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TOXICOLOGICAL REVIEW

OF

1,1,1-TRICHLOROETHANE

(CAS No. 71-55-6)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

February 2007

NOTICE

This document is an **Agency Review draft**. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for review of its technical accuracy and science policy implications.

U.S. Environmental Protection Agency
Washington, DC

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FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to exposure to 1,1,1-trichloroethane. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of 1,1,1-trichloroethane.

In Section 6, *Major Conclusions in the Characterization of Hazard and Dose Response,* EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response by addressing knowledge gaps, uncertainties, quality of data, and scientific controversies. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

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This document and the accompanying IRIS Summary have been peer reviewed by EPA scientists and independent scientists external to EPA. Comments from all peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. During the finalization process, the IRIS Program Director achieved common understanding of the assessment among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Economics, and Innovation; Office of Children's Health Protection; Office of Environmental Information; and EPA's regional offices.

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Summaries of the external peer reviewers' comments *[and public comments, if applicable]* and the disposition of their recommendations are in Appendix A.

1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and dose-response assessment of 1,1,1-trichloroethane. IRIS Summaries may include oral reference dose (RfD) and inhalation reference concentration (RfC) values for chronic and less-than-lifetime exposure durations, and a carcinogenicity assessment.

The RfD and RfC provide quantitative information for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. The RfD (expressed in units of mg/kg-day) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation RfC (expressed in units of mg/m^3) is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). Reference values may also be derived for acute ($\leq$24 hours), short-term (>24 hours, up to 30 days), and subchronic (>30 days, up to approximately 10% of the life span) exposure durations, all of which are derived based on an assumption of continuous exposure throughout the duration specified.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral and inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is an upper bound on the estimate of risk per unit of concentration, either per μg/L drinking water or per $\mu g/m^3$ air breathed. Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

Development of these hazard identification and dose-response assessments for 1,1,1-trichloroethane has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines and technical reports that were used in the development of this assessment 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, 1991a), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988a), (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, 1995), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998b, 2000a, 2005c), *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 literature search strategy employed for this compound was based on the CASRN and at least one common name. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document. The relevant literature was reviewed through June 2006.

2. CHEMICAL AND PHYSICAL INFORMATION

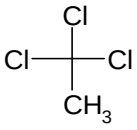
1,1,1-Trichloroethane is a colorless liquid with an odor resembling chloroform. Information on chemical identity is presented in Table 1. Physico-chemical properties for 1,1,1-trichloroethane are listed in Table 2.

1,1,1-Trichloroethane is produced most commonly by reaction of hydrochloric acid with vinyl chloride (from 1,2-dichloroethane) to obtain 1,1-dichloroethane, which can then undergo thermal and photochemical chlorination (U.S. EPA, 1991b; HSDB, 2002; ATSDR, 2006). Other methods of production include the catalyzed addition of hydrogen chloride to 1,1-dichloroethylene and the direct chlorination of ethane (U.S. EPA, 1991b; HSDB, 2002; ATSDR, 2006). In order to prevent reaction with aluminum and alloys, commercial grades of 1,1,1-trichloroethane contain an inhibitor such as nitromethane, N-methylpyrrole, 1,4-dioxane, butylene oxide, 1,3-dioxolane, or a secondary butyl alcohol (U.S. EPA, 1991b; ATSDR, 2006; Reid, 2001).

1,1,1-Trichloroethane was originally introduced as a replacement for other chlorinated and flammable solvents like carbon tetrachloride (U.S. EPA, 1991b; ATSDR, 2006). Although 1,1,1-trichloroethane was formerly used extensively in a range of industrial applications and consumer products, currently this chemical is used almost entirely as a precursor for hydrofluorocarbons (ATSDR, 2006). According to ATSDR (2006), use of 1,1,1-trichloroethane as of 1995 included as a hydrochloroflurorcarbon intermediate (60%), in vapor degreasing and cold cleaning (25%), as a solvent for adhesives (5%), in coatings and inks (3%), textiles (2%) and electronics and miscellaneous (5%). 1,1,1-Trichloroethane was used extensively in household products, including such products as adhesives and adhesive cleaners, lubricants, general purpose liquid cleaners and spray degreasers, oven cleaners, spot removers, shoe polish, and fabric finishes (IARC, 1999; Reid, 2001; ATSDR, 2006; HSDB, 2002); however, it is no longer used in common household products (ATSDR, 2006). This chemical was formerly used as a food and grain fumigant (ATSDR, 2006; HSDB, 2002).

1,1,1-Trichloroethane is one of the compounds addressed by the Montreal Protocol, which stipulates that the production and consumption of these potentially ozone-depleting substances in the stratosphere are to be phased out. Under the Montreal Protocol, the final phase-out for developed countries for 1,1,1-trichloroethane was 1996, with selected exceptions for existing stocks and essential uses; developing countries have until 2015 for their ban to take effect (Doherty, 2000a; Doherty, 2000b; UNEP, 2000; Krol et al., 2003).

Table 1. Chemical Identity of 1,1,1-Trichloroethane

Characteristic	Value	Reference
Chemical name	1,1,1-Trichloroethane	Budavari, 2001
Synonyms	Methyl chloroform; alpha-Trichloroethane; Methyltrichloromethane	HSDB, 2002
Trade names	Alpha-T; Aerothene MM; Aerothene TT; Algylen; Baltana; CF 2; Chloroethane-NU; Chlorotene; Chlorothane NU; Chlorothene NU; Chlorothene SM; Chlorothene VG; Chlorylen; Dowclene LS; Gemalgene; Genklene; ICI-CF 2; Inhibisol; Solvent 111; TCEA; Trichloran; Trielene	HSDB, 2002
Chemical formula	$C_2H_3Cl_3$	Budavari, 2001
Chemical structure		Verschueren, 2001
CAS Registry	71-55-6	Budavari, 2001
Shipping name / DOT number	UN 2831; IMO 6.1	HSDB, 2002
Standard Transportation Number	49 633 75	HSDB, 2002
NIOSH RTECS	KJ2975000	HSDB, 2002
EPA Hazardous Waste	U226; F002	HSDB, 2002
OHM/TADS	No data	

CAS = Chemical Abstracts Service; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substances Data Bank

Table 2. Physico-chemical Properties of 1,1,1-Trichloroethane

Property	Value	Reference
Molecular weight	133.40	Lide, 2000
Color	Colorless	Lewis, 1997
Physical state	Liquid	Budavari, 2001
Melting point	-30.4 °C	Lide, 2000
Boiling point	74.0 °C	Lide, 2000
Density at 20 °C	1.3390 g/cm^3	Lide, 2000
Odor	Mild, chloroform-like odor	NIOSH, 1997
Odor threshold:		
Air	100 ppm	Weiss, 1986
Saturation concentration in air	726 g/m^3 at 20 °C; 1,088 g/m^3 at 30 °C	Verschueren, 2001
Solubility:		
Water	1,500 mg/L at 25 °C	ATSDR, 2006
Organic solvents	Soluble in ethanol and chloroform; miscible in ether	Lide, 2000
Partition coefficients:		
Log octanol/water	2.49	Hansch et al., 1995
Log Koc	2.02 to 2.03	ATSDR, 2006
Vapor pressure	100 mm Hg at 20 °C; 155 mm Hg at 30 °C	Verschueren, 2001
Vapor density	4.6	Verschueren, 2001
Critical temperature	311.5 °C	HSDB, 2002
Henry's law constant	8 x 10^{-3} atm-m^3/mol	HSDB, 2002
Refractive index at 20 °C	1.4379	Lide, 2000
Heat of combustion	110x10^5 J/kg	HSDB, 2002
Heat of vaporization at 25 °C	32.50 kJ/mol	HSDB, 2002
Autoignition temperature	500 °C	Weiss, 1986
Flashpoint	None	Lewis, 1997
Flammability limits	7%-16%	Weiss, 1986
Conversion factors	1 mg/m^3 = 0.18 ppm; 1 ppm = 5.46 mg/m^3	IARC, 1999

3. TOXICOKINETICS

3.1. ABSORPTION

In humans and experimental animals, 1,1,1-trichloroethane is well absorbed by all routes of exposure. At least by inhalation, the rate of uptake is driven initially by tissue loading (i.e., accumulation in blood and tissues), and by metabolism once steady state conditions have been reached.

Studies in humans exposed to 1,1,1-trichloroethane demonstrate that 1,1,1-trichloroethane is rapidly and efficiently absorbed by the respiratory tract. Expired alveolar air from a human subject who held breaths of air containing ^{38}Cl-labeled 1,1,1-trichloroethane for durations ranging from 15 to 40 seconds contained only 2-5% of the concentration of the inhaled compound (based on activity of the radiolabel) (Morgan et al., 1970, 1972a, 1972b). 1,1,1-Trichloroethane was detected in arterial blood as soon as 10 seconds after the start of exposure in human subjects exposed to approximately 250 ppm (1370 mg/m^3) of 1,1,1-trichloroethane (Astrand et al., 1973).

Concentrations of 1,1,1-trichloroethane in blood and expired air increased rapidly in human subjects (n=6) exposed continuously to 35 or 350 ppm (190 or 1900 mg/m^3) 1,1,1-trichloroethane for 6 hours; after only 1.5 hours, blood and expired air concentrations were already about 90% of the concentrations later observed after 6 hours of exposure (Nolan et al., 1984). Using a physiologically-based pharmacokinetic (PBPK) model[1], it was predicted that the subjects retained respective averages of 101.6 and 1005 mg 1,1,1-trichloroethane during the 6 hours of exposure, and that these amounts represented about 25% of the 1,1,1-trichloroethane that was inhaled (Nolan et al., 1984). Monster et al. (1979) exposed human subjects (n=6) for 4 hours to 70 or 145 ppm (380 or 790 mg/m^3) 1,1,1-trichloroethane while at rest or 142 ppm (780 mg/m^3) while experiencing alternating periods of rest and work (two 30-minute periods on a bicycle ergometer at 100W). Minute volumes and concentration in exhaled air were measured at various times during and after exposure. Uptake of 1,1,1-trichloroethane during the exposure period ranged from 140 to 240 mg for 70 ppm (380 mg/m^3) at rest, 305 to 520 mg for 145 ppm (790 mg/m^3) at rest, and 435 to 610 mg for 142 ppm (780 mg/m^3) with alternating periods of rest and work; average uptakes across subjects were 193, 429, and 538 mg, respectively. Alveolar retention was reported to be about 30% at the end of exposure (Monster et al., 1979). Based on measurements of 1,1,1-trichloroethane in expired air and ventilation rates, estimates of alveolar

[1] Developed from data for concentrations of 1,1,1-trichloroethane and its principal metabolites, trichloroethanol and trichloroacetic acid, in blood and urine collected from the 6 human subjects exposed to 35 or 350 ppm for 6 hours (Nolan et al., 1984).

retention ranged from 26.1 to 35.6% in human subjects (n=2-3) exposed to 72 or 213 ppm (390 or 1160 mg/m^3) 1,1,1-trichloroethane for 8 hours (Humbert and Fernandez, 1977).

Studies in rats and mice provide supporting evidence that inhaled 1,1,1-trichloroethane is rapidly and efficiently absorbed by the respiratory tract. Groups of male Fischer 344 rats (n=16) and male B6C3F1 mice (n=16) were exposed to 150 or 1500 ppm (820 or 8190 mg/m^3) of [2-^{14}C]-labeled 1,1,1-trichloroethane for 6 hours (Schumann et al., 1982a). Following exposure, the urine, feces, and expired air were collected at regular intervals. Groups of 4 animals per species were sacrificed at 0, 24, 48, and 72 hours post-exposure for collection of tissues. Amounts of radioactivity were measured in expired air (as unchanged 1,1,1-trichloroethane and as CO_2), feces, urine, skin, liver, kidney, fat, and the remaining carcasses. Absorption of 1,1,1-trichloroethane was indicated by the detection of considerable radioactivity in the rat and mouse liver, kidney, and fat tissues immediately after termination of exposure, and by the increased concentration of 1,1,1-trichloroethane equivalents in these tissues with increasing exposure level (Table 3 in Section 3.2.). In a companion experiment in which 1,1,1-trichloroethane was measured in blood samples collected at intervals during and after 6-hour exposure to 1,1,1-trichloroethane, blood concentrations of 1,1,1-trichloroethane were about 2 and 20 μg/g blood in rats immediately after termination of exposure to 150 or 1500 ppm (820 or 8190 mg/m^3), respectively; in mice, blood concentrations were about 13 and 105 μg/g blood immediately after termination of exposure to the same air concentrations (Schumann et al., 1982a).

The percent uptake of inhaled 1,1,1-trichloroethane (i.e., pulmonary retention) has been demonstrated to be time dependent. Monster et al. (1979) reported that percent uptake by humans was approximately 95% at the onset of a 4-hour exposure to 70 or 145 ppm (380 or 790 mg/m^3) 1,1,1-trichloroethane and decreased to approximately 30% at the end of exposure. Similar results have been reported for male Sprague-Dawley rats exposed to 50 or 500 ppm (270 or 2730 mg/m^3) for 2 hours; percent uptake was about 80% at the onset of exposure and declined to about 50% at the end of exposure (Dallas et al., 1989). Initial uptake of inhaled 1,1,1-trichloroethane is expected to be primarily influenced by tissue loading, but, once steady state conditions are reached, uptake of 1,1,1-trichloroethane is expected to be driven primarily by the decrease in the parent concentration in body fluids as a result of metabolism. Dallas et al. (1989) noted that once steady state is reached, percent uptake of 1,1,1-trichloroethane is expected to be low, since 1,1,1-trichloroethane is slowly metabolized and readily excreted predominately as unchanged compound in exhaled air (see Sections 3.2, 3.3, and 3.4).

No data on the extent or rate of absorption of 1,1,1-trichloroethane in the gastrointestinal tract of humans are available, but results from animal studies indicate that absorption is rapid and almost complete (≥90%) (Mitoma et al., 1985; Reitz et al., 1988; RTI, 1988).

In studies of male Fischer 344 rats (n=3-4 per dose) given single gavage doses of 100,

300, or 1000 mg/kg of [2-^{14}C]-labeled 1,1,1-trichloroethane in vegetable oil, radioactivity in exhaled air trapped in cold ethanol during a 24-hour post-administration period represented 96.7, 92.0, and 98.9% of the administered doses, respectively (RTI, 1988). In female B6C3F1 mice (n=3) given single doses of 100 or 300 mg/kg of the same material, radioactivity in trapped exhaled air represented 96.7 and 92.0% of the administered doses, respectively. Rapid absorption was indicated in both species by observations that radioactivity in air trapped in the first hour after administration accounted for 7.8 to 11.2% of administered doses in rats, and 10.6 to 18.5% of administered doses in mice (RTI, 1988).

Similar results indicating nearly complete gastrointestinal absorption were obtained in another study in which groups of male Osborne-Mendel rats (n=4) and male B6C3F1 mice (n=4) were given [1,2-^{14}C]-labeled 1,1,1-trichloroethane (in corn oil) at dose levels of 3000 mg/kg and 4000 mg/kg, respectively (Mitoma et al., 1985). In this study, animals were placed in metabolism cages for 48 hours following dose administration to collect excreta (urine and feces) and expired air (expired radioactivity was separated into volatile organic compounds, which was assumed to be 1,1,1-trichloroethane, and expired CO_2). In rats, the amounts of recovered radioactivity (expressed as percentages of the administered dose) were 85.13% in trapped expired organic compounds, 0.87% in trapped expired CO_2, 2.05% in excreta, and 1.20% in carcasses; in mice, the respective percentages were 92.94%, 2.01%, 3.36%, and 0.72%.

