investigated, but the levels may be attributed to consumer products used in the home or out gassing of the chemical from construction materials or household furnishings.

A survey of 1159 common household products was performed by the EPA in an effort to identify the potential for household products to pollute indoor air (Sack et al., 1992). Two-hundred and sixteen of the products contained 1,1,2,2-tetrachloroethane. Trace amounts were commonly found in adhesives, oils, greases, and lubricants. Concentrations in the products were uniformly near detection limits (detection limits not reported); thus, Sack et al. (1992) concluded that 1,1,2,2-tetrachloroethane has a low potential to pose unacceptable human exposure risks in indoor air.

1,1,2,2-Tetrachloroethane was detected in air at five National Priorities List (NPL) Superfund hazardous waste sites in New Jersey. The mean levels reported ranged from 0.01-0.59 ppb, and the maximum levels ranged from 0.17-11.38 ppb. An urban landfill receiving municipal waste and non-hazardous industrial waste had a mean of 0.01 ppb and the maximum was 0.19 ppb (LaRegina et al., 1986). Air samples from the Kin-But waste disposal site near Edison, New Jersey contained up to 2.1 ppb of 1,1,2,2-tetrachloroethane. Air concentrations of 0.226 ppb of 1,1,2,2-tetrachloroethane were found in Iberville Parish, Louisiana, along the Mississippi River, where many organic chemical production and storage facilities are located (Pellizzari, 1982).

5.2.2 Intake of 1,1,2,2-Tetrachloroethane from Air

There was no information found in the literature reviewed concerning current average levels of 1,1,2,2-tetrachloroethane in ambient or indoor air. Accordingly it is not possible to estimate a current exposure level for the general population. In the most recent measurement of ambient air (Shah and Heyerdahl, 1988), the median concentration measured was less than the detection limit.

5.3 Exposure from Soil

1,1,2,2-Tetrachloroethane is released to soil when it is disposed of in landfills or from accidental spills of products or wastes containing 1,1,2,2-tetrachloroethane. 1,1,2,2-Tetrachloroethane released to soils and landfills may be mixed wastes; therefore, estimation of the overall releases to the soil is limited. 1,1,2,2-Tetrachloroethane's volatility and biodegradation suggest that it will not accumulate in the soil.

5.3.1 Concentration of 1,1,2,2-Tetrachloroethane in Soil

Relatively little information was available on general background or monitoring data of 1,1,2,2-tetrachloroethane in soil. Most studies are about hazardous waste sites. An analysis of test wells around Resources Conservation and Recovery Act (RCRA) disposal sites, determined that 25 of 479 sites had levels above the 1,1,2,2-tetrachloroethane detection limit (Plumb, 1991). A waste disposal site in Pennsylvania had 2.4 ppm 1,1,2,2-tetrachloroethane in soil (Sable and Clark, 1984).

Sediment monitoring data from rivers, lakes, and other aquatic systems from the U.S. EPA's national STORET database illustrate that less than 1% of the samples contained 1,1,2,2-tetrachloroethane levels above the detection limit of approximately 5 µg/kg (Staples et al., 1985). Based on ATSDR's HazDat database (HazDat, 2006), at least 135 of 1678 current or past NPL sites with 1,1,2,2-tetrachloroethane contamination had the chemical in its soil or sediment.

5.3.2 Intake of 1,1,2,2-Tetrachloroethane from Soil

Humans are unlikely to be exposed to 1,1,2,2-tetrachloroethane through soils. Exposure by inhalation of airborne soil particles, by ingestion of household dust, or by direct ingestion of soil might be possible for those living near a hazardous waste site contaminated with 1,1,2,2-tetrachloroethane. Infants and toddlers ingest soil and household dust by hand-to-mouth transfer

during everyday activities. They may therefore be exposed to higher levels than adults living in the same contaminated environment. However, in most locations 1,1,2,2-tetrachloroethane is not likely to be present in soils. The TRI release data for land disposal (Table 3-1) show no releases for all but three of the last ten years. There was a large reported discharge to land (941 pounds) in 2001; the other reported releases were 1 and 15 pounds.

5.4 Other Residential Exposures

1,1,2,2 tetrachloroethane can be introduced into household air from cigarette smoke. Bi et al (2005) found that 3-6 µg tetrachloroethane/cigarette were released into the atmosphere from smoking.

5.5 Occupational (Workplace) Exposures

The National Institute for Occupational Safety and Health (NIOSH) conducted a field survey of 4,490 facilities to estimate the exposure of chemicals in the workplace (1981-1983). This was a nationwide survey based on a statistical sample of virtually all workplace environments in the United States where 8 or more persons are employed. The survey was based on all Standard Industrial Classification (SIC) code workplace types except mining and agriculture (Sieber et al., 1991). The National Occupational Exposure Survey (NOES) estimated that 4,145 workers were potentially exposed to 1,1,2,2-tetrachloroethane in the United States. They also estimated that 3666 workers were in occupations involving work in chemical research and development laboratories, and the other exposures involved jobs in industrial chemical plants (NIOSH, 2006). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of the number of workers potentially exposed to chemicals in the workplace. This survey was conducted prior to the decrease in production and use of 1,1,2,2-tetrachloroethane in the United States.

According to the Occupational Safety and Health Administration (OSHA) (1998), the current 8-hour time-weighted average (TWA) permissible exposure level (PEL) for 1,1,2,2-tetrachloroethane is 5 ppm (35 mg/m^3). The prior standard of 1 ppm (7 mg/m^3) was abandoned, however, it is reported that several states continue to follow this guideline (HSDB, 2004). According to NIOSH, the recommended exposure level for a 10-hour TWA is 1 ppm (7 mg/m^3) 1,1,2,2-tetrachloroethane (HSDB, 2004).

5.5.1 Description of Industries and Workplaces

The NOES estimated that workers potentially exposed to 1,1,2,2-tetrachloroethane in the U. S. were in occupations involving work in chemical research and development laboratories and in industrial chemical plants (NIOSH, 2006).

5.5.2 Types of Exposure (Inhalation, Dermal, Other)

1,1,2,2-Tetrachloroethane is a volatile substance with a vapor pressure of about 6 mm Hg at 25°C. Accordingly, most workplace exposure is likely to result from inhalation, except for those working directly with 1,1,2,2-tetrachloroethane. Some dermal exposure could result from direct contact, if proper industrial hygiene practices were not followed.

5.5.3 Exposure in the Work Environment

Information concerning other sources of occupational exposure to 1,1,2,2-tetrachloroethane was not found in the literature reviewed.

5.6 Summary

Exposures are possible for individuals who smoke cigarettes and those living near waste disposal facilities where 1,1,2,2-tetrachloroethane site contamination has occurred. Higher inhalation exposures also would occur for workers at chemical plants where 1,1,2,2-tetrachloroethane is still produced as a chemical intermediate. Other populations with higher exposures could include people living close to NPL or other waste sites where leachates or runoff from contaminated soils could affect groundwater used for drinking water. Little or no 1,1,2,2-tetrachloroethane was found in foods or ambient air.

6.0 TOXICOKINETICS

6.1 Absorption

There are relatively few quantitative data for absorption of 1,1,2,2-tetrachloroethane by the gastrointestinal or respiratory tracts in humans or animals. 1,1,2,2-Tetrachloroethane is a small lipophilic molecule (log K_{ow} = 2.39) (ATSDR, 2006) and would be able to diffuse through the lipid matrix of cell membranes. Data from studies that administered radiolabeled compound and measured its presence in tissue and excretory products, along with the adverse health effects observed after exposure, demonstrate absorption for all routes of exposure.

Oral Exposure

The recovery of radioactivity in the expired air and urine from rats and mice administered 150 mg/kg oral doses of the 1,1,2,2-tetrachloroethane by gavage in corn oil was 65% to 73% for both species after 72 hours; 4 to 6% was recovered in the feces with the remainder in the skin and carcass (20 to 30%). This indicates that the compound is almost completely absorbed orally (Dow, 1988). Another study showed that rats given an oral dose of 100 mg/kg of radiolabeled 1,1,2,2-tetrachloroethane by gavage metabolized approximately 80% of the dose within 48 hours while mice given a 200 mg/kg dose metabolized approximately 70% (Mitoma et al., 1985). The percent metabolized was determined by adding the amounts of label in expired carbon dioxide, excreta, and that remaining in the carcass. These data are supportive of the conclusion that a large fraction of an oral dose of 1,1,2,2-tetrachloroethane is absorbed. Since absorption is likely to be diffusion-limited, the percent of the dose absorbed would be higher at low environmental doses than at the higher doses used in the experimental studies.

Inhalation Exposure

A study in human volunteers was carried out in which a bulb containing ^{38}C1-labeled 1,1,2,2-tetrachloroethane was inserted into their mouths. The volunteers immediately inhaled deeply, held their breath for 20 seconds, and then exhaled through a trap containing granulated charcoal. The excretion of the radiolabel in the exhaled breath, and the partition coefficients between blood and air were measured. The study indicated that 97% of a single breath of 1,1,2,2-tetrachloroethane was absorbed systemically (Morgan et al., 1970).

The recovery of radiolabeled 1,1,2,2-tetrachloroethane from rats and mice exposed to a vapor concentration of 10 ppm (70 mg/m^3) for 6 hours was 52 to 60% in expired air and urine and 29 to 42% in the skin and carcass. Only 5 to 6% was found in the feces indicating nearly complete absorption (Dow, 1988).

Dermal Exposure

Up to 1 mL (1.6 mg based on a density of 1.595 at 20°C) of 1,1,2,2-tetrachloroethane applied to the skin of mice or guinea pigs was absorbed or adsorbed within one-half hour (Jakobson et al., 1982; Tsuruta, 1975). The application site was sealed to prevent evaporation.

6.2 Distribution

No studies of the systemic distribution of 1,1,2,2-tetrachloroethane in humans were identified for any exposure route. Available data from animal studies for oral and inhalation exposures generally lacked quantitative measurements in individual tissues. There were no distribution data in animals for the dermal route of exposure (ATSDR, 2006).

Oral Exposure

Hepatic protein-binding was seen in rats and mice administered 1,1,2,2-tetrachloroethane by gavage for five days per week for five weeks, followed by a single dose of ^{14}C-1,1,2,2-tetrachloroethane (Mitoma et al., 1985). The doses in rats were 25 or 100 mg/kg, while those given to mice were 50 and 200 mg/kg. These doses are equivalent to the maximum tolerated dose (MTD) and one quarter of the MTD used in the National Cancer Institute (NCI, 1978) bioassays of 1,1,2,2-tetrachloroethane. The protein binding in rats was generally comparable to that for mice and was directly related to dose. The protein binding in rats receiving doses of 25 or 100 mg/kg was 3.31 and 12.93 nmol eq/mg purified liver protein at the low and high dose, respectively, while the binding in mice receiving doses of 50 or 200 mg/kg was 7.22 and 25.09 nmol eq/mg, respectively. The presence of the radiolabel in protein could represent either binding to the protein or incorporation of the radiolabeled carbon from dechlorinated 1,1,2,2-tetrachloroethane into nonessential amino acids.

The binding of label from inhaled 1,1,2,2-tetrachloroethane to liver proteins after inhalation exposure to 10 ppm for 6 hours was also examined (Dow, 1988). Samples of precipitated protein were subjected to acid hydrolysis to determine if the label was bound to the protein through a hydrolyzable bond. About 85 to 90 percent of the label was found to be incorporated into the protein and was not removed by acid hydrolysis. This suggests incorporation of some of the DCA metabolites (possibly glycine or serine; see Figure 3-1) into the protein structure. The amount of label present in the proteins from mice was 1.9 times greater than that for rats.

Mitoma et al. (1985) examined the radiolabel remaining in the carcass 48 hours after administration of radiolabeled 1,1,2,2-tetrachloroethane. The data were only reported for the 100 mg/kg dose in rats and the 200 mg/kg dose in mice. The amount of radiolabel remaining in the carcass was 31% for the rats and 27% for the mice.

Adverse effects were observed following oral exposures in the liver, kidney, and testes in mice and rats indicating distribution to these tissues (NCI, 1978; NTP, 1996, 2004). No data were identified that provided measurements of 1,1,2,2-tetrachloroethane concentrations in these or other tissues.

Inhalation Exposure

No studies were located regarding distribution in humans or animals following inhalation exposure to 1,1,2,2-tetrachloroethane. However, adverse effects have been observed in liver and kidney for animals exposed via inhalation (Deguchi, 1972; Horiuchi et al., 1962; Price et al. 1978; Schmidt et al., 1980b) demonstrating systemic distribution of inhaled 1,1,2,2-tetrachloroethane.

Other Routes of Exposure

Three days after an intraperitoneal dose of 0.21 to 0.32 g/kg of ^{14}C-1,1,2,2-tetrachloroethane, a mean of 15.5% of the administered radiolabel was present in the carcass of female albino mice (Yllner, 1971). This finding supports a possible mechanism for the retention of the radiolabel, through binding of 1,1,2,2-tetrachloroethane metabolites to tissue macromolecules or incorporation of the label into other compounds. The results were similar after intravenous injection of ^{14}C-1,1,2,2-tetrachloroethane into female C57B1 mice. Bound radiolabel was identified by autoradiography in the olfactory and tracheobronchial mucosa, oral cavity, nasopharynx, esophagus, forestomach, liver, biliary bladder, adrenal cortex, and testes between 1 and 4 hours after injection (Eriksson and Brittebo, 1991).

6.3 Metabolism

When administered by the oral or inhalation routes, 1,1,2,2-tetrachloroethane appears to be extensively metabolized although quantitative data that identify metabolites are limited. In the 72 hours after a gavage exposure to a dose of 150 mg/kg, 9.39% was recovered from expired air as unmetabolized 1,1,2,2-tetrachloroethane in Osborne-Mendel rats and 0.68% of the dose was recovered in B6C3F1 mice. After inhalation exposure for 6 hours to 10 ppm 1,1,2,2,tetrachloroethane, 7.73% was recovered unmetabolized from expired air in Osborne-Mendel rats and 1.78% in B6C3F1 mice 72 hours later (Dow, 1988). Additional, unmetabolized 1,1,2,2-tetrachloroethane could have been distributed to the adipose tissues and retained in the carcass.

The initial stages of metabolism are believed to involve cytochrome (CYP) P450, but the specific isoforms involved have not been identified. Biotransformation reactions were increased by chronic ethanol consumption and fasting, preconditions that are known to induce the levels of cytochrome P-450 isoform CYP 2El (Johansson et al., 1988; Soucek and Gut, 1992). Sapigni et al. (1992) found a seven-fold induction of hepatic CYP 2B1 following gavage treatment of groups of 6 CD1 mice for 3 days with doses of 6.5%, 12%, 25%, or 50% of the LD_{50} in corn oil. The degree of enhancement was not dose-related, but may indicate a role for CYP 2B1 in 1,1,2,2-tetrachloroethane metabolism. Conversely, *in vitro* responses of hepatic microsomes from CD1 mice after exposure to a single dose of either 300 or 600 mg/kg 1,1,2,2-tetrachloroethane (20% or 40% of the LD_{50}) were indicative of reduced activities for CYPs 1A1, 1A2, 2B1, 2E1, and 3A; the CYP1A1 isoform was affected the least (-26.6%) and the CYP 3A isoform the most (-57.5%) (Paolini et al., 1992). Eriksson and Brittebo (1991) found that metabolite binding to liver tissue slices was decreased by about 60% when metyrapone, an inhibitor of CYP 3A4 was added to the culture medium, but only about 15% when α-naphthoflavone a CYP 1A1 inhibitor was added to the culture medium, implicating CYP 3A4 in the metabolic activation of 1,1,2,2-tetrachloroethane.

It has been hypothesized that the first step in the metabolism of 1,1,2,2-tetrachloroethane is the loss of a chlorine generating a 1,2,2-trichloroethyl free radical. A carbon-centered radical was detected in lipid extracts from the livers of mice treated with a single dose of 600 mg/kg 1,1,2,2-tetrachloroethane by Paolini et al. (1992). Tomasi et al. (1984) found evidence of a free radical intermediate in rats. A free radical can combine with oxygen to form a peroxide free

radical and subsequently react with the unsaturated bonds of membrane lipids diverting some of the 1,1,2,2-tetrachloroethane from further catabolic reactions. Paolini et al. (1992) were able to measure cis-trans and trans-trans diene hydroperoxide products in microsomes from animals exposed to 300 and 600 mg/kg 1,1,2,2-tetrachloroethane. In addition, Halpert (1982) reported the formation of dichloroacetylated protein adducts. The reactive moiety in this instance was postulated to be dichloroacetyl chloride formed by oxidation of the free radical carbon.

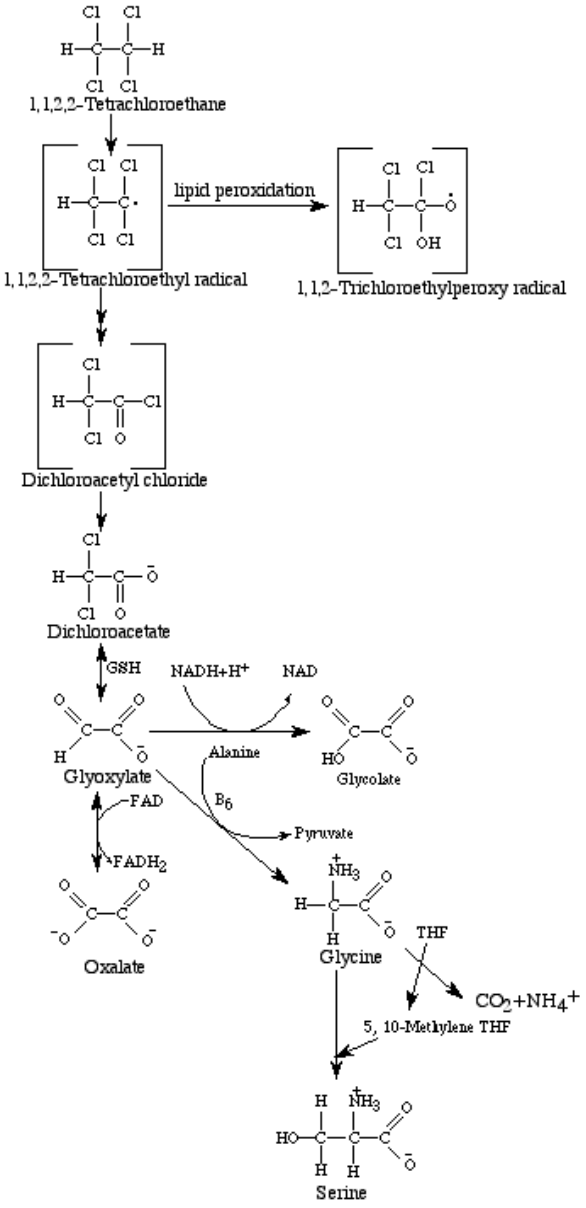
Dichloroacetic acid (DCA) appears to be the major metabolite of 1,1,2,2-tetrachloroethane (Yllner, 1971). This suggests loss of a second chlorine from carbon 1 of the parent compound which would be consistent with a reactive acyl chloride intermediate. Dichloroacetic acid is metabolized by cytosolic glutathione-S-transferase zeta (GSTZ) forming glyoxylate, glycolate, and oxalate; transamination of glycolate produces glycine (U.S. EPA, 2003b). Complete oxidation of the chlorine free intermediates produces carbon dioxide (Figure 6-1).

Among humans there are known polymorphisms in GSTZ which may account for differences in the ability to metabolize DCA and other halogenated compounds. The GSTZ variants are designated GSTZ1a-1a, GSTZ1b-1b, GSTZ1c-1c, GSTZ1d-1d, and GSTZ1e-1e (Blackburn et al., 2000, 2001; Tzeng et al., 2000). Analysis of blood samples from 128 Caucasian, Australians of European origin showed a variant distribution of 0.086, 0.285, 0.473, 0.156 and 0 for GSTZ1a-1a, GSTZ1b-1b, GSTZ1c-1c, GSTZ1d-1d, and GSTZ1e-1e, respectively. GSTZ1a-1a has been demonstrated to have 4-5-fold higher activity toward DCA than the other variants. However, excluding the GSTZ 1e-1e variant it has the lowest frequency in the population studied by Blackburn et al. (2001). The most common variant, GSTZ1c-1c, had the highest activity toward the isomerization of maleylacetoacetate and lower activity toward DCA as a substrate.

The most comprehensive metabolite study was conducted by Yllner (1971). Individual female albino mice were given single doses of 210 to 320 mg/kg ^{14}C-labeled and unlabeled 1,1,2,2-tetrachloroethane in olive oil by intraperitoneal injection. Urine, feces and exhaled air were collected over 72 hours in three 24-hour aliquots; label recovery was almost complete. Trapped carbon dioxide accounted for 37 to 51% of the label in the first 24-hours, 5 to 6% of the label in the second 24 hours and 2 to 4% in the last 24-hours. Unmetabolized 1,1,2,2-tetrachloroethane and other volatile chlorinated hydrocarbons accounted for 3 to 4% of the dose for the first 24 hours and negligible amounts thereafter. The total 72-hour collected urine accounted for 23 to 34% of the label with about 90% of that total excreted in the first 24 hours.

In a separate study, 24-hour urine samples were collected from mice given intraperitoneal doses of from 160 to 320 mg/kg (Yllner, 1971). The urinary metabolites were identified by paper chromatography. Dichloroacetic acid was the primary metabolite identified, accounting for about 27% of the labeled urinary metabolites. Trichloroethanol (10%), oxalic acid (7%), glycolic acid (0.9%), trichloroacetic acid (4%)and urea (2%) were also found to contain the radiolabel. Almost half of the urinary activity was not identified.

Figure 6-1 Postulated Metabolism of 1,1,2,2-Tetrachloroethane



The authors hypothesized that much of the residual label in the carcass after 72 hours represented glycine formed as a metabolite of DCA. Accordingly, three mice were given intraperitoneal doses of 1,1,2,2-tetrachloroethane (200-310 mg/kg; 35.8 -52.1 µmol) and 156 µmol sodium benzoate. The reaction of glycine with benzoate produces hippuric acid which is excreted in urine. Under these conditions about 50% of the 1,1,2,2-tetrachloroethane dose was present in the urine after 24 hours as opposed to about the 23% to 34% excreted in the absence of

benzoate. The authors estimated that 20 to 23% of the 1,1,2,2-tetrachloroethane had been converted to glycine. Some of the glycine derived from DCA may become incorporated into proteins as glycine or serine (See Figure 6-1).

Studies by Dow (1988) found only a slight decrease in hepatic level of non-protein sulfhydryl groups in B6C3F1 mice in the 12-hour period after oral exposure to a dose of 500 mg/kg 1,1,2,2-tetrachloroethane. The reduction in sulfhydryl groups was 10 to 15% in the first hour after dosing and returned to a level the same or slightly higher than that observed in controls.

Eriksson and Brittebo (1991) demonstrated that radiolabeled 1,1,2,2-tetrachloroethane is metabolized in mice by cytochrome P-450 to products that bind to the epithelium of the respiratory and upper alimentary tracts following intravenous administration (3 mg/kg) to mice. High levels of radiolabel were also identified in the liver and gallbladder. The bound metabolites and the modified membrane constituents (phospholipids or proteins) were not identified in the study. However, there was a dose-related decrease in hepatic binding in tissue slices when glutathione was added to the medium. This is consistent with the dichloroacetic acid route of metabolism, since this pathway requires glutathione. It is also consistent with the formation a peroxide free radical since reduced glutathione participates in free radical detoxification.

Small quantities of trichloroethanol and trichloroacetic acid have been identified as 1,1,2,2-tetrachloroethane metabolites (Ikeda and Ohtsuji, 1972; Mitoma et al., 1985; Yllner, 1971). Production of a trisubstituted number 2 carbon in trichloroacetic acid from the disubstituted carbons of 1,1,2,2-tetrachloroethane would require rearrangement of the chlorine substituents during metabolism. Yllner (1971) found that an aqueous solution of 1,1,2,2-tetrachloroethane at pH=7 when heated to body temperature (37°C) in sealed ampules was dehydrohalogenated to form trichloroethylene (12%) over a 24-hour period. Hydration of trichloroethylene to form trichloroethanol followed by oxidation could account for the presence of both trichloroethylene and trichloroacetic acid in urine after exposure to 1,1,2,2-tetrachloroethane.

An alternate source of trichloroethanol and trichloroacetic acid in urine after exposure to 1,1,2,2-tetrachloroethane would be the presence of its isomer, 1,1,1,2-tetrachloroethane, as an impurity in the 1,1,2,2-tetrachloroethane used for dosing. The purity of commercially available 1,1,2,2-tetrachloroethane ranges from 97 to 99.5% (Aldrich Handbook, 1994). The analysis of the 1,1,2,2-tetrachloroethane used in the NTP study (2004) by gas chromatography found one major impurity and four minor unidentified impurities even though the sample was reported to be 99% 1,1,2,2- tetrachloroethane. The presence of 1,1,1,2-tetrachloroethane as an impurity in the dosed material could account for some of the trichloroacetic acid in the urine.

Unfortunately there is no study of 1,1,2,2-tetrachloroethane that examined metabolism after repeated dosing. Based on the single dose study of metabolism conducted by Yllner (1971) and supported by studies that looked at respiratory elimination of unmetabolized tetrachloroethane and labeled carbon dioxide, it can be concluded that, in a naive mouse, there is complete metabolism of about 50 to 60% of the dose to carbon dioxide, DCA and its intermediary metabolites (glycine, glyoxylic acid and oxalate) account for 25 to 30%. Small amounts 1-2% are

exhaled as unmetabolized 1,1,2,2-tetrachloroethane. A small fraction of the dose and may be slowly converted to trichloroethylene through spontaneous dehydrohalogenation and be further metabolized to trichloroethanol and trichloroacetic acid. Some unmetabolized parent compound may partition to adipose tissues and some may become bound to macromolecules as a result of free radical reactions. Rats exhaled a larger portion (10%) of the dose as unmetabolized 1,1,2,2-tetrachloroethane than mice (Dow, 1988).

Based on studies of DCA, the amounts of DCA that does not become metabolized should increase as the dose and/or duration of exposure increases because of GSTZ inhibition (U.S. EPA 2003b). The amount of unmetabolized parent compound is small in a naive animal but may increase as dose and duration of exposure increases.

6.3.1 Metabolic Rate Constants

Gargus and Anderson (1989) used the level of exhaled 1,1,2,2-tetrachloroethane from rats in conjunction with a physiologically-based pharmacokinetic (PBPK) model to determine metabolic kinetic constants for inhalation exposure. Two rats were exposed to 350 ppm (2243 mg/m^3) 1,1,2,2-tetrachloroethane in an inhalation chamber for 6 hours. The animals were then placed in a special chamber where the exhaled air was collected over an 18-hour period and the 1,1,2,2-tetrachloroethane concentration measured. The levels of 1,1,2,2-tetrachloroethane in exhaled air were fit using a PBPK model which had been developed from rat blood:air, liver:blood, muscle:blood, and fat:blood partition coefficients.

The PBPK model was fit to the data on the concentrations in exhaled air to determine the Michaelis-Menton constant (K_m) and maximum velocity (V_{max}) for the metabolism of 1,1,2,2-tetrachloroethane. A portion of the 1,1,2,2-tetrachloroethane in the exposure chamber adhered onto the fur, causing an initial spike in measured post-exposure chamber air concentrations when it was released that could not be predicted by the model. This effect disappeared after 3 hours. The optimized metabolic rate (V_{max}) for 1,1,2,2-tetrachloroethane was estimated as 12.9 mg/kg/hour and the K_m was 0.8 mg/L. The V_{max} was higher than that for other tri- through hexa-chloroethanes studied. The reaction was classified as high affinity by the authors based on the K_m, and they concluded that hepatic metabolism would be subject to flow-limited behavior at low concentrations as would be expected based on intrinsic hepatic clearance characteristics. However, it is important to remember that these estimations are based on whole animal data and a single 6-hour exposure. Thus, the model does not account for the changes that would occur when continued exposure led to enzyme inhibition nor for the fact that there may be more than one metabolic pathway for 1,1,2,2-tetrachloroethane.

6.4 Excretion

No data were available regarding the excretion of 1,1,2,2-tetrachloroethane or its metabolites from studies of human exposure for oral and dermal routes of exposure. A single human inhalation study was identified (ATSDR, 2006), as described in the *Inhalation Exposure* section below.

Oral Exposure

The excretion of 1,1,2,2-tetrachloroethane was followed for 72 hours after oral administration of a 150-mg/kg single radiolabeled dose to rats and mice (Dow, 1988). More than 90% of the dose was metabolized or excreted unchanged in both species. In rats, 41% was excreted in breath (9% as unmetabolized tetrachloroethane and 32% as CO_2), 23% in urine, and 4% in feces. Thirty percent was retained in the skin and carcass. In mice, 51% was excreted in breath (1% as unmetabolized tetrachloroethane and 50% as CO_2), 22% in urine, and 6% in feces. Twenty percent was retained in the skin and carcass.

Mice given an oral dose of 200 mg/kg radiolabeled 1,1,2,2-tetrachloroethane excreted about 10% of the dose unchanged or as volatile metabolites in the breath. Ten percent of the dose was metabolized and excreted in the breath as CO_2. The amount excreted in the urine and feces, measured together, was 30% after 48 hours. The remainder was retained in the carcass (27%) suggesting deposition in adipose tissues or metabolism and incorporation into or binding to biological molecules, such as proteins or lipids (Mitoma et al., 1985). When the same protocol was applied to rats given a dose of 100 mg/kg radiolabeled compound, the exhaled 1,1,2,2-tetrachloroethane and volatile metabolites accounted for 7% of the dose, while 46% of the dose was found in the excreta. Only 2% was exhaled as CO_2.

Inhalation Exposure

A study with human volunteers showed that 3% of inhaled chlorine-labeled 1,1,2,2-tetrachloroethane was excreted in the breath within one hour, and that the urinary excretion rate was 0.015% of the absorbed dose/min (Morgan et al., 1970).

The excretion of ^{14}C-1,1,2,2-tetrachloroethane was tracked for 72 hours following exposure of rats and mice to vapor concentrations of 10 ppm (70 mg/m^3) of the radiolabeled chemical for 6 hours (Dow, 1988). More than 90% of the absorbed dose was metabolized in both species. The percentage of the recovered radioactivity in rats was 33% in breath (8% as unmetabolized tetrachloroethane and 25% as CO_2), 19% in urine, and 5% in feces. In mice the amounts were 34% in breath (2% as unmetabolized tetrachloroethane and 32% as CO_2), 26% in urine, and 6% in feces.

Dermal Exposure

A study describing the elimination of 1,1,2,2-tetrachloroethane in guinea pigs demonstrated that the half-life of the 1,1,2,2-tetrachloroethane in the blood was about two hours following dermal absorption (Jakobson et al., 1982).

Other Exposure Routes

Following intraperitoneal injections of doses ranging from 210 to 320 mg/kg ^{14}C-labeled 1,1,2,2-tetrachloroethane in rats and mice, about 4% of the radioactivity was expired unchanged in the breath after 72 hours and 50% was expired as CO_2. Another 28% of the radioactivity was excreted in the urine, 1% was in the feces, and 16% remained in the carcass (Yllner, 1971).