In a study of male Fischer 344 rats (n = 4) with free access to drinking water containing [2-^{14}C]-labeled 1,1,1-trichloroethane for 8 hours, radioactivity in expired air, urine, and selected tissues (liver, kidney, skin, and carcass homogenate) represented 95.2% of the average dose of 116 mg/kg (Reitz et al., 1988). Samples of expired air and urine were collected during exposure and up to 48 hours after exposure, when rats were sacrificed.

Absorption of 1,1,1-trichloroethane by the skin has been demonstrated in human subjects (Fukabori et al., 1977; Kezic et al., 2000, 2001; Riihimaki and Pfaffli, 1978; Stewart and Dodd, 1964). Immersing the thumb or hand in 1,1,1-trichloroethane for 30 minutes resulted in mean peak alveolar air concentrations in human subjects of 1 or 22 ppm (5.5 or 120 mg/m^3), respectively (Stewart and Dodd, 1964). In another study, three subjects received two daily one-hour occluded applications of 1,1,1-trichloroethane to forearm skin for five days (Fukabori et al., 1977). Mean alveolar air concentrations of 1,1,1-trichloroethane after the second of two daily concentrations ranged (across 5 consecutive days) from 1.9 to 4.8 ppm. Blood samples collected immediately after the end of the last exposure on day 5 showed concentrations of 1,1,1-trichloroethane ranging (among the three subjects) from 1.1 to 8.8 μg/mL (average = 5.4 μg/mL). In another experiment with three subjects similarly exposed to 1,1,1-trichloroethane for one hour only, average blood concentrations of 1,1,1-trichloroethane were 4.8, 3.4, and 3.4 μg/mL at 0, 30, and 60 minutes post-exposure; average alveolar air concentrations at the same intervals after

exposure were 3.1, 1.8, and 1.2 ppm, respectively (Fukabori et al., 1977).

Kezic et al. (2001) calculated an average dermal absorption flux of 56 nmol 1,1,1-trichloroethane/cm^2/minute in human subjects (n=3) exposed for 3 minutes to liquid 1,1,1-trichloroethane on a 3-cm^2 area of forearm skin. Dermal permeation rates were calculated from time courses of exhaled air concentration measured after dermal exposure and after a reference inhalation exposure. Using the average dermal absorption flux, a daily intake of 0.5 mmoles 1,1,1-trichloroethane was calculated for an exposure scenario that involved immersion of a 360-cm^2 area of skin for 3 minutes, eight times a day. This intake represented about 5% of an estimated respiratory intake of 1,1,1-trichloroethane (9.6 mmoles) resulting from an 8-hour inhalation exposure to 1910 mg/m^3, assuming an alveolar minute volume of 7 L/minute and a respiratory retention percentage of 20%.

Riihimaki and Pfaffli (1978) estimated that absorption of airborne 1,1,1-trichloroethane by the skin of human subjects represented 0.08% of the amount of 1,1,1-trichloroethane absorbed by the respiratory tract. These investigators exposed 2 human subjects wearing thin cloth pajamas, socks, and respiratory protection to 600 ppm of 1,1,1-trichloroethane for 3.5 hours. During exposure, the subjects cycled on a bicycle ergometer for 10 minutes of each full hour of exposure. Expired air samples were collected at several intervals during and after exposure. Based on 1,1,1-trichloroethane concentrations in expired air, the average amount of 1,1,1-trichloroethane absorbed by the skin was estimated to be 15.9 μmoles. It was calculated that, in the absence of respiratory protection, 20,399 μmoles of 1,1,1-trichloroethane would have been absorbed by the respiratory tract, assuming a ventilation rate of 10 L/minute and an average pulmonary retention of 40%.

Dermal absorption of airborne 1,1,1-trichloroethane was also measured in 5 human subjects exposed to a concentration of 1.57 mmol/L (about 38,380 ppm) (Kezic et al., 2000). In this study, a forearm and hand (about 1000-cm^2 area) were enclosed in a chamber with 1,1,1-trichloroethane vapor for 20 minutes, and exhaled alveolar air samples were collected at intervals during and up to 6 hours after exposure. Concentrations of 1,1,1-trichloroethane in exhaled air were determined by gas chromatography and flame ionization detection. From these measurements (and measurements of exhaled air following a short-term inhalation exposure of the subjects), the average absorption rate into the skin during the 20-minute exposure (normalized to 1 nmol/L and 1000 cm^2) was calculated to be 0.021 ± 0.003 cm/hour. Using this absorption rate and assuming a whole-body skin area of 20,000 cm^2, the amount of 1,1,1-trichloroethane absorbed into the skin from a 20-minute whole-body exposure to 1 nmol/L of 1,1,1-trichloroethane was calculated to be 0.1% of the amount absorbed by the respiratory tract during the same period.

Rapid dermal absorption has been demonstrated in male Fischer 344 rats exposed to pure

1,1,1-trichloroethane, or one-third, two-thirds, or fully saturated aqueous solutions of 1,1,1-trichloroethane (Morgan et al., 1991). In these studies, 2 mL of test material were applied to an occluded 3.1-cm^2 area of shaved dorsal skin for 24 hours. Blood samples were collected at 0, 0.5, 1, 2, 4, 8, 12, and 24 hours and concentrations of 1,1,1-trichloroethane were determined by gas chromatography. With exposure to pure 1,1,1-trichloroethane, near maximum blood levels of 1,1,1-trichloroethane (about 10 μg/mL blood) were attained within 0.5 hours and remained essentially constant through 24 hours. With exposure to aqueous solutions, maximum blood concentrations were attained between 4 and 8 hours of exposure and declined thereafter. Maximum blood concentrations were about 20, 50, and 120 ng of 1,1,1-trichloroethane/mL blood for one-third, two-thirds, and fully saturated solutions, respectively.

Skin:air partition coefficients for 1,1,1-trichloroethane and other volatile solvents have been measured *in vitro* using strips of dorsal skin from 8- to 16-week-old Fischer 344 rats (Mattie et al., 1994). These coefficients can be used in PBPK models describing the uptake of a chemical from air or solutions into the skin (see Section 3.5). The coefficient for 1,1,1-trichloroethane (10.8±0.6) was near the lower end of the range of coefficients measured for 11 common solvents. Hexane had the lowest coefficient (1.9±0.1), and styrene had the highest (91.9±6.8).

3.2. DISTRIBUTION

Results from studies of animals exposed by inhalation or gavage indicate that following absorption, 1,1,1-trichloroethane is distributed to tissues throughout the body, with preferential distribution to fat. Disposition in the body is similar in animals exposed once or repeatedly to 1,1,1-trichloroethane. Studies in pregnant animals show that distribution to the placenta and developing fetus is relatively low.

Immediately following 6-hour inhalation exposure of rats or mice to 150 or 1500 ppm (820 or 8190 mg/m^3) of [2-^{14}C]-labeled 1,1,1-trichloroethane (Schumann et al., 1982a), the tissue concentrations of 1,1,1-trichloroethane equivalents showed the order of fat > kidney > liver (see Table 3).

Table 3. Distribution and Clearance of Radioactivity in Rat and Mouse Tissues Following a 6-hour Inhalation Exposure to 150 or 1500 ppm [2-^{14}C]-labeled 1,1,1-Trichloroethane

Exposure Level and Tissue	nmol-equivalents 1,1,1-trichloroethane/g of tissue[1]			
	0 hour	24 hour	48 hour	72 hour
Mouse 150 ppm				
Liver	76.0±7.5	5.0± 0.8	2.8± 1.0	4.4± 0.7
Kidney	74.6± 6.7	7.0± 2.0	5.8± 0.6	3.0±1.5 (3)[2]
Fat	1329±123	10.2 (1)	7.6 (1)	ND[3]
Mouse 1500 ppm				
Liver	631±144	ND[4]	ND[4]	ND[4]
Kidney	1103±579	ND[4]	ND[4]	ND[4]
Fat	16,198±1792	ND[4]	ND[4]	ND[4]
Rat 150 ppm				
Liver	68.2 ±4.4	4.5±0.9	4.2±0.4	3.1±0.4
Kidney	225±31	9.3±1.6	7.5± 0.6	5.3±0.7
Fat	724±236	14.1±5.6	ND	ND
Rat 1500 ppm				
Liver	504 ±33	19.1±1.5	13.2±1.4	9.8±1.3
Kidney	994±261	28.5±6.6	17.9±4.8	11.1±3.8
Fat	8403 ±1780	60.1±51.7	21.7±10.6 (2)	12.1 (1)

[1] Values are means ±SD of data from 4 animals, unless otherwise noted.
[2] Some determinations were below the detection limit. When not all determinations were above the detection limit, the number in parentheses represents the number of animals with values above the detection limit.
[3] Not detectable.
[4] The authors stated that the inability to detect ^{14}C activity in the tissues of mice 24 hours after the 1500 ppm exposure reflected the lower specific activity of [^{14}C] 1,1,1-trichloroethane used relative to the other exposures.

Source: Schumann et al., 1982a

Takahara (1986a) reported that immediately following exposure of female mice to 1000 ppm (5460 mg/m3) of 1,1,1-trichloroethane for 2 hours, tissue concentrations of 1,1,1-trichloroethane showed the following decreasing order: fat > liver > kidney > spleen ≈blood > lung ≈heart ≈ brain. In male hybrid dogs (n=3) that were exposed (under continuous anesthesia) to 10,000 ppm (54,600 mg/m3) of 1,1,1-trichloroethane for 3 minutes (four times at 4-hour intervals), wet weight concentrations of 1,1,1-trichloroethane, 4 hours after the last exposure, showed the following order: abdominal fat > renal fat> brain≈liver≈kidney≈lungs (Katagiri et al., 1997). In mice, 2 hours after oral administration of 1000 mg/kg of [2-14C]-labeled 1,1,1-trichloroethane, amounts of radioactivity in tissues showed the following order: fat (53% of body burden for those tissues analyzed) > muscle > stomach > liver > skin > blood > kidney > lung (RTI, 1988). Similarly in rats, one hour after oral administration of 1000 mg/kg labeled 1,1,1-trichloroethane, amounts of radioactivity in tissues showed the following order: fat (62% of body burden) > muscle > liver > skin > blood ≈ kidney ≈ lung > thyroid (RTI, 1988). The preferential accumulation of 1,1,1-trichloroethane in fatty tissues following a single exposure is not

persistent, as demonstrated by the rapid decline in rat and mouse tissue concentrations within 72 hours after exposure (Table 3).

Schumann et al. (1982b) compared the fate of inhaled 1,1,1-trichloroethane following single or repeated exposure in male Fischer 344 rats and B6C3F1 mice. Rats and mice were exposed by inhalation to 1500 ppm 1,1,1-trichloroethane for 6 hours/day, 5 days/week for approximately 16 months. On the last day of exposure, animals were exposed to ^{14}C-labeld 1,1,1-trichloroethane. The fate of ^{14}C-1,1,1-trichloroethane in the repeat-exposure animals was compared to a group of rats and mice that had been exposed concurrently to chamber air (i.e., age-matched controls) prior to receiving the single 6-hour exposure to 1500 ppm ^{14}C-1,1,1-trichloroethane. Animals were followed for 72 hours after their final exposure. ^{14}C activity was measured in liver, kidney and fat. Tissue concentrations of ^{14}C activity were similar between the singly and repeatedly exposed rats and mice. In mice immediately after a 6-hour exposure to ^{14}C-1,1,1-trichloroethane, tissue concentrations (in nmole equivalent of 1,1,1-trichloroethane/g tissue) in single and repeated exposure animals, respectively, were: liver—1794±302 and 1489±415; kidney—877±186 and 817±214; fat—10,603±1528 and 8789±2259. At 72 hours post exposure, concentrations in mouse tissues were: liver—50.5±9.8 and 45.9±16.8; kidney—47.3±14.4 and 36.5±4.0; fat—both non-detectable. In rats immediately after a 6-hour exposure, tissue concentrations in single and repeated exposure animals, respectively, were: liver—606±75 and 641±83; kidney—480±146 and 490±128; fat—5685±1424 and 4591±1226. At 72 hours post exposure, concentrations were: liver—both non-detectable; kidney—30.0 and 76.5; fat—191±113 and 144±1.9. The authors concluded that repeated exposure of rats and mice to 1500 ppm 1,1,1-trichloroethane did not significantly alter the disposition of the chemical.

Schumann et al. (1982b) compared tissue concentrations of ^{14}C activity in these older rats and mice that received a single exposure to 1,1,1-trichloroethane (age 18 months) with those from a single exposure study in younger (age 2.5-3.5 months) rats and mice (Schumann et al., 1982a). This comparison revealed an age-related increased body burden (1.3-fold in rats and 2- to 3-fold in mice) and increased amount metabolized (1.6-fold in rats and 5- to 6-fold in mice) in aged versus young animals. The authors suggested that the increased body burden and extent of metabolism in the older animals may be a function of the greater fat content of the older rodents.

Studies with pregnant C57BL mice indicate that distribution of radioactivity from [2-^{14}C]-labeled 1,1,1-trichloroethane to the placenta and developing fetus is low relative to other tissues and organs (Danielsson et al., 1986). On day 17 of gestation, four groups of mice were exposed by inhalation for 10 minutes in glass chambers into which volatilized 1,1,1-trichloroethane was introduced by heating corn oil solutions containing 100 µCi of radiolabeled compound with a specific activity of 0.5 µCi/µmol. Concentrations in the exposure chambers were not determined. Groups of four mice were killed at 0, 0.5, 4, and 24 hours after exposure,

and concentrations of total and non-volatile radioactivity in brain, lung, liver, kidney, fetus, and placenta were determined. Immediately following exposure, concentrations of total radioactivity in fetal and placental tissue samples were about 10-fold lower than concentrations in other sampled tissues (Table 4). Concentrations in all tissues declined to very low levels at the 24-hour sampling period (Table 4). At the 0-hour period, tissue concentrations of non-volatile radioactivity, taken as a measure of metabolized 1,1,1-trichloroethane, were only small fractions (< about 10%) of the concentrations of total radioactivity, with the exceptions of liver and lung, in which concentrations of non-volatile radioactivity were about 31% and 23% of total radioactivity concentrations, respectively (data not shown in Table 4).

Table 4. Tissue Concentrations of Radioactivity (dpm/mg tissue) at Several Time Periods after 10-Minute Inhalation Exposure of Pregnant Mice to [2-^{14}C]-Labeled 1,1,1-Trichloroethane[1]

	0 hour	0.5 hour	4 hour	24 hour
Brain	123±50	15±2	1.4±0.2	0.3±0.03
Lung	114±44	17±2.3	6.6±0.7	2.0±0.3
Liver	143±74	39±4.8	13±1.5	5.3±1.0
Kidney	97±4.2	49±8.7	7.2±1.1	1.4±0.3
Fetus	9.3±1.7	7.8±0.5	2.1±0.1	0.7±0.1
Placenta	14±2.7	12±1.0	2.6±0.1	0.9±0.2

[1] Values are means±SE of tissue samples from four mice at each time interval. Tissues were sampled at low temperatures to prevent loss of volatile radioactivity. Separate sets of tissue samples were heated to 50°C before determination of radioactivity to assess non-volatile radioactivity (data not shown above).