7.0 HAZARD IDENTIFICATION

7.1 Human Effects

7.1.1 Short-Term Studies and Case Reports

Intentional and Accidental Acute Ingestion

There are several case study reports of individuals who committed suicide by ingesting 1,1,2,2-tetrachloroethane. The amount consumed varied among individuals, making a lethal dose difficult to determine. The approximate lethal doses were estimated to be 4100 mg/kg (Hepple, 1927), 357 mg/kg (Lilliman, 1949), 1100 to 9600 mg/kg (Mant, 1953). Death following suicidal ingestion of 1,1,2,2-tetrachloroethane generally occurred within 3 to 20 hours. The presence of food in the gastrointestinal tract appeared to increase the time to death. Subjects usually lost consciousness within about an hour of exposure. Postmortem examination showed congestion in the lungs along with epicardial- and endocardial- anoxic hemorrhaging in some cases (ATSDR, 2006). In one situation (Lilliman, 1949), there was slight congestion of the liver tissues.

Several men and women were accidentally given oral doses (approximately 70 to 117 mg/kg) of undiluted 1,1,2,2-tetrachloroethane as a treatment for intestinal parasites (round worms) in an African clinic. The subjects lost consciousness within an hour. While unconscious they experienced shallow breathing, a faint pulse, and pronounced lowering of blood pressure (60/46) (Sherman, 1953; Ward, 1955). There were no fatalities and the subjects, understandably, refused further treatment at the clinic.

Acute and Short-Term Inhalation Exposure

A study was conducted during which two volunteers inhaled 1,1,2,2-tetrachloroethane vapors in a chamber at concentrations of 20, 30, or 90 mg/m^3 for 10 minutes; 800 mg/m^3 for 20 minutes; 900 mg/m^3 for 10 minutes; 1000 mg/m^3 for 30 minutes; 1800 mg/m^3 for 10 minutes, and 2300 mg/m^3 for 10 minutes (Lehmann and Schmidt-Kehl, 1936). After 10 minutes, 1,1,2,2-tetrachloroethane odor was detectable at concentrations of 20 mg/m^3 and above. Mild nausea and vomiting were observed at the lowest exposure concentration (20 mg/m^3) after 20 minutes. At concentrations of 90 mg/m^3 and above, minor respiratory effects were experienced. Dizziness and eye irritation were reported at concentrations of 800 mg/m^3 and above. The study lacks detail on the sequencing of exposure episodes. Ideally, adequate recovery periods would have been allowed between exposures to each increasing 1,1,2,2-tetrachloroethane concentration. This experimental detail was not reported.

Gastrointestinal and neurological distresses were reported following occupational exposure (inhalation and most likely dermal) to a cellulose acetate varnish with 1,1,2,2-tetrachloroethane as the solvent while covering fabric airplane wings during the early years of aviation (Willcox et al., 1915). Although most workers recovered, at least 4 of 14 workers later became confused, delirious, comatose, and finally died. Autopsies revealed extreme liver damage including areas of fatty degeneration. Fatty degeneration and congestion of the kidney were found in one female who died after a 2-3 month exposure. The levels of 1,1,2,2-tetrachloroethane in the air were not measured, so inhaled concentrations and total exposures are not known.

One worker was exposed to an unknown amount of 1,1,2,2-tetrachloroethane by a combination of the inhalation and dermal routes while cleaning up a spill. The exposure proved to be fatal. The subject experienced nausea, vomiting, loss of appetite, headache, fatigue and jaundice within six days of the incident. He died 20 days after exposure despite treatment. Autopsy records demonstrated liver cirrhosis and inflamation, enlargement of the heart and spleen, and bleeding in the gastrointestinal tract (Coyer, 1944).

7.1.2 Long-Term and Epidemiological Studies

Several occupational case reports and epidemiology studies of human exposures to 1,1,2,2-tetrachloroethane have been published. Most of them provide limited exposure data.

Humans exposed to 1,1,2,2-tetrachloroethane in the workplace developed gastric distress including pain, nausea, vomiting, loss of appetite, loss of body weight, jaundice, and an enlarged liver (Horiguchi et al., 1964; Jeney et al., 1957; Koelsch, 1915; Willcox et al., 1915). However, it was not possible to correlate specific adverse effects with specific exposure levels. Clinical signs generally disappeared when the workers changed employment.

Norman et al. (1981) retrospectively studied mortality records of a group of 1,099 white male civilians who worked for the army during World War II and were exposed dermally and/or by inhalation to tetrachloroethane solvent vapors in chemical processing plants where clothing was impregnated with N,N-dichlorohexachlorodiphenylurea for protection against mustard gas. The exposed workers were compared to 1319 non-exposed workers (i.e., individuals working in chemical processing plants using a water-based solvent instead of tetrachloroethane). Exposure levels were not measured; the exposure durations ranged from about 5 weeks to 1 year, with an average of about 5 months. The period between exposure and the epidemiology study was 31 years (1946-1976).

The exposed group showed a very slight, non-significant increase in the incidence of deaths due to genital cancers (relative risk [RR] =4.56), leukemia (RR=1.77), and other lymphatic cancers (RR=5.19), when compared to similar workers not exposed. The increased incidences were not statistically significant. Overall, cancer mortality for exposed workers was 1.26 times that of unexposed workers. There were no significant increases of death from liver cirrhosis. Several confounding factors may have influenced the study results (i.e., exposure to the N,N-dichlorohexachlorodiphenylurea and dry cleaning solvents), and there were no occupational histories recorded for the 31-year period after exposure. The authors concluded that the results are difficult to interpret, and the observed incidences of cancer may not have been due to tetrachloroethane exposure. This information is inconclusive as to whether tetrachloroethane causes cancer in humans.

Jeney et al. (1957) studied a group of about 50 penicillin plant workers who used 1,1,2,2-tetrachloroethane as an extractant for 3 years. During the first year, air concentrations were reported to range from 2.3 to 247 ppm (16 to 1724 mg/m^3) for most of the work shift. Approximately half of the workers developed hepatitis (diagnosed by palpation and liver function tests). Liver dysfunction occurred at a lower frequency and severity. Liver enlargement was found in 5% of the workers, urobilinogenuria in 12%, and increased serum bilirubin in 7.6%.

Exposure-related neurological or hematological changes were not reported. It is not clear whether the workers had direct dermal contact with the 1,1,2,2 tetrachloroethane in addition to the inhalation exposure. There was no control group for this study.

Lobo-Mendonca (1963) studied 380 workers who were exposed to 1,1,2,2-tetrachloroethane during the manufacture of bracelets from waste cellulose acetate film at 23 factories in Bombay, India. Eighty-five of the workers had dermal contact with a 1:1 liquid mixture of 1,1,2,2-tetrachloroethane and acetone, 107 had dermal contact with undiluted 1,1,2,2-tetrachloroethane, and 188 were exposed only by inhalation of vapor. Average breathing zone concentrations of 1,1,2,2-tetrachloroethane ranged from 9 to 98 ppm (63 to 684 mg/m^3), with most samples ranging between 20 and 65 ppm (140 and 454 mg/m^3). Neurological signs were reported to occur in exposed workers, primarily finger tremors (in 35% of the exposed workers), and appeared to be dose-related. Controls were not evaluated and the reported air concentrations may not have been representative of actual exposures (WHO, 1998).

An increase in the number of large mononuclear cells, white blood cells, and platelets, and slight anemia were found in workers in an artificial silk factory who were exposed both dermally and via inhalation of 1,1,2,2-tetrachloroethane vapors (Minot and Smith, 1921). Neurological symptoms, including fatigue, irritability and headache were also observed. Accurate measures of exposure concentrations were not available.

7.2 Animal Studies

7.2.1 Acute Toxicity

Oral Exposure

Estimates of the oral LD_{50} of 1,1,2,2-tetrachloroethane in rats fall in a narrow range (ATSDR, 2006): 319 mg/kg (Smyth et al., 1969), 250 mg/kg (Gohlke et al., 1977), and 330 mg/kg (Schmidt et al., 1980a). However, the LD_{50} identified by Paolini, et al. (1992) using gavage exposures to groups of six CD-1 mice gave a considerably higher value of 1,476 mg/kg.

Ten male Wistar rats that received a single oral dose of 100 mg/kg of 1,1,2,2-tetrachloroethane in peanut oil were found to have hepatic necrosis and fatty degeneration 20 to 22 hours after exposure, but no changes in relative liver weight or body weight. Levels of liver serum leucine aminopeptidase, ascorbic acid, and triglyceride were increased (Schmidt et al., 1980a). In another study, single doses of 143.5, 287, 574, or 1148 mg/kg were administered by gavage in corn oil to groups of male Sprague-Dawley rats. The animals were sacrificed 24 hours later and the liver excised for analysis. Levels of aspartate amino transferase (AST) and alanine amino transferase (ALT) were significantly elevated at doses of 287 mg/kg and above (Cottalasso et al., 1998). When the levels of AST and ALT were evaluated at different time points (5, 15, 30, or 60 minutes) after administration of the 574-mg/kg dose, the increases reached a level of significance ($p<0.05$) 30 minutes after dosing ($n=4-6$). Significant increases in liver triglycerides also were seen at this same dose.

A lethal dose of 300 mg/kg-day was identified when groups of male Osborne-Mendel rats were exposed for 4 days to doses of 0, 25, 75, 150, or 300 mg/kg/day by gavage in corn oil (Dow,

1988). After sacrifice, enlargement of hepatic cells in the centrilobular region and hyperplasia were seen at doses of 75 mg/kg/day and above. Body weight was depressed at doses of 150 mg/kg/day and above, reaching a 16% difference in the highest dose group. The animals in the highest dose group exhibited central nervous system depression which could have contributed to the death of some rats in this dose group. When groups of male B6C3F1 mice were exposed under the same conditions, there were no deaths (Dow, 1988). Centrilobular hepatic swelling was noted at doses of 75 mg/kg/day and hepatic mitosis was observed at the highest dose. The no observed adverse effect level (NOAEL) in this study was the 25-mg/kg/day doses for both mice and rats and the lowest observed adverse effect level (LOAEL) was the 75-mg/kg/day dose.

Inhalation Exposure

Concentrations of 1,1,2,2-tetrachloroethane in air that cause death in rats following 4- to 6-hour exposures have been consistently reported to be near 1000 ppm (6980 mg/m^3) (Carpenter et al., 1949; Deguchi, 1972; Schmidt et al., 1980b; Smyth et al., 1969).

Groups of 10 rats and 10 guinea pigs were exposed to concentrations of 0, 576 ppm (3951 mg/m^3), 5050 ppm (32,249 mg/m^3), or 6310 ppm (44,044 mg/m^3) for 30 minutes. Three of the rats died at the 5050-ppm concentration; labored respiration and eye irritation were observed. Post mortem evaluations did not reveal any lesions of the livers or kidneys. Myocardial damage was found in 1 of 10 rats following the 30-minute exposure to 6310 ppm. There were three deaths in the guinea pigs at the highest dose; labored respiration became apparent at the 5050-ppm dose and above and lacrimation was observed at the 576-ppm dose and above. Histological changes in the liver, kidney, and heart were not observed in the guinea pigs (Price et al., 1978).

Adult male Wistar rats (6/group) exposed to 0, 10, 100, or 1000 ppm (equivalent to 0, 70, 700, 7000 mg/m^3, respectively) 1,1,2,2-tetrachloroethane for 6 hours showed a dose-related increased serum AST levels 24 to 72 hours after exposure when compared with controls (Deguchi, 1972). There were no trends found in serum ALT over a 120-hour period after exposure. No pathological changes were observed in the liver, kidney, brain, heart, spleen, or bone marrow after the 6-hour exposure to 100 ppm. Four of the 6 rats exposed to 1000 ppm died within 18 hours following exposure.

Schmidt et al. (1980b) observed fine droplet fatty degeneration in the liver when groups of 5 to 10 male Wistar rats were exposed to concentrations of 0, 0.41, 0.7, 1.03, 2.10, or 4.2 mg/L (410, 700, 1030, 2000, or 4200 mg/m^3) 1,1,2,2-tetrachloroethane vapor for 4 hours and sacrificed after 24 hours. There was a concentration-related increase in liver triglycerides and liver ascorbic acid at doses $\geq$700 mg/m^3 when measurements were taken 24 hours after the exposure. The serum triglycerides appeared to decrease compared to controls but the decrease was not concentration-related. Alkaline phosphatase and succinic dehydrogenase were increased in the liver at the highest exposure concentration. Fine droplets of fat were seen in the liver at the 700-mg/m^3 concentration. The histological effects at the highest concentration were manifest as inflamation and necrotic cells with tiny fat droplets and ceroid pigments. Histological results were reported only for the 700 and 4200 mg/m^3 exposure concentrations.

In mice, the acute exposures that caused death were reported to be approximately 5000 to 6000 ppm (i.e., 34,900 to 41,880 mg/m^3) (Horiuchi et al., 1962; Lazarew, 1929; Pantelitsch,

1933). In animals surviving more than a few days, fatty degeneration of the liver was seen at necropsy (Horiuchi et al., 1962). Mice exposed to 600 or 800 ppm (i.e., 4188 to 5584 mg/m^3) 1,1,2,2-tetrachloroethane for 3 hours had increased levels of hepatic triglycerides (Tomokuni, 1969, 1970).

Dermal/Ocular Exposure

The dermal LD_{50} reported for 1,1,2,2-tetrachloroethane in rabbits was 6360 mg/kg (Smyth et al., 1969). Direct application of 514 mg/cm^2 1,1,2,2-tetrachloroethane for 16 hours damaged the skin of guinea pigs, causing karyopyknosis (compaction of the chromatin observed after cell death) and pseudoeosinophilic infiltration (Kronevi et al., 1981). Application of 1,1,2,2-tetrachloroethane (concentration not reported) to the shaved abdomen of rabbits caused hyperemia, edema, and severe blistering (Dow, 1944).

Guinea pigs were found to be more sensitive to ocular irritation from 1,1,2,2-tetrachloroethane vapors than rats (Price et al., 1978). Five minutes after exposure to a 576-ppm concentration, eye squinting, and closure were observed; lacrimation had begun by 15 minutes of exposure. Rats did not exhibit these responses until the exposure concentration had reached 5050 ppm and above.

7.2.2 Short-Term Studies

Oral Exposure

The NTP study (2004) conducted a 15-day range finding study of 1,1,2,2-tetrachloroethane in F344/N rats and B6C3F1 mice using a dietary route of exposure. The chemical was administered through microcapsules incorporated in the feed. The microcapsules were made from a combination of corn starch and sucrose granules. Groups of 5 male and female rats or mice were fed dietary levels of 0, 3325, 6650, 13,300, 26,600, or 53,200 ppm in their food. The animals were examined for clinical signs. Body weights were recorded initially, on day 8, and at the end of the dosing period. Food consumption was measured for the two highest dose groups at on days 1, 8, 11, and 15. At termination, the animals were subjected to gross necropsy and histopathological examination of any lesions identified. Selected major organ weights (heart, liver, lung, thymus, right kidney, and right testes) were recorded. Controls were either completely untreated or received diets with the tetrachloroethane-free microcapsules.

All of the rats in the two highest dose groups were sacrificed on day 11 of the study because of their poor physical condition and were not evaluated for changes in body weight or organ weights. Weight gain in all surviving animals was significantly less than that of the controls; all animals except the males in the 3325-ppm low dose group lost weight during the study. Relative liver weights were significantly increased among the surviving animals in the lowest dose group but not at higher doses. Relative kidney weights were significantly increased in all dose groups except the low dose females; relative thymus weights were significantly decreased in the highest two dose groups. A small number of animals in each dose group, including the untreated controls, had hepatodiaphragmatic nodules and mild or moderate centrilobular degeneration. The LOAEL in this study was 3325 ppm (273 mg/kg/day for females and 326 mg/kg/day for males based on food consumption and initial body weights). The initial weights were used for the dose calculation because all animals except the low dose males lost

weight over the 15-day period and no information was given for the weight loss time course. The effects associated with the LOAEL were increased relative liver weight, increased kidney weight, and body weight loss for the females; there was no NOAEL.

In mice, all animals receiving the highest dose and the males in the penultimate dose group died or were sacrificed before the end of the study and were not evaluated for body weights or organ weights. Body weights for all surviving animals were significantly lower than the controls and all groups, except the low-dose females that lost weight during the study. Relative liver weights were significantly increased in all surviving males and the females receiving the 13,300 and 26,000 ppm. Relative kidney weights were significantly increased and thymus weights were decreased for females receiving concentrations $\geq$13,300 ppm.

All exposed animals had mottled livers with cellular swelling, cytoplasmic rarefaction, single paranuclear vacuoles, and hepatocellular necrosis. The extent of liver damage increased with dose. There was some pooling of sinusoidal erythrocytes and infiltration with mononuclear cells. The lowest dose (579 mg/kg/day in males and 623 mg/kg/day for females based on food intake and initial body weights) was an LOAEL in mice. There was considerable scattering of feed, especially at the higher doses, preventing an accurate measure of food intake. Accordingly, the calculated dose is only an estimate of the actual dose. The effects associated with the LOAEL were decreased body weight, increased relative liver weight (males), decreased relative thymus weight (females), and histopathological lesions of the liver; there was no NOAEL in the study.

In a study examining the potential renal toxicity of orally administered halogenated ethanes, groups of five male F344/N rats received 0, 0.62, or 1.24 mmol/kg-day 1,1,2,2-tetrachloroethane in corn oil (0, 104, 208 mg/kg/day) by gavage daily for 21 days (NTP, 1996). All animals were examined for body weights, clinical signs, urinalysis, organ weights, and gross pathology. Histology was conducted on the liver and right kidney. Gross lesions were examined histopathologically. Rats in the high-dose group died or were killed before the end of the study. Clinical observations among the high-dose animals included an emaciated appearance and lethargy (5/5 animals), diarrhea (4/5 animals), abnormal breathing (3/5 animals), and ruffled fur (3/5 animals). In the low-dose group, no effects on survival, body weight gain, urinalysis, absolute and relative kidney weights, or kidney histopathology were observed. Absolute and relative liver weights of all dosed groups were greater than those for the controls. Mild to moderate cytoplasmic vacuolization (multifocal areas of hepatocytes with clear droplets within the cytoplasm) was observed among all rats in the low-dose group. The NTP did not consider the cytoplasmic vacuolization observed at 104 mg/kg/day to be an adverse effect. However, the 104 mg/kg/day dose could be regarded as a marginal LOAEL in rats exposed to 1,1,2,2-tetrachloroethane for 21 days based on the increased liver weights and hepatocyte vacuolization. The 208-mg/kg/day dose was a frank effect level (FEL).

The National Cancer Institute (NCI, 1978) conducted range-finding studies in rats and mice. In this study, groups of five male and five female Osborne-Mendel rats received gavage doses of 0 (vehicle control group), 56, 100, 178, 316, and 562 mg/kg of 1,1,2,2-tetrachloroethane in corn oil 5 days/week for 6 weeks followed by a 2-week observation period. Groups of five male and five female B6C3F1 mice were similarly exposed to 0, 32, 56, 100, 178, and 316 mg/kg of 1,1,2,2-tetrachloroethane. Mortality and body weight gain were the only endpoints used to

assess toxicity. In the rats, mortality was observed in one male exposed to 100 mg/kg, and all five females exposed to 316 mg/kg (mortality rates in the 562-mg/kg group were not provided). Decreases in body weight gain were observed in the rats at the 56, 100, and 178 mg/kg doses; the differences were 3, 9, and 38% for the males and 9, 24, and 41% for the females compared to the controls. No deaths were observed in the mice and there were no significant alterations in body weight gain. The limited number of endpoints examined in this study precludes identifying NOAELs and/or LOAELs.

Inhalation Exposure

Hepatic effects (fine-droplet fatty degeneration, inflammatory changes in the liver, and necrotic foci) were described in a study in which male rats were exposed to 2 ppm (14 mg/m^3) 1,1,2,2-tetrachloroethane for 4 hours per day, for a total of 8 exposures in 10 days (Gohlke and Schmidt, 1972). This study, however, had a number of limitations, including maintaining the rats at elevated room temperatures, a lack of a defined dose-response or duration-response relationships, and inconsistencies in the reported results (ATSDR, 2006).

7.2.3 Subchronic Studies

Oral Exposure

In a subchronic study conducted for the NTP (2004), groups of 10 male and 10 female F344 rats were fed diets containing microencapsulated 1,1,2,2-tetrachloroethane for 14 weeks at concentrations of 0, 268, 589, 1180, 2300, and 4600 ppm. One control group was untreated and a second received food containing the starch microcapsules. The estimated doses based on food intake and body weights were 0, 20, 40, 80, 170, or 320 mg/kg/day for males and females. Satellite groups of 10 males and 10 females received the same doses as the core group and were used for collection of blood samples.

The animals were examined for clinical signs daily. Body weights and food consumption were recorded weekly. Blood samples were collected on days 5 and 21, and week 13 for hematology and serum biochemistry measurements. A "Functional Observational Battery" (FOB) was given to the core study animals from the three lowest dose groups and controls during weeks 4 and 13. FOB results are reported in Section 7.2.4. Sperm motility and vaginal examinations and measurements of estrus cycles were conducted at the end of the study. The sperm and vaginal results are reported in Section 7.2.5. After sacrifice, all animals were subjected to gross necropsy. Complete histopathological examinations were conducted for the animals in the high dose group and for the liver, spleen, bone, and bone marrow in the lower dose groups. The testes and prostate in males and ovaries and clitoral gland in females were examined for all dose groups.

Statistically-significant decreases in final body weight were observed in the males and the females from the highest three dose groups ($\geq$1180 ppm). Animals in the highest dose group lost weight across the duration of the study, but all animals survived. Food consumption was notably decreased among the animals in the highest dose group (4600 ppm) and slightly decreased among animals in the 2300-ppm dose group. The maximum tolerated dose was exceeded for males and females in the 2300- and 4600-ppm dose groups and for females in the 1800-ppm dose group, since final body weights were more than 10% lower than that for the controls. For this reason, the

observations from the 2300- and 4600-ppm dose groups are not included in Table 7-1, the summary of the observed effects in the F-344 rats.

The blood samples taken on days 5 and 21 had a variety of statically significant changes in various red blood cell and other hematological parameters, especially at doses of 1800 ppm and greater. At the end of the study, dose groups exposed to concentrations ≥589 ppm had hematological changes indicative of a microcytic anemia. A lack of an increase in reticulocyte counts suggested that the anemia did not elicit an erythropoietic response. Some groups showed decreases in platelet counts early in the study (≥1800 ppm for males and ≥598 ppm for females). However, by the end of the study platelet counts were significantly decreased only in the ≥2300-ppm dose groups. Decreased leucocyte counts were seen in these same dose groups.

A number of significant changes were observed in serum biochemical parameters during the study; most were dose-related. ALT and sorbitol dehydrogenase (SDH) levels were significantly increased in males at doses ≥2300 ppm and in females at doses ≥1800 ppm. These parameters along with others are indicative of hepatic toxicity. [There was a significant increase of SDH in males at the lowest dose but the increase at the next higher dose was not significant.] Significant increases in bile acids, alkaline phosphatase, and 5'-nucleotidase were indicative of cholestasis (obstructed outflow of bile from the liver) at concentrations ≥2300 ppm. On day 5, cholesterol levels were significantly decreased in all dose groups but by the end of 14-weeks the levels were significantly decreased in females only at levels ≥1180 ppm and only in the highest dose group for males. At the early time points, there was evidence of hypoproteinuria accompanied by elevated levels of albumin and increased levels of creatinine kinase, suggesting muscle injury in the two highest dose groups. These conditions had resolved by the end of the study.

Among the animals in the lower dose groups (≤1180 ppm) relative liver weights were increased in a dose-related fashion. Decreased absolute organ weights at the higher doses were likely a consequence of exceeding the maximum tolerated dose.

Gross and histopathologic observations, combined with the clinical biochemistry parameters discussed above, implicate the liver as the primary target organ for 1,1,2,2-tetrachloroethane in this 14-week study. Hepatocyte vacuolization was seen in all dose groups. The number and type of liver lesions increased with dose. Necrosis and altered cell foci were observed at doses of ≥2300 ppm. Cell foci appeared as basophilic, eosinophilic, mixed cell, and/or clear cell clusters of cellular alterations. Bile duct hyperplasia and pigmentation appeared only in the highest dose group for the males but in the two highest dose groups for females. In males, atrophy of the spleen, bone, bone marrow, and male reproductive organs (prostate, seminal vesicle, and testes) were apparent only for the 4600-ppm dose group, but in the females, changes were observed in both the 2300- and 4600-ppm dose groups. The reproductive organs examined in females were the uterus, ovary, and clitoral gland. Organ atrophy was attributed to the body weight deficits in the affected groups. The results of the tests of sperm motility and estrus cycle are reported in section 7.2.5.

According to the authors, the 589-ppm dose level (40 mg/kg/day for males and females) was the LOAEL for systemic effects in this study. The only observed effect in the 268-ppm

group was hepatocyte cytoplasmic vacuolization of minimal severity in 7/10 males ($p<0.05$) but not in females. As mentioned earlier, the SDH levels in the 268-ppm males was significantly increased but the increase for the 589-ppm dose group was not significant. These minimal effects were not considered adverse by the authors. The effects that contributed to the identification of 589 ppm as the LOAEL were on hepatocyte cytoplasmic vacuolization (mild severity) in 9/10 males and 10/10 females (compared to 0/20 controls), increased relative liver weight, plus significantly decreased hemoglobin in males and hematocrit in females. It also is possible to classify the 268-ppm dose (20 mg/kg/day) as a marginal LOAEL for the male rats based on the cytoplasmic vacuolization in 7/10 male rats.

Table 7-1 Doses and Effects from the NTP 14-Week Study (2004) in F-344 Rats

Concentration in Diet (ppm)	Dose - Males (mg/kg/day)	Significant Effects	Dose - Females (mg/kg/day)	Significant Effects
0	0		0	
268	20	Increased SDH Increased hepatocyte cytoplasmic vacuolization (1.3)[1]	20	No observed effects
589	40	Decreased hemoglobin Increased SDH (not significant) Increased hepatocyte cytoplasmic vacuolization (2.0)[1] Increased relative liver weight Decreased sperm motility	40	Decreased manual hematocrit Increased hepatocyte cytoplasmic vacuolization (1.7)[1] Increased relative liver weight
1,180	80	Decreased body weight gain (5%) Increased ALT Increased SDH Decreased hemoglobin Decreased manual hematocrit Increased relative liver weight Increased relative kidney weight Increased hepatocyte cytoplasmic vacuolization (1.9)[1] Spleen pigmentation Decreased epididymal sperm motility Decreased left epididymis weight	80	Decreased body weight gain (8%) Decreased manual hematocrit Decreased hemoglobin Decreased mean cell volume Decreased mean cell hemoglobin Decreased cholesterol Increased hepatocyte cytoplasmic vacuolization (2.2)[1] Increased relative liver weight

Higher doses not shown because they clearly exceed the maximum tolerated dose
1. Severity scale for hepatocyte cytoplasmic vacuolization 1 = minimal; 2 = mild; 3 = moderate; 4 = severe

The protocol used for the NTP study (2004) in rats with slight modifications was used to study groups of 10 male and 10 female B6C3F1 mice. The dietary concentrations used for the mice were 0, 589, 1120, 2300, 4550, or 9100 ppm. These corresponded to doses of 0, 100, 200, 370, 700, and 1360 mg/kg/day for the males and 0, 80, 160, 300, 600, and 1400 mg/kg/day for the females. There were no measurements of hematology in mice; measurement of serum biochemical parameters were only conducted at the end of the study.

There was a significant difference from vehicle controls in body weight gain among mice for all exposure concentrations $\geq$2300 ppm, but as with the rats, there was no mortality. The exposed animals had final body weights that were more than 10% lower than the controls for each of the doses $\geq$4550 ppm, indicating that the maximum tolerated dose had been exceeded. For this

reason the effects observed in the two highest dose groups are not included in Table 7-2 on the effects observed in the NTP study (2004) of B6C3F1 mice.

The clinical signs of liver toxicity in mice were similar to those in rats. There was a dose-related increase in ALT in all female dose groups, which became significant at concentrations ≥1120 ppm. In males, the concentration of ALT did not begin to increase until the 1120 dose and became significant for concentrations ≥2300 ppm. SDH results were similar except that the increases attained significance at concentrations ≥589 ppm in females and ≥1120 ppm in males. Bile acids, alkaline phosphatase, and 5'-nucleotidase indicated cholestasis at concentrations of ≥1120 ppm in females and ≥2300 ppm in males. Serum protein levels were significantly decreased at doses of ≥2300 ppm, and cholesterol levels in females were significantly decreased at concentrations of ≥1120 ppm. The dose-related downward trend in cholesterol levels was reversed at the highest dose, but the cholesterol level still remained significantly lower than the controls.

On necropsy, the livers for all females and males were pale at concentrations ≥2300 ppm. One male had pale kidneys in each of the two highest dose groups. Relative liver weights were significantly elevated for all exposed female groups and males receiving the 1120- and 2300-ppm concentrations. Absolute and relative kidney weights were decreased in males at concentrations of ≥2300 ppm, and absolute thymus weights were decreased in males and females at the highest dose. The decreased absolute organ weights among the animals in the higher dose groups may be due to the deficits in body weight gain. An increase in focal lymphocyte cellular infiltration of the lung was observed in the female mice exposed to 4550 or 9100 ppm; however, the number of infiltrates was within the normal range and was not considered to be related to 1,1,2,2-tetrachloroethane exposure.

Hepatocyte hypertrophy was evident in males and females receiving concentrations ≥1120 ppm. Pigmentation and bile duct hyperplasia were significantly increased at concentrations ≥2300 ppm. A significant increase in liver necrosis was observed in males at concentrations ≥2300 ppm and in females for concentrations ≥4550 ppm. Based on observations of significant changes in the parameters measured, the 1120-ppm concentration (a dose of 160 mg/kg/day in females and 200 mg/kg/day in males) was a clear LOAEL for this study and the 589-ppm concentration (80 mg/kg/day for females and 100 mg/kg/day for males) was the NOAEL.

There was a significant dose-related increase in SDH levels for females at doses of 589 ppm and higher that could indicate that the 589-ppm concentration is a marginal LOAEL, rather than a true NOAEL. The authors of the study did not identify an NOAEL and/or LOAEL for the mice because of the tumor response that was seen in mice in a cancer study conducted by NCI (see Sections 7.2.6 and 7.2.7).

Table 7-2 Doses and Effects from the NTP 14-Week Study (2004) in B6C3F1 Mice

Concentration in Diet (ppm)	Dose - Males (mg/kg/day)	Significant Effects	Dose - Females (mg/kg/day)	Significant Effects
0	0		0	
589	100	No significant effects	80	Increased SDH Increased relative liver weight
1120	200	Decreased total protein Increased SDH Hepatocyte hypertrophy[1] (1.0)[1]	160	Increased ALT Increased SDH Increased 5' nucleotidase Increased bile acids Decreased cholesterol Hepatocyte hypertrophy (1.0)[1] Increased relative liver weight
2300	370	Decreased body weight gain (13%) Decreased total protein Increased ALT Increased AP Increased SDH Increased 5' nucleotidase Increased bile acids Hepatocyte hypertrophy (2.2)[1] Hepatocyte necrosis Focal liver pigmentation Bile duct hyperplasia Increased relative liver weight	300	Decreased total protein Increased ALT Increased AP Increased SDH Increased bile acids Decreased cholesterol Hepatocyte hypertrophy (1.9)[1] Focal liver pigmentation Bile duct hyperplasia Increased relative liver weight Increased relative heart weight

Higher doses not shown because they clearly exceed the maximum tolerated dose
1. Severity scale for hepatocyte hypertrophy 1 = minimal; 2 = mild; 3 = moderate; 4 = severe

Inhalation Exposure

Fifty-five female rats were exposed to 130 ppm (907 mg/m^3) 1,1,2,2-tetrachloroethane for 5 hours/day, 5 days/week for 15 weeks. They exhibited increased relative liver weight and signs of hyperplasia (including increased numbers of binuclear cells), granulation, and vacuolization of the liver cells. Histological examination of the lungs revealed no treatment-related lesions (Truffert et al., 1977). The rats also showed slightly decreased hematocrit levels, but statistical significance was not reported.

Exposure to 1,1,2,2-tetrachloroethane at 50 mg/m^3 four hours/day, 5 days/ week, or 130 mg/m^3 for 15 minutes, 5 times/day and 5 days/week, both for approximately 5 weeks, resulted in alterations in biochemical parameters and organ weights in male rats (strain and number not specified). Although no "morphological changes" were noted upon examination, the nature and extent of the histopathological examination were not specified (Schmidt et al., 1975).

Brown, Norway and Wistar rats were exposed to 516 ppm (3602 mg/m^3) 1,1,2,2-tetrachloroethane for 5 hours/day, 5 days/week for 13 weeks. The animals had depressed body weights compared with controls. There were small glomerular lesions in the kidneys and the levels of protein in the urine were lower than those for controls (Danan et al., 1983).

7.2.4 Neurotoxicity

There have been a number of indications of neurotoxicity in humans exposed to 1,1,2,2-tetrachloroethane by the inhalation route. Human volunteers who inhaled 800 mg/m^3 1,1,2,2-tetrachloroethane for 20 minutes or $\geq$900 mg/m^3 for 10 minutes reported being dizzy. These effects did not occur when the exposure was 90 mg/m^3 for 10 minutes (Lehmann and Schmidt-Kehl, 1936).

Humans exposed to 1,1,2,2-tetrachloroethane vapors in the workplace showed symptoms such as headache, tremors, dizziness, numbness, and drowsiness (Hamilton, 1917; Jeney et al., 1957; Lobo-Mendonca, 1963; Minot and Smith, 1921; Parmenter, 1921). Length of exposure was not noted, but the reports seem to indicate that the exposures generally were for a period of about 18 months or less. Exposure levels were noted in only one study, and these ranged from 9 to 98 ppm (63 to 684 mg/m^3), with significant skin exposure in addition to the inhalation exposure (Lobo-Mendonca, 1963). The incidence of tremors was higher among factory workers exposed to higher concentrations, suggesting a dose-response relationship. Workers in an artificial silk plant experienced fatigue, irritability, headache, and coma (Minot and Smith, 1921). Exposure levels were not reported. The data from the occupational studies are limited because most do not provide information on whether or not there might have been co-exposures to other chemicals with neurotoxic properties.

There are a variety of reports of short term inhalation exposures of rodents to 1,1,2,2-tetrachloroethane that are indicative of adverse effects on the central nervous system after short-term exposures. In acute duration experiments, rats showed a decrease in spontaneous motor activity after being exposed to 360 ppm (2513 mg/m^3) for 6 hours (Horvath and Frantik, 1973), and mice showed a loss of reflexes after being exposed to 1091 ppm (7615 mg/m^3) for 2 hours (Lazarew, 1929). As the concentration or duration of exposure to 1,1,2,2-tetrachloroethane

increased, mice, rats, and guinea pigs showed some combination of a loss of reflexes, loss of spontaneous motor activity, ataxia, prostration, and narcosis (Lazarew, 1929; Pantelitsch, 1933; Price et al., 1978). Rats exposed to 9000 ppm (62,820 mg/m^3) for 2 hours/day, twice a week for 4 weeks exhibited hyperactivity, ataxia, and then unconsciousness (Horiuchi et al., 1962).

Narcosis also was observed in a cat exposed to 8300 ppm (57934 mg/m^3) 1,1,2,2-tetrachloroethane for 5 hours (Lehmann, 1911). One monkey was exposed to 1,1,2,2-tetrachloroethane for 2 hours/day, 6 days/week for 9 months (190 exposures). For the first 20 exposures, the concentrations were 2000-4000 ppm (13960-27920 mg/m^3); for the next 140 exposures, the concentrations were 1000-2000 ppm (6980-13960 mg/m^3); and for the last 30 exposures, the concentrations were 3000-4000 ppm (20,940-27,920 mg/m^3). The monkey was rendered unconsciousness 20 to 60 minutes after each 2-hour exposure, starting with the fifteenth exposure (Horiuchi et al., 1962).

Rats receiving a single oral 50-mg/kg dose displayed significantly decreased avoidance learning. This effect was not detected at a dose of 25 mg/kg (Wolff, 1978). A single oral dose of 50 mg/kg body weight increased levels of several neurotransmitters in the brain of rats (Kanada et al., 1994). Rats receiving doses of 300 mg/kg-day for 3 to 4 days experienced significant central nervous system depression and debilitation (Dow, 1988).

During the 14-week NTP study (2004), F-344 rats in the 0-, 268-, 589-, and 1180-ppm exposure groups and B6C3F1 mice in the 0-, 1120-, 2300-, and 4550-ppm groups were given a FOB to examine the neurotoxic potential of 1,1,2,2-tetrachloroethane during weeks 4 and 13 of the study. The test battery included observations of general behavior, gait, coordination, movement patterns, convulsions, tremors, fighting, licking behavior, as well as piloerection, lacrimation, chromodacryorrhea (reddish corneal discharge without the presence of red blood cells), vocalization, diarrhea, and urination patterns. No significant dose-response increase in the incidence of any of these parameters were noted among the animals in any dose group.

Edefors and Ravn-Jonsen (1992) examined the effects of a variety of nonpolar halogenated and nonhalogenated solvents, including 1,1,2,2-tetrachloroethane, on the activity of the Ca^{2+}/Mg^{2+} ATPase from freshly isolated rat synaptosomal membrane preparations. The enzyme activity was monitored through the amount of ATP produced relative to the concentration of the dissolved solvent in the buffer solution. In the case of 1,1,2,2-tetrachloroethane, the maximum activity (105%) was observed with the 25% solution. The ATPase activity with the 12.5% solution was about 80% of the maximum, and that for the 50% solution was about 60% of the maximum. The biphasic response showed initial excitation (higher levels of ATP) as the concentration increased from 12.5% to 25% followed by a depression (lower levels of ATP) at concentrations greater than 25%. 1,1,2,2-Tetrachloroethane had no significant impact on the fluidity of the synaptosomal membrane.

7.2.5 Developmental/Reproductive Toxicity

No studies were located regarding reproductive or developmental effects in humans following exposure to 1,1,2,2-tetrachloroethane. In addition, there have been no standard multigeneration reproductive studies of 1,1,2,2-tetrachloroethane in animals. There are data from a limited single generation study (Schmidt et al., 1972) and a developmental study (Schmidt, 1976) using protocols that are now nonstandard. The NTP study (2004) examined the reproductive organs in males and females and measured sperm production in male rats. The data from these studies are reported below.

The data from animals studies on developmental toxicity are more complete, since studies have been completed in two species. The studies were conducted in pregnant Sprague-Dawley rats and CD-1 Swiss mice by Environmental Research and Testing, Inc. for NTP (1991a,b) but are more consistent with a range-finding methodology than a full developmental study.

Reproductive Effects

Oral Exposure

As part of the NTP study (2004), epididymal sperm samples were collected from rats receiving concentrations of 0, 589, 1180, or 2300 ppm 1,1,2,2-tetrachloroethane in their diets after 14 weeks. The left cauda, left epididymus, and left testis were weighed. In females, vaginal smears were collected for 12 days prior to the end of the study for vaginal cytology examinations. The percentage of time spent in various estrous stages and estrous cycle length were evaluated. There was a decrease in sperm motility at concentrations of 589 ppm and greater. The left epididymus weight was decreased at concentrations of $\geq$1180 ppm, and the weight of the left cauda epididymus was increased for the 2300-ppm concentration. Estrus cycles were altered in females receiving the 2300-ppm concentration. These females spent more time is the diestrus phase of the cycle and less time in other phases.

Mice receiving dietary 1,1,2,2-tetrachloroethane concentrations of 0, 1120, 4550, or 9100 ppm in the NTP study (2004) were examined using the same parameters described for the rats above. The results in mice were comparable to those in rats but occurred at a higher dose. In mice, with the exception of the weight of the left testis which was decreased in the group receiving the 4550-ppm concentration, changes in all measured parameters were significant for only the 9100-ppm concentration.

Longer-term oral gavage exposures of male or female rats or mice produced no gross or histological alterations in the reproductive organs in the chronic study by NCI (1978; see Section 7.2.6). In these 78-week gavage studies, male rats were dosed at levels up to 108 mg/kg-day, female rats were dosed at levels up to 76 mg/kg-day, and mice (both sexes) were dosed at levels up to 284 mg/kg-day.

Testicular effects were found in groups of 10 rats dosed by gavage at doses on 0, 3.2, or 8 mg/kg-day, 82 times in 120 days (Gohlke et al., 1977). A high incidence of interstitial edema of the testes, clumped sperm, and epithelial cells in the tubular lumen were observed. Partial necrosis and totally atrophied tubules, giant cells, and two-row germinal epithelial cells with

disturbed spermatogenesis also were observed (the incidence was not reported). Some of these changes (details not provided) persisted during the 2-week follow-up observation period. No other reproductive indices were examined. This study had a number of limitations, including an unusual experimental design in which the rats were exposed in the presence and absence of an elevated air temperature (35°C). Effects were observed at both 1,1,2,2-tetrachloroethane doses.

Inhalation Exposure

In a limited one-generation inhalation study, male rats were exposed to 13.3 mg/m^3 1,1,2,2-tetrachloroethane, 4 hours/day (days/ week not specified) for a 9-month period. One week before the end of the exposure period, groups of 7 exposed males and control males were mated with 5 unexposed females. Exposure of the males continued during the mating period. The F_1 generation was observed for 12 weeks postpartum. There were no statistically significant differences in the percentage of females having offspring (77.1% in controls vs. 62.9% in exposed), number of pups per litter, average birth weight, gestation length, sex ratio, offspring mortality at postnatal days 1, 2, 7, 14, 21, and 84, or average weight on postnatal day 84. No macroscopic malformations were observed (Schmidt et al., 1972).

In rats, no effects on the testes, epididymis, ovaries, or uteruses were seen after inhalation exposure for 30 minutes to 6310 ppm (44,044 mg/m^3) 1,1,2,2-tetrachloroethane (Price et al., 1978). In female rats, exposure to 130-ppm (907 mg/m^3) 1,1,2,2-tetrachloroethane vapors for 15 weeks (5-6 hours/day; 5 days/week) also had no effect on the histology of the reproductive organs (Truffert et al., 1977). Inhalation of 1,1,2,2-tetrachloroethane for 9 months to a TWA concentration of 1974 ppm (13,779 mg/m^3) produced no pathological changes in the testes of one monkey (Horiuchi et al., 1962).

Developmental Effects

Groups of 8 to 9 pregnant female Sprague-Dawley rats were exposed to doses of 0, 34, 98, 180, 278, or 330 mg/kg/day 1,1,2,2-tetrachloroethane (98% pure) through microcapsules incorporated in the diet starting on gestation day (gd) 4 in a range finding study (NTP, 1991a). The doses were estimated by the study authors based on the concentrations in the diet and food consumption. Gestation day 0 was defined as the day of mating. Food consumption, body weights and clinical signs were observed during treatment. The animals were sacrificed on gd 20. Live and dead pups, implantation sites, resorption sites, and fetal body weights were recorded.

There were no maternal deaths during the study. Clinical signs of toxicity (rough hair coat) were observed in the two highest dose groups and 3 of 9 rats from the highest dose group developed a hunched posture as well. Weight gain during treatment and weight gain corrected for gravid uteri weight were significantly decreased in all but the lowest dose group. Average feed consumption was significantly lower in the exposed animals than in the controls and demonstrated a dose-related pattern. The 34-mg/kg/day dose appeared to be an NOAEL for maternal toxicity. There was a significant difference in maternal body weight on gd 16 but not at other time points. In all other dose groups differences in body weight were significantly lower at all time points from day 9 to day 20.

At sacrifice, total pup resorption was seen in one animal from the 98-mg/kg/day dose group and 4 of 9 animals in the 330 mg/kg/day dose group. Significant decreases in average fetal body weights were observed for all dose groups except the 34-mg/kg/day group. The 98-mg/kg/day dose group was the LOAEL for fetal toxicity based on decreased fetal weights but confounded by maternal toxicity in the dams which was manifest as decreased weight gain during pregnancy. The NOAEL for the pups was 34 mg/kg/day based on the parameters evaluated. There was no evaluation for external, visceral or skeletal abnormalities.

NTP (1991b) conducted two studies, comparable to that described above, in Swiss CD-1 mice. In the first study, the doses (4 to 10% of the diet) the doses were lethal to the pregnant animals and, thus, a second study was conducted using lower doses. The target doses for the second study (0.5 to 3% of the diet) were 0, 987, 2120, 2216, or 4575 mg/kg/day. All animals in the 3% dose group died early in the study and, thus, a dose was not calculated for this group. Dose groups each included 5 to 10 pregnant animals.

Maternal mortality and clinical signs of toxicity were present in all but the lowest dose group. Daily feed consumption was significantly increased compared to controls in the 2216 mg/kg/day dose group for gd 6-11 but was lower than that for controls for gd days 11-16. Body weight gain and body weights were decreased at doses of 2120 mg/kg/day and above, but not in a dose-related pattern. The livers of the dams were discolored and enlarged for all dose groups except the lowest. The 987-mg/kg dose was an NOAEL for the dams based on an absence of clinical signs of toxicity, effects on body weight, and liver histopathology. The 2120-mg/kg/day dose group was the LOAEL.

The maternal mortality in the 2216- and 4575-dose groups made it difficult to evaluate the fetal toxicity in mice. There was only one dam left in the 2216-mg/kg dose group at sacrifice on day 17 and two in the 4575-mg/kg/day dose group. Embryos were completely resorbed in one dam in each dose group. Total resorptions were seen for 2 of 8 dams in the 2120-mg/kg/day dose group, but were not seen in the 987-mg/kg/day dose group. Accordingly, 987 mg/kg/day was determined to be an NOAEL for maternal and fetal toxicity in Swiss CD-1 mice based on the parameters evaluated. There was no evaluation for external, visceral or skeletal abnormalities.

In AB or DBA mice, single intraperitoneal injections of 700 mg/kg 1,1,2,2-tetrachloroethane in corn oil on day gd 9 or 400 mg/kg/injection on gd days 7 through 14 were not embryotoxic. However, injections of 300 mg/kg on gd 1 through 14 were embryolethal for the DBA strain. In the DBA mice the incidence of deformities (skeletal or visceral) in the 1,1,2,2-tetrachloroethane exposed mice was 3-5% compared to 2% for the corn oil exposed controls. The highest percentage of fetal malformation (9.39%) was seen when a 700 mg/kg ip. dose was administered on gd 9 to the AB mice. There is generally a low (< 2%) incidence of developmental abnormalities (exencephaly, cleft palate, anophthalmia, and fused ribs and vertebrae) in this strain (Schmidt, 1976).

7.2.6 Chronic Toxicity

Oral Exposure

NCI (1978) conducted a chronic study of the tumorigenic potential of 1,1,2,2-tetrachloroethane in groups of 50/sex/species Osborne-Mendel rats (7 weeks old at initiation) and B6C3F1 mice (5 weeks old at initiation). The animals were administered technical grade 1,1,2,2-tetrachloroethane (purity ≥90%) in corn oil via gavage, 5 days/week for 78 weeks. The doses were adjusted several times during the study.

In the male rats, the doses increased from an initial 50 mg/kg/day to 65 mg/kg/day after 14-weeks for the low-dose group. For the male high dose group the doses were raised from 100 mg/kg/day to 130 mg/kg/day. For the female rats in the low dose group the doses were lowered from 50 to 40 mg/kg/day after 25 weeks and from 100 to 80 mg/kg/day for the high dose group. the doses The 5 days/week time-weighted average doses were calculated as 62 or 108 mg/kg/day for male rats, 43 or 76 mg/kg/day for female rats. NCI (1978) did not normalize the doses for a 7 days/week exposure. The exposure period was followed by a 32-week period in which the rats were not exposed to 1,1,2,2-tetrachloroethane. The vehicle and untreated control groups included 20 animals/sex/species.

A statistically significant association between increased mortality and dose was observed in the female rats; 10 of the high-dose females died during the first 5 weeks of the study. The incidence of chronic murine pneumonia in the low- and high-dose female rats (8/20, 34/50, 38/50, respectively) was significantly increased compared to the controls ($p<0.05$, Fisher Exact Test). Eight of the 10 females that died had pneumonia; NCI (1978) considered the deaths to be related to 1,1,2,2-tetrachloroethane exposure. No significant effects of 1,1,2,2-tetrachloroethane on survival were observed in the low-dose female rats and in both male dose groups.

Clinical signs observed in the exposed rats, but not in the controls, included a hunched appearance in the high-dose females and squinted or reddened eyes. The investigators noted that there was a low or moderate incidence of labored breathing, wheezing, and/or nasal discharge in exposed and control animals during the first year of the study. Near the end of the study, these respiratory signs were observed more frequently in the 1,1,2,2-tetrachloroethane-exposed animals than in the controls; no additional information on this effect was provided.

Dose-related differences in body weight gain were observed in the rats; the differences between body weights of the vehicle control rats and the low- and high-dose rats were less than 10% for the low-dose group and 20% to 25% for the high-dose male and female rats, respectively. No significant increases in tumor incidence were observed in the rats. The tumor data are presented in Section 7.2.7. This study identifies an LOAEL of 43 mg/kg/day (31 mg/kg/day when normalized to account for a 7 day exposure per week) for an increased incidence of chronic murine pneumonia in female rats exposed to gavage doses of 1,1,2,2-tetrachloroethane for 78 weeks and an FEL of 76 mg/kg/day (55 mg/kg/day when normalized for the 7 days/week exposure).

The NCI (1978) protocol for the rats described above was also used for the B6C3F1 mice. The time weighted average doses were 0, 142, or 283 mg/kg for both male and female mice dosed

for 5 days/week. As was the case for the rats, the doses were adjusted during the study. At the low dose, the initial level was 100 mg/kg/day. The dose was increased to 150 mg/kg/day and then to 200 mg/kg/day; at 26 weeks it was lowered to 150 mg/kg/day. The high dose was initially 200 mg/kg/day. It was raised to first 300 mg/kg/day and then 400 mg/kg/day; after 26 weeks it was lowered to 300 mg/kg/day once more. The post-treatment observation period for the mice was 12 weeks.

A statistically significant association between mortality and dose was noted. There was a considerable decrease in survival after 45 weeks of exposure in the high-dose male and female mice. Acute toxic tubular nephrosis was determined to be the apparent cause of death in 33 high-dose males dying between weeks 69 and 70. There was a high incidence (95%) of pronounced abdominal distension among the high-dose animals beginning in week 60 and continuing throughout the recovery period, which was probably related to the liver tumors. The tumors could also have contributed to the early deaths among the females.

A slight decrease in body weight gain (less than 10%) was observed in the high dose male mice; no other effects on body weight gain were observed. Significant increases in the incidence of hepatocellular carcinoma were observed in the low- and high-dose male and female mice. Additional details on the tumorigenic effects of 1,1,2,2-tetrachloroethane are reported in Section 7.2.7. Increases in the incidence of nonneoplastic lesions were limited to hydronephrosis in the high-dose groups (0/20, 0/46, 16/46) and chronic inflammation in the kidneys of high-dose females (0/20, 0/46, and 5/46). This study identifies an NOAEL of 142 mg/kg for noncancer effects and a frank effect level of 283 mg/kg in mice exposed to 1,1,2,2-tetrachloroethane for 78 weeks. After applying a duration adjustment to normalize the 5-days/week exposure over a seven-day week, the NOAEL becomes 101 mg/kg/day and the LOAEL 202 mg/kg/day.

Inhalation Exposure

Schmidt et al. (1972) exposed groups of 105 male rats (strain not specified) to 0 or 13.3 mg/m^3 four hours/day for up to 325 days. Interim sacrifices of 7 animals per group were conducted on days 110 and 265 and at termination of exposure. After exposures ceased, the remaining animals were kept until they died naturally. The parameters evaluated at each sacrifice time were not consistent making it difficult to determine if there were any trends related to the duration of exposure.

At 110 days, body weight was decreased by 5% compared to the controls, a decrease that was reported as significant ($p< 0.01$). Leucocyte levels and $\beta 1$ globulins were significantly increased ($p<0.025$ and $p<0.02$ respectively) and adrenocorticotrophic hormone (ACTH) concentration in the pituitary was decreased ($p<0.001$). The change in ACTH was the only endpoint that was measured at each sacrifice point. The difference between the exposed and control animals decreased with time and was only slightly lower than controls at 325 days ($p<0.02$). At the 265 day-sacrifice, the fat content of the liver, segmented neutrophils and lymphocytes were measured in addition to ACTH. The fat content of the liver was increased ($p<0.05$) as were the segmented neutrophils ($p<0.05$). The percent lymphocytes was decreased ($p<0.01$). The only parameter measured at 235 days in addition to ACTH was γ-globulins which were slightly increased ($p<0.05$).

No histolopathological lesions were found in the lungs or heart of a monkey exposed to a time-weighted average of 1974-ppm (13,779 mg/m^3) 1,1,2,2-tetrachloroethane vapors 2 hours/day, 6 days/week for 9 months (Horiuchi et al., 1962). The monkey was reported to experience transient diarrhea and anorexia, and sporadic changes in hematocrit, red blood cell, and white blood cell counts, although these changes showed no clear dose-response trend (Horiuchi et al., 1962). Only one monkey was studied, and a control was not included.

Rabbits were exposed to 0.3, 1.5, or 15 ppm (equivalent to 2, 11, and 105 mg/m^3) 1,1,2,2,-tetrachloroethane for 3 to 4 hours daily for 7 to 11 months. The 15-ppm exposure group showed early signs (unspecified) of liver degeneration at necropsy (Navrotskiy et al., 1971).

7.2.7 Carcinogenicity

Oral Exposure

A highly significant dose-related trend in the incidence of hepatocellular carcinomas was observed in groups of 50 male and female B6C3F1 mice administered technical-grade 1,1,2,2-tetrachloroethane in corn oil by gavage (NCI, 1978). Full details of this study can be found in Section 7.2.6. The-5 days/week, time-weighted average daily doses were 142 or 283 mg/kg/day for 78 weeks followed by a 12-week recovery period. The doses were normalized by NCI for a 5-days/week exposure rather than for a 7 day exposure. When normalized for a 7-day per week exposure these doses are equivalent to doses of 101 or 202 mg/kg/day. Effects in the treatment groups compared to the control are summarized in Table 7-3. The increased hepatocellular incidences were statistically significant at both dose levels compared with vehicle controls. Tumors also appeared earlier in mice administered the higher dose than those given the low-dose. The first tumor in the high does male mice occurred on week 52 while that in the low dose occurred on week 84. For the female mice the first high-dose tumor occurred at 53 weeks and the first low-dose tumor at 58 weeks. Between week 69 and 70 of the study 33 of the high dose males died; all but one had tumors. Between week 52 and week 90, 34 of the female mice died. Tumors were considered to be the cause for most on the premature animal deaths.

The hepatocellular tumors in the mice were varied in appearance. Some were clusters of well-differentiated cells with a uniform arrangement of cords. Others were composed of anaplastic cells with large hyperchromic nuclei, vacuolated pale cytoplasm, many with eosinophilic inclusions. Mitotic figures were often present. Some tumors had a combined morphology where anaplastic areas were identified within well differentiated tumors.

There was no significant increase in the incidence of any type of neoplastic or preneoplastic lesions in groups of 50 male or 50 female Osborne-Mendel rats similarly administered technical-grade 1,1,2,2-tetrachloroethane in corn oil by gavage (NCI, 1978). The normalized time-weighted average doses (for 5 days/week) were 44 or 77 mg/kg/day (males) and 31 or 54 mg/kg/day (females) for 78 weeks. The control groups (untreated and vehicle) each consisted of 20 animals/sex. There were two high-dose males with hepatocellular carcinomas and one with a hepatic preneoplastic nodule, but these results were not significant. None-the-less, NCI considered the results in male rats to be equivocal because hepatocellular carcinomas are rare tumors in Osborne-Mendel rats. One papilloma and one carcinoma of the stomach were also observed in the high-dose males.

Table 7-3 Summary of Liver Tumor Incidence, 78-Week Study in Mice

	Normalized Time Weighted Average Doses Dose[1] (mg/kg/day)	Liver Tumor Incidence
Male	0 (untreated)	2/18[2]
	0 (vehicle)	1/18
	101	13/50[3]
	202	44/49[3]
Female	0 (untreated)	½0[2]
	0 (vehicle)	0/20
	101	30/48[3]
	202	43/47[3]

Source: NCI (1978)

1. Doses were derived from the data in the NCI report (Table 2) and duration adjusted to accommodate the 5 out of 7 day weekly exposure. The calculation of the high dose exposure using the formula given by NTP with Table 2 and data in exposures and durations indicated that the high dose exposure before 5-days/week normalization was 283.3 mg/kg/day rather than 284 mg/kg/day as indicated in Table 6 of the NCI report or 282 mg/kg/day as indicated in the NCI study summary.

2. The data on the numbers of animals with tumors were obtained from Tables 6 and 7 of the NCI report and differ for the male and female untreated control group from the values given in the NCI study summary. Any animals that died prior to the appearance of the first tumor are not included in the statistical evaluation.

3. Significantly increased compared to control, $p < 0.05$.

In an initiation/promotion assay, groups of 10 male Osborne-Mendel rats were administered a gavage dose of 100 mg/kg body weight in corn oil followed by dietary exposure to phenobarbital for 7 weeks and were sacrificed a week later. 1,1,2,2-Tetrachloroethane caused a significant ($p < 0.05$) increase in the formation of γ-glutamyl transpeptidase-positive (GGT+) foci in the liver (a preneoplastic indicator) when compared to the corn oil control but not the phenobarbital control. When 1,1,2,2-tetrachloroethane was administered for 7 weeks after diethylnitrosamine initiation, the number of GGT+ foci (4.4 ±0.8) were greater than those that formed when the tetrachloroethane was administered as the initiator (1.2 ±0.4). Accordingly, the data suggest that 1,1,2,2-tetrachloroethane may act as a weak initiator of GGT+ foci and as a stronger promoter for foci initiated by a different chemical (Story et al., 1986).

Other Routes of Exposure

The development of pulmonary tumors in groups of 20 male Strain A mice following intraperitoneal administration of 80, 200, or 400 mg/kg-day of 1,1,2,2-tetrachloroethane in tricaprylin three times per week for up to 8 weeks was studied by Theiss et al. (1977). Tricaprylin served as the vehicle control and urethane as a positive control. The number of injections was as follows: 5 injections for the 80-mg/kg/day group, 18 injections for the 200-mg/kg/day group, and 16 injections for the 400-mg/kg/day group. Preliminary testing identified the highest dose as a maximally tolerated dose. The animals were sacrificed at 24 weeks and the

number of surface lung-adenomas was evaluated. A marginally significant increase (p=0.059) in pulmonary tumors in mice was reported at 400 mg/kg-day, but not at lower doses. Mortality, however, was high in this study. Only 5 of 20 mice survived to the end of the study in the 400-mg/kg dose group. Animal deaths also occurred in the low-dose (10/20) and mid-dose (5/20) groups.

Colacci et al. (1993) used BALB/c 3T3 cells that had been transformed *in vitro* through exposure to 1,1,2,2-tetrachloroethane (see Section 7.3.1) and injected them subcutaneously into groups of 5 athymic Charles River CD1/BR mice. The BALB/c 3T3 cell line is derived from the mouse embryo and is fibroblast-like in its properties. It is used in tumorigenicity and viral transformation assays (HyperCLDB, 2004). Two concentrations were tested. In the absence of S9, a concentration of 1000 μg/mL was necessary to achieve transformation while in the presence of S9, a concentration of 500 μg/mL was sufficient. Separate pools of cells were prepared for the transformation assay, two without S9 (pools A and B) and two with S9 (pools C and D).

Transformed cells were injected subcutaneously at concentrations of 1×10^6 or 5×10^6 transformed cells. The mice were observed weekly for tumor formation for up to 4 months. All animals injected with the higher concentration of transformed cells (19/19) and 8 of 9 animals receiving the lower concentration developed tumors within 3 months. At 3 months there were no tumors in the controls injected with untreated BALB/c 3T3 cells; after 4 months there were tumors in 3 of 10 controls.

In a second phase of this same study, transformed cells (5×10^5) were injected intravenously into groups of 8 or 9 mice. The control group received untreated BALB/c 3T3 cells. After 8 weeks the animals were sacrificed; 25% of the controls had pulmonary nodules while the incidence among the 4 treated groups ranged from 55.5% to 88.9%. Table 7-4 summarizes the tumors and metastasises observed in each group. Cells transformed with 1,1,2,2-tetrachloroethane in the presence and absence of S9 had increased tumors and metastasises. The authors concluded that 1,1,2,2-tetrachloroethane was able to transform weakly tumorigenic BALB/c 3T3 cells to fully tumorigenic and invasive cells and that both genotoxic and nongenotoxic events may have been involved with this change (Colacci et al., 1993).

Table 7-4 Experimental Metastasises in Athymic Mice Injected with Transformed BALB/c 3T3 Cells

Test Material	Animals with Tumors	Range of Observed Metastasises per Mouse	Median for Metastasises
BALB/c 3T3 cells	4/16	0 - 10	0
1,1,2,2-Tetrachloroethane; 1000 μg/mL - no S9 - Pool A	7/8	1 - 17	8
1,1,2,2-Tetrachloroethane; 1000 μg/mL - no S9 - Pool B	8/9	0 - 7	2
1,1,2,2-Tetrachloroethane; 500 μg/mL with S9 - Pool C	7/8	0 - 8	5
1,1,2,2-Tetrachloroethane; 500 μg/mL with S9 - Pool D	5/9	0 - 56	1

Adapted from Colacci et al. (1993)
Note: There seems to be an error in the Table in the published paper from which these data are abstracted. The transformed cell pools with S9 are identified as Pool A and B. The methodology section clearly identifies these as pools C and D. Accordingly they are identified as such in this table.

7.3 Other Key Data

7.3.1 Mutagenicity and Genotoxicity

1,1,2,2-Tetrachloroethane has shown mixed results in assays for gene mutation, chromosomal aberration, DNA repair and synthesis, and cell transformation.

Results of selected *in vitro* studies are summarized in Table 7-5. Predominantly negative results have been reported for the induction of gene mutation in prokaryotic systems with or without metabolic activation, whereas both positive and negative results have been observed for gene conversions in yeast and fungi. 1,1,2,2-Tetrachloroethane induced sister chromatid exchange but not chromosomal aberrations, DNA repair, or unscheduled DNA synthesis in mammalian cells *in vitro*. *In vivo* micronucleus results in mice were positive in both males and females.