Source: Danielsson et al., 1986

Several investigators have explored the effect of duration of exposure on the body burden of 1,1,1-trichloroethane. Using data from human volunteers exposed to 1,1,1-trichloroethane, Nolan et al. (1984) simulated repeated 8-hour daily exposures based on a three compartment pharmacokinetic model. The simulation indicated that at the end of the fifth daily exposure, the expired air and blood concentrations of 1,1,1-trichloroethane would be within 4 and 8%, respectively, of the concentrations after a single 8-hour exposure, and that the amount of 1,1,1-trichloroethane in the body would be 1.8 times that following a single exposure. This simulation is in agreement with the results of a repeated exposure study in humans (Stewart et al., 1969), in which the concentration of 1,1,1-trichloroethane in expired air increased very little over 5 consecutive days of exposure to 507 ppm (2770 mg/m^3) of 1,1,1-trichloroethane. The simulation predicted that twelve daily exposures would be required to reach 95% of steady state concentrations of 1,1,1-trichloroethane in the body (Nolan et al., 1984). At steady state, the body would contain 3.6 times the amount of 1,1,1-trichloroethane as after a single 8-hour exposure; about 70% of this would be in the fat. This percentage in fat is generally consistent with the findings of RTI (1988), which reported a body burden in fat of 53 to 62% of the dose

retained in tissues one to two hours after gavage dosing. [Single-exposure inhalation studies in animals generally presented tissue distribution data in terms of concentrations and not percent total dose in a given tissue.] Thus, the available date suggests a possible increase in body burden of 1,1,1-trichloroethane with repeated exposure; however, any increase in tissue concentrations at steady state as compared with the concentration at the end of a single exposure is predicted to be modest.

3.3. METABOLISM

1,1,1-Trichloroethane is metabolized oxidatively, albeit to a limited extent, to trichloroethanol and trichloroacetic acid by the cytochrome P450 mixed function oxidase system. These metabolites are excreted in the urine; other minor metabolites (carbon dioxide and acetylene) are excreted in expired air. Studies in animals and humans demonstrate that only a small fraction of absorbed 1,1,1-trichloroethane (<10%) is metabolized; a large fraction of the absorbed dose is excreted unchanged in exhaled air. Some, but not all studies, have found evidence of cytochrome P450 enzyme induction by 1,1,1-trichloroethane.

1,1,1-Trichloroethane is metabolized at low rates to trichloroethanol (and its glucuronide conjugate) and trichloroacetic acid; these metabolites are excreted in the urine in both humans and experimental animals. A minor metabolite, carbon dioxide (CO_2), is eliminated in expired air (Johns et al., 2006; Reitz et al., 1988; Mitoma et al., 1985; Nolan et al., 1984; Schumann et al., 1982a; Monster et al., 1979; Hake et al., 1960). A general metabolic scheme for 1,1,1-trichloroethane is presented in Figure 1.

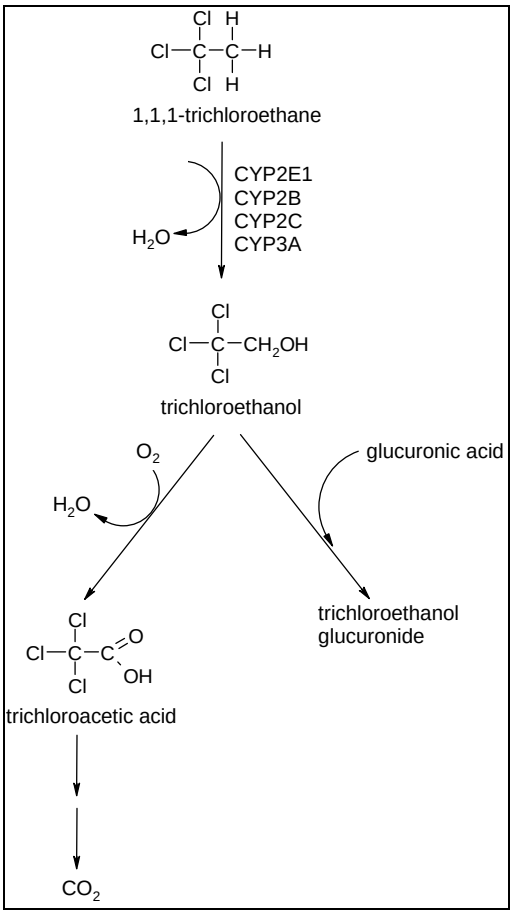


Figure 1. Metabolic Scheme for 1,1,1-Trichloroethane

The initial step in metabolism of 1,1,1-trichloroethane involves cytochrome P450 (CYP) monooxygenases, with several isozymes of P450 shown as contributing to metabolism. Evidence that the ethanol-inducible CYP isozyme CYP2E1 contributes to the catalysis of the initial step comes from studies in humans and animals. A group of volunteers was administered ethanol (0.35 mg/kg body weight) daily for 7 days, and was then exposed to 175 ppm (950 mg/m^3) 1,1,1-trichloroethane for 2 hours (Johns et al., 2006). Prior ethanol consumption resulted in a significant increase in metabolic clearance (mean increase = 25.4%). Ethanol pretreatment of male Wistar rats (n=5 per exposure group) increased the cumulative urinary excretion of trichloroacetic acid and trichloroethanol following inhalation exposure to 50, 100, or 500 ppm (270, 550, 2730 mg/m^3) of 1,1,1-trichloroethane for 6 hours (Kaneko et al., 1994); mean *in vitro* metabolic rates for 1,1,1-trichloroethane were 1.8 nmol/g liver-minute for liver microsomes from ethanol-pretreated Wistar rats compared with 0.5 nmol/g liver-minute for microsomes from control Wistar rats (Sato et al., 1980); and antibody to purified human liver CYP2E1 inhibited *in vitro* metabolism of 1,1,1-trichloroethane by human liver microsomes (Guengerich et al., 1991).

Phenobarbital-inducible CYP isozymes (CYP2B, 2C, or 3A) may also be involved in the initial metabolic step. Rates of 1,1,1-trichloroethane metabolism by liver microsomes from phenobarbital-treated rats were 2-4-fold greater than rates by microsomes from control rats (Ivanetich and Van den Honert, 1981; Koizumi et al., 1983).

Conversion of trichloroethanol to trichloroacetic acid appears to involve the intermediate formation of chloral hydrate and may involve alcohol and aldehyde dehydrogenases or cytochrome P-450 mixed function oxidases (Casciola and Ivanetich, 1984; Ivanetich and Van der Honert, 1991).

Under conditions of hypoxia, evidence for reductive dechlorination of 1,1,1-trichloroethane via CYP to form acetylene has been reported in rats (Albano et al., 1985; Dürk et al., 1992). This pathway is not expected to be biologically important except under conditions of tissue hypoxia, and is not presented in Figure 1.

Humans metabolize absorbed 1,1,1-trichloroethane to a limited extent (Monster et al., 1979; Nolan et al., 1984). In humans (n=6 per exposure scenario) exposed for 4 hours to 70 or 145 ppm (380 or 790 mg/m^3) of 1,1,1-trichloroethane while at rest, or 142 ppm (780 mg/m^3) while alternating periods of rest with intermittent work loads, about 60-80% of absorbed compound was estimated to have been excreted unchanged in exhaled breath during a 163-hour post-exposure period (Monster et al., 1979). Excretion of the metabolites, trichloroethanol and trichloroacetic acid, in urine collected for 70 hours after exposure accounted for about 2% and 0.5%, respectively, of the estimated amount of absorbed 1,1,1-trichloroethane. In humans exposed to 35 or 350 ppm (190 or 1900 mg/m^3) of 1,1,1-trichloroethane for 6 hours, it was estimated that 91% of absorbed 1,1,1-trichloroethane was excreted unchanged by the lungs, 5-6% was metabolized and excreted in urine as the metabolites trichloroethanol or trichloroacetic acid, and less than 1% remained in the body after 9 days (Nolan et al., 1984). These estimates were made with a PBPK model that was developed with measurements of 1,1,1-trichloroethane in exhaled breath samples and of trichloroacetic acid and trichloroethanol in urine samples collected from 6 human subjects at several intervals during a 9-day post-exposure period (Nolan et al., 1984).

Experiments with laboratory animals similarly indicate that ingested and inhaled 1,1,1-trichloroethane is slowly metabolized and predominantly excreted unmetabolized in exhaled breath. In male Osborne-Mendel rats and male B6C3F1 mice treated by gavage with 1,1,1-trichloroethane in corn oil, 5 days/week for 4 weeks, followed by a single dose of [1,2-^{14}C]-labeled compound, recovery of the applied dose 48 hours after exposure (for rats and mice, respectively) was as follows: 85.1 and 92.9% as unchanged compound in expired air; 0.9 and 2.0% as CO_2 in expired air; 2.1 and 3.4% as metabolites in urine; and 1.2 and 0.7% as presumed metabolites remaining in the carcass (Mitoma et al., 1985). In male Fischer 344 rats supplied

with drinking water for 8 hours containing [2-^{14}C]-labeled 1,1,1-trichloroethane, 90.5% of the dose was expired as unchanged 1,1,1-trichloroethane, 2.2% was expired as CO_2, and 2.2 and 1.3% were accounted for by metabolites in urine and carcasses, respectively (Reitz et al., 1985). In male Fischer 344 rats (n=4 per group) exposed by inhalation to 150 or 1500 ppm (820 or 8190 mg/m^3) of [2-^{14}C]-labeled 1,1,1-trichloroethane for 6 hours, 94.2 and 97.9% of recovered radioactivity (during a 72-hour post exposure period) was accounted for by unchanged 1,1,1-trichloroethane in expired air, respectively (Schumann et al., 1982a). Similar results were obtained for male B6C3F1 mice exposed according to the same exposure protocol, except that average rates of metabolism in mice, calculated on a body weight basis, were two to three times rates in rats (Schumann et al., 1982a). Following exposure to 150 ppm (820 mg/m^3), average metabolic rates were 8.87±1.79 and 24.26±10.28 μmol/kg for rats and mice, respectively; after exposure to 1500 ppm (8190 mg/m^3), the rates were 24.64±1.15 and 42.06±8.61 μmol/kg, respectively.

In vitro data provide supporting evidence that 1,1,1-trichloroethane is slowly metabolized compared with several other small molecular weight chlorinated hydrocarbons. For example, with rat liver microsomes, rates of metabolism were 0.5 nmol/g liver/minute for 1,1,1-trichloroethane compared with 21.0, 31.1, 19.1, and 18.9 nmol/g liver/minute for 1,1,2-trichloroethane, 1,1-dichloroethylene, 1,1-dichloroethane, and trichloroethylene, respectively (Sato et al., 1980).

Studies by Fuller et al. (1970), Lal and Shah (1970) and Shah and Lal (1976) demonstrated induction of drug metabolizing enzymes by acute inhalation of 1,1,1-trichloroethane in rats and mice; they showed 1) concentration- and duration-related decreases in sleeping time induced by the parent-active, CYP-metabolized drugs hexobarbital, meprobamate, and zoxazolamine, 2) increased microsomal metabolism of these drugs, 3) no effect on sleeping time produced by barbital (not metabolized) or chloral hydrate (metabolized by alcohol dehydrogenase), indicating that the effect on hexobarbital sleeping time was not due to a general reduction in CNS sensitivity to depressants, 4) increased cytochrome P450 and NADPH cytochrome c reductase (although not liver microsomal protein), 5) increased absolute and relative liver weight, and 6) inhibition of these effects by the protein synthesis inhibitors cycloheximide and actinomycin D, suggesting that 1,1,1-trichloroethane increases the activity of drug metabolizing enzymes by inducing synthesis of new enzyme protein. With 24-hour exposure, the maximum inductive effect occurred at 3000 ppm; lower concentrations were ineffective and higher concentrations were progressively less effective, possibly due to toxicity. Bruckner et al. (2001) found significant dose-related increases in CYP2E1 and CYP2B1/2 in male Sprague-Dawley rats given single oral doses ≥2500 mg/kg, but no effect on CYP1A1 or total cytochrome P450 levels at doses up to 10,000 mg/kg. Peak activity for CYP2E1 and

CYP2B1/2 were reached at 6 and 12 hours after dosing, respectively; return to pre-exposure levels was fairly rapid (within 36-48 hours). With repeated oral exposure for 7 days, Platt and Cockrill (1969) found significant increases in microsomal protein concentration and cell-sap protein concentration in the liver of rats treated with 1650 mg/kg-day.

Other studies, however, failed to find evidence of enzyme induction by 1,1,1-trichloroethane. Wang et al. (1996) found that 6-hour exposure to 4000 ppm (21,840 mg/m^3) of 1,1,1-trichloroethane had no effect on microsomal protein, cytochrome P450 (total or specific isozymes), or specific monooxygenase activities in male Wistar rats. Subchronic inhalation exposure (6 hours/day, 5 days/week for 4 weeks) to 820 ppm (4480 mg/m^3) had no effect on microsomal cytochrome P450 in male Sprague-Dawley rats (Toftgard et al., 1981). Savolainen et al. (1977) exposed groups of 10 adult male Sprague-Dawley rats to 0 or 500 ppm (2730 mg/m^3) of 1,1,1-trichloroethane vapor 6 hours per day for 4 consecutive days. On the 5th day, 2 rats from each group were sacrificed after 0, 2, 3, 4 or 6 hours of additional exposure. Liver microsomal cytochrome P450 was similar to controls in the rats sacrificed without exposure on the 5th day, but was progressively decreased in rats with an additional 2-6 hours of exposure. Significantly reduced hepatic cytochrome P450 activity was also reported in male Wistar rats treated with a single dose of 1375 mg/kg by gavage in olive oil and sacrificed 24 hours later (Vainio et al., 1976). An explanation for the different findings regarding enzyme induction by 1,1,1-trichloroethane has not been postulated. It is possible, however, that the differences in enzyme induction observed by different investigators may be a function of the differences in dose level tested, number of hours after dosing CYP activity was measured, and whether the activity of total P450 or specific CYP isozymes was measured.

It is unclear whether 1,1,1-trichloroethane may enhance its own biotransformation via CYP induction. Koizumi et al. (1983) reported that exposing rats to 200, 400, or 800 ppm (1090, 2180 or 4370 mg/m^3) 1,1,1-trichloroethane (24 hours/day for 10 days) increased the ability of liver microsomes to metabolize 1,1,1-trichloroethane, compared to microsomes from fresh-air controls. In contrast, repeated preexposure of rats and mice to 1500 ppm (8190 mg/m^3) 1,1,1-trichloroethane for 16 months did not alter the routes of excretion, the extent of metabolism, or the concentrations of radioactivity in tissues after a 6-hour inhalation exposure to 1500 ppm (8190 mg/m^3) of [2-^{14}C]-labeled 1,1,1-trichloroethane, compared with age-matched rats given only a single 6-hour exposure (Schumann et al., 1982b).

Loizou et al. (1996) observed statistically significant and apparently dose-related reductions in liver glutathione levels in male Wistar rats exposed to 4000 to 25,000 ppm (21,840 to 136,500 mg/m^3) of 1,1,1-trichloroethane for 3 hours; liver glutathione levels were approximately 77% of the control at 4000 ppm and 58% of the control at 25,000 ppm. Lung glutathione and liver and lung glutathione disulfide were unaffected. There was no evidence of

toxicity associated with the observed glutathione depletion. The mechanism by which glutathione would be depleted by 1,1,1-trichloroethane is unclear, as the compound is little metabolized and binding of reactive intermediates by glutathione is not known for this chemical. The researchers allowed that reductive dechlorination could lead to intermediates that would react with glutathione, but indicated this could not explain the observed glutathione depletion, given the very low rate of reductive dechlorination of 1,1,1-trichloroethane. They suggested that their finding may be related to uncoupling of the P-450 system, leading to hydrogen peroxide production, a phenomenon that has been associated with 1,1,1-trichloroethane *in vitro* (Ivanetich and Van den Honert, 1981; Takano et al., 1988).

3.4. ELIMINATION

Most 1,1,1-trichloroethane, whether received either by inhalation or oral exposure, is excreted unchanged by the lungs in expired air. Only a small fraction is excreted in the urine as trichloroacetic acid or trichloroethanol. Studies in animals and humans indicate that 1,1,1-trichloroethane is unlikely to accumulate to any significant extent with repeated exposure.

Results from human and animal studies indicate that most inhaled 1,1,1-trichloroethane is rapidly excreted unchanged by the lungs in expired air (Monster et al., 1979; Nolan et al., 1984; Schumann et al., 1982a); the same elimination path has been demonstrated to be important following drinking water exposure in rats (Reitz et al., 1988) or gavage administration in rats and mice (Mitoma et al., 1985; RTI, 1988). In rats and mice, urinary excretion of metabolites accounted for only small fractions (1-2%) of orally administered doses (Mitoma et al., 1985; Reitz et al., 1988).

In a study of exposed human volunteers, Nolan et al. (1984) found that the concentration of 1,1,1-trichloroethane in blood rose rapidly during the initial portion of the exposure period such that by 1.5 hours it was 90% of the mean concentration at 6 hours of exposure. [A similar pattern of initial rapid increase followed by an apparent leveling off in blood concentration was seen in 12 men exposed for 3 hours to 175 or 350 ppm (950 or 1900 mg/m^3) of 1,1,1-trichloroethane (Mackay et al., 1987).] Based on blood and expired air concentrations, elimination of 1,1,1-trichloroethane was described as triexponential, with estimated half times of 44 minutes, 5.7 hours and 53 hours for the initial, intermediate, and terminal phases (Nolan et al., 1984). Measured blood concentrations at 1.5, 16, and 40 hours after exposure were 59%, 7%, and 3%, respectively, of the concentration at the end of exposure.

In rats, elimination of 1,1,1-trichloroethane was rapid and diexponential, with estimated half lives of 10.5-36 minutes for the initial and 139-258 for the terminal phase, and was triexponential in mice, with estimated half lives of 2, 13, and 169-193 minutes for the initial, intermediate, and terminal phases (Schumann et al., 1982a).

Several studies have described quantitative relationships between time-weighted average workplace air concentrations and urinary excretion of metabolites (Kawai et al., 1991; Mizunuma et al., 1995; Seki et al., 1975) or 1,1,1-trichloroethane itself (Mizunuma et al., 1995). ACGIH (2002) recommends several biological exposure indices to monitor occupational exposure to 1,1,1-trichloroethane (methyl chloroform): 1) 40 ppm of 1,1,1-trichloroethane in end-exhaled air, prior to last shift of workweek; 2) 10 mg/L of trichloroacetic acid in urine at end of workweek; 3) 30 mg/L of total trichloroethanol in urine at end of shift at end of workweek; and 4) 1 mg/L of total trichloroethanol in blood at end of shift at end of workweek.

3.5. PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS

3.5.1. Summary of Available Models

Fourteen physiologically based pharmacokinetic (PBPK) models for 1,1,1-trichloroethane in adult rodents or humans have been published. These models were reviewed by Yang (2006) and are summarized in Table 5. Selected models are more fully described below.

Table 5. Summary of Available Models for 1,1,1-Trichloroethane in Rats and Humans

Model	Structure
Caperos et al. (1982)	Fat, muscle, lung, & rapidly perfused tissues; clearance from rapidly perfused tissues
Nolan et al. (1984)	Fat, muscle, lung, & well perfused tissues; first-order metabolism in well perfused tissues
Gargas et al. (1986)	Liver, viscera, muscle/skin, & fat; first-order metabolism in liver
Reitz et al. (1987, 1988)	Liver, fat, and slowly & rapidly perfused tissues; saturable metabolism in liver
Bogen and Hall (1989)	Liver, fat, skin, & slowly & rapidly perfused tissues; saturable metabolism in liver
Dallas et al. (1989)	Blood, lung, liver, muscle, fat, & rapidly perfused tissues; first order metabolism in liver
Leung (1992)	Fat, liver, & slowly & rapidly perfused tissues; saturable metabolism in liver
Yoshida (1993)	Fat, liver, & slowly & rapidly perfused tissues; saturable metabolism in liver
Lapare et al. (1995)	Lungs, liver, gastrointestinal tract, fat, muscle & skin, & rapidly & slowly perfused tissues; saturable metabolism in liver
Loizou et al. (1996)	Fat, liver, & rapidly & slowly perfused tissues; first-order metabolism in liver
DeJongh et al. (1998)	Fat, liver, brain, & rapidly & slowly perfused tissues; first-order metabolism in liver
Tardif and Charest-Tardif (1999)	Liver, fat, & slowly & rapidly perfused tissues; saturable metabolism in liver
Poet et al. (2000)	Fat, skin, liver, & rapidly & slowly perfused tissues; saturable metabolism in liver
Dobrev et al. (2001, 2002)	Fat, liver, & other tissues lumped into one or two compartments; saturable metabolism in liver

Source: Yang, 2006

Reitz et al. (1988) Model

Reitz et al. (1988) developed a four-compartment (liver, rapidly perfused tissue, slowly perfused tissue, and fat) perfusion limited PBPK model for 1,1,1-trichloroethane in rats, mice, and humans. The model predicts 1,1,1-trichloroethane tissue concentrations following exposure via inhalation, intravenous administration, oral gavage, or drinking water administration. The model parameter values are shown in Table 6, and are updated numbers from previous versions (Reitz et al., 1987). Tissue:blood partition coefficients (Table 6) were derived using a vial-equilibration technique for rat blood, liver, fat, and muscle tissue. Blood:air partition coefficients were determined with human and mouse blood (further details not reported). Metabolism was restricted to the liver compartment, and was represented with standard terms for Michaelis-Menten kinetics. Metabolic parameters, V_{max} and K_m (Table 6), were optimized to fit the parent blood concentration data for rats exposed to 150 or 1500 ppm (820 or 8190 mg/m^3) 1,1,1-trichloroethane via inhalation for 6 hours (Schumann et al., 1982a).

The predictive capability of the model was evaluated by comparing various dose metrics from the PBPK model simulations with the experimentally derived values from studies with 2-3 month-old rats and mice following drinking water (116 mg/kg-day) or inhalation exposures (150 or 1500 ppm). Dose metrics evaluated included concentrations of parent 1,1,1-trichloroethane in blood, liver and fat; and total amount of metabolite in liver. Comparison of simulations and data sets revealed the following.

- Rat inhalation study: Schumann et al. (1982a) determined the venous blood concentrations of 1,1,1-trichloroethane in male Fischer 344 rats during and after 6-hour exposure to 150 or 1500 ppm 1,1,1-trichloroethane in a head-only exposure system. The Reitz et al. (1988) model simulated the postexposure data reasonably well, but the concentrations during exposure were overpredicted by a factor of about 2.

- Rat intravenous study: The model predicted the shapes of the venous blood concentration profiles (data obtained by Reitz et al., 1988), but somewhat underpredicted from about 1 hour postexposure.

- Rat oral gavage study: The model simulation did not follow the shape of the time-venous blood concentration curve (data collected by Reitz et al., 1988) satisfactorily.

- Rat drinking water study: The model simulation of the rate of elimination of ^{14}C-1,1,1-trichloroethane in exhaled air of the rats was comparable with the experimental data by Reitz et al. (1988). In addition, the predicted amount metabolized (5.49 µmol, about 2% of ingested 1,1,1-trichloroethane) was also comparable with the experimental measurement in urine and CO_2 (8.19 µmol, about 3% of ingested 1,1,1-trichloroethane).

- Mouse inhalation study: B6C3F1 mice had the same exposure scenario as the rats did in the Schumann et al. (1982a) study. The model predicted well the venous blood

concentrations of 1,1,1-trichloroethane in mice (experimental data collected by Schumann et al. (1982a) under the same experimental conditions as rats).

- Human volunteer inhalation study: The human inhalation data were collected by Nolan et al. (1984) (exposed to 35 or 350 ppm for 6 hours). The model overpredicted the venous blood concentrations during exposure by a factor of about 2 and predicted the postexposure concentrations well. The predictions of 1,1,1-trichloroethane concentrations in expired air agreed with the data.

Reitz et al. (1988) used their rat and mouse PBPK models to calculate average concentrations of 1,1,1-trichloroethane in the liver over the lifetime of the animal (ACL), i.e., the dose surrogate. The ACL for rats exposed by inhalation (6 hours/day, 5 days/week for 2 years) to 875 ppm (4780 mg/m^3) was 28 μmol/L and for mice exposed to 1500 ppm (8190 mg/m^3) was 95 μmol/L. These exposure levels were reported to have produced no effects on liver histopathology in 1-year rat (Quast et al., 1978) and 2-year mouse bioassays (Quast et al., 1984, 1988). This PBPK model was parameterized for humans and used to calculate the human ACL from ingestion of 2 L of water per day with varying concentrations of 1,1,1-trichloroethane. The human ACL for a drinking water concentration of 300 ppb 1,1,1-trichloroethane (a concentration reported to have been the highest detected in some finished drinking-water supplies) was predicted to be 0.01 μmol/L (Reitz et al., 1988). Comparison of this predicted human ACL (0.01 μmol/L) with the ACLs derived from PBPK model runs at the rat drinking water NOAEL (28 μmol/L) and the mouse NOAEL (95 μmol/L) yielded margins of exposure of 2800 and 9500, respectively. The human PBPK model also predicted that the ACL for a person drinking water containing 10 ppb of 1,1,1-trichloroethane for 100 days would be 2.7 times higher than the ACL after one day of drinking 10 ppb water, indicating only limited accumulation of 1,1,1-trichloroethane in the liver after continuous long-term drinking water exposure.

Table 6. Parameters Used in PBPK Models for 1,1,1-Trichloroethane Developed by Reitz et al. (1988)[a]

	Human	Rat	Mouse
Weights			
Body wt (kg)	83.0 [b]	0.215 [b]	0.029
Liver	3.1%	4.0%	4.0%
Rapidly perfused	3.7%	5.0%	5.0%
Slowly perfused	61.1%	75.0%	78.0%
Fat	23.1%	7.0%	4.0%
Flows (L/hour)			
Alveolar ventilation	348.0 [c]	5.11 [c]	1.26
Cardiac output (COP)	348.0 [c]	5.11 [d]	1.26
Liver (% COP)	24.0	24.0	24.0
Rapidly perfused (% COP)	49.0	53.0	56.0

Table 6. Parameters Used in PBPK Models for 1,1,1-Trichloroethane Developed by Reitz et al. (1988)[a]

	Human	Rat	Mouse
Slowly perfused (% COP)	18.0	18.0	18.0
Fat (% COP)	9.0	5.0	2.0
Partition coefficients			
Blood/air	2.53	5.76	10.8
Liver/air	8.6	8.6	8.6
Rapidly perfused/air	8.6	8.6	8.6
Slowly perfused/air	3.15	3.15	3.15
Fat/air	263	263	263
Biochemical constants [e]			
$V_{max}C$	0.419	0.419	0.419
K_m (mg/L)	5.75	5.75	5.75
K_a (hr^{-1}) (1^{st}-order rate constant for GI absorption)	-	1.25	-

[a] Parameter values in Reitz et al. (1988) were used in the current IRIS assessment except as noted in the footnotes to this table.

[b] Modeling performed in the current assessment used the following body weight values (rather than those in this table from Reitz et al.):
Human: actual weight of study subjects (if reported) or 70 kg if not reported.
Animal: actual reported body weights.

[c] In the current assessment, alveolar ventilation was scaled (rather than those in this table from Reitz et al.): (alveolar ventilation rate constant = 15 L/hr/kg) x $BW^{0.74}$.

[d] In the current assessment, cardiac output rate was scaled (rather than those in this table from Reitz et al.): (cardiac output rate = 15 L/hr/kg) x $BW^{0.74}$.

[e] $V_{max}C$ and K_m were obtained for the rat from the blood level data of Schumann et al. (1982a) by computer optimization. $V_{max}C$ is an allometric measure of maximum velocity of metabolism showing the following relationship with maximum enzyme rate: $V_{max} = V_{max}C$ x (body wt) $^{0.7}$.

Gargas et al. (1986) Model

Gargas et al. (1986) developed a model for rats based on the styrene model by Ramsey and Anderson (1984) comprised of four tissue compartments (liver, viscera, muscle/skin, and fat) and a chemical exchange compartment (lung). Time-course concentrations and tissue and blood:air partition coefficients (at 37 °C) were obtained from close-chamber gas uptake studies. Male Fischer 344 rats were exposed to 1,1,1-trichloroethane at initial chamber concentrations of 0.2, 1.0, 10 and 210 ppm. The model assumed equilibrium between the concentrations in blood leaving the lung and in alveolar air, controlled by the blood:air partition coefficient, and that the tissue uptake of 1,1,1-trichloroethane was flow-limited. The chemical was eliminated through exhalation and first-order metabolism in the liver. Metabolic parameters used in the model were obtained from optimization against gas uptake data by visual inspection. The model simulated the chamber concentration data from their own gas uptake pharmacokinetic studies in rats very well, but the PBPK model was not further verified with external data.

Bogen and Hall (1989) Model

Bogen and Hall (1989) developed a PBPK model for 1,1,1-trichloroethane in gerbils by

scaling parameters of the Reitz et al. (1987) rat model with a gerbil:rat body weight ratio to the 0.7 power. A fifth compartment for skin was also added and parameterized for a reference human weighing 70 kg. Parameter values for the gerbil and five compartment human models are listed in Table 7. Parameter values for tissue-specific volumes and blood-perfusion rates, as well as cardiac output, were taken from U.S. EPA (1988b) reference values, except that values for skin were assumed to be 6% of the reference value for poorly perfused tissues. Blood:air and tissue:blood partition coefficients, and the K_m, were the same as those used in the Reitz et al. (1987) human model. The human V_{max} value from Reitz et al. (1987) of 5.84 mg/hour was multiplied by a factor of $4(70/83)^{0.7}$ (= 3.55) to scale for body weight differences and an hypothesized underestimation of the parameter of the total amount of 1,1,1-trichloroethane metabolized. As the basis for the factor of 4, Bogen and Hall (1989) noted that the Reitz et al. (1987) model underestimated urinary excretion of metabolites by a factor of 2, and that an additional factor of 2 is needed to adjust for a proposed underestimation of the extent of metabolism based only on urinary excretion due to non-excreted metabolites and metabolites exhaled as CO_2 that would not be detected in the urine.

Table 7. Parameter Values in PBPK Models for 1,1,1-Trichloroethane Presented by Bogen and Hall (1989)

	Gerbil	Reference Human
Weights		
Body weight (kg)	0.059	70.0
Liver (% of body weight)	4%	2.6%
Rapidly perfused	5%	5%
Slowly perfused	79%	58.3%
Fat	4%	19%
Skin	-	3.7%
Flows (L/hour)		
Alveolar Output	2.07	378.0
Cardiac Output (COP)	2.07	372.0
Liver (% COP)	24	26
Rapidly perfused (% COP)	53	44
Slowly perfused (% COP)	21	23.5
Fat (% COP)	2	5
Skin (% COP)	-	1.5
Partition coefficients		
Blood/air	10.8	2.53
Liver/blood	0.796	3.4
Rapidly perfused/blood	0.796	3.4
Slowly perfused/blood	0.292	1.25
Fat/blood	24.4	104
Skin/blood	-	53
V_{max} (mg/hour)	0.0356	20.7
K_m (mg/L)	6.43	6.43

Bogen and Hall (1989) used the mouse, rat, and gerbil PBPK models to estimate the internal dose resulting from exposure to the no-effect levels for liver effects in mice, neurological effects in gerbils, and developmental effects in rats from exposure to 1,1,1-trichloroethane. The dose metrics used were assumed to be directly applicable to humans, and were used in the human PBPK model to calculate corresponding applied doses for a reference 70-kg human. Three endpoints from three different studies were considered with a different dose metric used for each – liver metabolite for liver effects (at steady state) and parent compound in arterial blood for effects on the central nervous system and fetus (peak and time-weighted average). Bogen and Hall (1989) noted that drinking water concentrations predicted to be nontoxic to humans by this PBPK approach were lower than drinking water concentrations predicted to be nontoxic by the traditional "safety factor" approach without cross-species dosimetric adjustment.