Studies using *Salmonella typhimurium* strains that detect base pair (TA100 and TA1535) and frame shift (TA98, TA1537, and TA1538) mutations were negative in almost all assays (Haworth et al., 1983; Milman et al., 1988; Nestmann et al., 1980) using concentrations that range from those with no associated cytotoxicity to those high enough to cause cytotoxicity. Exceptions to the negative results are the studies by Mersch-Sundermann (1989a) and Brem et al. (1974). Mersch-Sundermann (1989a) obtained positive results in TA97 and TA98 in the absence of microsomal activation; Brem et al. (1974) reported positive results in TA1530 and TA1535 in the presence of microsomal activation.

Inhalation exposure to 1,1,2,2-tetrachloroethane at 349 mg/m^3 (51 ppm) for 5 days did not induce dominant lethal mutations in rats, and results for chromosomal aberrations in rat bone marrow cells were equivocal. This concentration did not induce cytotoxicity (McGregor, 1980). 1,1,2,2-Tetrachloroethane did not induce unscheduled DNA synthesis in hepatocytes of mice exposed to doses of 200, 500, or 600 mg/kg body weight by gavage. Results for the induction of S-phase synthesis (an indicator of chemically induced cell proliferation) were negative in hepatocytes from male mice dosed with 200 or 600 mg/kg and were equivocal in female mice dosed with 500 mg/kg (Mirsalis et al., 1989).

Table 7-5 Genotoxicity of 1,1,2,2-Tetrachloroethane *In Vitro*

Species (test system)	End-point	With activation	Without activation	Reference
Saccharomyces cerevisiae D7	Mitotic gene conversion	nt	+	Callen et al., 1980
	Recombination	nt	+	
Saccharomyces cerevisiae D7	Gene conversion and reversion	nt	–	Nestmann and Lee, 1983
XV185-14C		nt	–	
Salmonella typhimurium	Reverse mutations			Brem et al., 1974
TA1530, TA1535		nt	+	
TA1538		nt	–	
Salmonella typhimurium TA 98, TA 100, TA1535, TA 1537, TA 1538	Reverse mutations	–	–	Nestmann et al., 1980
Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537	Reverse mutations	–	–	Milman et al., 1988
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Reverse mutations	–	–	Haworth et al., 1983
Salmonella typhimurium TA100	Reverse mutations	–	–	Warner et al., 1988
Salmonella typhimurium	Reverse mutations			Mersch-Sundemann et al., 1989a
TA 97, TA 98		+	–	
TA 100, TA 102		–	–	
Salmonella typhimurium	Forward mutations	–	–	Roldan-Arjona et al,

Species (test system)	End-point	With activation	Without activation	Reference
BA13/BAL13				1991
Escherichia coli (polymerase deficient pol A+/pol A–)	DNA damage	nt	+	Brem et al., 1974
Escherichia coli PQ37	Gene mutation	–	–	Mersch-Sundemann et al., 1989b
Escherichia coli	Induction of prophage lambda	+	–	DeMarini and Brooks, 1992
Aspergillus nidulans	Mitotic malsegregation	nt	+	Crebelli et al., 1988
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Galloway et al., 1987
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Galloway et al., 1987
BALB/c3T3 cells (mouse)	Sister chromatid exchange	+	+	Colacci et al., 1992
Mouse hepatocytes	DNA growth, repair, or synthesis	nt	–	Williams, 1983
Mouse hepatocytes	DNA repair	nt	–	Milman et al., 1988
Rat hepatocytes	DNA growth, repair, or synthesis	nt	–	Williams, 1983
Rat hepatocytes	DNA repair	nt	–	Milman et al., 1988
Human embryonic intestinal cells	Unscheduled DNA synthesis	–	–	McGregor, 1980

nt = not tested

Radio label from 1,1,2,2-Tetrachloroethane has been reported to bind to or become incorporated into cellular macromolecules (DNA, RNA, and/or proteins) from several organs in rodents, following *in vivo* exposure (Mitoma et al., 1985; Colacci et al., 1987; Eriksson and Brittebo, 1991). Results for cell transformation in mammalian cells have been mixed, with positive results (Colacci et al., 1992, 1993) and negative results (Little, 1983; Tu et al., 1985; Milman et al., 1988) reported. 1,1,2,2-Tetrachloroethane did not induce sex-linked recessive lethal mutations or mitotic recombination in *Drosophila melanogaster* in three studies (McGregor, 1980; Woodruff et al., 1985; Vogel and Nivard, 1993).

An *in vivo* mouse micronucleus test was conducted for NTP (2004) using dietary levels of 1,1,2,2-tetrachloroethane equivalent to those employed in the subchronic study. Groups of 5 male

and 5 female mice were used for each of the five dose groups. There was a dose-related increase in the number of micronucleated normochromatic erythrocytes per thousand cells and a significant difference from controls for the males and females. Accordingly the test results were considered positive.

Colacci et al. (1992) concluded that 1,1,2,2-tetrachloroethane was able to initiate genetic changes in an *in vitro* two-stage BALB/c 3T3 cell culture. The cells were treated with subeffective or transforming concentrations of 1,1,2,2-tetrachloroethane (31.25 to 500 μg/mL) in the presence of an S9 activating system and in the absence or presence of tetradecanoylphorbol acetate (TPA), a promoter. In the level I analysis, the number of transformed foci were double those of the controls for concentrations of 62.5 μg/mL and above in the absence of TPA, but lower than the benzo(a)pyrene used as a positive control. In the presence of TPA, the difference between the 1,1,2,2-tetrachloroethane and controls was increased and the number of transformed foci were similar to the benzo(a)pyrene positive control. The level II analysis examined the potential for amplification of the response through a replating of the transformed cells allowing for additional rounds of cell division. In the level II analysis, all 1,1,2,2-tetrachloroethane concentrations tested showed statistically significant increases in the mean number of transformations per plate in both the presence and absence of TPA.

Colacci et al (1992) also examined the ability of 1,1,2,2-tetrachloroethane to induce chromosomal aberrations in BALB/c 3T3 cells using 500 μg/mL in the absence of S9 and 1000 μg/mL in the presence of S9. DMSO (1%) was the solvent control and 3-methylcholanthrene and benzo(a)pyrene were the positive controls. Responses for the 1,1,2,2-tetrachloroethane were comparable to the positive controls in both cases.

The *in vitro* studies of mutagenicity suggest that 1,1,2,2-tetrachloroethane either does not alter DNA structure or, is at best, a weak mutagen. The mouse micronucleus results in conjunction with the *in vitro* tests for sister chromatid exchange indicate that 1,1,2,2-tetrachloroethane can have clastogenic effects.

7.3.2 Immunotoxicity

Rabbits exposed to 1.5 ppm of 1,1,2,2-tetrachloroethane vapor 3 hours/day for 8 months and then immunized with a typhoid vaccine showed a decrease in antibody titers and an increase in the electrophoretic mobility of the specific antibodies when compared to rabbits that were not exposed to 1,1,2,2-tetrachloroethane (Shmuter, 1977).

The elevated incidence of chronic murine pneumonia among treated female rats (40%, 68%, and 76% for control, low dose, and high dose animals, respectively) in the NCI (1978) cancer study, along with the elevated white cell counts (90% higher than controls) seen by Schmidt et al. (1972) after 110 days of exposure to 13.3 mg/m^3, are suggestive of possible effects on the immune system. In the NTP studies (2004), significantly decreased relative thymus weights were observed in female rats at the highest dose, but not in male rats or male or female mice.

7.3.3 Physiological or Mechanistic Studies

7.3.3.1 Noncancer Effects

Impaired Heme Synthesis. There are limited mechanistic data that relate to the effects of 1,1,2,2-tetrachloroethane on heme synthesis. The data come from a study conducted to determine if heme effects may have contributed to decreased levels of CYP P450 enzymes. Paolini et al. (1992) treated groups of 6 male and female Swiss albino mice with doses of 0, 300, or 600 mg/kg 1,1,2,2-tetrachloroethane in corn oil. The animals were fasted for 16 hours before dosing, and sacrificed 24 hours after exposure. The livers were removed and analyzed for the activity of γ-aminolevulinic acid (ALA) synthetase (a critical enzyme for heme synthesis) and heme oxygenase (a critical enzyme for heme degradation). The activity of ALA synthetase was decreased by 35% at the lower dose and by almost 60% at the higher dose. The lower dose had no significant effect on heme oxygenase activity, but activity was increased by about 35% at the higher dose. At the 600-mg/kg dose, the total heme content of the liver was reduced by about 33%. The authors concluded that the decrease in heme level in the liver was, in part, responsible for a decrease in the levels of CYP 450 (58-73%) observed during other portions of this same study (see Section 6.3).

Decreased hemoglobin or hematocrit levels were identified in several short term studies of 1,1,2,2-tetrachloroethane (NTP, 2004; Minot and Smith, 1921). The study of hepatic heme synthesis by Paolini et al. (1992) did not examine the impact of 1,1,2,2-tetrachloroethane on hematopoiesis. Accordingly the results are not directly applicable to the observation of decreased red-blood cell parameters measured in the whole animal studies.

Lipid Peroxidation. Paolini et al. (1992) used electron spin resonance spectroscopy in conjunction with a spin trapping agent to determine if free radicals were formed in the liver of 5 male mice exposed to a single intraperitoneal dose of 600 mg/kg 1,1,2,2-tetrachloroethane and sacrificed 24 hours later. The observed signal was interpreted as being evidence for the presence of a $CHCl_2CHCl$ free radical. Mice treated with 180 mg/kg phenyl-T-butylnitrone served as a positive control. In addition, lipid extracts from the treated mouse livers gave spectroscopic evidence that conjugated dienes and hydroperoxides from lipid peroxidation of polyunsaturated fatty acids were present in the endoplasmic reticulum.

Dolichols are long chain polyisoprenoid units found in mammalian tissues in their free form or esterified to phosphate or fatty acids. They are located in the endoplasmic reticulum and Golgi apparatus and function in the glycosylation of glycoproteins and in the process of membrane translocation of activated glycosyl units. Cottalasso et al. (1998) hypothesized that the dolichols would be substrates for attack by free radicals produced in the metabolism of 1,1,2,2-tetrachloroethane and that their inactivation would impact the glycoslylation of secretory proteins, particularly the very low density lipoproteins. Accordingly, this study investigated whether 1,1,2,2-tetrachloroethane affects glycosylation mechanisms by changing the dolichol levels and distribution in rat liver microsomes and Golgi apparatus. Analysis for free-radical modified or peroxidized dolichols was not a component of the protocol.

Male Sprague-Dawley rats received a single dose of 0 or 574 mg/kg 1,1,2,2-tetrachloroethane in mineral oil and groups of 5 animals were sacrificed 5, 15, 30, and 60 minutes later. Samples of the endoplasmic reticulum (microsomes) and Golgi apparatus (three fractions) were collected from homogenized liver samples and analyzed for their total dolichol, free dolichol and dolichol phosphate concentrations. Total dolichol levels decreased in all organelle samples at 60 minutes after dosing. The decreases were greatest in microsomes and the secretory fraction of the Golgi apparatus (a decrease of 56% and 57%, respectively). There was a continual decrease in both free dolichol and dolichol phosphate in microsomes at all time points. Decreases were significant in the 15-minute and later samples. If this phenomenon were linked to the assembly of very low density lipoproteins (VLDLs), it could help to explain the hypocholesteremic effects of 1,1,2,2-tetrachloroethane in rats and mice. VLDLs are responsible for the systemic transport of endogenous cholesterol from the liver to other tissues.

7.3.3.2 Cancer Effects

As part of a study to determine if BALB/c 3T3 cells exposed to 1,1,2,2-tetrachloroethane were capable of inducing tumor formation in treated mice, Colacci et al. (1993) examined the invasive properties of the transformed cells using a reconstituted basement membrane matrigel derived from an Engelbrecht-Holm-Swarm tumor. In order to become invasive and metastasize, most tumor types must be able to cross basement membranes. Very few control BALB/c 3T3 cells were able to cross the membrane matrigel. However, a large number of the transformed cells were able to penetrate the membrane barrier. The transformed cells were also able to display invasive growth in a three dimensional gel formed from the reconstituted membrane.

7.3.3.3 Interactions with Other Chemicals

In an *in vitro* study of the synergistic effects of 15 xenobiotic chemicals with 2,4-D, 1,1,2,2-tetrachloroethane was one of the materials evaluated. The toxicity of the 2,4-D was enhanced when a no effect concentration (NOEC) of 1,1,2,2,-tetrachloroethane was combined with it. In one study, Jacobi et al. (1995) found that there was a decrease in the concentration of 2,4-D that caused a 20% growth inhibition in human fibroblasts when it was combined with the no effect concentration of 1,1,2,2-tetrachloroethane. In a second study, the binary combination of an NOEC concentration of 1,1,2,2,-tetrachloroethane with 2,4-D decreased DNA synthesis by 48% in cultured fibroblasts compared to 2,4-D alone (Jacobi et al., 1996). The authors hypothesize that lipophilic substances like 1,1,2,2,-tetrachloroethane are synergistic in combination with a hydrophylic compound like 2,4-D at much lower concentrations than hydrophilic chemicals because of their capacity to damage membranes and enhance cellular uptake of both compounds.

7.3.4 Structure-Activity Relationship

1,1,2,2-Tetrachloroethane is one of a series of chlorinated ethanes that have been studied for their toxicity. Most of them (1,1-dichloroethane, 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,1,2-tetrachloroethane, and hexachloroethane), like 1,1,2,2-tetrachloroethane, are associated with tumor development in at least one species (U.S. EPA, 1986d,e,f, 1987, 1989a,b). All of them have caused liver precancerous nodules, adenomas, and/or carcinomas in mice; 1,1-dichloroethane and 1,2-dichloroethane also caused mammary tumors and hemangiosarcomas in female rats. Hepatic toxicity, and in some cases, renal toxicity, are characteristics of many of these related chlorinated ethanes and were often identified as the critical effects that provided the basis for the their IRIS RfD values. A number of these chlorinated alkanes and alkenes also share common metabolites (i.e., DCA and TCA). DCA has been demonstrated to cause tumors in both rats and mice (mice are more sensitive) and TCA has caused tumors in mice.

7.4 Hazard Characterization

7.4.1 Synthesis and Evaluation of Major Noncancer Effects

Human exposure data for 1,1,2,2-tetrachloroethane consist of one experimental inhalation study, case reports of suicidal or accidental ingestion, and occupational studies. Many of the occupational reports are dated and complicated by uncertainties in levels of exposure to 1,1,2,2-tetrachloroethane and other chemicals. The human case studies suffer from similar deficiencies in the quantification of exposure and the reporting of effects. Autopsy findings in suicide cases included congestion and edema in the lungs, mucosal congestion of the esophagus and upper stomach, and epicardial- and endocardial- anoxic hemorrhaging (ATSDR, 2006).

Respiratory, mucosal, and eye irritation, nausea, vomiting, and dizziness were reported by humans volunteers exposed to 1,1,2,2-tetrachloroethane vapors under controlled chamber conditions (Lehmann and Schmidt-Kehl, 1936). In a few occupational situations, death resulted from inhalation exposure to 1,1,2,2-tetrachloroethane. The subjects who died had fatty degeneration and necrosis of the liver as well as effects on the kidney, spleen, and heart (Coyer, 1944; Willcox et al., 1915). Effects from non-lethal occupational exposures included gastric distress (including pain, nausea and vomiting), loss of appetite, and loss of body weight (Jeney et al., 1957; Lobo-Mendonca 1963; Minot and Smith 1921). There also were increases in the number of white blood cells, jaundice, an enlarged liver, cirrhosis, and neurological symptoms such as headache, tremors, dizziness, numbness, and drowsiness.

There have been a variety of animal studies in rats and mice using both the inhalation and oral exposure routes. Some of the early work does not follow current standards for good laboratory practices. Several of these studies were reported in German and the study descriptions were obtained from translation of the German papers or from secondary sources (ATSDR, 2006; Cal EPA, 2003). Studies by the NTP (2004) provide a detailed evaluation of the short-term and subchronic oral toxicity of 1,1,2,2-tetrachloroethane and confirm many of the early observations.

In rats and mice exposed orally, the liver appears to be the principal target organ. Effects on the liver were seen in subchronic studies and included: histopathological alterations consisting

of basophilic, eosinophilic, mixed cell, and/or clear cell foci of cellular alterations; hepatocyte necrosis; mitotic alterations in hepatocytes; liver pigmentation; bile duct hyperplasia; hepatocyte hypertrophy; cytoplasmic vacuolization and increased liver weight (NTP, 2004; Schmidt et al., 1980a). Biomarkers of the damage to the liver include elevated serum levels of ALT and/or SDH (NTP, 2004). Data on hepatic effects after short-term exposures (Dow, 1988; NTP, 1996, 2004: Schmidt et al., 1980a) are limited, but are consistent with the observations following subchronic oral exposure. Rats seem to exhibit these effects at lower doses than mice.

In addition to effects on the liver, rats exposed to 1,1,2,2-tetrachloroethane exhibited decreased leucocyte counts and changes in red blood cell parameters indicative of a microcytic anemia (NTP, 2004). Effects on the kidney were suggested by increased relative kidney weights in rats and mice in short-term and/or subchronic studies (NTP, 1996, 2004) and acute tubular nephrosis in mice after chronic exposures (NCI, 1978). Decreased relative thymus weights in female rats at high doses (NTP, 2004) suggested the possibility of immunological effects. In mice, there were no hematological effects and kidney weights were decreased at doses above 2300 ppm in males (NTP, 2004). Significant non-neoplastic effects in the NCI (1978) studies were limited to the kidney in mice.

Death was a frequent consequence of high-dose exposure of animals to 1,1,2,2-tetrachloroethane. In such instances, the animals exhibited clear clinical signs of distress. Weight gain was impeded and, in some cases, weight loss was observed (NTP, 2004). In short-term high dose studies, the distressed animals became emaciated, had a poor quality coat and some showed patches of hair loss (NTP, 1996, 2004). Neurological effects occurred primarily after inhalation exposures and included decreased motor activity, loss of reflexes, ataxia, prostration, and narcosis (Horvath and Frantek, 1973; Lazarew, 1929; Price et al., 1978).

Information on the reproductive effects of 1,1,2,2-tetrachloroethane is limited. There is a single one-generation study that does not follow a standard methodology and examined a small number of animals (5 females and 7 exposed males) exposed via inhalation to one dose (13 mg/m^3). There were no statistically-significant differences in the percentage of females having offspring (77.1% in controls vs. 62.9% in exposed animals), number of pups per litter, average birth weight, gestation length, sex ratio, offspring mortality at postnatal days 1, 2, 7, 14, 21, and 84, or average weight on postnatal day 84. No macroscopic malformations were observed (Schmidt et al., 1972).

There was a decrease in sperm motility in the NTP study (2004) following an oral 14-week exposure at concentrations of 27 mg/kg/day and greater. At higher doses ($\geq$149 mg/kg/day) the left epididymus weight was decreased and the weight of the left cauda epididymus was increased. Similar effects were seen in mice, although, at higher doses (1525 mg/kg/day).

Range-finding studies for developmental toxicity conducted for NTP (1991a, b) found that 1,1,2,2-tetrachloroethane was toxic to the dams and pups of Sprague-Dawley rats and CD-1 Swiss mice. Rats were more sensitive than mice. The NOAEL in the rats for both maternal toxicity and associated fetal toxicity was 34 mg/kg/day with an LOAEL of 98 mg/kg/day for decreased maternal weight gain and decreased fetal body weight (NTP, 1991a). In mice the NOAEL was 987 mg/kg/day and the LOAEL was 2120 mg/kg/day for mortality and fetal resorptions (NTP,

1991b). These studies did not include evaluations of the pups for visceral or skeletal abnormalities.

7.4.2 Synthesis and Evaluation of Carcinogenic Effects

There is only one study that examined the relationship between 1,1,2,2-tetrachloroethane and cancer in humans. An epidemiological study on the relationship between occupational exposure of soldiers to 1,1,2,2-tetrachloroethane during World War II and subsequent development of tumors over the 30+ year period after the exposure was carried out by Norman et al. (1981). It showed a weak correlation between inhalation exposure to 1,1,2,2-tetrachloroethane and development of genital tumors and leukemia. The soldiers were exposed to other chemicals in addition to 1,1,2,2-tetrachloroethane during their military service and there were no post-military records on employment, so no definite conclusions could be drawn from the study.

The ability of 1,1,2,2-tetrachloroethane to induce cancer in animals was tested in an oral gavage study and an intraperitoneal injection study. NCI (1978) looked for tumors in B6C3F1 mice and Osborne-Mendel rats following oral gavage administration of 1,1,2,2-tetrachloroethane in corn oil for 78 weeks, followed by 32 weeks of observation for the rats and 12 weeks for the mice. A significant increase in the incidence of hepatocellular carcinomas in B6C3F1 mice was reported. Rats had no significant increase in tumor incidence, but there were two males with hepatocellular carcinomas and one with a preneoplastic hepatic nodule in the high-dose group. According to (NCI, 1978), these are rare tumors for Osborne-Mendel rats. The 7-days/week, normalized time-weighted average doses were 44 and 78 mg/kg/day for male rats, 31 and 55 mg/kg/day for female rats, and 101 and 202 mg/kg/day for both male and female mice.

Haseman (1984) reported that an increased incidence of hepatocellular carcinomas in B6C3F1 mice is not unusual because many chemicals increase the spontaneous rate of such tumors in these mice, but do not produce them in other sites in mice or in rats. Since this species of mouse has a high rate of spontaneous incidence of liver tumors, the data may not be indicative of carcinogenic risk in humans (ATSDR, 1996). Osborne-Mendel rats have been shown to have a low incidence of liver tumors when treated with carbon tetrachloride as a positive control (NCI, 1978). This indicated to the study authors that rats may not be sensitive enough to detect tumors caused by 1,1,2,2-tetrachloroethane.

The second study that resulted in carcinogenic effects in animals focused on the development of pulmonary tumors in male Strain A mice following intraperitoneal administration of 80 to 400 mg/kg-day of 1,1,2,2-tetrachloroethane for 2 to 6 weeks (Theiss et al., 1977). A marginally significant increase in pulmonary tumors in mice was reported at 400 mg/kg/day, but not at lower doses (Theiss et al., 1977). The results from this study were confounded by a small number of animals in each dose group (20 males) and high mortality during the study.

7.4.3 Mode of Action and Implications in Cancer Assessment

Story et al. (1986) examined the effect of 1,1,2,2-tetrachloroethane in a rat liver GGT+ foci assay for its initiating and promoting potential in male rats. The results indicated that 1,1,2,2-tetrachloroethane was a weak initiator and a somewhat stronger tumor promoter. Colacci et al. (1992, 1993) confirmed tumor initiation by 1,1,2,2-tetrachloroethane using an *in vitro* two-stage BALB/c 3T3 cell transformation assay combined with an *in vivo* phase which demonstrated the tumorigenic impact of the injected transformed cells in athymic CD1/BR mice. The results of these studies suggest that 1,1,2,2-tetrachloroethane can act as a complete carcinogen, although it seems to have a stronger influence as a promoter of tumors initiated by other factors.

7.4.4 Weight of Evidence Evaluation for Carcinogenicity

Evidence of carcinogenicity was seen in male and female mice in a study conducted by the NCI (1978). The evidence for tumorigenicity in male rats in the same study was equivocal. Mechanistic studies of initiation and promotion using the production of GGT + foci in the livers of male Osborne-Mendel rats and an *in vitro* two-stage BALB/c3T3 cell transformation assay in athymic CD1/BR mice indicate that 1,1,2,2-tetrachloroethane is a weak initiator that also can function as a tumor promoter (see Section 7.4.3 above). Studies of gene mutation in *Salmonella* have mostly been negative, but a few positive results were observed. Results with *Saccharomyces cerevisiae* and *Escherichia coli* were also mixed. The mouse micronucleus assay (NTP, 2004) was positive for males and females as were *in vitro* assays for sister chromatid exchange (Galloway et al., 1987; Colacci et al., 1992).

Following the U.S. EPA (2005a) guidelines for carcinogen risk assessment, 1,2,2,2-tetrachloroethane can be classified as *likely to be carcinogenic to humans*. Information from animal studies is adequate, but supporting data from human studies are lacking. The IRIS classification for 1,1,2,2-tetrachloroethane (U.S. EPA, 1986e) under the U.S. EPA (1986c) guidelines for cancer assessment is Group C. However, the IRIS assessment is presently being updated through the IRIS program. The International Agency for Research on Cancer (IARC, 1999) classifies 1,1,2,2-tetrachloroethane in Group 3. The data in humans are inadequate and there is limited evidence for carcinogenicity in experimental animals. The Agency IRIS assessment for DCA, the principal 1,1,2,2-tetrachloroethane metabolite classified DCA as *likely to be carcinogenic to humans* (U.S. EPA, 2005a).

7.4.5 Potentially Sensitive Populations

No populations with unusual susceptibility to the health effects of 1,1,2,2-tetrachloroethane could be identified based on the available literature. Factors that could increase individual susceptibility include chronic alcohol consumption, diabetes, and fasting (Soucek and Gut, 1992). Individuals with pre-existing liver and kidney damage would likely be sensitive to 1,1,2,2-tetrachloroethane exposure. Low intake of antioxidant nutrients (Vitamin E, Vitamin C, and selenium) would be a predisposing factor for liver damage if free radicals play a role in the hepatic toxicity of 1,1,2,2-tetrachloroethane.

No data were available that could be used to evaluate sensitivity to children. Fetotoxicity observed during pregnancy appeared to be a consequence of maternal toxicity (NTP, 1991a,b). In the NTP studies (2004) , males appeared to demonstrate hepatic toxicity at lower doses than those affecting females.

Dichloroacetic acid (DCA) is the principal metabolite of 1,1,2,2-tetrachloroethane and also causes hepatic toxicity and liver tumors. DCA is a disinfection by-product that is often present in disinfected potable water. If continuous exposure to DCA in disinfected water inhibited GSTZ, it could increase the toxicity of the 1,1,2,2-tetrachloroethane.

Populations differ in their ability to convert DCA to oxalic acid. Five separate isozymes of the rate controlling enzyme (GSTZ) with differing catalytic capabilities have been identified (e.g., GSTZ1a-1a, GSTZ1b-1b, GSTZ1c-1c, GSTZ1d-1d, and GSTZ1e-1e) (U.S. EPA, 2003b). Differences in GST zeta activity could render some populations more sensitive to 1,1,2,2-tetrachloroethane than others. However, it will be necessary to have a more complete understanding of the mode of action for DCA and 1,1,2,2-tetrachloroethane hepatic toxicity in order to predict how differing GST isozymes might influence sensitivity.

8.0 DOSE-RESPONSE ASSESSMENT

8.1 Dose-Response for Noncancer Effects

The derivation of the reference dose (RfD) for 1,1,2,2-tetrachloroethane is described below. The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Table 8-1 summarizes the available dose-response data for oral subchronic and chronic animal studies of 1,1,2,2-tetrachloroethane. The available data indicate that the liver seems to be the principal target organ and rats are more susceptible to the noncancer effects of 1,1,2,2-tetrachloroethane than mice after oral exposures (NCI, 1978; NTP, 2004). The NTP subchronic study (2004) provides the most complete data set for noncancer effects and is the study that identified the lowest LOAEL. Accordingly, this study was selected for use in derivation of the RfD. The NCI (1978) study is an inadequate basis for the development of an RfD because it did not examine a full range of noncancer endpoints and lacked an NOAEL. The LOAELs were the same or greater than the LOAELs in the NTP study (2004) .

Table 8-1 NOAEL/LOAEL Data for Oral Subchronic and Chronic Studies of 1,1,2,2 - Tetrachloroethane

Species	Study Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Critical Effect(s)	Reference
Rats	14 weeks	20 (M, F)	40 (M, F)	Hepatocyte cytoplasmic vacuolization, Increases in SDH, increased relative liver weight, decreased hemoglobin (males), decreased hematocrit (females), decreased sperm motility.	NTP, 2004
Mice	14 weeks	100 (M) 80 (F)	200 (M) 160 (F)	Hepatocyte hypertrophy, increased relative liver weight	NTP, 2004
Rats	6 weeks	100 (M) 56 (F)	178 (M) 100 (F)	Decreased body weight gain;	NCI, 1978
Mice	6 weeks	316	None	Decreased body weight gain	NCI, 1978
Rats	78 weeks	None	31 (M)	Increased incidence of chronic murine pneumonia	NCI, 1978
Mice	78 weeks	None	101 (M/F)	Liver tumors	NCI, 1978

In the NTP study (2004), groups of male and female F344 rats (10/sex) were fed diets containing microencapsulated 1,1,2,2-tetrachloroethane for 14 weeks at concentrations of 0, 268, 589, 1180, 2300, and 4600 ppm. One control group was untreated and a second received food containing the starch microcapsules. Doses were 0, 20, 40, 80, 170, or 320 mg/kg/day for the males and females. Statically significant decreases in body weight gain were observed in the

males from the two highest dose groups and the females from the three highest dose groups (≥1,180 ppm for females and ≥2,300 ppm in males). Animals in the highest dose group lost weight across the duration of the study, but all animals survived. Doses of 2300 and 4600 ppm exceeded the maximum tolerated dose based on changes in body weight.

The blood samples taken on days 5 and 21 had a variety of statistically significant changes in various red blood cell and other hematological parameters, especially at doses ≥1800 ppm. At the end of the study, dose groups exposed to concentrations ≥589 ppm had hematological changes indicative of a microcytic anemia. Some groups showed decreases in platelet counts early in the study (≥1800 ppm for males and ≥598 ppm for females). However, by the end of the study, platelet counts were significantly decreased only in the ≥2300-ppm dose groups. Decreased leucocyte counts were seen in these same dose groups.

A number of significant changes were observed in serum biochemical parameters during the study; most were dose-related. ALT and/or SDH levels were increased in males at doses ≥268 ppm and in females at doses ≥1800 ppm (in most cases increases were significant). Significant increases in bile acids, alkaline phosphatase, and 5'nucleotidase were indicative of cholestasis (obstructed outflow of bile from the liver) at concentrations ≥2300 ppm. Significant dose-related hypocholesterolemia was present in male and female rats receiving concentrations of ≥589 ppm during the early stages of exposure; however, by the end of 14 weeks, the levels were significantly decreased only at the doses ≥1180 ppm in the females and at the highest dose in the males. At the early time points, there was evidence of hypoproteinuria accompanied by elevated levels of albumin and increased levels of creatinine kinase (suggesting possible muscle injury) in the two highest dose groups. These conditions had resolved by the end of the study. There were no neurological effects identified in the exposed animals using a FOB evaluation.

Among the animals in the lower dose groups, absolute and relative liver weights were increased in a dose-related fashion. For animals in the 1180 ppm and greater dose groups, the absolute liver weights decreased, but the relative weights were elevated. Relative kidney weights were significantly increased in the 2300- and 4600-dose groups and relative thymus weights in females were decreased for the 4600-ppm dose group. Decreased absolute organ weights at the higher doses were evidently a consequence of the decreased weight gain in the 2300-ppm group and weight loss in the 4600-ppm group. Gross and histopathologic observations revealed hepatocyte vacuolization in all dose groups. The number and severity of liver lesions increased with dose. Necrosis and altered cell foci were observed at doses of ≥2300 ppm. Cell foci appeared as basophilic, eosinophilic, mixed cell, and/or clear cell clusters of cellular alterations.