Poet et al. (2000) Model

In order to describe dermal uptake of 1,1,1-trichloroethane in rats and humans from soil or water, Poet et al. (2000) modified the PBPK models developed by Reitz et al. (1988) to include a separate skin compartment that was assumed to be a simple, "well-stirred" single compartment. Equations to describe the rate of change of 1,1,1-trichloroethane across the skin incorporated Fick's Law, and included parameters for surface area, blood flow to the skin, skin:matrix (skin:soil or skin:water) partition coefficients, and the permeability coefficient. Values of model parameters are listed in Table 8. Skin:air partition coefficients were determined by Mattie et al. (1994). Soil:air and water:air partition coefficients were determined by the vial-equilibration technique.

Table 8. Parameter Values in PBPK Models for 1,1,1-Trichloroethane Developed by Poet et al. (2000)

	Rat	Human
Weights		
Body weight (kg)	0.189-0.219	68.4-95.3
Liver (% of body weight)	4%	3.1%
Rapidly perfused	5%	3.7%
Slowly perfused	75%	61.1%
Fat	7%	11.2-24.5%
Skin	10%	3.5%
Flows (L/hour)		
Alveolar Output	5.11	348
Cardiac Output (COP)	5.11	348
Liver (% COP)	24	24
Rapidly perfused (% COP)	53	49
Slowly perfused (% COP)	18	18

Table 8. Parameter Values in PBPK Models for 1,1,1-Trichloroethane Developed by Poet et al. (2000)

	Rat	Human
Fat (% COP)	5	9
Skin (% COP)	0.058	0.058
Partition coefficients		
Blood/air	5.8	2.5
Liver/air	8.6	8.6
Rapidly perfused/air	8.6	8.6
Slowly perfused/air	3.2	3.2
Fat/air	263	263
Skin/air	10.8	10.8
Water/air	2.0	2.0
Soil/air	8.3	8.3
V_{max} (mg/kg/hour)	0.419	0.419
K_m (mg/L)	5.75	5.75

Breath elimination data were obtained from rats exposed to 1,1,1-trichloroethane-containing soil in a dermal exposure cell designed to capture volatilized 1,1,1-trichloroethane and prevent contamination of exhaled breath. Breath elimination data for rats were also obtained for 1,1,1-trichloroethane in an aqueous solution; the applied aqueous solution was occluded. Humans were exposed by immersing one hand in 0.1% 1,1,1-trichloroethane aqueous solutions or 0.75% 1,1,1-trichloroethane in soil. Rat and human skin permeability coefficients (K_p) were optimized to fit the exhaled breath data. Resulting rat skin K_p's were 0.25 and 0.15 cm/hour for the water and soil matrices, respectively. The estimated human K_p for water matrix exposures (0.006 cm/hour) was about 40-fold lower than the corresponding rat K_p. This human value was based on data from 3 subjects whose hands were not prehydrated: 0.0064, 0.0069 and 0.0057 cm/hour. The estimated water-matrix K_p for a fourth subject whose hand was prehydrated by immersing his hand in water for 2 hours was much higher, 0.528 cm/hour; this observation is consistent with the hypothesis that skin hydration results in an increased permeability to many compounds. The optimized values of the human K_p's for 1,1,1-trichloroethane in soil (0.002 $\pm$ 0.0005 cm/hour) were approximately one-third of the water matrix K_p's. Poet et al. (2000) used the PBPK models to simulate dermal exposures to 1,1,1-trichloroethane-contaminated water and soil in children and adults using worst-case EPA default assumptions. The simulation results indicated insignificant dermal absorption from non-occluded exposures (i.e., exposures not involving an impermeable covering over the test material), independent of the length of exposure.

Dobrev et al. (2001, 2002) Interaction-based Models for Mixtures of Trichloroethylene, Tetrachloroethylene, and 1,1,1-Trichloroethane

Dobrev et al. (2001, 2002) developed human and rat PBPK models to evaluate interactions for mixed exposures to trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane by incorporating terms for various types of competitive metabolism in the liver. The Reitz et al. (1988) PBPK model was adapted for 1,1,1-trichloroethane. Metabolic kinetic constants (K_i's for competitive, uncompetitive, and non-competitive mechanisms of interaction) were estimated by optimizing parameter values to fit data from gas uptake experiments in which rats were exposed to different initial concentrations of each mixture component singly, or as mixtures, and air concentrations of the chemicals were measured in the exposure chamber. Competitive inhibition was considered to be the most plausible interaction, since competitive K_i values for tetrachloroethylene and 1,1,1-trichloroethane (on trichloroethylene metabolism) were much closer to the individual Michaelis-Menten affinity constants (i.e., K_m) than K_i values for uncompetitive or non-competitive inhibition. The competitive inhibition model for the ternary mixture adequately described data from 12 gas uptake experiments with Fischer 344 rats exposed to mixtures of all three chemicals at various concentrations. The PBPK model predicted that concurrent exposure to occupational exposure limits for each of the three chemicals (50 ppm for trichloroethylene; 350 ppm for 1,1,1-trichloroethane; 25 ppm for tetrachloroethylene) would produce a 22% and 15% increase in trichloroethylene blood concentrations in rats and humans, respectively, compared with exposure to 50 ppm trichloroethylene alone. Dobrev et al. (2002) speculated that these mixture-induced changes would lead to higher bioavailability of trichloroethylene and increased amounts available to a glutathione-conjugation pathway that has been associated with kidney damage.

Fisher et al. (1997) Model for a Lactating Woman

A PBPK model for a lactating woman has been developed to estimate the amount of common volatile solvents (including 1,1,1-trichloroethane) that a nursing infant may receive for a given nursing schedule and maternal occupational exposure scenario (Fisher et al., 1997). To develop the model, human blood/air and milk/air partition coefficients were determined *in vitro* for 1,1,1-trichloroethane as 4.23 (SD=1.61, n=9) and 13.21 (SD=4.80, n=34), respectively. Samples of blood and milk were collected from nine lactating women; partition coefficients were determined using a modification of the vial equilibrium method. The model predicted that partitioning to milk (and excretion via the milk during nursing) was a minor physiological fate of inhaled 1,1,1-trichloroethane in a lactating woman exposed under a plausible occupational exposure scenario.

3.5.2. Model Selection

A review by Yang (2006) reveals that a number of the models in Table 5 are variants of the models by Gargas et al. (1986) and Reitz et al. (1988) (including Dallas et al., 1989; Leung, 1992; Yoshida, 1993; DeJongh et al., 1998; Bogan and Hall, 1989; Tardif and Charest-Tardif (1999); Poet et al., 2000; and Dobrev et al., 2001, 2002). The models by Bogan and Hall (1989) and Poet et al. (2000) added a skin compartment, a feature not relevant to the development of RfD and RfC values. Dobrev et al. (2001, 2002) was developed specifically to examine interactions among 1,1,1-trichloroethane, trichloroethylene, and tetrachloroethylene. Caperos et al. (1982) and Nolan et al. (1984) are earlier models that lump the liver compartment into the well perfused tissue compartment; because 1,1,1-trichloroethane undergoes metabolism in the liver, this lumping was not considered appropriate. The Lapare et al. (1995) model did not predict data sets as well as Reitz et al. (1988), and the Loizou et al. (1996) model results could not be successfully simulated by Yang (2006). Reitz et al. (1988) and Gargas et al. (1986) were identified as the most appropriate PBPK models for 1,1,1-trichloroethane. These two models were then further evaluated against 11 data sets.

The 11 data sets used for the further evaluation of the Reitz et al. (1988) and Gargas et al. (1986) models were the following:

Experimental rat pharmacokinetic data sets:
- Schumann et al. (1982a) – inhalation data
- Gargas et al. (1986) – inhalation data
- Reitz et al. (1988) – iv, gavage, and inhalation data
- Loizou et al. (1996) – inhalation data
- You and Dallas (1998) – inhalation data
- Warren et al. (1998) – inhalation data
- Bruckner et al. (Yang, 2006, personal communication) – gavage data

Human pharmacokinetic data sets (all inhalation):
- Savolainen et al. (1981)
- Nolan et al. (1984)
- Mackay et al. (1987)
- Lapare et al. (1995)

Both models performed similarly on inhalation data sets (Yang, 2006). The Reitz et al. (1988) model was designed to describe the disposition of 1,1,1-trichloroethane after multiple routes of exposure (inhalation, oral, and iv injection), whereas the Gargas et al. (1986) model described 1,1,1-trichloroethane disposition by the inhalation route only. Because it addressed interspecies extrapolation as well as route-to-route extrapolation, the Reitz et al. (1988) model was considered more versatile than Gargas et al. (1986). Therefore, Reitz et al. (1988) was used in the current assessment for PBPK modeling applications. Parameter values for experimental

animal species and humans are those shown in Table 6. For the most part, parameter values used in the current assessment are those from Reitz et al.; values used in the current assessment other than those from Reitz et al. are indicated in footnotes to Table 6.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

4.1.1. Oral Exposure

Stewart and Andrews (1966) reported the case of a man who accidentally ingested one ounce (≈600 mg/kg) of 1,1,1-trichloroethane and experienced an immediate burning sensation in the mouth and throat, nausea after 30 minutes, severe vomiting and diarrhea after 1-6 hours, and slightly elevated serum bilirubin levels after 48 hours (serum transaminase, blood urea nitrogen [BUN] and other clinical pathology indices were normal). The subject showed no signs of CNS depression (disorientation, incoordination or drowsiness), and thorough neurological examinations (details not reported) revealed no abnormalities.

Several epidemiological studies have investigated the potential relationship between exposure to 1,1,1-trichloroethane in drinking water and pregnancy outcome. Bove et al. (1995) studied birth outcomes over a 3-year period in 75 towns in northern New Jersey, where some water supplies were contaminated with 1,1,1-trichloroethane and other chemicals. When the data were analyzed on the basis of exposure specifically to 1,1,1-trichloroethane, odds ratios (ratio of risk of a defect in the population with the specified exposure to risk of the defect in the portion of the study population without the specified exposure) exceeding one were found for neural tube defects (OR = 1.21; 50% CI: 0.96-1.55) in the study population exposed to >1 ppb of 1,1,1-trichloroethane and for oral cleft defects (OR = 1.39; 50% CI: 0.97-1.93) in the study population exposed to >2 ppb of 1,1,1-trichloroethane. However, the confidence intervals show that the odds ratios for neither of these defects differed significantly from one (no association).

A series of studies was conducted to assess pregnancy outcomes over a 2-year period in a portion of Santa Clara County, California where one of the public drinking water wells was contaminated with 1,1,1-trichloroethane (and smaller quantities of other chemicals) from a leak in an underground storage tank (Deane et al., 1989; Swan et al., 1989; Shaw et al., 1990; Wrensch et al., 1990a,b). There were statistically significant increases in relative risk for spontaneous abortion (RR = 2.3; 95% CI: 1.3-4.2) and total congenital malformations (RR = 3.1; 95% CI: 1.1-10.4) in the initial study area during the 2-year exposed period. Follow-up studies found a significant increase in relative risk for major congenital cardiac anomalies (RR = 2.2; 95% CI: 1.2-4.0) during the exposed period in the service area of the water company that operated the contaminated well (a larger area than the initial study area), and that the risk of congenital cardiac anomalies increased with increasing consumption of home tap water during the exposed period. However, hydrogeological modeling and analysis of the spatial and

temporal distribution of cases showed that water from the contaminated well was unlikely to be responsible for any of the observed increases in adverse pregnancy outcomes (Wrensch et al., 1990a). In addition, a second study area that received more of the contaminated well water than the initial study area had no increase in any adverse pregnancy outcomes. Therefore, this series of studies did not establish a causal association between 1,1,1-trichloroethane exposure in drinking water and adverse pregnancy outcomes.

Isacson et al. (1985) found no association between the presence of detectable levels of 1,1,1-trichloroethane in the ground water drinking supply of Iowa towns (population 1000 to 10,000) and the incidence of bladder, colon, rectum, prostate, lung, or breast cancer in town residents over age 55 for the years 1969-1981. 1,1,1-Trichloroethane concentrations were characterized only as <0.1 μg/L or ≥0.1 μg/L. Given the low doses that would result from a 0.1 μg/L concentration (e.g., a 70 kg adult who drank 2 L water/day would receive a 1,1,1-trichloroethane dose of 0.003 μg/kg-day), the study is unlikely to have been sufficiently sensitive to pick up an association between chemical exposure and cancer.

4.1.2. Inhalation Exposure

CNS depressant effects are the predominant signs of acute inhalation exposure to 1,1,1-trichloroethane in humans. These effects become more severe as exposure duration and concentration increase. Acute exposure to 500-1000 ppm (2730-5460 mg/m^3) causes dizziness, lightheadedness and disturbances in equilibrium and coordination (Stewart et al., 1961, 1969; Torkelson et al., 1958), and general anesthesia occurs at ≥10,000 ppm (54,600 mg/m^3) (Dornette and Jones, 1960). Aside from a transitory increase in urinary urobilinogen in 2 of 4 subjects tested 6 hours after 15 minute exposure to 2650 ppm (14,470 mg/m^3) (Stewart et al., 1961), these controlled exposure studies found no evidence that acute inhalation exposure to 1,1,1-trichloroethane produces hepatotoxicity or other systemic effects in humans, as determined by liver function tests and serum chemistry, hematology and urinalysis measurements (Stewart et al., 1961, 1969; Torkelson et al., 1958; Dornette and Jones, 1960). Although effects on blood pressure and electrocardiogram were not found at subanesthetic levels (Stewart et al., 1961, 1969; Torkelson et al., 1958), induction of anesthesia was accompanied by a slight decrease (5-10 mm Hg) in systolic blood pressure in about half of the 50 patients tested and a large decrease in 3 patients (60 mm Hg in one) (Dornette and Jones, 1960). Other observations in patients under anesthesia that may have been related to 1,1,1-trichloroethane were premature ventricular contractions in several patients and cardiac arrest (and subsequent death) in one patient (Dornette and Jones, 1960).

Numerous case reports have documented the potentially lethal consequences of acute overexposure to 1,1,1-trichloroethane vapor (Stahl et al., 1969; Stewart, 1971; Travers, 1974;

Caplan et al., 1976; Macdougall et al., 1987; D'Costa and Gunasekera, 1990; Sullivan, 1994; del Amo et al., 1996; Winek et al., 1997). Simulations performed by some researchers estimated lethal levels in such cases to range from approximately 6000 ppm (32,760 mg/m^3) to as high as 70,000 ppm (382,200 mg/m^3) (Hatfield and Maykoski, 1970; Mercier 1977 [cited in Northfield, 1981], Northfield, 1981; Droz et al., 1982; Silverstein, 1983; Jones and Winter, 1983). Death due to 1,1,1-trichloroethane was usually attributed to respiratory arrest secondary to CNS depression (Hall and Hine, 1966; Jones and Winter, 1983; Wise et al., 1983), or to cardiac arrhythmias presumed to result from sensitization of the heart to epinephrine (Bass, 1970; Guberan et al., 1976; Garriott and Petty, 1980 [cited in Banathy and Chan, 1983]; Ranson and Berry, 1986).

Case reports have also produced suggestive evidence for persistent CNS effects (Gresham and Treip, 1983; Garnier et al., 1991), persistent ventricular arrhythmias (Wright and Strobl, 1984; McLeod et al., 1987), myocardial injury secondary to coronary spasm (Wodka and Jeong, 1991; Bailey et al., 1997), distal sensory peripheral neuropathy (Liss, 1988; Howse et al., 1989; House et al., 1994, 1996), hepatotoxicity (Halevy et al., 1980; Gerace, 1981; Thiele et al., 1982; Cohen and Frank, 1994; Gitelman and Dement, 1996; Hodgson et al., 1989), renal toxicity (Halevy et al., 1980), acute pulmonary eosinophilic pneumonia (Kelly and Ruffing, 1993), and biliary-pancreatic cancer (Zarchy, 1996) associated with high-level 1,1,1-trichloroethane exposure. Suggestive evidence from case reports, however, is inadequate to conclusively establish any relationship between these effects and 1,1,1-trichloroethane exposure.

4.1.2.1. *Experimental Human Exposure Studies*

Controlled studies in humans exposed to 1,1,1-trichloroethane concentrations below those causing gross CNS depression provide evidence of subtle neurological and nasal inflammatory effects. The findings of these studies are summarized in Table 9.

Neurobehavioral performance was assessed in 12 adult male subjects (students or employees of the Department of Occupational Medicine at the Swedish National Board of Occupational Safety and Health, 20-30 years of age) who were exposed to progressively increasing concentrations of 250, 350, 450 and 550 ppm (1370, 1900, 2450 and 3000 mg/m^3) of 1,1,1-trichloroethane (purity not reported) in four successive 30-minute periods via respiratory valve and mouthpiece (Gamberale and Hultengren, 1973). The taste and smell of the gas were disguised using menthol crystals. Review of the publication does not provide information on the human subjects research ethics procedures undertaken in this study, but there is no evidence that the conduct of the research was fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. The study was conducted by the Swedish National Board of Occupational Safety and Health at exposure concentrations

below, or only briefly (30 minutes) above the occupational limit for repeated exposure (threshold limit value, TLV, of 350 ppm). Increases in concentration from 250 ppm to 350 ppm and 450 ppm to 550 ppm were performed without interruption in exposure, and the increase from 350 ppm to 450 ppm was made after a 5-minute pause in exposure. Half of the subjects were exposed to 1,1,1-trichloroethane on one day, followed by exposure to control conditions (pure air) 7 days later; the remaining subjects were exposed similarly, but in reverse order. Tests of manual dexterity (wire spiral), perceptual speed (identical number and spokes tests), and simple and choice reaction time were conducted in the final 20 minutes of each exposure period. Performance was impaired in all five tests at ≥350 ppm (1900 mg/m^3), with deficits that were concentration-related. Mean performance values in the wire spiral, identical number, spokes, simple reaction time and choice reaction time tests ranged from 6.4-9.8%, 6.8-10.9%, 14.5-22.6%, 3.7-12.8% and 1.7-6.8% lower than control values, respectively, at 350-550 ppm (1900-3000 mg/m^3). Statistical analysis revealed that at 350 ppm (1900 mg/m^3) only performance on the identical number test differed significantly from the control; at 450 ppm (2450 mg/m^3), performance differed significantly for four of the five tests, and at 550 ppm (3000 mg/m^3) for all five of the tests. At 250 ppm (1370 mg/m^3), mean performance values were 1.8%, 0.9%, 3.1%, 1.6% and 1.7% lower than control values, respectively. Mean performance at 250 ppm (1370 mg/m^3) was not statistically significantly different from the control for any of the tests. These findings suggest that the NOAEL and LOAEL for acute neurotoxic effects in this study were 250 ppm (1370 mg/m^3) and 350 ppm (1900 mg/m^3), respectively.

Table 9. Summary of Human Controlled-Exposure Studies and Findings for 1,1,1-Trichloroethane

Reference Exposure Duration / # of Subjects	Experimental Design/ NOAEL and LOAEL	Measurement for 1,1,1-TCA?	Neurobehavioral Test Findings																	
			Simple reaction time	Choice reaction time	Stroop test	Digital step-input tracking	Stress arousal check list	EEG	Tiredness score	Visual evoked potential (VEP)	Body sway	Perception test (tachistoscopic task)	Wechsler memory scale	Complex reaction times	Manual dexterity	Perceptual speed (ident #)	Perceptual speed (spokes)	Hand tapping speed	Critical flicker fusion threshold	Gaze deviation nystagmus
Mackay et al. (1987) 3.5 hr / 12 M	0, 175, 350 ppm, 3.5 hours, continuous exposure NB testing: @ 0, 20, 60, 120 & 180 min. NOAEL: ND LOAEL: 175 ppm	Blood: 20, 60, 120 & 180 min.	X	X	X	X	neg													
Muttray et al. (2000) 4 hr / 12 M	20, 200 ppm, 4 hours, continuous exposure NB testing: @ 0 & 3.7 hours NOAEL: ND LOAEL: 200 ppm	Venous blood: 0 & 3.7 hours							X											
Laine et al. (1996) 5 hr / 9 M	Exposure day 1: 200 ppm, 3 hrs exposure → 40-minute break → 40 min exposure. 10 minutes of exercise (bicycle ergometer) at beginning of morning and afternoon sessions. Exposure day 2: 135 ppm (baseline exposure) combined with transient peak concentration (400 ppm) Exposure day 3: control NB testing: EEG during 1st 20-min period (peak), body sway & reaction times during 2nd 20-min period (2nd peak). Repeated after 120 min in chamber and in afternoon session. NOAEL: 200 ppm LOAEL: ND	Venous blood: @ (morning session) 7, 9, 11, 13, 15, 20, 40, 60, 120, 180, (afternoon session) 220, 227, 229, 231, 233, 235, 240, 260 & 290 minutes	X					neg		neg	neg									

Reference Exposure Duration / # of Subjects	Experimental Design/ NOAEL and LOAEL	Measurement for 1,1,1-TCA?	Neurobehavioral Test Findings																	
			Simple reaction time	Choice reaction time	Stroop test	Digital step-input tracking	Stress arousal check list	EEG	Tiredness score	Visual evoked potential (VEP)	Body sway	Perception test (tachistoscopic task)	Wechsler memory scale	Complex reaction times	Manual dexterity	Perceptual speed (ident #)	Perceptual speed (spokes)	Hand tapping speed	Critical flicker fusion threshold	Gaze deviation nystagmus
Savolainen et al. (198 1982a,b) 4 hr / 9 M	200, 400 ppm, 4 hours, continuous. NB testing: prior to exposure, between 20 min & 1 1/2 hour, and between 3 hours & 3 3/4 hours. NOAEL: 400 ppm LOAEL: ND	Venous blood: pre-exposure, 1 hour, 2 hours, 3.5 hours	neg								neg							neg	neg	neg
Salvini et al. (1971) 8 hr / 6 M	350, 450 ppm, 4 hours exposure → 1 ½ hr break → 4 hours exposure (8 hours total exposure time). Alternated activities as follows: 1 hr at rest, then 20 minutes physical exercise. NB testing: 0 & 8 hours (immediately after entering exposure room and before leaving exposure room). NOAEL: 450 ppm LOAEL: ND	–										neg	neg	neg	neg[1]					
Gamberale & Hultengren (1973) 0.5 hr / 12 M	250 ppm (30 min) → 350 ppm (30 min) → 450 ppm (30 min) → 550 ppm (30 min). NB testing: final 20 minutes of each exposure period. NOAEL: 250 ppm LOAEL: 350 ppm	Alveolar air: every other minute. Arterial blood (2 subjects): 37 measurements parallel to alveolar air samples.	X	X											X[2]	X	X			

[1] threading needles in hole
[2] wire spiral
X – positive finding

In a study using similar endpoints, 12 adult male volunteers were chamber-exposed to 0, 175 and 350 ppm (950 and 1900 mg/m^3) of 1,1,1-trichloroethane (purity not reported) for 3.5 hours (Mackay et al., 1987). Volunteers were recruited from the Health and Safety Executive staff of the Occupational Medicine and Hygiene Laboratories, UK. The exposure chamber program adhered to the protocol approved by the local Brent and Harrow Area Health Authority Ethical Committee and the study appears to have been conducted consistent with the ethical standards prevailing at the time of the study. Each subject's three exposures were separated by at least 14 days. Peppermint oil was introduced into the chamber to mask the odor of the solvent. Neurobehavioral tests were performed 25 minutes before exposure and four times during exposure starting at 20, 60, 120 and 180 minutes. Each test battery took 20-25 minutes to complete. Testing included 5 psychomotor performance tests [simple reaction time, four-choice reaction time, Stroop test (a test that measures susceptibility to distraction)[2], syntactic reasoning (via analysis of grammatical statements) and digital step-input tracking (a test that measures eye-hand coordination)], and a subjective measure of mood (stress-arousal checklist). Measurements of 1,1,1-trichloroethane in blood, performed after 0, 20, 60, 120 and 180 minutes of exposure, showed that levels rose rapidly during the first 20 minutes and began leveling off after about 120 minutes. Blood levels were similar at 120 and 180 minutes; levels were ~12 μmol/L blood at an exposure concentration of 950 mg/m^3 and ~24 μmol/L blood at 1900 mg/m^3 (as estimated from a graph). None of the subjects complained of headache, discomfort or nausea. Changes in neurobehavioral performance were observed at both exposure levels, including increased simple reaction time, increased choice reaction time, impaired performance in the tracking test, and improved performance in the Stroop Test. The reaction time tests appeared to be the most sensitive; however, only simple reaction time was adequately quantified. The change in simple reaction time reportedly represented a 10-15% increase over baseline performance; the magnitudes of change in the other tests are unclear due to a lack of reported baseline performance values. For all tests, statistical analysis included analysis of variance to determine the main effects of exposure and duration (and their interaction), but did not include pair-wise tests to identify the specific exposure level at which a statistical difference from controls was achieved. Differences between exposure levels for the various tests were depicted graphically. When adjusted for both baseline (pre-exposure) and control (0 ppm) exposures, performance changes in the more sensitive tests (e.g., simple reaction time) followed the time-course of 1,1,1-trichloroethane levels in blood and correlated with absolute blood levels. Based on impaired psychomotor performance, particularly increased reaction time, the low dose of 175 ppm

[2] In the Stroop test, subjects are required to select the color of ink in which a color-word was written and then choose the appropriate color from four alternatives in the presence of highly distracting stimuli.

(950 mg/m^3) is a LOAEL for acute CNS effects.

Psychomotor effects were not reported in other acute studies conducted under similar exposure conditions (Salvini et al., 1971; Savolainen et al., 1981, 1982a,b). In the Salvini et al. (1971) study, 6 adult males (University of Pavia students, age 20-23 years) were exposed to 0 and 450 ppm (0 and 2450 mg/m^3) of 1,1,1-trichloroethane (Chlorothene® NU) for 8 hours (two 4-hour periods separated by a 1.5 hour interval with no exposure). Review of the publication does not provide information on the human subjects research ethics procedures undertaken in this study, but there is no evidence that the conduct of the research was fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. The study was conducted by the Institute of Preventive Medicine for Workers and Applied Psychology at the University of Pavia, Italy, using a single exposure at or just above the TLV. In this study, each subject served as his own control by being exposed to control air 4 days following exposure to 1,1,1-trichloroethane. Three of the six subjects were first exposed to 1,1,1-trichloroethane and secondly to a control atmosphere. The remaining three subjects were exposed in the reverse order The following were conducted immediately after the start of exposure and again just prior to termination of exposure: a complex reaction time test, a manual dexterity test, a perception test with tachistoscopic presentation and Wechsler memory scale (to evaluate instantaneous memory). The extent of impairment in performance in the 1,1,1-trichloroethane-exposed subjects was as follows: perception test – 20% decrease; immediate memory test – 6% decrease; complex reaction time – 2.5% decrease; and manual ability and dexterity – no effect. None of the decrements in any of the tests were statistically significant. There were, however, some transient complaints of dizziness and slight excitation that were limited to the first 30 minutes of exposure, as well as some complaints of eye irritation at the periods of peak exposure. The perception test revealed an interaction between 1,1,1-trichloroethane and mental stress. Based on eye irritation and slight dizziness, 450 ppm (2450 mg/m^3) was considered a LOAEL in this study.

In the Savolainen et al. (1981, 1982a,b) study, 9 adult male volunteers (age 20-25 years) were exposed to 0, 200 and 400 ppm (0, 1090 and 2180 mg/m^3) of 1,1,1-trichloroethane (containing 0.5% dioxane stabilizer) for 4 hours with 1 or 2 week intervals between exposures; each subject served as his own control. The nine subjects were divided into two groups; the sequence of exposures was reversed for the two groups to minimize the effects of learning. Peppermint oil vapor was used to mask the presence or absence of solvent odor. The study was conducted in accordance with the ethical principles adopted by the World Medical Association in the 1964 Declaration of Helsinki. The following tests were conducted before exposure, soon after the start of exposure and just before the end of exposure: simple reaction time, hand tapping speed, critical flicker fusion threshold, gaze deviation nystagmus and body sway. No clear

exposure-related effects on reaction time or other pyschomotor tests were found. Exposure to 200 ppm (1090 mg/m^3) 1,1,1-trichloroethane tended to improve performance, whereas exposure to 400 ppm tended to have the opposite effect, although differences at 400 ppm (2180 mg/m^3), with the exception of one measurement for body sway (closed eyes only), were not statistically significantly different from control. Therefore, the high dose of 400 ppm (2180 mg/m^3) is considered a NOAEL for acute CNS effects in this study.

A subsequent study by these researchers investigated the neurological effects of 1,1,1-trichloroethane exposure combined with physical exercise (Laine et al., 1996). The study was conducted in accordance with the ethical principles adopted by the World Medical Association in the 1975 Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Institute of Occupational Health in Helsinki, Finland. Nine healthy male volunteers (university students, ages 21-24 years) were divided into 3 groups of 3 subjects, with each group studied under three different exposure patterns on separate days. The experiments were conducted over consecutive weeks so that the time interval between exposures was at least 5 days. One exposure pattern consisted of exposure to a constant concentration of 200 ppm (1090 mg/m^3) 1,1,1-trichloroethane for 3 hours (morning), followed by a 40 minute lunch break and another 40 minute (afternoon) exposure period. A second consisted of exposure to a time-weighted average concentration of 200 ppm (1090 mg/m^3) as a baseline of 135 ppm (740 mg/m^3) with transient peaks up to 400 ppm (2180 mg/m^3) for 20 minutes at the start of the morning and afternoon exposure periods. The third exposure pattern comprised the unexposed controls. The sequence of exposures was reversed to minimize the effects of learning. Peppermint oil vapor was used to mask the presence or absence of solvent odor. In all 3 groups, the subjects exercised on a stationary bicycle for 10 minutes at the start of the morning and afternoon sessions. Electroencephalograms (EEG) and body sway measurements were recorded before, several times during, and 45 minutes after exposure. Visual evoked potentials were measured before exposure and immediately after the morning and afternoon exposure periods. Subjects reported no subjective symptoms, and no signs of respiratory irritation were observed. No consistent, statistically significant effects on EEG, visual evoked potentials, or equilibrium were found. Some deviations from control were observed, but were not considered by the investigators to be significant. These included: short-lived (but statistically significant) effects on EEG beta activity during the morning exposure session that was not observed during the afternoon exposure session despite higher blood 1,1,1-trichloroethane concentrations; and sporadic changes in VEP values that were not statistically significant or not consistent. The 200 ppm (1090 mg/m^3) level was therefore considered a NOAEL in this study.