According to the authors, the 589-ppm dose group (27 mg/kg/day for males and 31 mg/kg/day for females) was the LOAEL for systemic effects in this study. The only observed effect in the 268-ppm group was hepatocyte cytoplasmic vacuolization in 7/10 males but not females and a significant increase in SDH for the males that did not remain significant at the next highest dose. The hepatic vacuolization was not considered adverse by the authors because the changes were considered to be mild (severity grade 1.3) but were regarded by EPA as a marinal LOAEL. The effects that contributed to the identification of the 589-ppm dose as the LOAEL included: hepatocyte cytoplasmic vacuolization in 9/10 males and 10/10 females (compared to 0/20 control; severity grade 2.0); increased relative liver weight and significantly decreased

hemoglobin in males and hematocrit in females; and decreased sperm motility. There was a dose-related trend towards increased levels of ALT and SDH at 14 weeks in male rats, which reached significance for the 1180 ppm concentration.

There are no adequate data on reproductive toxicity for 1,1,2,2-tetrachloroethane. The studies of the male and female reproductive organs and estrus cycling included in the NTP study (2004) all showed effects only at dose levels above the LOAEL for liver and hematological effects (doses of $\geq$1180 ppm for males and $\geq$2300 ppm for females). Sperm motility was significantly decreased at doses greater than or equal to the LOAEL. There was a limited one-generation inhalation study using 7 males and 5 females exposed to 13.3 mg/m^3 1,1,2,2-tetrachloroethane for 4 hours/day for an unspecified number of times over a nine-month period (Schmidt et al., 1972). There were no statistically significant differences in the percentage of females having offspring (77.1% in controls versus 62.9% in exposed groups), number of pups per litter, average birth weight, gestation length, sex ratio, offspring mortality at postnatal days 1, 2, 7, 14, 21, and 84, or average weight on postnatal day 84. No macroscopic malformations were observed .

The NTP (1991a,b) conducted range-finding studies of developmental toxicity in rats and mice using 10 pregnant females per dose group. The animals were exposed orally through microcapsules in feed starting on gd 4 and continuing until sacrifice on gd 20 for rats and gd 17 for mice. Both studies identified an NOAEL that was greater than the LOAEL in the NTP subchronic study (2004) . In both cases, embryo/fetotoxicity was accompanied by maternal toxicity. There was no evaluation of the pups for visceral or skeletal abnormalities.

8.1.1 RfD Determination

8.1.1.1 Benchmark Dose Approach

The NTP study (2004) provided dose-response information for the hematological, biochemical, body weight, organ weight, and histological effects. Based on the data provided and the clear indication that the liver was the primary target organ for 1,1,2,2-tetrachloroethane, three liver-related data sets were selected for modeling using the benchmark dose approach:

- Relative liver weights
- ALT levels
- SDH levels

Each of these endpoints are reflective of hepatic toxicity and are early indicators for possible necrosis.

ALT is a vitamin B-6-requiring enzyme that functions in the transfer of the amino functional group from an amino acid to pyruvate, forming alanine. This is an important reaction in the catabolic pathway for amino acids and in the synthesis of nonessential amino acids. In general, increases in serum activities of ALT are considered to be a liver-specific event in rodents and can be used as a marker of hepatocellular necrosis or increased cell membrane permeability (Clampitt

and Hart, 1978; Boyd, 1983). SDH is the enzyme that converts sorbitol (the alcohol sugar formed by reduction of glucose and fructose) to glucose. It is a cytosolic enzyme with a more limited tissue distribution than ALT. Accordingly, it also is an appropriate indicator for damage to liver cells. Serum levels of both of these enzymes showed a dose-related trend towards increased levels, especially in male rats, which made them appropriate candidates for benchmark dose (BMD) modeling. Travelose et al. (1996) found that there was a treatment-related association between increases in either or both enzymes and the presence of histopathological changes in the liver at study termination by examining the data from 61 NTP 13-week toxicity studies. SDH had higher predictive properties than ALT when only one enzyme was considered. Increases in the activity of both enzymes were more predictive than either enzyme independently.

There was some evidence of cytoplasmic vacuolization in hepatocytes in 7of 10 male rats but no females at the lowest dose. However, this endpoint was never graded at a level of greater than mild in any dose group, even those with marked hepatocellular necrosis, and was not considered at toxicologically relevant by the NTP pathology work group. Accordingly, this endpoint was felt to be inappropriate as a point of departure.

Relative liver weight was also increased in both males and females. Increases in relative liver weight, when unaccompanied by other signs of toxicity, is generally not considered adverse. In this study, however, the increase in relative weight was accompanied by increased levels of SDH in males and vacuolization of the hepatocytes in males and females. Increased relative liver weight also is one of the hallmarks of DCA toxicity in animals studies and is attributed to glycogen accumulation in the liver (U.S. EPA, 2003b). Although most 1,1,2,2-tetrachloroethane studies did not examine the liver for glycogen deposits, an increase was observed in the short term study in rats conducted by Dow (1988).

Hemoglobin levels and decreased sperm motility were also modeled. Hematological effects have been reported in humans and several rodent studies in addition to the NTP study (2004). There was a dose-related decrease in hemoglobin levels across all male dose groups at the end of the study which reached statistical significance for the animals receiving the 589-ppm dietary concentration. There was a similar trend in females which became statistically significant for the animals receiving the 1180-ppm concentration. Significant dose-related decreases in sperm motility were reported in the NTP study (2004) and effects on the testes were seen in the oral 27-week study by Gohlke et al. (1977).

The data for each of the endpoints discussed above are continuous. They were modeled using the U.S. EPA Benchmark Dose Software (BMDS) Version 1.3.2 (U.S. EPA, 2003c) and options appropriate for continuous data, namely the linear, polynomial, power, and Hill models. Data for the two highest dose groups were not included in the modeling because the differences in body weights compared to controls indicated that the maximum tolerated dose had been exceeded. The BMD levels were determined using a difference of one standard deviation from the control mean.

The BMD and BMDL for those models that adequately fit the data (Chi-square, $p>0.10$) with the lowest Akaike's Information Criterion (AIC) values are summarized in Table 8-2. Based on Agency guidelines for the use of continuous data, the results for a change of one standard

deviation in the relative liver weight for males was selected as the point of departure for determination of the RfD. Figure 8-1 shows the model fit to the relative liver weight data. The full modeling results are provided in Appendix B.

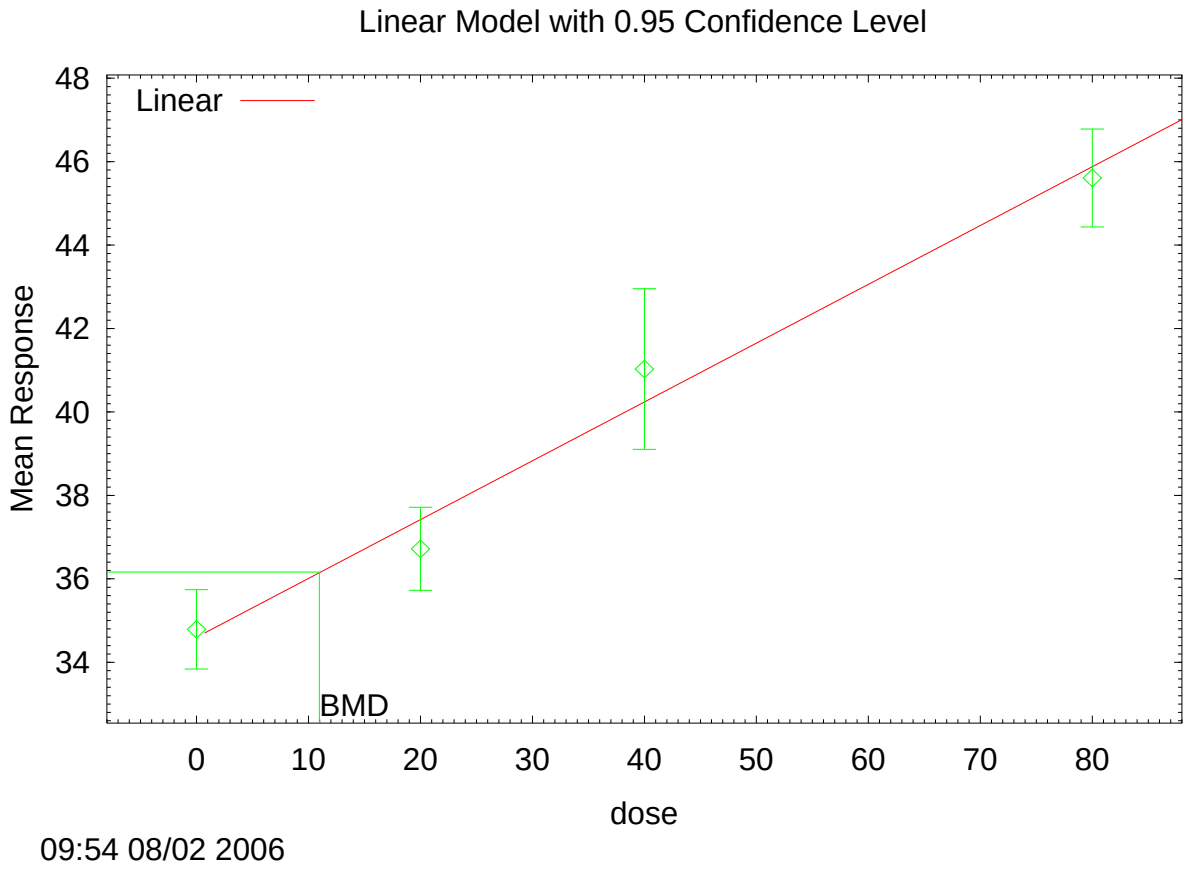
Table 8-2 Benchmark Modeling Results for Noncancer Endpoints in the NTP Study (2004) With Rats

Endpoint	Model	Sex	BMD	BMDL
One Standard Deviation Change				
ALT	Polynomial	male	46.61	29.13
ALT	Polynomial	female	86.31	76.13
SDH	Linear	male	45.73	31.69
SDH	Linear	female	167.33	67.40
Relative Liver Weight	Linear	male	13.08	10.71
Relative Liver Weight	Polynomial	female	24.21	16.09
Hemoglobin	Linear	male	45.47	31.56
Hemoglobin	Polynomial	female	48.69	29.74
Sperm motility	No models fit	male	-	-

The modeling results indicate that the increase in relative liver weight is the most sensitive indicator of liver damage in male rats (BMDL of 10.71 mg/kg/day). The use of increased relative liver weight as a biomarker for liver damage is supported by the increase in ALT and AST and hematological effects at BMDL values about three-fold higher than the relative liver weight BMDL and vacuolization of the cytoplasm in 7/10 male rats at the lowest dose tested (20 mg/kg/day). The leakage of ALT and SDH from the hepatic cells is a biomarker for a breakdown in the cytoplasmic membrane, which is an early stage in the progression to cellular necrosis. They are highly predictive (>75%) individually and combined for histopathological changes in the liver (Travelos et al., 1996).

The BMD/BMDL values for the females suggest that they are more resistant to the hepatotoxic effects of 1,1,2,2-tetrachloroethane than the male rats. The BMDL for increased relative liver weight is 16.09 mg/kg/day in females, and the BMDL values for increases in ALT and SDH are 76.13 mg/kg/day and 76.40 mg/kg/day, respectively. The BMDL for the decreased hemoglobin value in females is 29.74 mg/kg/day.

Figure 8-1 BMD Modeling Results for Male Relative Liver Weight



The liver endpoints were also modeled in male and female mice. Model fits were achieved for ALT in males and ALT and SDH in females. In all cases, the BMDL values in mice (from 92 to 170 mg/kg/day) were greater than those for the rats.

The RfD is calculated from the BMDL for a one standard deviation change in relative liver weight as follows:

$$\text{RfD} = \frac{10.71 \text{ mg/kg/day}}{1000} = 0.01071 \text{ mg/kg/day} = \text{rounded to } 10 \text{ µg/kg/day}$$

where:

10.71 mg/kg/day	=	The BMDL value for an increase in relative liver weight
1000	=	The net uncertainty factor (UF) developed according to EPA guidelines (Dourson and Stara, 1983; U.S. EPA, 2002a).

The net uncertainty factor was derived as follows:

UF_H A tenfold factor was applied allowing for differences in sensitivity among the human population. 1,1,2,2-Tetrachloroethane is at least partially metabolized by the CYP P450 system. There are known genetic differences within the populations for specific CYP P450 isoforms and the activity of the CYP P450 isoforms is influenced by diet and other lifestyle practices introducing greater diversity in human response. In addition, dichloroacetic acid is an intermediate in the metabolism of 1,1,2,2-tetrachloroethane. There are four to five-fold population differences in the activity of the five human GSTZ isoforms that are responsible for the metabolism of dichloroacetic acid to glyoxylate.

UF_A A tenfold factor was applied to account for differences between animals and humans. There is little to no dose-response data from studies where adverse effects have been observed in humans. High-dose acute case studies of accidental or suicide exposures to 1,1,2,2-tetrachloroethane identify the liver as a target tissue in humans. Lacking quantitative data on the responses of humans, a full adjustment for interspecies differences have been applied.

UF_L An uncertainty factor of 1 is applied for NOAEL/LOAEL extrapolation. The point of departure lower is the bound dose for a one standard deviation increase in relative liver weight, an early biomarker for liver damage. Evidence that these effects are not purely adaptive is provided by the increase in serum ALT and SDH at a BMDL that is only three-fold higher than the point of departure for the increase in liver weight. The increases in ALT and SDH are indicative of damage to the hepatocellular membrane. Given the fact that the BMDL for the increase in relative liver weight occurs early in the progression of liver effects and has been determined using the BMD approach, a UF_L adjustment is not necessary.

UF_S An uncertainty factor of 3 is applied for extrapolation from a subchronic to a chronic duration. There are data from a 78-week exposure study in male and female Osborne-Mendel rats (NCI, 1978) using higher dose levels that indicate that the liver damage did not proceed to cirrhosis or other major liver problems. However, the NCI (1978) study did find two rare liver tumors and one preneoplastic nodule in the livers of male Osborne-Mendel rats and did not monitor for hematological effects. Significant decreases in hemoglobin were observed after 14 weeks in Fischer-344 male rats in the subchronic NTP study (2004) . Accordingly, an UF of 3 is justified for the subchronic to chronic adjustment, because of the differences in the rat strains used in the subchronic and chronic studies and the limited monitoring of effects in the chronic study.

UF_D An uncertainty factor of 3 was applied for database deficiencies. There is no adequate study of reproductive toxicity, although a very limited one-generation inhalation study with exposure to 13.3 mg/m^3 did not identify reproductive effects in rats. The NTP study (2004) demonstrated a significant decrease in sperm motility at the LOAEL but the data demonstrate that the RfD will be protective of this effect. Range-finding developmental studies in rats and mice indicated that 1,1,2,2-tetrachloroethane only causes embryo or

fetotoxicity at doses that are maternally toxic. However, these studies are limited because there was no evaluation for skeletal and visceral abnormalities.

8.1.1.2 NOAEL/LOAEL Approach

It is also possible to determine an RfD using the NOAEL/ LOAEL approach. The LOAEL from the NTP study (2004) was the 20 mg/kg/day (268 ppm) dose for the males based on increased cytoplasmic vacuolization and a significant increase in SDH. However, the authors of the NTP study considered that dose to be an NOAEL because the SDH increase was not significant at the next higher dose and the cytoplasmic vacuolization was mild and could have reflected a variety of changes that were not necessarily adverse. If the 20-mg/kg/day dose is accepted as an NOAEL, the uncertainty factor used for the benchmark dose-RfD above is appropriate. The RfD would be calculated as follows:

$$RfD = \frac{20 \text{ mg/kg/day}}{1000} = 0.020 \text{ mg/kg/day (rounded to 20 µg/kg/day)}$$

where:

20 mg/kg/day	=	The NOAEL for adverse effects on the liver in male rats
1000	=	The net uncertainty factor (UF) developed according to EPA guidelines (Dourson and Stara, 1983; U.S. EPA, 2002a).

An alternate interpretation of the data would be to consider the 268-ppm concentration (20-mg/kg/day dose) as a marginal LOAEL. Under those circumstances, the uncertainty factor for the calculation would increase by a factor of 3 for the UF_L uncertainty, and the RfD would be calculated as follows:

$$RfD = \frac{20 \text{ mg/kg/day}}{3000} = 0.00666 \text{ mg/kg/day (rounded to 7 µg/kg/day)}$$

where:

20 mg/kg/day	=	The LOAEL for adverse effects on the liver in male rats
1000	=	The net uncertainty factor (UF) developed according to EPA guidelines (Dourson and Stara, 1983; U.S. EPA, 2002a). A three-fold factor (UF_L) was used fo the NOAEL/LOAEL adjustment because the effects observed and the LOAEL were of marginal toxicologic significance.

EPA prefers the benchmark dose approach for derivation of the RfD because it uses the dose-response properties for increased relative liver weight. The increase in liver weight is supported by two enzyme biomarkers for liver damage (ALT and SDH) at slightly higher BMDL values and mild cytoplasmic vacuolization seen in almost all (7/10) of the exposed animals in the 20-mg/kg dose group. Each of these factors increases the confidence that liver toxicity is the

critical effect and that the BMDL for the increase in relative liver weights should be used as the basis for the RfD.

8.1.2 RfC Determination

The reference concentration (RfC) is an estimate of the daily inhalation exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime. The U.S. EPA has not developed an RfC for 1,1,2,2-tetrachloroethane because the available data are inadequate. There are no studies in human populations that provided quantification of the concentration in air associated with adverse effects. However, early occupational reports indicate that 1,1,2,2-tetrachloroethane is associated with nausea, dizziness, headache, fatigue, eye irritation, vomiting, mild anemia, and elevated white cell and platelet counts (Jeney et al., 1957; Lehman and Schmidt-Kehl, 1936; Lobo-Mendonca, 1963; Minot and Smith, 1921; Willcox et al., 1915). Some subjects that were occupationally exposed had enlargement of the liver or cirrhosis (Jeney et al., 1957). In a controlled human exposure study (Lehman and Schmidt-Kehl, 1936), using two volunteers, a 20-minute exposure to a concentration of 20 mg/m^3 was sufficient to cause mild nausea and vomiting.

There are no chronic inhalation data for 1,1,2,2-tetrachloroethane and the few studies of subchronic duration (Danan et al., 1973; Schmidt et al., 1975; Truffert et al., 1977) are inadequate for determination of an RfC because they examined only a single dose and did not provide complete information on study design and observed effects. The lowest subchronic dose tested was 50 mg/m^3.

8.2 Dose-Response for Cancer Effects

8.2.1 Choice of Study

NCI (1978) found significant, dose-related increases in the incidence of hepatocellular carcinomas in groups of 50 male and 50 female B6C3F1 mice exposed to 5 days/week, time-weighted average concentrations of 142 or 282 mg/kg-day 1,1,2,2-tetrachloroethane in corn oil administered via gavage for 78 weeks followed by a 12-week observation period. These doses are equivalent to 101 and 202 mg/kg/day, respectively, when normalized over a 7-days/week period. NCI (1978) did not find any significant increases in the incidence of neoplasms in Osborne-Mendel rats similarly exposed to 5 days/week time-weighted average doses of 44 or 77 mg/kg-day (males) or 31 and 54 mg/kg-day (females) when normalized for a 7-days/week exposure. However, there were two male rats with hepatocellular carcinomas in the high dose group and one with a hepatic preneoplastic nodule. Because these tumors are rare in Osborne-Mendel rats, the NCI considered the results in male rats to be equivocal.

Based on the results of available *in vivo* and *in vitro* assays, 1,1,2,2-tetrachloroethane has, at most, a weak mutagenic potential. Studies of mutagenicity in *Salmonella typhimurium*, *Escherichia coli* and *Saccharomyces cerevisiae* were predominantly negative but some positive results were observed both with and without activation (see Table 7-5). Several studies (Colacci et al., 1992; Galloway et al., 1987) found positive results for sister chromatic exchange both with and without S9 activation, and a mouse micronucleus assay was positive for males and females (NTP, 2004).

1,1,2,2-Tetrachloroethane was a stronger promoter than an initiator of GGT+ foci in the liver of rats (Story et al., 1986). Additional support for the classification of 1,1,2,2-tetrachloroethane as a weak initiator was provided by the results of Colacci et al. (1992, 1993) using an *in vitro* two-stage BALB/c 3T3 cell transformation assay and implantation of the transformed cells into athymic CD1/BR mice. In both the GGT+ and cell transformation assays the promotion potential of 1,1,2,2-tetrachloroethane was stronger than its initiation potential. This profile for tumor induction by 1,1,2,2-tetrachloroethane is similar to that of dichloroacetic acid, its primary metabolite (U.S. EPA, 2003b).

The critical study for quantification of the tumor dose response is the mouse study by NCI (1978).

8.2.2 Dose-Response Characterization

Groups of male and female B6C3F1 mice (50/sex/dose) were administered technical-grade 1,1,2,2-tetrachloroethane in corn oil by gavage at normalized, 7 days/week, time-weighted average daily doses of 101 or 202 mg/kg body weight for 78 weeks. The doses were not normalized beyond the actual exposure period because of the variations in the doses across the duration of the study and the link between DCA and 1,1,2,2 tetrachloroethane. DCA carcinogenicity appears to be related to the inhibition of GSTZ in some, yet to be defined, fashion. Modeling of DCA toxicokinetics in mice indicates that for drinking water exposures, the area under the curve (AUC) for liver DCA is nonlinear (Barton et al., 1999). In animals pre-treated with DCA, the modeled liver AUC was about 8-fold higher than in the naive animals with drinking water concentrations of 0.01 to about 0.8 g/L reflecting the impact of the enzyme inhibition. At higher doses, the difference between the naive and pre-treated animals increased rapidly. Accordingly, the magnitude of the dose at the time it is given may play a role in the carcinogenic potency of DCA and 1,1,2,2-tetrachloroethane. For this reason artificially lowering the administered dose, beyond the normalization for the irregular dosing pattern and the 5-day per week normalization did not seem appropriate. Uncertainty introduced by the decreases and increases in the doses given during the actual period of compound administration is most likely greater than any uncertainty introduced by a failure to normalize for the estimated full life span of the animals.

Effects in treated animals were compared to the untreated- and vehicle control animals. A highly significant dose-related trend in the incidence of hepatocellular carcinomas was observed in males and females that received the chemical when compared to the respective controls (Table 8-3). These tumors also appeared earlier in mice administered the higher dose. Slightly decreased body weight gain and increased mortality also were observed in exposed mice; there were no increases in the incidences of non-neoplastic lesions (NCI, 1978).

Table 8-3 Summary of Liver Tumor Incidence, 78-Week Study in Mice

	Normalized doses[1] (mg/kg/day)	Liver Tumor Incidence[2]
Male	0	3/36 (sum of 2 control groups)
	101	13/50*
	202	44/49*
Female	0	1/40 (sum of 2 control groups)
	101	30/48*
	202	43/47*

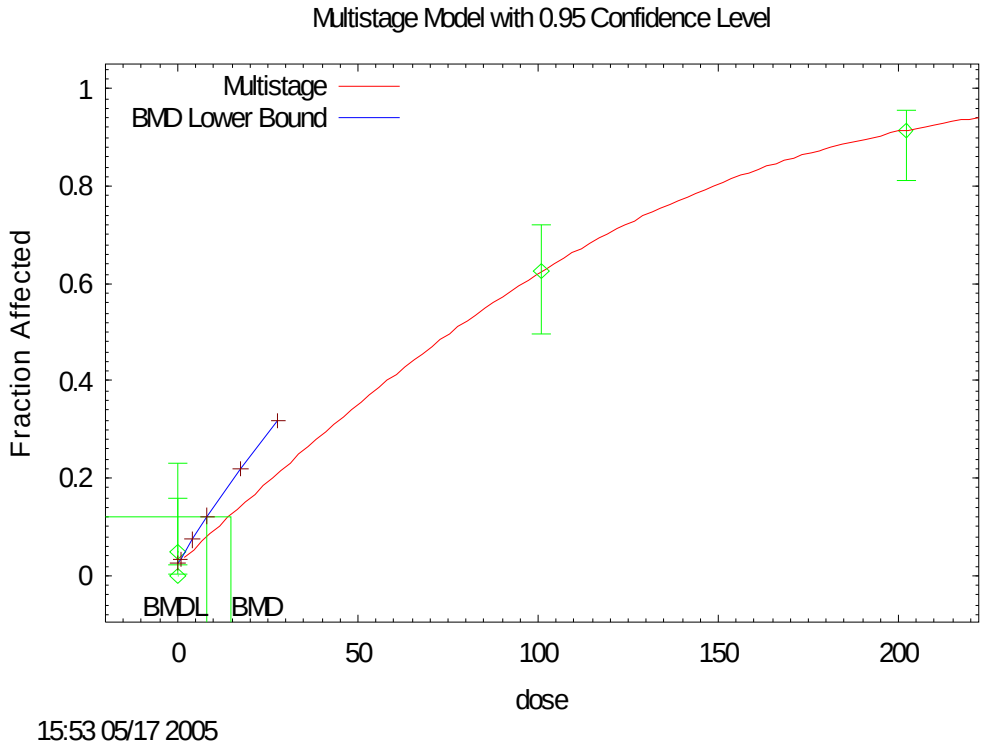
Source: NCI (1978)

*Significantly increased compared to control, $p < 0.05$

1. Doses were derived from the dose duration data in the NCI report (Table 2) and calculated according to the NCI formula. The doses were normalized to accommodate the 5 out of 7 day weekly exposure. The calculation indicated that the high dose exposure was 283.3 mg/kg/day rather than 284 mg/kg/day shown in NCI Table 6 or 282 mg/kg/day as indicated in the NCI study summary. Animals that died prior to 52 weeks, the time at which the first tumor was observed were not included in the statistical analysis of the data.

2. The data on the numbers of animals with tumors were obtained from NCI Tables 6 and 7 and differ for the male and female untreated control groups from the values given in the NCI summary.

Figure 8-2 Multistage Model Fit to Bioassay Tumor Data for Female Mice



8.2.3 Cancer Potency and Unit Risk

U.S. EPA used the ED_{10} of 15 mg/kg/day and LED_{10} of 8 mg/kg/day for the tumor response in female mice to derive a slope factor from both the point of departure and its lower bound for 1,1,2,2-tetrachloroethane. The rodent ED_{10} and LEd_{10} values were converted to human equivalent doses (HED) by using a body weight to the 3/4 power scaling factor as required by the U.S. EPA Guidelines for Carcinogen Risk Assessment Guidelines (2005a). This resulted in HED ED_{10} and HED LED_{10} values of 2.08 and 1.17 mg/kg/day. The point of departure and lower bound slope factor estimates for tumorigenicity are calculated from these values as follows:

Slope Factor Based on the Point of Departure

$$\text{Slope Factor (SF)} = \frac{\text{Response}}{BMD_{10}} = \frac{0.1}{2.08 \text{ mg/kg/day}} = 4.8 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$$

Slope Factor Based on the Lower Bound Estimate for the Point of Departure

$$\text{Slope Factor} = \frac{\text{Response}}{BMDL_{10}} = \frac{0.1}{1.17 \text{ mg/kg/day}} = 8.5 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$$

The lower bound value is in fairly good agreement with the central tendency and lower bound slope factors for the principal metabolite, dichloroacetic acid, which has a slope factor of 1.5×10^{-2} (mg/kg/day)$^{-1}$ and 7×10^{-2} (mg/kg/day)$^{-1}$, respectively (U.S. EPA, 2003b).

The Health Reference Level (HRL) serves as the benchmark for examining the occurrence data for 1,1,2,2-tetrachloroethane in the Regulatory Determination process. It is the concentration in drinking water equivalent to a one-in-a million risk (10^{-6}) of cancer above background. For 1,1,2,2-tetrachloroethane, the concentration equivalent to a 10^{-6} risk is calculated as follows:

Lower Bound Estimate

$$10^{-6}\ \text{risk} = \frac{\text{risk x body weight}}{\text{SF x drinking water intake}} = \frac{0.000001 \times 70\ \text{kg}}{0.085\ (\text{mg/kg/day})^{-1} \times 2\text{L/day}} = 4.12 \times 10^{-4}\ \text{mg/L}$$

The HRL is rounded to one significant figure and becomes 0.4 µg/L.

Point of Departure Estimate

$$10^{-6}\ \text{risk} = \frac{\text{risk x body weight}}{\text{SF x drinking water intake}} = \frac{0.000001 \times 70\ \text{kg}}{0.048\ (\text{mg/kg/day})^{-1} \times 2\text{L/day}} = 7.29 \times 10^{-4}\ \text{mg/L}$$

The Point of Departure Estimate rounded to one significant figure is 0.7 µg/L

Prior Cancer Slope Factor

EPA evaluated the carcinogenicity for 1,1,2,2-tetrachloroethane under the Guidelines for Cancer Risk Assessment (U.S. EPA, 1986c) using the linearized multistage model (U.S. EPA, 1986e). The oral slope factor using this approach is 2.0×10^{-1} per (mg/kg-day) using administered doses that were adjusted for frequency and length of exposure, and human equivalent dose based on body weight using a 2/3 power scaling factor (U.S. EPA, 1986e; see Table 8-4). The HRL calculated from the IRIS slope factor is 0.2 µg/L. The IRIS documentation for 1,1,2,2-tetrachloroethane is currently being updated by the Agency.

Table 8-4 Factors Used to Derive the Oral Slope Factor

Administered Dose (mg/kg/day)	Administered Dose, Adjusted[1] (mg/kg/day)	Human Equivalent Dose[2] (mg/kg/day)	Tumor Incidence (Female mice)
0	0	0	0/20
142	87	6.56	30/48[3]
284	174	13.12	43/47[3]

Source: U.S. EPA (1986e)

1. Adjusted for frequency (5/7 days) and length of exposure (546 days of an assumed life span of 637 days).
2. Human Equivalent Dose = Administered Dose x $(0.03\text{kg}/70\text{kg})^{1/3}$; 0.03 kg = Assumed Animal Weight.
3. Increase is statistically significant compared to controls, $p < 0.05$.

The U.S. EPA (1986e) assessment on IRIS differs from the revised assessment presented in this document in a number of respects, most related to application of the 2005 cancer guidelines. The differences in the approach are summarized as follows:

- The 1986 Human Equivalent Dose (HED) was determined using a 2/3 power scaling factor for body weight as required by the EPA Guidelines for Cancer Risk Assessment (U.S. EPA, 1986c). The new assessment uses a 3/4 power scaling factor for body weight as required by the EPA Revised Guidelines for Carcinogen Risk Assessment (U. S. EPA, 2005a).

- The control values for the 1986 assessment were those for the untreated controls. The new assessment combined the untreated and vehicle controls. There was one tumor in the vehicle control group.

- The highest dose for the 1986 assessment was 284 mg/kg/day as indicated in the NCI (1978) reports. The revised assessment used 283 mg/kg/day as the highest dose since that is the result from using the NCI dose and duration information and the equation provided by NCI for obtaining the time-weighted average doses.