EEG was also evaluated in 12 healthy male volunteers (non-smokers, mean age 27.0 years $\pm$1.9 years) exposed to 22 (control) and 200 ppm (120 and 1090 mg/m^3) 1,1,1-

trichloroethane (99.8%) in 4-hour exposure chamber sessions one week apart (Muttray et al., 2000). Exposure to 22 ppm (odor detectable by humans), rather than 0 ppm, was used as the control condition in an attempt to blind subjects and staff to the exposure conditions. The study was performed in accordance with the ethical principles of the Declaration of Helsinki (1989 Hong Kong version), and the protocol was approved by the local ethics committee (Mainz, Germany). EEG was recorded before (baseline) and during the last 15 minutes of exposure, with eyes open and closed and during a choice reaction time test (Color Word Stress test). EEG spectral power was expressed as percentage absolute spectral power relative to baseline and was calculated for each of 17 electrodes and each frequency band (δ, θ, α_1, α_2, β_1, β_2) Subjective symptoms were also recorded before, during and after exposure. Scores for tiredness were statistically significantly increased at the end of exposure to 200 ppm (1090 mg/m^3), compared with 22 ppm (120 mg/m^3). No other symptoms were associated with 1,1,1-trichloroethane exposure. EEG changes consistent with an increase in drowsiness (indicating a slight sedative effect) were noted in the closed eye test at 200 ppm, in comparison to 22 ppm. In the closed eye condition at 200 ppm compared to 22 ppm, the median percentage of spectral power increased at all electrodes of the δ-band, statistically significantly at temporo-occipital leads. Percentage of spectral power was elevated at most electrodes in the θ-band, was lower at the temporo-parietal-occipital electrodes in the α_1-band (statistically significant at one electrode), and was lower at all electrodes in the α_2-band (statistically significant at two electrodes). These differences were not seen in the open eye or Color Word Stress tests, but these tests are not as sensitive to changes in vigilance. As part of the same experiment, nasal secretions were collected for determination of inflammatory mediators, mean ciliary beat frequency of nasal respiratory cells was measured, and mucociliary transport time was recorded (Muttray et al., 1999). The concentrations of interleukines (IL-1β, IL-6, IL-8) in nasal secretions were statistically significantly increased after exposure to 200 ppm, compared with 22 ppm. There were no changes in prostaglandin E_2 levels in nasal secretions, mucociliary transport time, ciliary beat frequency of nasal respiratory cells, or subjective symptoms related to irritation. The increased levels of proinflammatory cytokines in nasal secretions in the absence of related effects indicates a slight irritant response in the nasal mucosa characterized by subclinical inflammation. This study identified a LOAEL of 200 ppm (1090 mg/m^3) for subtle neurological (tiredness and EEG changes) and nasal irritant (increased levels of proinflammatory cytokines in nasal secretions) effects of 1,1,1-trichloroethane. A NOAEL was not identified (the low concentration of 22 ppm (120 mg/m^3) served as the control for this study).

4.1.2.2. *Epidemiological Studies*

Epidemiology studies of workers occupationally exposed to 1,1,1-trichloroethane have

also found neurological effects. Workers exposed to 1,1,1-trichloroethane at a factory in Singapore reported neurological symptoms more frequently than matched controls from a factory without 1,1,1-trichloroethane exposure (Tay and Pinnagoda, 1994). The study group comprised 50 workers exposed only to 1,1,1-trichloroethane at 7 factories that used 1,1,1-trichloroethane in their cleaning and degreasing process. Controls were 50 workers from a single factory without 1,1,1-trichloroethane exposure, and were matched for age, sex, ethnic group and education. There were statistically significant increases in the prevalences of certain symptoms, including tiredness, inability to concentrate, and memory impairment, in the exposed group. This study is limited by reliance on subjective reporting of symptoms and possible introduction of bias because the interviewer who collected the survey data was not blinded to exposure status. Exposure was not quantified.

Kelafant et al. (1994) evaluated a group of 28 workers from a single employer, all of whom had long-term exposure to "moderate to high" concentrations of 1,1,1-trichloroethane by work history, for complaints of impaired short-term memory, inability to concentrate, moodiness, irritability, and disequilibrium that had been occurring for an average of 3 years. Other complaints were headaches, anxiety, fatigue, changed olfaction, and disturbed sleep. Exposures occurred over a 10-year period. Work practices included use of 1,1,1-trichloroethane in poorly ventilated areas, washing arms and hands in the concentrated solvent, and spraying material to be cleaned with compressed air sprayers, all without respiratory protection. Monitoring was not performed, but levels were high enough so that workers regularly reported becoming light-headed, vertiginous, nauseated and fatigued, and had on occasion observed co-workers become unconscious. Although few of the workers had been exposed to other solvents, many had been exposed to asbestos, silica and/or concentrated alkali cleaning agents. The subjects averaged 42.0 years of age and 17.6 years of employment. Subjects received a physical exam, chest radiograph, pulmonary function tests, electrocardiogram, hepatic function tests, neuropsychological evaluation (questionnaire and test battery), magnetic resonance imaging (MRI) of the brain, posture sway tests (posturography), and if indicated, tests for thyroid function, electroencephalogram, electromyogram/nerve conduction velocity, and electronystagmography. No control group was included; subject data were compared to published test normative data. Chest radiographs and pulmonary function tests were consistent with early pneumoconiosis, presumably due to silica and/or asbestos exposure. Physical examinations, electrocardiograms, hepatic function tests, and brain MRI were normal. Some subjects displayed increased sway in the Romberg test and difficulty with tandem gait; almost all were unable to maintain a monopedal stance for 5 seconds. In the posturography tests, posture sway deficits were found in 24 of the 26 subjects tested; the number of subjects testing abnormal increased with increasing difficulty of the postural task. Vestibular, somatosensory and ocular

components of balance were all affected. Consistent, statistically significant deficits were found for memory, intermediate memory, rhythm and speed in the neuropsychological test battery. This study suggests an association between neurobehavioral effects and prolonged exposure to high concentrations of 1,1,1-trichloroethane in an occupational environment. However, NOAEL and LOAEL values cannot be identified because exposures were not quantified.

Other studies did not find neurological effects in workers exposed to 1,1,1-trichloroethane. Maroni et al. (1977) investigated 22 female factory workers (mean age 32.4 years) who were exposed to 1,1,1-trichloroethane for a mean duration of 6.7 years via its use as a lubricating and degreasing agent (other solvents had not been used). The workers were divided into three groups of 7-8 according to workplace levels of 1,1,1-trichloroethane and compared with a reference group of 7 females from the same factory who had no past or present exposure to any solvent. Based on limited area monitoring data, the exposure groups were 110, 140-160 and 200-990 ppm (600, 760-870 and 1090-5400 mg/m^3); 7 of 8 workers in the high concentration group were exposed to 200-345 ppm (1090-1880 mg/m^3). The investigation included a questionnaire on subjective symptoms and work conditions, a general physical examination, neurological examinations (signs of peripheral neuropathy, maximal conduction velocity and slow fiber conduction velocity in motor nerves) and a psychological test battery (23 variables including intelligence, psychomotor ability and memory tests). Reaction time was not evaluated. No exposure-related effects were found, indicating that the NOAEL is 200 ppm (1090 mg/m^3). Confidence in this neurotoxicity NOAEL is low because of the small study population (7-8 per group), limited exposure data, and lack of data on some CNS endpoints known to be sensitive in acute studies (e.g., reaction time).

Cherry et al. (1983) conducted neurological tests on workers engaged in paint manufacture. Fifteen male workers (mean age 32.2 years) were studied over a 48-hour period during which they were engaged in the manufacture of a special batch of paint. Air measurements showed exposure to 1-46 ppm of 1,1,1-trichloroethane, as well as low concentrations of toluene (1-4 ppm) and xylene (0-7 ppm). Neurological tests (visual analogue scales to measure mood, digit symbol substitution test from the Wechsler Adult Intelligence Scale, and simple reaction time) of each worker were administered for 20 minutes at the beginning and end of a work shift. Referents comprised 36 workers without solvent exposure from two other factories that followed the same shift pattern; the researchers noted that the controls were poorly matched for age with the exposed workers. Of the measures of mood examined, only physical tiredness showed statistically significantly greater deterioration in exposed than control workers on the morning shift; no differences reached statistical significance for night shift workers. No consistent association was found between blood 1,1,1-trichloroethane levels and mood changes. Performance test results (digit symbol substitution test

and simple reaction time test) showed no consistent evidence of an effect. Morning shift workers (at beginning and end of shift) had slower reaction times than controls, but no differences in performance were observed for afternoon or night shift workers. Overall, the study did not demonstrate exposure-related effects. Because air concentrations in the plant were identified as a broad range, a NOAEL could not be identified.

Kramer et al. (1978) studied primarily systemic endpoints in 151 matched pairs of employees from two neighboring textile plants. One of the factories was reported to use large quantities of 1,1,1-trichloroethane (Chlorothene NU, ≈94-96% 1,1,1-trichloroethane) as a cleaning solvent. In the second plant, equipment cleaning was reported to be minimal and was performed with unspecified unchlorinated solvents (lack of exposure to 1,1,1-trichloroethane was verified by industrial hygiene survey). Air samples were collected for 1,1,1-trichloroethane analysis from various work stations within the "exposed" plant several times during a two-year period preceding the health surveys and physical examinations. Physical examinations included determination of blood pressure, heart rate, spirometric parameters, electrocardiogram, limited neurological endpoints (Romberg test), urinalysis, and serum chemistry (alkaline phosphatase [AP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transpeptidase [GGT], bilirubin, lactate dehydrogenase [LDH], BUN, protein) and hematology indices. From the analysis of the air samples and the work histories of the subjects, exposed workers were classified in one of five exposure groups: <15, 15-49, 50-99, 100-149 and 150-249 ppm (<81, 81-269, 270-540, 550-810, and 820-1360 mg/m^3). Exposed subjects were employed at the factory for ≤6 years. There were no significant exposure-related differences in health histories or measured parameters between the exposed and unexposed workers. This study showed no evidence of effects on cardiovascular, hepatic, or blood measures in workers exposed to up to 150-249 ppm of 1,1,1-trichloroethane for up to 6 years, making this level (150 ppm or 820 mg/m^3) a NOAEL for the systemic effects evaluated in this study. The limited neurological evaluation in this study was inadequate to identify a NOAEL or LOAEL for neurological effects.

Garabrant et al. (2003) conducted a case-control study to examine the relationship between solvent exposure (or jobs/hobbies with potential solvent exposure) and the development of scleroderma among women diagnosed with scleroderma between 1980 and 1992 in Michigan or Ohio. Six hundred sixty cases and 2227 controls matched for race, age, and geographic region were interviewed by telephone; solvent exposure was self-reported. The study found a statistically significant increased odds ratio for "other chlorinated solvents" (OR = 2.0, 95% CI: 1.3-3.1) and "any solvent" (OR = 2.0, 95% CI: 1.5-2.5). This study found no significant association between exposure to 1,1,1-trichloroethane (self-reported) and scleroderma (OR = 1.5; 95% CI: 0.7-3.2) or exposure verified by expert review (OR = 0.9; 95% CI: 0.3-2.8). The number of cases exposed to 1,1,1-trichloroethane was small (9 self reported; 4 confirmed by

expert review).

Radican et al. (2006) conducted a retrospective occupational cohort study of end-stage renal disease (ESRD) in aircraft workers exposed to 16 individual solvents and two solvent mixtures. An occupational database was matched to the U.S. Renal Data System, a database that captures the incidence of ESRD from 1973 onward. For the period 1973 to 2000, there was an approximate 2-fold increased risk of ESRD among workers exposed to 1,1,1-trichloroethane (as well as trichloroethylene and JP4 gasoline) [adjusted hazard ratio for 1,1,1-trichloroethane (95% CI) = 2.31 (1.04-5.10); Cox regression model]. When 2001-2002 data were included in the analysis, the association was no longer significant [adjusted OR (95% CI) = 1.53 (0.75-3.11); logistic regression model]. Investigators noted that uncertainty regarding the mechanism for increased risk of ESRD, the observed attenuation in risk in 2001-2002, and the overlap of exposures complicated the interpretation of the results.

Several case-control studies of spontaneous abortion and one longitudinal study of time to pregnancy were conducted to examine the potential relationship between exposure to 1,1,1-trichloroethane (and other organic solvents) and adverse reproductive outcomes. The case control studies investigated the risk of spontaneous abortion in women exposed to 1,1,1-trichloroethane at work in Finland (Lindbohm et al., 1990) or through the use of household products in Santa Clara County, CA (Windham et al., 1991), or of the wives of male workers occupationally exposed to 1,1,1-trichloroethane in Finland (Taskinen et al., 1989). The longitudinal study examined fertility (as measured by number of menstrual cycles required for wife to become pregnant) in Finnish male workers with exposure to 1,1,1-trichloroethane (Sallmen et al., 1998). All studies looked at multiple solvents, of which 1,1,1-trichloroethane was only one. None of the studies found any statistically significant association between adverse reproductive outcome and 1,1,1-trichloroethane exposure; however, small sample sizes (4-15 cases in an exposure group) limited the power of these studies to find any association. Further, exposure was not quantified in any of these studies.

Occupational exposure to 1,1,1-trichloroethane was not found to be associated with cancer risk in case-control studies for astrocytic brain cancer in white males from 3 U.S. states with prominent workforce representation in the petroleum refining and chemical manufacturing industries (Heineman et al., 1994), renal cell carcinoma in Minnesota residents (Dosemeci et al., 1999), pancreatic cancer in residents from 24 U.S. states (Kernan et al., 1999), or esophageal or stomach cancer in workers at an industrial facility in Chula Vista, CA (Garland, 1987; Garabrant, 1986). A study of a cohort of Finnish workers found statistically significantly increased standardized incidence ratios for cancer of the nervous system (SIR = 6.05; 95% CI: 1.25-17.7) and multiple myeloma (SIR = 15.98; 95% CI: 1.93-57.7) in male and female workers exposed to 1,1,1-trichloroethane (exposure assessed by blood monitoring) (Anttila et al., 1995).

However, these results are based on only 3 observed cases for nervous system tumors and 2 (both females) for multiple myeloma. Because of the small number of cases and the author's acknowledgment that all or most of the solvent workers were exposed to more than one solvent, the findings of this study are difficult to interpret. An increased risk of multiple myeloma was also observed in workers exposed to 1,1,1-trichloroethane at an aircraft maintenance facility in Utah (SMR = 56.6; 95% CI: 6.85-204.45), but again this result was based on only 2 observed cases, was seen only in females (no observed cases in males) and was found in workers with multiple, overlapping exposures to many chemicals (Spirtas et al., 1991). Spirtas et al. (1991) found no association between non-Hodgkin's lymphoma and 1,1,1-trichloroethane exposure in these workers. An environmental study found no significant correlation between release of 1,1,1-trichloroethane in 26 Florida counties in 1987 (as recorded in the U.S. EPA Toxics Release Inventory) and age adjusted incidence of childhood brain tumors in these counties in 1992-1993 (Mulla, 1996). Infante-Rivard et al. (2005) carried out a population-based case-control study to examine the association between maternal exposure to occupational solvents, including 1,1,1-trichloroethane, and childhood acute lymphoblastic leukemia (ALL). Exposure coding was conducted by a team of chemists and industrial hygienists based on questionnaire responses. Increased risks for ALL were observed for 1,1,1-trichloroethane, but the increases were not statistically significant. Cancer epidemiological studies are summarized in Table 10.