- The 1986 IRIS Assessment normalized doses to adjust for the 5 of 7 days weekly exposure pattern and then also adjusted the dose for exposures for 546 days out of a 637-day life span. The revised assessment normalized for the 7-days/week exposure but did not do the lifetime normalization. The raising and lowering of dose levels during the study are problematic. Studies of 1,12,2-tetrachloroethane indicate that it is at best a weak tumor initiator. This also is true for its principle metabolite DCA. In the case of DCA, the tumorigenic appears to be multifaceted but does not rely on a hyperplastic response of the liver to tissue damage. For both 1,1,2,2-tetrachloroethane and DCA it is possible that enzyme inhibition of GST zeta may be an important feature of the mode of action. Accordingly, artificially lowering the doses by normalizing for a lifetime longer that the period of exposure may not be appropriate.

- The linearized multistage model used for the IRIS assessment derived a slope by fitting the dose-response data to a straight line that passes through the zero point for the X and Y axises. The Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) determine the slope factor by drawing a straight line from the lower bound on the 10 percent response level to zero.

Despite the difference in cancer risk assessment approaches listed above, the responses are remarkably similar. The revised and original IRIS slope factors are 8.5×10^{-2} and 2×10^{-1} $(mg/kg/day)^{-1}$ $(mg/kg/day)^{-1}$, respectively. The revised and original IRIS HRL values are 0.4 µg/L and 0.2 µg/L respectively.

9.0 REGULATORY DETERMINATION AND CHARACTERIZATION OF RISK FROM DRINKING WATER

9.1 Regulatory Determination for Chemicals on the CCL

The SDWA, as amended in 1996, required the EPA to establish a list of contaminants to aid the Agency in regulatory priority setting for the drinking water program. EPA published a draft of the first Contaminant Candidate List (CCL) on October 6, 1997 (62 FR 52193, U.S. EPA, 1997). After review of and response to comments, the final CCL was published on March 2, 1998 (63 FR 10273, U.S. EPA, 1998c).

On July 18, 2003, EPA announced final Regulatory Determinations for one microbe and 8 chemicals (68 FR 42897, U.S. EPA, 2003d) after proposing those determinations on June 3, 2002 (67 FR 38222, U.S. EPA, 2002c). The remaining 40 chemicals and ten microbial agents from the first CCL became CCL 2 and were proposed in the Federal Register (FR) on April 2, 2004 (69 FR 17406, U.S. EPA 2004c) and finalized on February 24, 2005 (70FR:9071, U.S. EPA, 2005b).

EPA proposed Regulatory Determinations for 11 chemicals from CCL2 on May 1, 2007 (72FR 24016) (U.S. EPA, 2007). Determinations for all 11 chemicals were negative based on a lack of national occurrence at levels of health concern. The Agency is given the freedom to determine that there is no need for a regulation if a chemical on the CCL fails to meet one of three criteria established by the SDWA and described in section 9.1.1. After review of public comments and submitted data, the negative determinations for the 11 contaminants have been retained. Each contaminant will be considered in the development of future CCLs if there are changes in health effects and/or occurrence.

9.1.1 Criteria for Regulatory Determination

These are the three criteria used to determine whether or not to regulate a chemical on the CCL:

- The contaminant may have an adverse effect on the health of persons.
- The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern.
- In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The findings for all criteria are used in making a determination to regulate a contaminant. As required by the SDWA, a decision to regulate commits the EPA to publication of a Maximum Contaminant Level Goal (MCLG) and promulgation of a National Primary Drinking Water Regulation (NPDWR) for that contaminant. The Agency may determine that there is no need for a

regulation when a contaminant fails to meet one of the criteria. A decision not to regulate is considered a final Agency action and is subject to judicial review. The Agency can choose to publish a Health Advisory (a nonregulatory action) or other guidance for any contaminant on the CCL, independent of the regulatory determination.

9.1.2 National Drinking Water Advisory Council Recommendations

In March 2000, the EPA convened a Working Group under the National Drinking Water Advisory Council (NDWAC) to help develop an approach for making regulatory determinations. The Working Group developed a protocol for analyzing and presenting the available scientific data and recommended methods to identify and document the rationale supporting a regulatory determination decision. The NDWAC Working Group report was presented to and accepted by the entire NDWAC in July 2000.

Because of the intrinsic difference between microbial and chemical contaminants, the Working Group developed separate but similar protocols for microorganisms and chemicals. The approach for chemicals was based on an assessment of the impact of acute, chronic, and lifetime exposures, as well as a risk assessment that includes evaluation of occurrence, fate, and dose-response. The NDWAC protocol for chemicals is a semi-quantitative tool for addressing each of the three CCL criteria. The NDWAC requested that the Agency use good judgment in balancing the many factors that need to be considered in making a regulatory determination.

The EPA modified the semi-quantitative NDWAC suggestions for evaluating chemicals against the regulatory determination criteria and applied them in decision-making. The quantitative and qualitative factors for 1,1,2,2-tetrachloroethane that were considered for each of the three criteria are presented in the sections that follow.

9.2 Health Effects

The first criterion asks if the contaminant may have an adverse effect on the health of persons. Because all chemicals have adverse effects at some level of exposure, the challenge is to define the dose at which adverse health effects are likely to occur and estimate a dose at which adverse health effects are either not likely to occur (threshold toxicant), or have a low probability for occurrence (non-threshold toxicant). The key elements that must be considered in evaluating the first criterion are the mode of action, the critical effect(s), the dose-response for critical effect(s), the RfD for threshold effects, and the slope factor for nonthreshold effects.

A full description of the health effects associated with exposure to 1,1,2,2-tetrachloroethane is presented in Chapter 7 of this document and summarized below in Section 9.2.2. Chapter 8 and Section 9.2.3 present dose-response information.

9.2.1 Health Criterion Conclusion

The available toxicological data indicate that 1,1,2,2-tetrachloroethane has the potential to cause adverse health effects in humans and animals. Liver effects are the most common manifestation of 1,1,2,2-tetrachloroethane toxicity. Dose information is lacking in almost all of the human studies or case reports. The HRL (0.4 µg/L) for 1,1,2,2-tetrachloroethane is based on the occurrence of liver tumors in mice following chronic exposures (NCI, 1978). The RfD (10 µg/kg/day) is based on evidence for liver damage, decreased hemoglobin levels, and decreased sperm motility in male rats after subchronic exposures (NTP, 2004). Inhalation, but not oral exposures, are associated with neurological effects (e.g., headaches dizziness, fatigue, tremors). Based on these considerations, the evaluation of the first criterion for 1,1,2,2-tetrachloroethane is positive: 1,1,2,2-tetrachloroethane may have an adverse effect on human health.

9.2.2 Hazard Characterization and Mode of Action Implications

Data on the toxicity of 1,1,2,2-tetrachloroethane in humans are limited, consisting of one experimental inhalation study, a few case reports of suicidal or accidental ingestion, and dated occupational studies. In most cases, there was no quantification of the exposure. Respiratory, mucosal, eye irritation, nausea, vomiting, and dizziness were reported by human volunteers exposed to 1,1,2,2-tetrachloroethane vapors under controlled chamber conditions (Lehmann and Schmidt-Kehl, 1936). Effects from non-lethal occupational exposures included gastric distress (i.e., pain, nausea, vomiting), headache, loss of appetite, an enlarged liver, and cirrhosis (Jeney et al., 1957; Lobo-Mendonca 1963; Minot and Smith 1921).

There have been a variety of animal studies in rats and mice using both the inhalation and oral exposure routes. Recent studies by the National Toxicology Program (NTP, 2004) provide a detailed evaluation of the short-term and subchronic oral toxicity of 1,1,2,2-tetrachloroethane and confirm many of the observations from earlier studies. In rats and mice exposed orally, the liver appears to be the principal target organ.

A National Cancer Institute (1978) bioassay of 1,1,2,2-tetrachloroethane found evidence of carcinogenicity in male and female B6C3F1 mice based on a dose-related statistically significant increase in liver tumors. There was equivocal evidence for carcinogenicity in Osborne-Mendel rats because of the occurrence of a small number of rare-for-species neoplastic and preneoplastic lesions in the livers of the high dose animals.

Information on the reproductive effects of 1,1,2,2-tetrachloroethane is limited. There is a single one-generation study that does not follow a standard methodology and examined a small number of animals (five females and seven males) exposed via inhalation to one dose (13.3 mg/m^3). There were no statistically significant differences in the percentage of females having offspring, number of pups per litter, average birth weight, sex ratio, or post natal offspring mortality (Schmidt et al., 1972). Effects on sperm in male rats were seen after oral exposure (27mg/kg/day; NTP, 2004)

Developmental range-finding studies conducted for NTP (1991a,b) found that 1,1,2,2-tetrachloroethane was toxic to the dams and pups of Sprague Dawley rats and CD-1 Swiss

mice. Rats were more sensitive than mice. The NOAEL in the rats for both maternal toxicity and associated fetal toxicity was 34 mg/kg/day with an LOAEL of 98 mg/kg/day. In mice, the NOAEL was 987 mg/kg/day and the was LOAEL 2120 mg/kg/day.

EPA also evaluated whether health information is available regarding the potential effects on children and other sensitive populations. Individuals with preexisting liver and kidney damage would likely be sensitive to 1,1,2,2-tetrachloroethane exposure. Low intake of antioxidant nutrients (e.g., Vitamin E, Vitamin C, and selenium) could be a predisposing factor for liver damage. In addition, individuals with a genetically low capacity to metabolize dichloroacetic acid (a principal metabolite of 1,1,2,2-tetrachloroethane) may be at greater risk than the general population as a result of 1,1,2,2-tetrachloroethane exposure. There are no data that can inform whether or not children would be more sensitive to the effects of 1,1,2,2-tetrachloroethane than the general population.

9.2.3 Dose-Response Characterization

The results from the NTP subchronic study (2004) in F-344 rats were chosen to serve as the basis of the RfD for 1,1,2,2-tetrachloroethane. The preponderance of the animal data indicates that rats are more sensitive than mice to the noncancer effects of 1,1,2,2-tetrachloroethane and the subchronic NTP data (2004) provide the best available dose-response data for a variety of important endpoints. The LOAEL of 40 mg/kg/day was identified based on an increased incidence of hepatocyte hypertrophy, increased relative liver weight, reduced hemoglobin levels and decreased sperm motility in male rats at the end of the 14-week study. There was also a dose-related trend towards increased levels of ALT and SDH, biomarkers for liver necrosis, that reached statistical significance at higher doses. The NOAEL was 20 mg/kg/day. Because there was a mild increase in hepatocyte vacuolization at the NOAEL that was not seen in the controls, it is possible that the NOAEL is a marginal LOAEL, an early sign of liver effects, rather than simply an adaptive response. Female rats were found to be less sensitive to adverse effects from 1,1,2,2-tetrachloroethane than the males.

Changes in relative liver weight, ALT and SDH levels, hemoglobin, and sperm motility were modeled using the EPA Benchmark Dose Software Version 1.3.2. Cytoplasmic vacuolization of the hepatocytes was not modeled because of the weak dose-response for the severity of the effect and the high response (7 of 10 animals at the NOAEL and 10 of 10 animals at the LOAEL). The severity of the response at the NOAEL was considered by the NTP to be mild and nonadverse. The dose-response data for the selected endpoints were modeled as continuous end points using a change of one standard deviation from the controls to identify the BMD and BMDL. The data from the highest two dose groups were not used for the modeling because the maximum tolerated dose was clearly exceeded in both dose groups.

The BMDL for a one standard deviation change in relative liver weight provided the most conservative estimate for the point of departure (10.71 mg/kg/day) and was used for the derivation of the RfD. The models were not able to obtain an adequate fit for the sperm effects. The RfD (10.71 µg/kg/day rounded to 10 µg/kg/day) for 1,1,2,2-tetrachloroethane was calculated using a 1000-fold uncertainty factor. The composite uncertainty factor (1000) included consideration of intraspecies variability (10), interspecies variability (10), database deficiencies (3), and an

adjustment for extrapolating from a subchronic to a chronic exposure (3). The 3-fold duration adjustment was justified based on the results from the NCI (1978) cancer bioassay which did not show a distinct worsening of liver effects in rats with age. The NCI study did not examine a full array of noncancer endpoints and used a different rat strain from NTP, justifying the 3-fold UF for the duration adjustment.

The dose-response assessment for the cancer effects of 1,1,2,2-tetrachloroethane utilized the tumor data from the NCI (1978) study in B6C3F1 mice. The tumor incidences for male and female mice were modeled using the multistage model from the EPA Benchmark Dose Software Version 1.3.2. The tumor data for both the untreated and vehicle controls were combined for the assessment. The data for the male mice did not achieve adequate model fit. The ED_{10} and LED_{10} for female mice were 15 mg/kg/day and 8 mg/kg/day respectively. After converting the doses to HEC values, the slope factors were 4.8 10^{-2} $(mg/kg/day)^{-1}$ and 8.5 10^{-2} $(mg/kg/day)^{-1}$, respectively. The concentration equivalent to a one-in-a-million risk level (10^{-6}) (0.4 µg/L) calculated from the lower bound slope factor was used as the HRL in the analysis of the 1,1,2,2-tetrachloroethane occurrence data.

9.3 Occurrence in Public Water Systems

The second criterion asks if the contaminant is known to occur or if there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern. In order to address this question, the following information was considered:

- Monitoring data from public water systems
- Ambient water concentrations and releases to the environment
- Environmental fate

Data on the occurrence of 1,1,2,2-tetrachloroethane in public drinking water systems were the most important determinant in evaluating the second criterion. EPA looked at the total number of systems that reported detections of 1,1,2,2-tetrachloroethane, as well those that reported concentrations of 1,1,2,2-tetrachloroethane above an estimated drinking water health reference level (HRL). For noncarcinogens, the estimated HRL level was calculated from the RfD assuming that 20% of the total exposure would come from drinking water. For carcinogens, the HRL was the 10^{-6} risk level (i.e., the probability of 1 excess tumor in a population of a million people). The HRLs are benchmark values that were used in evaluating the occurrence data while the risk assessments for the contaminants were being developed. The HRL for 1,1,2,2-tetrachloroethane is 0.4 µg/L based on the c equivalent to a one-in-a-million extra risk for tumors.

The available monitoring data, including indications of whether or not the contaminant is a national or a regional problem, are included in Chapter 4 of this document and summarized below. Additional information on production, use, and fate are found in Chapters 2 and 3.

9.3.1 Occurrence Criterion Conclusion

The available data for 1,1,2,2-tetrachloroethane production, use, and environmental releases all show a downward trend. Between Round 1 (1987-1992) and Round 2 (1992-1997) of drinking water monitoring, the 99th percentile concentration for detections for Cross Section reporting states declined from 112 µg/L to 2 µg/L and the percent of systems with detections declined from 0.45% to 0.08%. 1,1,2,2-Tetrachloroethane was not detected in ambient U. S. surface waters in two surveys of VOCs in ground water at a level of detection that was lower than the HRL. The physicochemical properties of 1,1,2,2-tetrachloroethane suggest that concentrations in surface water will volatilize to the atmosphere where it is relatively stable. In soils and ground water, acclimatized bacteria are able to metabolize 1,1,2,2-tetrachloroethane to simpler compounds. Based on these data, it is unlikely that 1,1,2,2-tetrachloroethane will occur in public water systems at frequencies or concentration levels that are of public health concern. Thus, the evaluation for the second criterion is negative.

9.3.2 Monitoring Data

Occurrence data for 1,1,2,2-tetrachloroethane were collected through the unregulated contaminant monitoring (UCM) program from 1987 to 1997. In Round 1, the percent of public 20,407 PWS with detections of 1,1,2,2-tetrachloroethane was 0.45% for cross section states. For Round 2 monitoring, 0.08% of 24,800 systems reported detections for the cross section states. Unfortunately for some states, the analytical method reporting limit (MRL) was greater than the HRL of 0.4 µg/L. MRL values reported for the states ranged from 0.01 to 10 µg/L for Round 1 and 0.01 to 2.5 µg/L for Round 2. The modal value in both cases was 0.5 µg/L. The median concentration for the detections in both cases was also 0.5 µg/L. The 99th percentile concentration for Round 1 was 112 µg/L for the cross section states. In Round 2, the 99th percentile concentrations for detections were 2 µg/L for the cross section states. The data show a decline in the occurrence of 1,1,2,2-tetrachloroethane in finished water between Round 1 and Round 2. The decline is supported by the fact that the MRL maximum for Round two was lower than that for Round 1increasing the confidence in the Round 2 results.

Because of the variable MRL values, the number of systems reporting concentrations exceeding the HRL must be viewed with some caution because not all systems and states were able to detect 1,1,2,2-tetrachloroethane at the HRL. Accordingly, estimates based on the HRL may under report the actual occurrence. Detections greater than the HRL occurred in approximately 0.2% of PWS in cross section states in Round 1. In Round 2, there were detections greater than the HRL in 0.07% of the PWS in the cross section states. Despite the limitation of the MRL, the trend toward decreased occurrence of 1,1,2,2-tetrachloroethane in finished water between Round 1 and Round 2 is clear.

Although 1,1,2,2-tetrachloroethane appears to occur in finished water at least occasionally throughout the U.S., it does not currently appear to have a distinct geographic pattern. Twenty-five of 47 States had at least one public water system with at least one analytical detection of this contaminant. There is also no apparent geographic trend among the States with the highest proportion of analytical detections. The state with the highest number of detections in Round 2 (the most representative of current conditions) was North Carolina. The States with HRL

exceedances in Round 2 were Maine, Massachusetts, Michigan, North Carolina, Ohio, Oklahoma, and Texas. Ohio was the only state that had HRL exceedances in both Round 1 and Round 2.

1,1,2,2-Tetrachloroethane was monitored through the U.S. Geological Service (USGS) National Water Quality Assessment (NAWQA) program in two separate studies of VOC occurrence. One survey (Grady, 2003), sampled source waters for community water systems between 1999 and 2000. The levels of detection (0.2 µg/L) were less than the HRL. 1,1,2,2-Tetrachloroethane was not detected in any of the samples. The second survey (Delzer and Ivahnenko, 2003) was conducted during the same time period and focused on source waters that might be contaminated with methyl tertiary-butyl ether (MtBE). Samples were also analyzed for other VOCs. Again, no 1,1,2,2-tetrachloroethane was detected.

9.3.3 Use and Fate Data

Prior to the 1980s, 1,1,2,2-tetrachloroethane was commonly used in the production of other chemicals, primarily TCE, PCE, and 1,2-dichloroethylene (ATSDR, 2006). It was also used as a metal degreaser and solvent. Production of 1,1,2,2-tetrachloroethane fell from approximately 440 million pounds in 1967 to 34 million pounds in 1974 and commercial production ceased in the United States by the late 1980s; imports are thought to be minimal (ATSDR, 2006).

Although 1,1,2,2-tetrachloroethane is no longer produced as a commercial product in the United States, it is still used as an intermediate and/or by-product in the manufacturing of other synthetic chemicals. It can occur as a trace contaminant in these and other chlorinated alkanes, and in the waste stream of facilities that produce them. Reports of environmental releases from the Toxic Release Inventory show a major decline between 1988 and 2001 (U.S. EPA, 2004b). The reported total releases to the environment in 1988 were 175,000 lbs, while in 2001 the releases totaled 5240 lbs. In all years, releases to the atmosphere exceeded those for land and water. In 2001, only 56 lbs were reported to be released to surface water.

There is little current information on the levels of 1,1,2,2-tetrachloroethane in environmental media. The monitoring data from finished water are supportive of a decline in its presence in the environment. Most of the monitoring data on ambient air are from periods of more wide-spread use of this material as a solvent. A low log K_{oc} indicates that 1,1,2,2-tetrachloroethane does not accumulate in sediments. Half-life measurements and biodegradation information suggest that anthropogenic releases of 1,1,2,2-tetrachloroethane from decades ago have likely been degraded and do not constitute a current problem.

DCA is the primary intermediary metabolite in the mammalian metabolism of 1,1,2,2-tetrachloroethane. DCA also is a disinfection byproduct in finished water treated with chlorine-containing disinfectants. Thus, the presence of 1,1,2,2-tetrachloroethane in water that also contains DCA would increase the total endogenous exposure (internal dose) of DCA. To the extent that other chlorinated two carbon compounds such as trichloroethylene, 1,1,2-trichloroethane, tetrachloroethylene, and 1,1, dichloroethane produce DCA during metabolism, they too would increase endogenous exposure were they to co-occur with 1,1,2,2-

tetrachloroethane. However, given the low levels of 1,1,2,2-tetrachloroethane found in finished water, it is unlikely to be a major contributor to total internal DCA exposure.

9.4 Risk Reduction

The third criterion asks if, in the sole judgment of the Administrator, regulation presents a meaningful opportunity for health risk reduction for persons served by public water systems. In evaluating this criterion, EPA looked at the total exposed population, as well as the population exposed to levels above the estimated HRL. Estimates of the populations exposed and the levels to which they are exposed were derived from the monitoring results. These estimates are included in Chapter 4 of this document and summarized in Section 9.4.2 below.

In order to evaluate risk from exposure through drinking water, EPA considered the net environmental exposure in comparison to the exposure through drinking water. For example, if exposure to a contaminant occurs primarily through ambient air, regulation of emissions to air provides a more meaningful opportunity for EPA to reduce risk than does regulation of the contaminant in drinking water. In making the regulatory determination, the available information on exposure through drinking water (Chapter 4) and information on exposure through other media (Chapter 5) were used to estimate the fraction that drinking water contributes to the total exposure. The EPA findings are discussed in Section 9.4.3 below.

In making its regulatory determination, EPA also evaluated effects on potentially sensitive populations, including the fetus, infants, and children. Sensitive population considerations are discussed in Section 9.4.4.

9.4.1 Risk Criterion Conclusion

Approximately 5.6 million people were served by systems with detections greater than the MRL for 1,1,2,2-tetrachloroethane based on the national extrapolations of the results from Round 2 cross section monitoring. A detection in one large system serving a population of 1.5 million contributed to this total. An estimated 168,000 of these individuals were served by systems with detections greater than the HRL on at least one occasion.

Drinking water is probably the largest contributor to total exposure in situations where 1,1,2,2 tetrachloroethane is present. Recent levels detected in ambient air have been very low and it has not been detected in foods. However, even its presence in water is relatively rare. On the basis of these observations, the impact of regulating 1,1,2,2-tetrachloroethane concentrations in drinking water on health risk reduction is likely to be small. Thus, the evaluation of the third criterion is negative.

9.4.2 Exposed Population Estimates

The variability in the MRL values for both Round 1 and Round 2 data indicate that the monitoring results must be viewed with some caution and that the Round 2 results are more likely to give a clearer picture of current occurrence than the Round 1 results. In Round 2, 2.61% of the population of the cross section states was exposed to 1,1,2,2-tetrachloroethane at least once during the monitoring period. The exposed population served by surface water systems was far larger than that served by ground water systems (4.06% vs. 0.09% respectively for the cross sections states. When extrapolated to a national exposure these results equate to 5 million people exposed by way of surface water systems and 80 thousand people exposed from ground water systems. A detection on 1,1,2,2-tetrachloroethane in one large system serving 1.5 million people contributed substantially to the surface water total.

When looking at the population exposed at concentrations greater than either ½ the HRL or the HRL in Round 2 monitoring, the numbers decline (Table 9-1). As mentioned previously, these values have to be viewed with caution because the modal MRL is slightly above the HRL. The decline in the populations exposed at ½ the HRL and the HRL in Round 1 versus Round 2 is additional evidence of the decline in the environmental levels of 1,1,2,2-tetrachloroethane. In Round 1, the estimated population exposed at ½ the HRL was about 4 million people the cross section states, compared to approximately 1 million in Round 2. The Round 1 estimate for exposure above the HRL in the cross section states was 3.5 million people compared to 168 thousand people in Round 2.

Table 9-1 Populations Exposed to 1,1,2,2-Tetrachloroethane at ½ HRL or HRL

System Type	Cross Section States %	All States %	National Extrapolation Cross Section States	National Extrapolation All States
½ HRL				
All PWS	0.51	0.44	1,082,000	936,000
Surface Water	0.75	0.63	950,000	803,000
Groundwater	0.09	0.11	80,000	94,000
HRL				
All PWS	0.08	0.08	168,000	166,000
Surface Water	0.07	0.06	90,000	76,000
Groundwater	0.09	0.11	80,000	94,000

9.4.3 Relative Source Contribution

A Relative Source Contribution (RSC) analysis compares the magnitude of exposure expected via drinking water to the magnitude of exposure from intake of 1,1,2,2-tetrachloroethane in other media, such as food, air, and soil. In situations where 1,1,2,2-tetrachloroethane occurs in drinking water, the water is likely to be the major source of exposure, unless there is also contamination at a local hazardous waste site. There are no national data for occurrence in foods and ambient air levels have declined in concert with the decline in production and use based on TRI data. Lack of recent quantitative monitoring data for air, foods, and soils would lead to a default 20% RSC as described by U.S. EPA (2000f), were a lifetime Health Advisory (HA) to be developed for noncancer effects.

9.4.4 Sensitive Populations

There are no data that indicate that the fetus is affected by oral exposure to 1,1,2,2-tetrachloroethane at levels below those that have maternal effects or to inform an evaluation on whether or not infants or children would be more sensitive than adults. Individuals with preexisting liver and kidney damage would likely be more sensitive than the general population to 1,1,2,2-tetrachloroethane exposure. To the extent that lipid peroxidation plays a role in the liver damage caused by 1,1,2,2-tetrachloroethane, low intake of antioxidant nutrients (Vitamin A, Vitamin E, Vitamin C, and selenium) could be a predisposing factor for liver damage. Individuals with a genetically low capacity to metabolize dichloroacetic acid might also be at greater risk than the general population as a result of 1,1,2,2-tetrachloroethane exposure.

9.5 Regulatory Determination Decision

As stated in Section 9.1.1, a positive finding for all three criteria is required in order to make a determination to regulate a contaminant. In the case of 1,1,2,2-tetrachloroethane, only the finding for the criterion on health effects is positive. 1,1,2,2-tetrachloroethane may have an adverse effect on the health of people. Based on monitoring conducted between 1987 to 1997, 1,1,2,2-tetrachloroethane was detected at least once in some PWS, but the number of detections and the concentrations detected have declined as many of the commercial uses of 1,1,2,2-tetrachloroethane have been phased out. Accordingly, it appears that 1,1,2,2-tetrachloroethane does not occur in public water systems at a frequency and at levels of public health concern at the present time. Based on the low occurrence of 1,1,2,2-tetrachloroethane in the potable water and in the environment, regulation of 1,1,2,2-tetrachloroethane does not present a meaningful opportunity for health risk reduction for persons served by public water systems at this time.

10.0 REFERENCES

Note: Multiple secondary sources are cited only when both were used to summarize a particular article.

Aldrich Handbook. 1994. Catalogue Handbook of Fine Chemicals. Milwaukee, WI: Sigma-Aldrich Company.

Archer, W.L. 1979. In: Grayson H. and D. Eckroth (eds.). Kirk-othmer Encyclopedia of Chemical Technology. 3rd ed. Vol. 5:722-742 (as cited in ATSDR, 2006).

ASTER (Assessment Tools for the Evaluation of Risk). 1995. ASTER Ecotoxicity Profile. U.S. Environmental Protection Agency. Environmental Research Laboratory- Duluth MN. October 11, 1995 (as cited in ATSDR, 2006).

Atkinson, R. 1987. A structure-activity relationship for the estimation of rate constants for gas-phase reaction of OH radicals with organic compounds. Int. J. Chem Kinetics 19:799-828 (as cited in ATSDR, 2006).

ATSDR (Agency for Toxic Substances and Disease Registry). 2006-draft. Toxicological Profile for 1,1,2,2-Tetrachloroethane. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA..

ATSDR (Agency for Toxic Substances and Disease Registry). 1996. Toxicological Profile for 1,1,2,2-Tetrachloroethane. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

Barrows, M.E., S.R. Petrocelli, K.J. Macek, et al. 1980. Bioconcentration and elimination of selected water pollutants by bluegill sunfish (*Lepomis macrochirus*). In: Haque, R. (ed.). Dynamics, Exposure, and Hazard Assessment of Toxic Chemicals. Ann Arbor, MI: Ann Arbor Science. pp. 379-392 (as cited in ATSDR, 2006).

Barton, H.A., R. Bull, I. Schultz, et al. 1999. Dichloroacetate (DCA) dosimetry: interpreting DCA-induced liver cancer dose response and the potential for DCA to contribute to trichloroethylene-induced liver cancer. Toxicol. Lett. 106:9-21.

Bi, X, G Sheng, Y Feng, et al. 2005. Gas-and particulate-phase specific tracer and toxic organic compounds in environmental tobacco smoke. Chemosphere 61(10):1512-1522. As cited in ATSDR, 2006.

Blackburn, A.C., H-F. Tzeng, M.W. Anders, et al. 2000. Discovery of a functional polymorphism in human glutathione transferase zeta by expressed sequence tag database analysis. Pharmacogenetics 10:49-57.

Blackburn, A.C., M. Coggan, H-F. Tzeng, et al. 2001. GSTZ1d: a new allele of glutathione transferase zeta and maleylacetoacetate isomerase. Pharmacogenetics 11:671-678.

Boyd, J.W. 1983. The mechanisms relating to increases in plasma enzymes and isoenzymes in diseases of animals. Vet. Clin. Pathol. 12:9-24.

Brem, H., A.B. Stein, and H.S. Rosenkranz.1974. The mutagenicity and DNA-modifying effect of haloalkanes. Cancer Res. 34:2576–2579 (as cited in WHO, 1998).

Brodzinsky, R. and H.B. Singh. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Menlo Park, CA: Atmospheric Science Center, SRI International, Contract No. 68-02-3452 (as cited in ATSDR, 2006).

Cal EPA (California Environmental Protection Agency). 2003. Public health goal for 1,1,2,2-tetrachloroethane in drinking water. Office of Environmental Health Hazard Assessment. Available from: <http:// www.oehha.ca.gov/water/phg/pdf/Ph41122TCA92603.pdf>.

Callen, D.F., C.R. Wolf, and R.M. Philpot. 1980. Cytochrome P-450 mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in *Saccharomyces cerevisiae*. Mutat. Res.77:55–63 (as cited in WHO, 1998).

Carpenter, C.P., H.F. Smyth, and U.C. Pozzani. 1949. The assay of acute vapor toxicity and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Tox. 31:343-346 (as cited in ATSDR, 2006).

Chiou, C.T., L.J. Peters, and V.H. Freed. 1979. A physical concept of soil-water equilibria for nonionic organic compounds. Science 206:83 l-832 (as cited in ATSDR, 2006).

Clampitt, R.B. and R.J. Hart. 1978. The tissue activities of some diagnostic enzymes in ten mammalian species. J. Comp. Pathol. 88:607-621.

Class, T. and K. Ballschmiter. 1986. Chemistry of organic traces in air. VI: Distribution of chlorinated Cl-C4 hydrocarbons in air over the northern and southern Atlantic Ocean. Chemosphere 15:413-427 (as cited in ATSDR, 2006).

Colacci, A., S. Grilli, G. Lattanzi, et al. 1987. The covalent binding of 1,1,2,2-tetrachloroethane to macromolecules of rat and mouse organs. Teratogenesis, Carcinogenesis, and Mutagenesis 7:465–474 (as cited in WHO, 1998).

Colacci, A., P. Perocco, S. Bartoli, et al. 1992. Initiating activity of 1,1,2,2-tetrachloroethane in two-stage BALB/c 3T3 cell transformation. Cancer Lett. 64:145–153.

Colacci, A., A. Albini, A. Melchiori, et al. 1993. Induction of malignant phenotype in BALB/c 3T3 cells by 1,1,2,2-tetrachloroethane. Int. J. Oncol. 2:937–945.

Cooper, W.J., M. Mehran, D.J. Riusech, et al. 1987. Abiotic transformations of halogenated organics. 1. Elimination reaction of 1,1,2,2-tetrachloroethane and formation of 1,1,2-trichloroethene. Environ. Sci. Technol. 21:1112-1114 (as cited in ATSDR, 2006).

Cottalasso, D., A. Bellocchio, C. Domenicotti, et al. 1998. 1,1,2,2-Tetrachloroethane-induced early decrease of dolichol levels in rat liver microsomes and Golgi apparatus. J. Tox. Env. Health 54:133-144.

Coyer, H.A. 1944. Tetrachloroethane poisoning. Ind. Med. 13:230-233 (as cited in ATSDR, 2006 and Cal EPA, 2003).

Crebelli, R., R. Benigni, J. Franekic, et al. 1988. Induction of chromosome malsegregation by halogenated organic solvents in *Aspergillus nidulans*: unspecific or specific mechanism? Mutat. Res. 201:401–411 (as cited in WHO, 1998).

Danan, M., S. Hirbec, C. Girard-Wallon, et al. 1983. Glomerulopathies and organic solvents of fates: review of the literature and animal experimental study with 1,1,2,2-tetrachloroethane. Arch. Mal. Prof. Med. Trav. Secur. Soc. 44(4):235-245 (as cited in EPA, 1989).

Deguchi, T. 1972. A fundamental study of the threshold limit values for solvent mixtures in the air--Effects of single and mixed chlorinated hydrocarbons upon the level of serum transaminases in rats. Osaka City Med. J. 21: 187-209 (as cited in ATSDR, 2006 and EPA, 1989).

Delzer, G.C. and T. Ivahnenko. 2003. Occurrence and temporal variability of methyl tert-butyl ether (MTBE) and other volatile organic compounds in select sources of drinking water: Results of the focused survey. U.S. Geological Survey Water-Resources Investigations Report WRIR 02-4084, p. 65. Available from: <http://sd.water.usgs.gov/nawqa/pubs/wrir/wrir02_4084.html>. Link to document from: <http://sd.water.usgs.gov/nawqa/vocns/nat_survey.html>.

DeMarini, D.M. and H.G. Brooks. 1992. Induction of prophage lambda by chlorinated organics: detection of some single-species/single-site carcinogens. Environ. Mol. Mutagen. 19:98–111 (as cited in WHO, 1998).

Dourson, M.L and J.F. Stara. 1983. Regulatory history and experimental support of uncertainty (safety) factors. Regul .Toxicol. Pharmacol. 3:224-238.

Dow Chemical Company. 1944. The toxicity of tetrachloroethane. Document D002192 (as cited in ATSDR, 2006).

Dow Chemical Company. 1988. The metabolism and hepatic macromolecular interactions of 1,1,2,2-tetrachloroethane (TCE) in mice and rats. D002628.

Edefors, S. and A Ravn-Jonsen, 1992. Effect of organic solvents on nervous cell membrane as measured by changes in the (Ca2+/Mg 2+) ATPase activity and fluidity of synaptosomal membrane. Panrm. Toxicol. 70(3):181-187.

Eriksson, C. and E.B. Brittebo. 1991. Epithelial binding of 1,1,2,2-tetrachloroethane in the respiratory and upper alimentary tract. Arch. Toxicol. 65:10-14.

Fleming-Jones, M.E. and R.E .Smith. 2003. Volatile organic compounds in foods: A five year study. J. Agric. Food Chem. 51:8120-8127.

Galloway, S.M., M.J. Armstrong, C. Reuben, et al. 1987. Chromosome aberrations and sister chromatid exchange in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ. Mol. Mutagen. 10(Suppl. 10):1–175 (as cited in NTP, 2004).

Gargas, M.L. and M.E. Andersen. 1989. Determining kinetic rate constants of chlorinated ethane metabolism in the rat from rates of exhalation. Toxicol. Appl. Pharmacol. 99:344-353.

Gohlke, R. and P. Schmidt. 1972. Subacute action of low concentrations of chlorinated ethanes with and without additional ethanol treatment in the rat [article in German]. Int. Arch. Arbeitsmed. 30:299-312 (as cited in ATSDR, 2006).

Gohlke R., P. Schmidt, and H. Bahmann. 1977. 1,1,2,2-Tetrachloroethane and heat stress in animal experiment. Morphological results [article in German]. Z. Gesamte. Hyg. IHRE Grenzgeb. 20:278-282.

Grady, S.J. 2003. National survey of methyl tert-butyl ether and other volatile organic compounds in drinking-water sources: Results of the random survey. U.S. Geological Survey Water-Resources Investigations Report WRIR 02-4079, p. 85. Available from: <http://sd.water.usgs.gov/nawqa/pubs/wrir/wrir02_4079.html>. Link to document from: <http://sd.water.usgs.gov/nawqa/vocns/nat_survey.html>.

Gupta, K.C., A.G. Ulsamer, and R. Gammage. 1984. Volatile organic compounds in residential air: Levels, sources and toxicity. Proc. APCA Annual Meeting 77:84-1.3, 9 (as cited in ATSDR, 2006).

Haag, W.R. and T. Mill. 1988. Effect of a subsurface sediment on hydrolysis of haloalkanes and epoxides. Environ. Sci. Technol. 22:658-663 (as cited in ATSDR, 2006).

Hallen, R.T., J.W. Pyne Jr., and P.M. Molton. 1986. Transformation of chlorinated ethenes and ethanes by anaerobic microorganisms. In: 192nd National Meeting ACS Division Environmental Chemistry. pp. 344-346 (as cited in ATSDR, 2006).

Halpert, J. 1982. Cytochrome P-450 dependent covalent binding of 1,1,2,2-tetrachloroethane *in vitro*. Drug Metab. Dispos. 10:465-468 (as cited in ATSDR, 2006).

Hamilton, A. 1917. Military medicine and surgery. J. Am. Med. Assoc. 69:2037-2039 (as cited in ATSDR, 2006).

Hamilton, P.A., T.L. Miller, and D.N. Myers. 2004. Water Quality in the Nation's Streams and Aquifers: Overview of Selected Findings, 1991-2001. USGS Circular 1265. Available from: <http://water.usgs.gov/pubs/circ/2004/1265/pdf/circular1265.pdf>. Link to document from: <http://water.usgs.gov/pubs/circ/2004/1265/>.

Harkov, R., R. Katz, J. Bozzelli, et al. 1981. Toxic and carcinogenic air pollutants in New Jersey: Volatile organic substances. In: McGovern, J.J. (ed.). Proceedings from International Technical Conference Toxic Air Contamination, 1980. Pittsburgh PA. APCA 104-l 19 (as cited in ATSDR, 2006).

Harkov, R., B. Kebbekus, J.W. Bozzelli, et al. 1983. Measurement of selected volatile organic compounds at three locations in New Jersey during the summer season. J. Air Pollut. Control Assoc. 33:1177-l 183 (as cited in ATSDR, 2006).

Harkov, R., B. Kebbekus, and J.W. Bozzelli. 1987. Volatile organic compounds at urban sites in New Jersey. In: Lioy and Daisey (eds). Toxic Air Pollutants. Chelsea, MI: Lewis Pub. pp. 69-88 (as cited in ATSDR, 2006).

Haseman, J.K. 1984. Results from 86 two-year carcinogenicity studies conducted by the National Toxicology Program. J. Toxicol. Environ. Health 14:621-637 (as cited in ATSDR, 1996).

Hawley, G.G. 1981. Condensed Chemical Dictionary. 10th ed. New York, NY: Van Nostrand Reinhold Co. (as cited in ATSDR, 1996).

Haworth, S., T. Lawlor, K. Mortelmans, et al. 1983. *Salmonella* mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1:3–142 (as cited in NTP, 2004).

HSDB (Hazardous Substance Data Bank). 2004. 1,1,2,2-Tetrachloroethane. Division of Specialized Information Services, National Library of Medicine. Available from: <http://toxnet.nlm.nih.gov/>.

HazDat (Hazardous Substance Release and Health Effects Database). 2006. 1,1,2,2-tetrachloroethane. HazDat Database: Agency for Toxic Substances and Disease Registry (ATSDR), Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/hazdat.html. July 5, 2006 (as cited in ATSDR, 2006).

Hepple, R.A. 1927. An unusual case of poisoning. J. Army Medical Corps. 49:442-445 (as cited in ATSDR, 2006).

Horiguchi, S., S. Morioka, T. Utsunomiya, et al. 1964. A survey of the actual conditions of artificial pearl factories with special reference to the work using tetrachloroethane. Jpn. J. Ind. Health 6:251-256 (as cited in ATSDR, 1996).

Horiuchi, K., S. Horiguchi, K. Hashimoto, et al. 1962. Studies on the industrial tetrachloroethane poisoning. Osaka City Medical J. 829-38 (as cited in ATSDR, 2006).

Horvath, M. and E. Frantik. 1973. To the relative sensitivity of nervous functions and behavior to nonspecific effects of foreign substances. Activ. Nerv. Super. 15:25-27 (as cited in ATSDR, 2006).

HyperCLDB. 2004. BALB 3T3 clone A 31 (mouse, BALB/c, embryo. Available from: <http//:www.biotech.ist.unige.it/cldb/c1386.html>.

IARC (International Agency for Research on Cancer). 1999. 1,1,2,2-Tetrachloroethane. IARC Summary and Evaluation. Volume 71. World Health Organization. Geneva. Switzerland. Available from: <http://www.inchem.org/documents/iarc/vol171/029-1122tetcheth.html>.

Ikeda, M. and H. Ohtsuj. 1972. Comparative study of the excretion of Fujiwara reaction-positive substances in urine of humans and rodents given trichloro-or tetrachloro-derivatives of ethane and ethylene. Br. J. Ind. Med. 29:99-184 (as cited in ATSDR, 2006).

Ivahnenko, T., Grady, S.J., and Delzer, G.C. 2001. Design of a national survey of methyl tert-butyl ether and other volatile organic compounds in drinking-water sources. U.S. Geological Survey Open-File Report OFR 01-271. p. 42. Available from: <http://sd.water.usgs.gov/nawqa/pubs/ofr/ofr01_271.html>. Link to document from: <http://sd.water.usgs.gov/nawqa/vocns/nat_survey.html>.

Jacobi, H., G. Leier, and I. Witte. 1996. Correlation of the lipophilicity of xenobiotics with their synergistic effects on DNA synthesis in human fibroblasts. Chemosphere 32(7):1251-1259.

Jafvert, C.T. and N.L. Wolfe. 1987. Degradation of selected halogenated ethanes in anoxic sediment-water systems. Environ. Toxicol. Chem. 6:827-837 (as cited in ATSDR, 2006).

Jakobson, I., J.E. Wahlberg, B. Holmberg, et al. 1982. Uptake via the blood and elimination of 10 organic solvents-following epicutaneous exposure of anesthetized guinea pigs. Toxicol. Appl. Pharmacol. 63:181-187 (as cited in ATSDR, 2006).

Jeney, E., F. Bartha, L. Kondor, et al. 1957. Prevention of industrial tetrachloroethane intoxication--Part III. Egeszsegtudomany 1:155-164 (as cited in ATSDR, 2006 and EPA, 1989).

Johansson, I., G. Ekstrom, B. Scholte, et al. 1988. Ethanol-, fasting- and acetone-inducible cytochromes P-450 in rat liver. Biochemistry 27:1925-1934 (as cited in ATSDR, 2006).

Kanada, M., M. Miyagawa, M. Sato, et al. 1994. Neurochemical profile of effects of 28 neurotoxic chemicals on the central nervous system in rats. (1) Effects of oral administration on brain contents of biogenic amines and metabolites. Ind. Health 32:145–164 (as cited in WHO, 1998).

Kincannon, D.F., A. Weinert, R. Padorr, et al. 1983. Predicting treatability of multiple organic priority pollutant wastewater from single-pollutant treatability studies. In: Bell, M.R. (ed.). Proceedings 37th Industrial Waste Conference. Ann Arbor, MI: Ann Arbor Science. pp. 641-650 (as cited in ATSDR, 2006).

Klecka, G.M. and S.J. Gonsior. 1983. Nonenzymatic reductive dechlorination of chlorinated methane and ethanes in aqueous solution. Midland, MI: Dow Chemical Co. Fiche No. 206367 (as cited in ATSDR, 2006).

Koelsch, F. 1915. Industrial poisonings by celluloid varnishes in the airplane industry. Muench Medizin Wochensch 62:1567-1569 (as cited in ATSDR, 2006).

Kolling, H.P., et al. 1987. Hydrolysis rate constants, partition coefficients and water solubilities for 129 chemicals. A summary of fate constants provided for the Concentration-Based Listing Program, Prepublication. U.S. EPA Environ. Res. Lab. Computer Sci. Corp. pp. 36 (as cited in HSDB, 2004).

Konietzko, H. 1984. Chlorinated ethanes: Sources, distribution, environmental impact, and health effects. Hazard Assess. Chem. Curr. Dev. 3:401-448 (as cited in ATSDR, 1996).

Kronevi, T., J.E. Wahlberg, and B. Holmberg. 1981. Skin pathology following epicutaneous exposure to seven organic solvents. Int. J. Tissue React. 3:21-30 (as cited in ATSDR, 2006).

LaRegina, J., J.W. Bozzelli, R. Harkov, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. An up-to-date review of the present situation. Environ. Prog. 5:18-27 (as cited in ATSDR, 2006).

Lazarew, N.W. 1929. The narcotic effect of the vapors of the chloride derivatives of methane, ethane and ethylene. Arch. Exper. Pathol. Pharmakol. 141:19-24 (as cited in ATSDR, 2006).

Leahy, P.P. and T.H. Thompson. 1994. The National Water-Quality Assessment Program. U.S. Geological Survey Open-File Report 94-70. pp. 4. Available from: <http://water.usgs.gov/nawqa/NAWQA.OFR94-70.html>.

Lehmann, K.B. 1911. Experimental studies on the influence of technology and hygienically important gases and vapors on the organism (XVI-XXIII)-Chlorinated aliphatic hydrocarbons and considerations on the one-stage and two-stage toxicity of volatile products. Arch. Hyg. 74:1-3,24-28,46-60 (as cited in ATSDR, 2006).

Lehman, K.B. and L. Schmidt-Kehl. 1936. Study of the 13 most important chlorohydrocarbons from the standpoint of industrial hygienics. Arch. Hyg. 116:132-268 (as cited in ATSDR, 2006 and EPA, 1989).

Lilliman, B. 1949. Suggested mechanism of poisoning by liquid tetrachloroethane. Analyst 74:510-511 (as cited in ATSDR, 2006).

Lioy, P.J., J.M. Daisey, A. Greenberg, et al. 1985. A major wintertime (1983) pollution episode in northern New Jersey: Analysis of the accumulation and spatial distribution of inhalable particulate matter, extractable organic matter and other species. Atmos. Environ. 19:429-436 (as cited in ATSDR, 2006).

Little, A.D. 1983. Cell transformation assays of 11 chlorinated hydrocarbon analogs (final report). US Environmental Protection Agency, Office of Toxic Substances (ICAIR Work Assignment No. 10; Document No. 40+8324457) (as cited in WHO, 1998).

Lobo-Mendonca, R. 1963. Tetrachloroethane - A survey. Br. J. Ind. Med. 20:51-56 (as cited in ATSDR, 2006 and EPA, 1989).

Lorah, M.M., M.A. Voytek, J.D. Kirshtein, et al. 2003. Anaerobic degradation of 1,1,2,2-tetrachloroethane and association with microbial communities in a freshwater tidal wetland, Aberdeen proving ground, Maryland: laboratory experiments and comparisons to field data. USGS Water-Resources Investigations Report 02–4157.

Mackay, D. and W.Y. Shiu. 1981. A critical review of Henry's Law constants for chemicals of environmental interest. J. Phys. Chem. Ref. Data 10(4):1175-l 199 (as cited in ATSDR, 1996).

Mant, A.K. 1953. Acute tetrachlorethane poisoning. A report on two fatal cases. Br. Med. J. 655-656 (as cited in ATSDR, 2006).

McGregor, D.B. 1980. Tier II mutagenic screening of 13 NIOSH priority compounds, individual compound report, 1,1,2,2-tetrachloroethane, Report No. 26. Inveresk Research International Limited, Musselburgh EH21 7UB Scotland. NIOSH, Cincinnati, OH (as cited in ATSDR, 1996 and WHO, 1998).

Mersch-Sundermann, V. 1989a. The mutagenicity of organic microcontamination in the environment. II. The mutagenicity of volatile organic halogens in the Salmonella microsome test (Ames test) with regard to the contamination of groundwater and drinking-water [article in German]. Zentralblatt für Bakteriologie und Mikrobiologie, Hygiene B 187:230–243.

Mersch-Sundermann, V. 1989b. Examination of mutagenicity of organic microcontamination of the environment. IV. Communication: The mutagenicity of halogenated aliphatic hydrocarbons with the SOS-chromotest [article in German]. Zentralblatt für Bakteriologie und Mikrobiologie, Hygiene B, 189:266–271.

Milman, H.A., C. Mitoma, C.Tyson, et al. 1984. Comparative pharmacokinetics/metabolism, carcinogenicity and mutagenicity of chlorinated ethanes and ethylenes (meeting abstract). International Conference on Organic Solvent Toxicity, October 15-17, Stockholm, Sweden, 19 (as cited in ATSDR, 2006).

Milman, H.A., D.L. Story, E.S. Riccio, A. Sivak, A.S. Tu, G.M. Williams, C. Tong, and C.A. Tyson. 1988. Rat liver foci and *in vitro* assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. Annals of the New York Academy of Sciences 534:521–530 (as cited in WHO, 1998).

Minot, G.R. and L.W. Smith. 1921. The blood in tetrachlorethane poisoning. Arch. Intern. Med. 28:687-702 (as cited in ATSDR, 2006).

Mirsalis, J.C., C.K. Tyson, K.L. Steinmetz, et al. 1989. Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following *in vivo* treatment; testing of 24 compounds. Environ. Mol. Mutagen. 14:155–164.

Mitoma, C., T. Steeger, S.E. Jackson, et al. 1985. Metabolic disposition study of chlorinated hydrocarbons in rats and mice. Drug Chem. Toxicol. 8(3):183–194.

Mohamed, MF, D Kang and VP Aneja. 202. Volatile organic compounds in some urban locations in the united states. Chemosphere 47:863-882. As cited in ATSDR, 2006.

Montgomery, J.H., and L.M. Welkom. 1990. Groundwater Chemicals Desk Reference. Chelsea, MI: Lewis Publishers. pp. 49l-495 (as cited in ATSDR, 2006).

Morgan, A., A. Black, and D.R. Belcher. 1970. The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. Ann. Occup. Hyg. 13:219 (as cited in ATSDR, 2006).

Mudder, T.I., and J.L. Musterman. 1982. Development of empirical structure biodegradability relationships and biodegradability testing protocol for volatile and slightly soluble priority pollutants. Presentation Amer. Chem. Sot. Division Environmental Chemistry, Kansas City MO, September 1982. pp. 52-53 (as cited in ATSDR, 2006).

Navrotskiy, V.K., L.M. Kashin, and I.L. Kulinskoya. 1971. Comparative assessment of the toxicity of a number of industrial poisons when inhaled in low concentrations for prolonged periods. Trudy S'ezda Gig Ukran 8:224-226 (as cited in ATSDR, 2006).

NCI (National Cancer Institute). 1978. Bioassay of 1,1,2,2-Tetrachloroethane for Possible Carcinogenicity. NTIS PB277 4537GA, DHEW/PUB/NIH-78-827, 90.

NIOSH (National Institute for Occupational Safety and Health). 2006. National occupational exposure survey 1981-83. U.S. Department of Health and Human Services, Public Health Service. Cincinnati, OH: Centers for Disease, July 1, 1990 (as cited in ATSDR 2006).

NRC (National Research Council). 1983. Risk Assessment in the Federal Government: Managing the Process. Washington, DC: National Academy Press.

NRC (National Research Council). 2002. Opportunities to Improve the U.S. Geological Survey National Water Quality Assessment Program. National Academy Press. 238 p. Available from: <http://www.nap.edu/catalog/10267.html>.

NTP (National Toxicology Program). 1991a. Range finding studies: developmental toxicity — 1,1,2,2-tetrachloroethane when administered via feed in CD Sprague-Dawley rats. Research Triangle Park, NC, US Department of Health and Human Services, National Institutes of Health, National Toxicology Program (NTP-91-RF/DT-017).

NTP (National Toxicology Program). 1991b. Range finding studies: developmental toxicity — 1,1,2,2-tetrachloroethane (repeat) when administered via feed in Swiss CD-1 mice. Research Triangle Park, NC, US Department of Health and Human Services, National Institutes of Health, National Toxicology Program (NTP-91-RF/DT-020).

NTP (National Toxicology Program). 1996. NTP Technical Report on renal toxicity studies of selected halogenated ethanes administered by gavage to F344/N Rats. U.S. DHHS, Public Health Service, National Institute of Health. NIH Publication 96-3935, Tox-45.

NTP (National Toxicology Program). 2004. Toxicity studies of 1,1,2,2-tetrachloroethane administered in microcapsules in feed to F344/N rats and B6C3F1 mice. National Institutes of Health, National Toxicology Program (NIH Publication 04-4414).

Nestmann, E.R., EG-H. Lee, T.I. Matula, et al. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the *Salmonella* mammalian-microsome assay. Mutat. Res. 79:203–212 (as cited in WHO, 1998).

Nestmann, E.R. and EG-H Lee. 1983. Mutagenicity of constituents of pulp and paper mill effluent in growing cells of *Saccharomyces cerevisiae*. Mutat. Res. 119:273–280 (as cited in WHO, 1998).

Nimitz, J.S. and S.R. Skaggs. 1992. Estimating tropospheric lifetimes and ozone-depletion potentials of one- and two-carbon hydrofluorocarbons and hydrochlorofluorocarbons. Environ. Sci. Tech. 26(4):739-744 (as cited in WHO, 1998).

Norman, J.E., Jr, C.D. Robinette, and J.F. Fraumeni, Jr. 1981. The mortality experience of Army World War II chemical processing companies. J. Occup. Med. 23:818-822.

OSHA (Occupational Safety and Health Administration). 1998. Air contaminants. Occupational standards permissible exposure limits. 29 CFR 1910.1000 (as cited in HSDB, 2004).

O'Loughlin, E., D. Burris, and C. Delcomyn. 1999. Reductive dechlorination of trichloroethene mediated by humic-metal complexes. Environ. Sci. Technol. 33: 1145-1147.

O'Loughlin, E., H. Ma, and D. Burris. 2003. Catalytic effects of Ni-humic complexes on the reductive dehalogenation of C_1 and C_2 chlorinated hydrocarbons. In Ghabbour, E.A. and G. Davies (eds.). Humic Substances: Nature's Most Versatile Materials. New York: Taylor and Francis, Inc. pp. 297-324.

Pantelitsch, M. 1933. Experiments concerning the effect of chlorinated methane and ethane on mice--The relative sensitivity of mice and cats to poisons. Inaugural Dissertation, Hygienischen Institute der Universitat Wurzburg, l-13 (as cited in ATSDR, 2006).

Paolini, M., E. Sapigni, R. Mesirca, et al. 1992. On the hepatotoxicity of 1,1,2,2-tetrachloroethane. Toxicol. 73:101-115.

Parmenter, D.C. 1921. Tetrachloroethane poisoning and its prevention. J. Ind. Hyg. 2:456-465 (as cited in ATSDR, 2006).

Pellizzari, E.D. 1982. Analysis for organic vapor emissions near industrial and chemical waste disposal sites. Environ. Sci. Technol. 16:88 l-785 (as cited in ATSDR, 2006).

Plumb, R.H. 1991. The occurrence of Appendix IX organic constituents in disposal site ground water. Ground Water Monit. Rev.11(2): 157-164 (as cited in ATSDR, 2006).

Pratt, GC, K Palmer, Cy Wu. 2000. An assessment of air toxics in Minnesota. Environ, Health. Perspect. 108(9):815-825. As cited in ATSDR, 2006.

Price, N.H., S.D. Allen, A.U. Daniels, et al. 1978. Toxicity data for establishing "immediately dangerous to life or health" (IDLH) values. NTIS PB87-163531 (as cited in ATSDR, 1996).

Roldan-Arjona, T., M.D. Garcia-Pedrajas, F.L. Luque-Romero, et al. 1991. An association between mutagenicity of the Ara test of *Salmonella typhimurium* and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. Mutagen. 6(3):199–205 (as cited in WHO, 1998).

Sable, G.V. and T.P. Clark. 1984. Volatile organic compounds as indicators of municipal solid waste leachate contamination. Waste Manage. Res. 2:119-130 (as cited in ATSDR, 2006).

Sack, T.M., D.H. Steele, K. Hammerstrom, et al. 1992. A survey of household products for volatile organic compounds. Atmos. Environ. 26A:1063- 1070 (as cited in ATSDR, 2006).

Sapigni, E., M. Paolini, R. Mesirca, P. Hrelia, P. Roncada, and G. Cantelli-Forti. 1992. Short-chain aliphatic halocompounds: *in vivo* effects of microsomal monooxygenase (P450-dependent) system. Pharmacol. Res. 25(S1):77-78 (as cited in Paolini et al., 1992).

Schmidt, R. 1976. The embryotoxic and teratogenic effect of tetrachloroethane experimental studies. Biol. Rundsch. 14:4220-223.

Schmidt, P., S. Binnevies, R. Gohlke, and R. Roth. 1972. Subacute action of low concentration of chlorinated ethanes on rats with and without additional ethanol treatment. I. Biochemical and toxicometrical aspects, especially results in subacute and chronic toxicity studies with 1,1,2,2-tetrachloroethane. Int. Arch. Arbeitsmed. 30:283-298.

Schmidt, P., I.P. Ulanova, G.G. Avilova, and S.M. Binnevis. 1975. Comparison of the processes of adaptation of the organism to monotonic and intermittent action of 1,1,2,2-tetrachloroethane. Gigiena Truda I Professional'nye Zabolevaniya 2:30–34 (as cited in WHO, 1998).

Schmidt, P., R. Gohlke, A. Just, et al. 1980a. Combined action of hepatotoxic substances and increased environmental temperature on the liver of rats. J. Hyg. Epidemiol. Microbial. Immunol. (Prague) 24:271-277 (as cited in ATSDR, 2006).

Schmidt, P., D. Burck, A. Buerger, et al. 1980b. On the hepatotoxicity of benzene, 1,1,2,2-tetrachloroethane and carbon tetrachloride. Gesamte Hyg IHre Grenzgeb.

Shah, J.J. and E.K. Heyerdahl. 1988. National ambient volatile organic compounds (VOCs) database update. Research Triangle Park, NC. U.S. Environmental Protection Agency, Atmospheric Sciences Research Laboratory (as cited in ATSDR, 1996).

Sherman, J.B. 1953. Eight cases of acute tetrachloroethane poisoning. J. Trop. Med. Hyg. 56:139-140 (as cited in ATSDR, 2006).

Shmuter, L.M. 1977. The effect of chronic exposure to low concentration of ethane series chlorinated hydrocarbons on specific and nonspecific immunological reactivity in animal experiments. Gig. Tr. Prof. Zabol. 8:38-43 (as cited in ATSDR, 2006).

Sieber, W.K., D.S. Sundin, T.M. Frazier, et al. 1991. Development use and availability of a job exposure matrix based on national occupational hazard survey data. Am. J. Ind. Med. 20:163- 174 (as cited in ATSDR, 2006).

Singh, H.B., L.J. Salas, A.J. Smith, et al. 1981. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos. Environ. 15:601-12 (as cited in HSDB, 2004).

Singh, H.B., L.J. Salas, and R.E. Stiles. 1982. Distribution of selected gaseous mutagens and suspected carcinogens in ambient air. Environ. Sci. Technol. 16:872-880.

Smyth, H.F., Jr, C.P. Carpenter, C.S. Weil, et al. 1969. Range-finding toxicity data-List VII. Am. Ind. Hyg. Assoc. J. 30:470-476 (as cited in ATSDR, 2006).

Soucek, P. and I. Gut. 1992. Cytochromes P-450 in rats: structures, functions, properties and relevant human forms. Xenobiotica 22:83-103 (as cited in ATSDR, 2006).

Squillace, P.J., M.J. Moran, W.W. Lapham, et al. 1999. Volatile organic compounds in untreated ambient groundwater of the United States, 1985-1995. Environ. Sci. Technol. 33(23):4176-4187. Available from: <http://sd.water.usgs.gov/nawqa/pubs/journal/EST.voc.squillace.pdf>. Link to document (and appendices) from: <http://sd.water.usgs.gov/nawqa/pubs/>.

SRI (Stanford Research Institute). 1988. Guide to chemical producers. United States of America. SRI International, Menlo Park, CA (as cited in ATSDR, 2006).

SRI (Stanford Research Institute). 1993. Stanford Research Institute. Directory of chemical producers. United States of America. SRI International, Menlo Park, CA (as cited in ATSDR, 2006).

Staples, C.A., A.F. Werner, and T.J. Hoogheem. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. Environ. Toxicol. Chem. 4:131-142 (as cited in ATSDR, 1996).

Story, D.L., E.F. Meierhenry, C.A. Tyson, et al. 1986. Difference in rat liver enzyme-altered foci produced by chlorinated aliphatics and phenobarbital. Toxicol. Ind. Health 2:351-362.

Tabak, H.H., S.A. Quave, C.I. Mashni, et al. 1981. Biodegradability studies with organic priority pollutant compounds. J. Water Pollut. Control Fed. 53:1503-1518 (as cited in ATSDR, 2006).

Theiss, J.C., G.D. Stoner, M.B. Shimkin, et al. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Res. 37(8):2717-2720.

Thomas, R.G. 1982. Volatilization from water (Ch. 15). In Lyman W.J., W.F. Reehl, and D.H. Rosenblatt (eds.). Handbook of Chemical Property Estimation Methods. New York, NY: McGraw-Hill Book Co. pp. 15-l to15-34 (as cited in ATSDR, 2006).

Tomasi, A., E. Albano, A. Bini, et al. 1984. Free radical intermediates under hypoxic conditions in the metabolism of halogenated carcinogens. Toxicol. Pathol. 12(3):240-6 (as cited in Paolini et al. 1992).

Tomokuni, K. 1969. Studies on hepatotoxicity induced by chlorinated hydrocarbons. Lipid and ATP metabolisms in the liver of mice exposed to 1,1,2,2-tetrachloroethane. Acta Med. Okayama 23:273-282 (as cited in ATSDR, 2006).

Tomokuni, K. 1970. Hepatotoxicity induced by chlorinated hydrocarbons. II. Lipid metabolism and absorption spectrum of microsomal lipids in the mice exposed to 1,1,2,2-tetrachloroethane. Acta Med. Okayama 24:315-322 (as cited in ATSDR, 2006).

Travis, C.C., et al. 1986. Assessment of inhalation and ingestion population exposures from incinerated hazardous wastes. Environ. Int. 12533-540 (as cited in ATSDR, 2006).

Truffert, L., C. Girard-Wallon, E. Emmerich, et al. 1977. Early experimental demonstration of the hepatotoxicity of some chlorinated solvents by the study of the synthesis of hepatic DNA. Arch. Mal. Prof. Med. Trav. Secur. Sot. 38:261-263 (as cited in ATSDR, 2006).

Tsuruta, H. 1975. Comparative study in the *in vivo* percutaneous absorptions of chlorinated solvents in mice. Ind. Health 13:227-236 (as cited in ATSDR, 2006).

Tu, A.S., T.A. Murray, K.M. Hatch, et al. 1985. *In vitro* transformation of BALB/c3T3 cells by chlorinated ethanes and ethylenes. Cancer Lett. 28:85–92 (as cited in WHO, 1998).

Tzeng, H-F., A.C. Blackburn, P.G. Board, et al. 2000. Polymorphism- and species-dependent inactivation of glutathione transferase zeta by dichloroacetate. Chem Res Toxicol 13:231-236.

U.S. EPA (United States Environmental Protection Agency). 1979. Water-related environmental fate of 129 priority pollutants-Volume 111. U.S. Environmental Protection Agency, Washington, DC. EPA-440/4-79-029B (as cited in ATSDR, 2006).

U.S. EPA (United States Environmental Protection Agency). 1986a. Guidelines for the health risk assessment of chemical mixtures. Fed. Reg. 51(185):34014-34025.

U.S. EPA (United States Environmental Protection Agency). 1986b. Guidelines for mutagenicity risk assessment. Fed. Reg 51(185):34006-34012.

U.S. EPA (United States Environmental Protection Agency). 1986c. Guidelines for carcinogen risk assessment. Fed. Reg. 51(185):33992-34003.

U.S. EPA (United States Environmental Protection Agency). 1986d. Integrated Risk Information System (IRIS): 1,2-dichloroethane (cancer assessment). Available from: <http://www.epa.gov/iris/subst/0149.htm>.

U.S. EPA (United States Environmental Protection Agency). 1986e. Integrated Risk Information System (IRIS): 1,1,2,2-tetrachloroethane (cancer assessment 1986). Available from: <http://www.epa.gov/iris/subst/0193.htm>.

U.S. EPA (United States Environmental Protection Agency). 1986f. Integrated Risk Information System (IRIS): 1,1,2-trichloroethane (cancer assessment 1986). Available from: http://www.epa.gov/iris/subst/0193.htm.

U.S. EPA (United States Environmental Protection Agency). 1987. Integrated Risk Information System (IRIS): hexachloroethane (cancer assessment 1986; RfD 1987). Available from: <http://www.epa.gov/iris/subst/0167.htm>.

U.S. EPA (United States Environmental Protection Agency). 1988. Recommendations for and documentation of biological values for use in risk assessment. EPA 600/6-87/008. Available from: National Technical Information Service, Springfield, VA; PB88-179874/AS.

U.S. EPA (United States Environmental Protection Agency). 1989a. Integrated Risk Information System (IRIS): 1,1-dichloroethane (cancer assessment 1989). Available from: <http://www.epa.gov/iris/subst/0149.htm>, <http://www.epa.gov/iris/subst/0409.htm>.

U.S. EPA (United States Environmental Protection Agency). 1989b. Integrated Risk Information System (IRIS): 1,1,1,2-tetrachloroethane (cancer assessment 1989; RfD 1987). Available from: <http://www.epa.gov/iris/subst/0265.htm>.

U.S. EPA (United States Environmental Protection Agency). 1989c. 1,1,2,2-Tetrachloroethane Drinking Water Health Advisory. Office of Water.

U.S. EPA (United States Environmental Protection Agency). 1991. Guidelines for developmental toxicity risk assessment. Fed. Reg. 56(234):63798-63826.

U.S. EPA (United States Environmental Protection Agency). 1994a. Interim policy for particle size and limit concentration issues in inhalation toxicity studies. Fed. Reg. 59(206):53799.

U.S. EPA (United States Environmental Protection Agency). 1994b. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F. Available from: National Technical Information Service, Springfield, VA; PB2000-500023, and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 1995a. Use of the benchmark dose approach in health risk assessment. U.S. Environmental Protection Agency. EPA/630/R-94/007. Available from: National Technical Information Service (NTIS) , Springfield, VA; PB95-213765, and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 1995b. The national listing of fish consumption advisories and bans. EPA 823-C-95-001Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (as cited in ATSDR, 1996).

U.S. EPA (United States Environmental Protection Agency). 1996a. Guidelines for reproductive toxicity risk assessment. Fed. Reg. 61(212):56274-56322.

U.S. EPA (United States Environmental Protection Agency). 1996b. 1996 Toxics Release Inventory: Public Data Release Report. Chapter 3: Year-to-Year Comparison of Toxics Release Inventory Data. Available from: <http://www.epa.gov/tri/tridata/tri96/pdr/chap3.pdf>. Link to chapter from: <http://www.epa.gov/tri/tridata/tri96/pdr/>.

U.S. EPA (United States Environmental Protection Agency). 1997. Draft Contaminant Candidate List (CCL). Fed. Reg. 62:52193.

U.S. EPA (United States Environmental Protection Agency). 1998a. Guidelines for neurotoxicity risk assessment. Fed. Reg. 63(93):26926-26954.

U.S. EPA (United States Environmental Protection Agency). 1998b. Science policy council handbook: peer review. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-98-001. Available from: National Technical Information Service, Springfield, VA; PB98-140726, and <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 1998c. Final Contaminant Candidate List (CCL). Fed. Reg.63:10273.

U.S. EPA (United States Environmental Protection Agency). 1999. Guidelines for carcinogen risk assessment [review draft]. Risk Assessment Forum, Washington, DC; NCEA-F-0644. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2000a. Science policy council handbook: peer review. 2nd edition. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-00-001. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2000b. Science policy council handbook: risk characterization. Prepared by the Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-00-002. Available from: http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA (United States Environmental Protection Agency). 2000c. Benchmark dose technical guidance document [external review draft]. EPA/630/R-00/001. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2000d. Supplemental guidance for conducting for health risk assessment of chemical mixtures. EPA/630/R-00/002. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2000e. Occurrence of unregulated contaminants in public water systems: an initial assessment. EPA Report 815-P-00-001. Office of Water. pp. 103.

U.S. EPA (United States Environmental Protection Agency). 2000f. Methodology for deriving ambient water quality criteria for the protection of human health. Office of Water, Office of Science and Technology.

U.S. EPA (United States Environmental Protection Agency). 2002a. A review of the reference dose and reference concentration processes. Risk Assessment Forum, Washington, DC; EPA/630/P-02/0002F. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2002b. Toxics Release Inventory (TRI). Factors to consider when using TRI data. EPA 260-F-02-017. Office of Environmental Information, Washington, DC. Available from: <http://www.epa.gov/triinter/2002_tri_brochure.pdf>.

U.S. EPA (United States Environmental Protection Agency). 2002c. Announcement of preliminary regulatory determinations for priority contaminants on the drinking water. Fed. Reg. 67:38222-38244.

U.S. EPA (United States Environmental Protection Agency). 2003a. How are the Toxics Release Inventory data used? EPA 260-R-02-004. Office of Environmental Information, Washington, DC. Available from: <http://www.epa.gov/tri/guide_docs/2003_dataU.S. EPAper.pdf>.

U.S. EPA (United States Environmental Protection Agency). 2003b. Toxicological review of dichloroacetic acid in support of summary information on Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, D.C. EPA/635/R-03/007.

U.S. EPA (United States Environmental Protection Agency). 2003c. Benchmark Dose Software (BMDS) Version 1.3.2. Available from: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167>.

U.S. EPA (United States Environmental Protection Agency). 2003d. Final regulatory determinations for one microbe and 8 chemicals. Fed. Reg. 68:42897.

U.S. EPA (United States Environmental Protection Agency). 2004a. OPPTS Chemical Ingredient Database (updated weekly). Available from: <http://www.cdpr.ca.gov/docs/epa/epachem.htm>.

U.S. EPA (United States Environmental Protection Agency). 2004b. TRI Explorer: Trends. Search for 1,1,2,2-tetrachloroethane. Available from: <http://www.epa.gov/triexplorer/trends.htm>.

U.S. EPA (United States Environmental Protection Agency). 2004c. Final Second Contaminant Candidate List (CCL2). Fed. Reg. 69:17406.

U.S. EPA (United States Environmental Protection Agency). 2005a. Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available from: <http://www.epa.gov/iris/backgr-d.htm>.

U.S. EPA (United States Environmental Protection Agency). 2005b. Drinking Water Contaminant Candidate List 2; final notice. Fed. Reg. 70:9071-9077.

U.S. EPA(United States Environmental Protection Agency). 2007. Drinking Water: Regulatory Determinations Regarding Contaminants on the Second Drinking Water Contaminant Candidate List - Preliminary Determinations: Proposed Rule Fed. Reg. 72(83):24016-24058.

U.S. FDA (Food and Drug Administration). 2003. Food and Drug Administration Total Diet Study: Summary of residues found, ordered by pesticide. 91-3 -01-4. Center for Food Safety and Nutrition. Washington, DC. Available from: <http://www.cfsan.fda.gov/~acrobat/tds1byps.pdf>.

U.S. FDA (Food and Drug Administration). 2004. Everything added to foods in the United States. Food and Drug Administration. Center for Food Safety and Nutrition. Washington, DC. Available from: <http://vm.cfsan.fda.gov/~dms/eafus.html>.

USGS (United States Geological Survey). 2001. Summary publications from 51 NAWQA study units sampled in 1991-2001. Available from: <http://water.usgs.gov/pubs/nawqasum>.

Valsaraj, K.T., R.R. Kommalapati, and E.D. Robertson. 1999. Partition constants and adsorption/desorption hysteresis for volatile organic compounds on soil from a Louisiana superfund site. Environ. Monit. Assess. 58:225-241 (as cited in ATSDR 2006).

Veith, G.D., K.J. Macek, S.R. Petrocelli, et al. 1980. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish. ASTM Spec. Tech. Pub. 707:116-129 (as cited in ATSDR, 1996).

Verschueren, K. 1983. Handbook of environmental data on organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Company (as cited in ATSDR, 1996).

Vogel, E.W. and M.J.M. Nivard. 1993. Performance of 181 chemicals in a *Drosophila* assay predominantly monitoring interchromosomal mitotic recombination. Mutagen. 8(1):57–81 (as cited in WHO, 1998).

Ward, J.M. 1955. Accidental poisoning with tetrachloroethane. Br. Med. J. 1:1136 (as cited in ATSDR, 2006).

Warner, J.R., T.J. Hughes, and L.D. Claxton. 1988. Mutagenicity of 16 volatile organic chemicals in a vaporization technique with *Salmonella typhimurium* TA100. Environ. Mol. Mutagen. 11(Suppl. 11):111 (as cited in WHO, 1998).

Willcox, W.H., B.H. Spilsbury, and T.M. Legge. 1915. An outbreak of toxic jaundice of a new type amongst aeroplane workers-Its clinical and toxicological aspect. Trans. Med. Soc. London 38: 129-156 (as cited in ATSDR, 2006).

Williams, G. 1983. DNA repair tests of 11 chlorinated hydrocarbon analogs. Final report. EPA Contract. US Environmental Protection Agency, Office of Toxic Substances (Document No. 40+8324292) (as cited in WHO, 1998).

Wolff, L. 1978. The effect of 1,1,2,2-tetrachloroethane on passive avoidance learning and spontaneous locomotor activity. Activ. Nerv. Sup. (Praha) 20:14-16 (as cited in ATSDR, 2006).

Woodruff, R.C., J.M. Mason, R. Valencia, et al. 1985. Chemical mutagenesis testing in *Drosophila*. 5. Results of 53 coded compounds tested for the National Toxicology Program. Environ. Mutagen. 7:677–702 (as cited in WHO, 1998).

WHO (World Health Organization). 1998. Concise international chemical assessment document; 1,1,2,2-tetrachloroethane. Geneva.

Yllner, S. 1971. Metabolism of 1,1,2,2-tetrachloroethane-^{14}C in the mouse. Acta Pharmacol. Toxicol. 29:499-5 12.

APPENDIX A: Abbreviations and Acronyms

ACTH	adrenocorticotropic hormone
AIC	Akaike's Information Criterion
ALA	γ-aminolevulinic acid (ALA)
ALT	alanine amino transferase
AST	aspartate amino transferase
ASTER	Assessment Tools for the Evaluation of Risk
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
CAS	Chemical Abstracts Registry
CCL	Contaminant Candidate List
CYP	cytochrome
DCA	dichloroacetic acid
EC20	effective concentration for a 20% effect
EPCRA	Emergency Planning and Community Right-to-Know Act
FDA	Food and Drug Administration
FEL	frank effect level
FOB	functional observation battery
FR	Federal Register
gd	gestation day
GGT+	γ-glutamyl transpeptidase-positive
GR	green rusts
GST	glutathione-S-transferase
HA	Health Advisory
HED	human equivalent dose
HRL	health reference level
IARC	International Agency for Risk of Carcinogens
IRIS	Integrated Risk Information System
LD_{50}	lethal dose for 50% of tested animals
LOAEL	lowest observed adverse effect level
MRL	analytical method reporting limit
MTD	maximum tolerated dose
MtBE	methyl turt-butyl ether
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NOEC	no effect concentration
NOES	National Occupational Exposure Survey
NIOSH	National Institute for Occupational Safety and Health
NPL	National Priorities List
NTP	National Toxicology Program

NAWQA	National Water Quality Assessment
NOEC	no effect concentration
OGWDW	Office of Ground Water and Drinking Water
OSHA	Occupational Safety and Health Administration
PBPK	physiologically-based pharmacokinetic
PCE	tetrachloroethylene
PEL	permissible exposure level
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PWS	public water systems
RCRA	Resources Conservation and Recovery Act
RfC	reference concentration
RfD	reference dose
RR	relative risk
RSC	relative source contribution
SDWA	Safe Drinking Water Act
SDH	sorbitol dehydrogenase
SIC	Standard Industrial Classification
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UCM	unregulated contaminant monitoring
USGS	U.S. Geological Service
U.S. EPA	U.S. Environmental Protection Agency
VLDL	very low density lipoprotein
VOC	volatile organic compound

APPENDIX B: Benchmark Dose Modeling Results for Non-Cancer Endpoints

Benchmark dose (BMD) modeling was performed to identify potential critical effect levels for derivation of the RfD for 1,1,2,2-trichloroethane. The modeling was conducted according to draft EPA guidelines (U.S. EPA, 2000c) using Benchmark Dose Software Version 1.3.2 (BMDS), which is available from EPA (U.S. EPA, 2002). The BMD modeling results are summarized in Tables C-1 through C-3, with selected output following. The table include results for all the endpoints and models for which (1) the BMDS model converged correctly, and (2) for which BMDL and BMDL estimates were successfuly generated.

BMD models were fit for all of the endpoints from the 14-week feeding study (NTP, 2004) that showed dose-related patterns of severity in rats and/or mice. These included serum alanine aminotransferase (ALT) and sorbitol dehydrogenase (SDH), as well as blood hemoglobin concentration, relative liver weight, and sperm motility in male rats. For BMD modeling, we excluded data from high-dose groups that showed significant body weight differences from controls and lower dose groups. This was done to exclude the potential that lower food consumption, generalized systemic effects, or acute toxicity might effect the dose-response relationships for the critical effects. For rats, this meant excluding all dose groups above 80 mg/kg-day. For female mice, all dose groups above 300 mg/kg-day were excluded, and for male mice, data from dose groups above 370 mg/kg-day were excluded.

Because the endpoints are continuous variables, the continuous models available with BMDS (linear, polynomial, power) were used. Because of the small number of data points available (four for most of the data sets, three for the male mice, the Hill Model was not used to fit data from the rat and mouse studies. For all of the modeling conducted, the BMR was defined as an excess risk of 1.0 control standard deviation, the default for continuous data (U.S. EPA, 2000c).

It can be seen from the data in Tables B1-B3, that the rat is the more sensitive species, as indicated by the lower BMD and BMDL values for rats as compared to mice, and that male rats seem to be more sensitive than females. For this reason, as noted in Section 8.1.1, the most sensitive endpoint in male rats (increase in relative liver weight, BMD) was selected as the point of departure for RfD Derivation. The best-fitting (Linear) model generates a BMD estimate of 13.1 mg/kg and a BMDL estimate of 10.7 mg/kg. Relative liver weight is also the most sensitive endpoint for female rats (BMDL = 24.2, BMDL = 16.1 with the best-fitting model.)

Table B-1 Benchmark Dose Modeling Summary for For Male Rats (NTP, 2004)

Endpoint(a)	Model	p - value	AIC	BMD	BMDL
ALT	Polynomial	0.965	200.09	46.6	29.1
ALT	Power	0.944	202.09	46.5	29.5
ALT	Linear	0.089	202.92	26.7	20.5
SDH	Linear	0.261	157.19	45.7	31.7
SDH	Polynomial	0.101	159.19	45.7	31.7
SDH	Power	0.101	161.19	45.7	31.7
RLW	Linear	0.148	92.26	13.1	10.7
RLW	Polynomial	0.059	94.02	11.8	8.5
RLW	Power	0.051	96.26	13.1	10.7
HEMO	Linear	0.709	-7.36	45.5	31.6
HEMO	Polynomial	0.526	-5.65	36.2	17.9
HEMO	Power	0.407	-3.36	45.5	31.6
MOT	Linear	0.0038	156.32	49.2	32.8

(a) ALT = alanine amino transferase, SDH = sorbitol dehydrogenase, RLW = relative liver weight, HEMO = hemoglobin, and MOT = sperm motility

Table B-2 Benchmark Dose Modeling Summary for Female Rats (NTP, 2004)

Endpoint(a)	Model	p - value	AIC	BMD	BMDL
ALT	Polynomial	0.96	180.83	86.3	76.1
ALT	Linear	0.01	188.74	125.7	59.3
ALT	Power	0.03	183.37	79.8	79.8
ALT	Polynomial (restricted)	0.01	185.90	83.1	63.2
SDH	Linear	0.44	156.17	167.3	67.4
SDH	Power	0.52	156.93	82.4	74.8
RLW	Polynomial	0.198	69.89	24.2	16.1
RLW	Power	0.138	72.43	26.0	17.6
RLW	Linear	0.003	77.56	13.3	10.9
HEMO	Linear	0.068	-28.76	29.4	22.3
HEMO	Polynomial	0.205	-30.54	48.7	29.7
HEMO	Power	0.211	-28.58	46.0	29.5

(a) See note to Table C-1.

Table B-3 Benchmark Dose Modeling Summary for Male and Female Mice (NTP, 2004)

MALE					
Endpoint(a)	**Model**	**p - value**	**AIC**	**BMD**	**BMDL**
ALT	Linear	0.591	253.03	770	169
SDH	Linear	0.0004	172.39	76.5	54.1
RLW	Linear	0.089	98.64	58.9	43.7
FEMALE					
Endpoint	**Model**	**p - value**	**AIC**	**BMD**	**BMDL**
ALT	Power	0.627	369.098	206	132
ALT	Polynomial	0.513	367.290	194	126
ALT	Linear	0.061	370.455	114.1	86.0
SDH	Linear	<.0001	319.403	56.6	46.0
SDH	Power	0.948	300.954	126	95.0
SDH	Polynomial	0.912	298.962	127	91.7
RLW	Polynomial	0.027	137.941	34.0	25.4
RLW	Linear	0.001	145.446	73.2	58.4
RLW	Power	0.000	149.446	73.2	58.4

(a) See note to Table C1.

BMDS Model Output for Critical Non-Cancer Effect (Relative Liver Weight in Male Rats)

```
================================================================
        Polynomial Model. Revision: 2.2  Date: 9/12/2002
        Input Data File: C:\BMDS DOCS\RE-ENTERED\MALE_RAT.(d)
        Gnuplot Plotting File:  C:\BMDS DOCS\RE-ENTERED\MALE_RAT.plt
                                                Mon Jul 17 13:45:46 2006
================================================================
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  The form of the response function is:
  Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

  Dependent variable = MEAN
  Independent variable = DOSE
  rho is set to 0
  Signs of the polynomial coefficients are not restricted
  A constant variance model is fit

  Total number of dose groups = 4
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

            Default Initial Parameter Values
                  alpha =       3.375
                    rho =           0   Specified
                 beta_0 =      34.646
                 beta_1 =    0.139757

                      Parameter Estimates

                                          95.0% Wald Confidence Interval
    Variable        Estimate       Std. Err.    Lower Conf. Limit   Upper Conf. Limit
       alpha         3.34192        0.747275             1.87728             4.80655
      beta_0          34.646        0.447789             33.7683             35.5237
      beta_1        0.139757      0.00977156            0.120605            0.158909

        Asymptotic Correlation Matrix of Parameter Estimates

               alpha       beta_0       beta_1
     alpha         1        1e-012   -1.1e-012
    beta_0    1e-012             1       -0.76
    beta_1  -1.1e-012         -0.76           1
```

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2 Res.
0	10	34.8	1.3	34.6	1.83	0.249
20	10	36.7	1.4	37.4	1.83	-1.25
40	10	41	2.7	40.2	1.83	1.37
80	10	45.6	1.6	45.8	1.83	-0.375

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-42.220696	5	94.441392
A2	-38.513709	8	93.027417
fitted	-44.130893	2	92.261785
R	-80.848861	2	165.697722

Test 1: Does response and/or variances differ among dose levels (A2 vs. R)
Test 2: Are Variances Homogeneous (A1 vs. A2)
Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	84.6703	6	<.0001
Test 2	7.41397	3	0.05981
Test 3	3.82039	2	0.1481

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels. It seems appropriate to model the data

The p-value for Test 2 is greater than .05. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .05. The model chosen appears to adequately describe the data

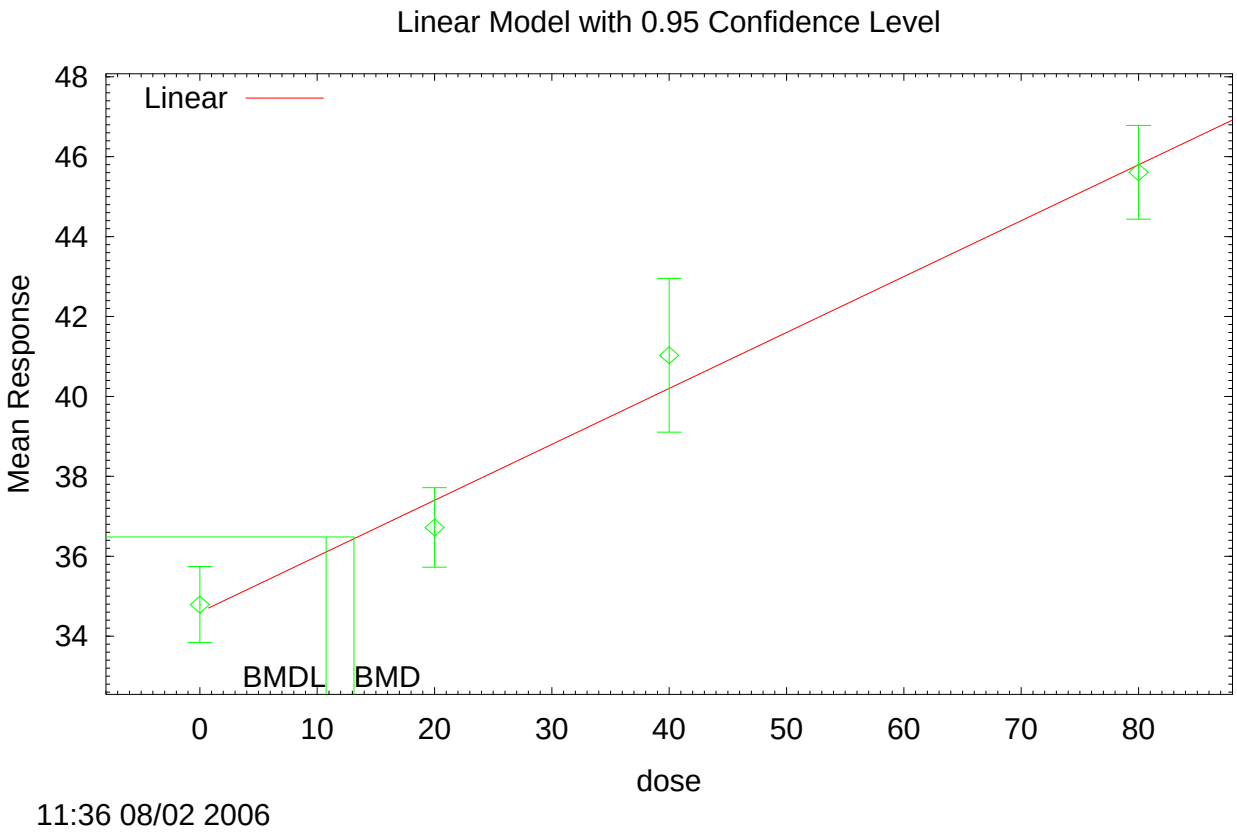
Benchmark Dose Computation
Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 13.0805

BMDL = 10.7147



APPENDIX C: Benchmark Dose Modeling Results for Cancer Risk Estimation

Benchmark dose (BMD) modeling was performed to identify a point of departure (POD) for derivation of the cancer risk estimates for 1,1,2,2-trichloroethane. The modeling was conducted according to EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) and draft EPA BMD guidelines (U.S. EPA, 2000c) using Benchmark Dose Software Version 1.3.2 (BMDS), which is available from EPA (U.S. EPA, 2002). The BMD modeling results are summarized in Table D-1, with selected output following. A brief discussion of the modeling results is presented below. Based upon current EPA policy, only the multistage model was used, with the BMR defined as a 10% increased incidence over control.

The increased incidence of liver tumors in female B6C3F1 mice given 1,1,2,2-trichloroethane in feed for 78 weeks (NCI, 1978) was chosen as the endpoint to model. These results are summarized in Table D-1. Fitting the 2-stage multistage model resulted in a BMD of 14.58 mg/kg-day and a BMDL of 8.22 mg/kg-day.

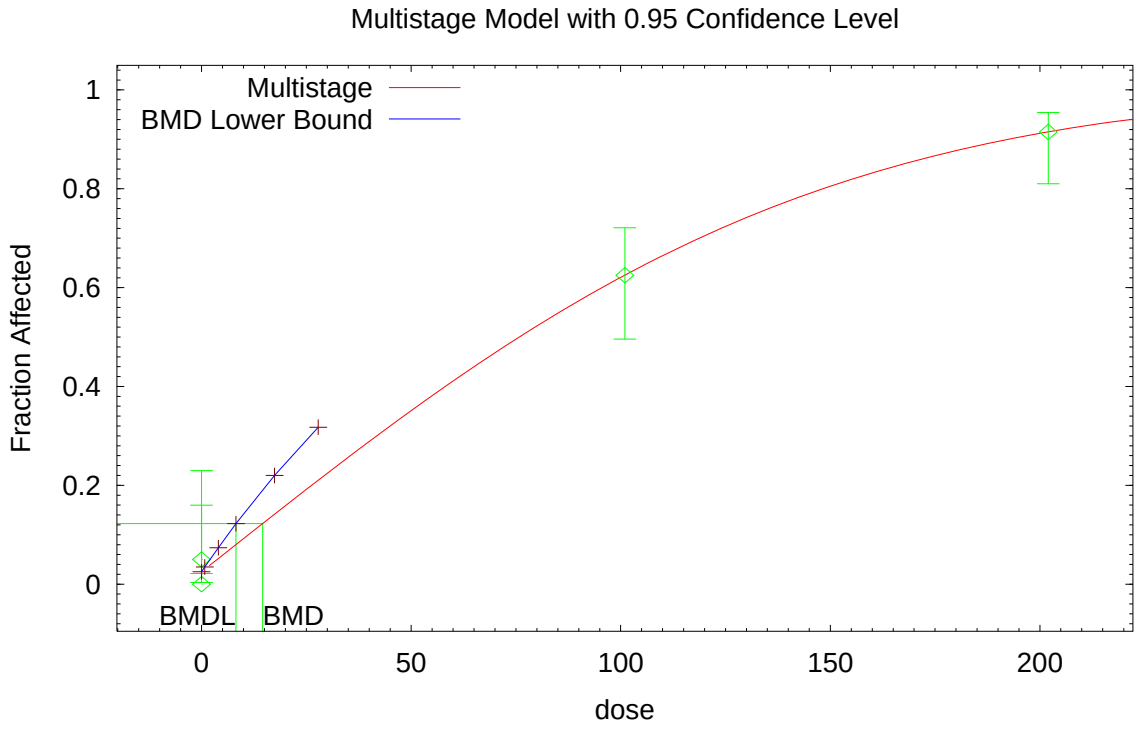
Table C-1 Benchmark Dose Estimates from NTP (2004) Male Rat Serum ALT Activity

Model	BMD	BMDL	Chi-square *p*-value	AIC[2]
Multistage (2)	**14.58**	**8.22**	**0.31**	**106**

[2]Akaike's Information Criterion (AIC) = -2L + 2p, where L is the log-likelihood at the maximum likelihood estimates for the parameters, and p is the number of model degrees of freedom. This can be used to compare models with different numbers of parameters using a similar fitting method (for example, least squares or a binomial maximum likelihood). Although such methods are not exact, they can provide useful guidance in model selection.

Benchmark Dose Modeling Output For 1122-TCE Cancer Endpoint

```
==========================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: E:\BMDS\DATA\TCE-HEPCARC.(d)
        Gnuplot Plotting File:  E:\BMDS\DATA\TCE-HEPCARC.plt
                                                  Tue Jun 14 11:02:53 2005
==========================================================================

BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

  The parameter betas are restricted to be positive

  Dependent variable = fmouse_hepcarc
  Independent variable = fmouse_dose

Total number of observations = 4
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

            Default Initial Parameter Values
              Background =     0.0253206
                 Beta(1) =    0.00684418
                 Beta(2) =   2.5872e-005

        Asymptotic Correlation Matrix of Parameter Estimates

          Background      Beta(1)      Beta(2)
Background          1        -0.41         0.23
  Beta(1)       -0.41            1        -0.93
  Beta(2)        0.23        -0.93            1
```



Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.025	0.156125
Beta(1)	0.00684906	0.00579368
Beta(2)	2.58559e-005	3.45846e-005

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-49.4055			
Fitted model	-50.1115	1.41194	1	0.2347
Reduced model	-92.948	87.085	3	<.0001

AIC: 106.223

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1					
0.0000	0.0250	0.500	1	20	1.026
i: 2					

```
    0.0000     0.0250        0.500        0         20      -1.026
i: 3
  101.0000     0.6250       30.000       30         48       0.000
i: 4
  202.0000     0.9149       43.000       43         47       0.000

 Chi-square =       1.03     DF = 1       P-value = 0.3112
```

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 14.5806

BMDL = 8.22427