Table 10. Summary of Cancer Epidemiology Studies

Study	Study Design	Source / No. of Subjects & Referents	Pertinent Findings	Comments
Garabrant (1986)	cohort	cohort: 14,067 employees at Rohr plant; worked ≥4 years by Dec. 1982. control: total US white and non-white populations and San Diego County population.	No statistically significant increase in risk was found for cancer of the esophagus or other digestive tract cancers.	Examination of the risk of esophageal cancer.
case-control		cases: 14 decedents of esophageal cancer and 8 decedents of stomach cancer identified in Rohr plant cohort. control: matched members of the cohort who were alive at the age of death of the case; 56 and 32 controls for esophageal and stomach cancer, respectively.	No statistically significantly elevated odds ratio (OR) found for cancer of the esophagus or stomach. OR (ever vs. never exposed): OR p-value Esophageal cancer 1.67 0.56 Stomach cancer 3.15 0.26	Examination of risk of esophageal and stomach cancer
Heineman et al. (1994)	case-control	cases: 300 cases with diagnosed astrocytic brain tumor (identified through death certificates in LA, NJ, or PA, 1978-81). control: 320 matched controls randomly selected from white male residents who died of causes other than brain tumor, cerebrovascular diseases, epilepsy, suicide, homicide.	Exposure to 1,1,1-trichloroethane showed little indication of an association with brain cancer. OR 95% CI Brain cancer 1.2 0.9-1.8	Risk of astrocytic brain cancer was examined for exposure to organic solvents (as a general class) and 6 individual chlorinated aliphatic hydrocarbons. 1,1,1-Trichloroethane exposure showed little indication of an association; risk increases were observed only among groups with low exposure probability.

Study	Study Design	Source / No. of Subjects & Referents	Pertinent Findings	Comments
Dosemeci et al. (1999)	case-control	cases: 438 white patients newly diagnosed with renal cell cancer (RCC), identified through the MN Cancer Surveillance System (1988-90) control: 687 population-based controls	The risk of RCC was not statistically elevated in subjects exposed to 1,1,1-trichloroethane: OR / 95% CI / # cases Men 0.88 0.6-1.3 53 Women 1.26 0.6-2.8 13 Total 0.94 0.7-1.3 66	Risk of RCC was examined for exposure to all organic solvents combined, all chlorinated aliphatic hydrocarbons (CHC) combined, and 9 individual CHCs using job exposure matrices.
Kernan et al. (1999)	case-control	cases: 63,097 persons who died from pancreatic cancer (1984-93), using NCI, National Center for Health Statistics (NCHS) data. control: 252,386 persons who died from causes other than cancer in same time period, using NCHS data.	The risk of pancreatic cancer was not statistically elevated in relation to intensity of exposure to 1,1,1-trichloroethane and showed no consistent pattern of elevation by probability of exposure across race and gender.	Relation between occupational exposure and pancreatic cancer mortality was examined. Specifically, odds ratios (OR) calculated for 36 occupations/industries and 11 solvent exposures.
Spirtas et al. (1991)	cohort	cohort: workers at an aircraft maintenance facility at Hill Air Force Base, Utah (1952-56); 27,223 person-years (men) and 1215 person-years (women) with 1,1,1-trichloroethane exposure control: mortality experience for white male and female population in US and state of Utah	The risk of multiple myeloma was statistically elevated in women only: Obs / person-yrs / SMR (95% CI) 2 1215 5660 (685-20445) No cases were observed in men.	Relationship between 28 industrial chemicals or chemical groups and multiple myeloma or non-Hodgkin's lymphoma was examined.

Study	Study Design	Source / No. of Subjects & Referents	Pertinent Findings	Comments
Antilla et al. (1995)	cohort	cohort: 2050 men & 1924 women biologically monitored for occupational exposure to three halogenated solvents at the Finnish Institute of Occupational Health (1967-92); follow-up for cancer through the Finnish Cancer Registry control: Finnish Cancer Registry	Overall cancer incidence was not statistically elevated. Elevated standardized incidence ratio (SIR) was observed for two cancer sites only: Cancer of the nervous system: Obs SIR 95%CI 3 6.05 1.25-17.7 Multiple myeloma: Obs SIR 95%CI 2 15.98 1.93-57.7	Relationship between exposure to trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane and cancer incidence (30 sites considered). Investigators noted that it was not possible to separate the effects of other solvents from the monitored ones, and that 1,1,1-trichloroethane contained 1,4-dioxane (<1-5%) as a stabilizer.
Infante-Rivard et al. (2005)	case-control	cases: 790 parents of children diagnosed with ALL between 1980 and 2000 in the province of Quebec, Canada; recruited from tertiary cancer centers. control: population-based controls from two Canadian government databases; children matched on sex and age at time of diagnosis.	The ORs for childhood ALL were elevated, but the increase was not statistically significant. OR 95% CI 2 years before pregnancy up to birth 7.55 0.92-61.97 During pregnancy 4.07 0.45-36.7	Analyses performed for 21 individual solvents and 6 solvent mixtures. Prevalence of exposure to individual solvents was low. Investigators considered power of the study to be an issue.

OR = odds ratio
SIR = standardized incidence ratio

4.2. LESS THAN LIFETIME AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Oral Exposure

4.2.1.1. *Acute Studies*

Lethality studies have reported single dose LD_{50} values for 1,1,1-trichloroethane of 9600-17,148 mg/kg in rats, 6000-11,240 mg/kg in mice, 9470 mg/kg in guinea pigs and 5660 mg/kg in rabbits (Torkelson et al., 1958; Kinkead and Wolfe, 1992; Walum, 1998).

Acute studies of systemic toxicity of 1,1,1-trichloroethane have focused on the liver as a potential target. Evidence of hepatotoxicity was reported by Xia and Yu (1992) and Tyson et al. (1983). In the Xia and Yu (1992) study, unspecified numbers of adult female Wistar rats (158 ± 14 g) were treated with single gavage doses of 0 or 5 mmol/kg (670 mg/kg) of 1,1,1-trichloroethane (purity not specified) in arachidic oil. Rats were sacrificed after 6, 12, 24, 36, 48 or 72 hours for collection of blood (analyzed for enzyme markers of hepatotoxicity: ALT, sorbitol dehydrogenase [SDH], and glutamate dehydrogenase [GDH]) and liver tissue (analyzed for histopathology). There was a statistically significant 1.5-fold increase in serum ALT in rats killed at 24 hours, although not before or after. Serum SDH and GDH were not affected by treatment. No liver lesions were found by light microscopy. The 1,1,2-trichloroethane isomer was also tested in this study, producing much more obvious liver toxicity (4-fold increase in ALT, large increases in SDH and GDH, microscopic lesions), but also with maximal effect 24 hours after dosing. The similar time course of ALT changes for the two isomers supports the position that the observed increase for 1,1,1-trichloroethane reflects a mild, treatment-related effect on the liver, and not a random event. The data suggest that serum ALT is a sensitive indicator of hepatotoxicity for 1,1,1-trichloroethane and that the dose of 670 mg/kg can be considered a LOAEL for this effect.

Tyson et al. (1983) also reported evidence of hepatotoxicity after acute oral exposure. Groups of 3-5 male Sprague-Dawley rats weighing 140-230 g were given single gavage doses of approximately 0, 2, 9.5 or 19 mmol/kg (0, 300, 1300, or 2500 mg/kg) of reagent grade 1,1,1-trichloroethane in corn oil. Blood was collected 6 and 24 hours after dosing and analyzed for ALT and AST as indicators of hepatotoxicity. Although there was no effect on serum ALT in this study, serum AST levels were increased roughly 2-fold 6 hours after treatment with 2500 mg/kg-day. The increase was no longer seen after 24 hours. This study, therefore, identified a NOAEL of 1300 mg/kg and LOAEL of 2500 mg/kg for mild hepatotoxicity.

In contrast to these studies, Bruckner et al. (2001) did not find evidence of hepatotoxicity in rats at doses up to 4000 mg/kg. Male Sprague-Dawley rats (group size not specified) weighing 200-220 g were given single doses of 0, 500, 1000, 2000, or 4000 mg/kg of 1,1,1-trichloroethane (>99% pure) by gavage in corn oil and sacrificed 24 hours later (Bruckner et al.,

2001). No mortality occurred, and there were no effects on liver weight or histopathology, serum enzyme indicators of hepatotoxicity (ALT, SDH, ornithine carbamoyl-transferase [OCT]), or hepatic nonprotein sulfhydryl levels or glucose-6-phosphatase activity (data not presented in the study report). The high dose of 4000 mg/kg was an apparent acute NOAEL for liver endpoints in this study.

4.2.1.2. *Short-Term Studies*

Liver and kidney effects were investigated in short-term oral studies (Bruckner et al., 2001; NTP, 1996). Bruckner et al. (2001) treated groups of approximately 15 male Sprague-Dawley rats (230-260 g) with 0, 500, 5000, or 10,000 mg/kg of 1,1,1-trichloroethane (>99% pure) by gavage in corn oil 9 times over 12 days (daily average doses of 0, 375, 3750, or 7500 mg/kg-day). Groups of up to 5 rats were weighed and sacrificed 1, 5, or 12 days after the start of dosing for clinical chemistry (ALT, SDH, OCT) and biochemistry (hepatic nonprotein sulfhydryl and glucose-6-phosphatase) evaluations and examination of the liver for histopathological changes. After each dosing, rats treated with 5000 or 10,000 mg/kg of 1,1,1-trichloroethane exhibited hyperexcitability for a brief period (20-30 minutes), followed by an extended period of narcosis. Three rats in the 5000 mg/kg group died during the study (2 in the first 24 hours), while only 1 rat in the 10,000 mg/kg group survived to terminal sacrifice (5/10 remaining after the 1-day sacrifice died before day 3 of the study). No clinical signs or deaths were seen in the 500 mg/kg group. Body weight was significantly lower than controls in the 5000 and 10,000 mg/kg groups at 5 days (≈15% reduction in both groups) and remained lower at 12 days (≈20% reduction in the 5000 mg/kg group and ≈37% reduction in the lone survivor from the 10,000 mg/kg group). Body weight was similar to controls in the 500 mg/kg group. No effect on the liver was found by serum chemistry, biochemistry, or histopathology evaluations at any dose level (data not presented in the study report). Absolute liver weight was about 20% lower than the control mean in the lone surviving rat at 10,000 mg/kg after 12 days. This change does not necessarily indicate a target organ effect on the liver, however, given the ≈37% reduction in body weight in this animal. Relative liver weights were not reported. This study identified an apparent short-term NOAEL of 500 mg/kg (375 mg/kg-day), although only the liver was investigated for target organ toxicity. The 5000 mg/kg (3750 mg/kg-day) dose level is a LOAEL for gross CNS depression and associated mortality. The wide spacing between the low-dose (375 mg/kg-day) at which no effects were observed and the mid-dose (3750 mg/kg-day), which was associated with an increased incidence of mortality, limit the study's usefulness in defining a NOAEL and LOAEL.

Consistent with the results of Bruckner et al. (2001), rats treated for 7 days with 0 or 1650 mg/kg-day of 1,1,1-trichloroethane by gavage in liquid paraffin had body and liver weights

similar to controls (Platt and Cockrill, 1969).

NTP (1996) investigated renal and hepatic endpoints in a short-term study in which groups of 5 male F344/N rats were administered 1,1,1-trichloroethane (purity 100%) by gavage in corn oil at doses of 0, 0.62 or 1.24 mmol/kg-day (0, 83 or 165 mg/kg-day) for 21 days. Evaluations included survival, body weight gain, clinical signs, urinalysis (creatinine, glucose, total protein, AST, GGT, *N*-acetyl-β-D-glucosaminidase, volume, specific gravity), organ weights (liver, right kidney, right testis) and limited histological assessment (liver, right kidney, gross lesions). The clinical and tissue pathology evaluations were limited in scope and centered on renal endpoints because this study was part of an investigation of structure-activity relationships involved in the induction of hyaline droplet nephropathy by halogenated ethanes. One rat in the 165 mg/kg-day group died on the second day of the study; the cause of death was not discussed. Otherwise, no clinical signs of toxicity were noted and body weights remained similar to controls throughout the study. Urinalysis revealed large, statistically significant increases in mean urinary protein (indicative of renal dysfunction, and possibly, tissue damage) and AST (indicative of renal tissue damage) in the survivors in the 165 mg/kg-day group (see Table 11). However, no histopathological lesions were found in the livers or kidneys of treated rats, including renal hyaline droplet nephropathy, tubule regeneration, or granular casts. Relative liver weight was significantly increased by ≈11% in the 165 mg/kg-day rats, and although not statistically significant, absolute liver weight was also ≈9% higher than controls in this group. There were no statistically significant changes in kidney or testis weight. NTP considered the urinalysis results to be highly suggestive of renal injury at 165 mg/kg-day, but also noted the lack of supporting histopathology data. The small group size (4 rats) in the 165 mg/kg-day group and the large standard errors for protein and AST concentrations in this group suggest that the increases in the corresponding means could be due to high levels in a single individual, and therefore, may not be related to treatment. Because of these questions about the urinalysis results and the lack of supporting histopathology data, it is not clear whether the observed urine changes indicate an adverse renal effect or whether any renal damage that did occur was related to treatment. Therefore, NOAEL/LOAEL values were not assigned.

Table 11. Effect of 1,1,1-Trichloroethane on Selected Urinary Parameters in Male Rats

	Dose (mg/kg-day)		
Parameter	0	83	165
Protein (μg/mg creatinine)	1227 ± 78 (5)[1]	1447 ± 130 (5)	2198 ± 584 (4)[2]
AST (mU/mg creatinine)	8 ± 1 (5)	16 ± 1 (5)	466 ± 444 (4)[2]

[1] mean ± standard error (n)
[2] significantly different from controls ($p \leq 0.05$)
Source: NTP, 1996

4.2.1.3. *Subchronic Studies*

Subchronic studies of 1,1,1-trichloroethane toxicity were conducted by gavage and dietary exposure. In the gavage study, groups of 15-20 male Sprague-Dawley rats (200-260 g) were treated with analytical grade 1,1,1-trichloroethane (>99% pure) at doses of 0, 500, 2500, or 5000 mg/kg by gavage in corn oil 5 days per week for up to 13 weeks (average daily doses of 0, 357, 1786, or 3571 mg/kg-day) (Bruckner et al., 2001). Blood for measurement of serum enzyme level activities (ALT, SDH, OCT) was collected from 5 randomly selected rats from each dose group on week 2 of the study. Subsequent collections of blood were performed on alternating sets of rats every other week throughout the study. Moribund rats were sacrificed and examined for gross pathology. On day 51 of the study, surviving rats in the 2500 and 5000 mg/kg groups were accidentally poisoned with 1,1-dichloroethene and all died within 24 hours from massive liver damage. Terminal sacrifice of the 0 and 500 mg/kg groups occurred on day 92, except for 5 rats from each group that were allowed to recover for 1 week and then sacrificed. At sacrifice, blood was collected for serum enzyme determination, and the livers were weighed and processed for histopathological examination.

Clinical signs of toxicity and death were observed in the rats treated with 2500 or 5000 mg/kg of 1,1,1-trichloroethane (Bruckner et al., 2001). Rats in these groups showed hyperexcitability followed by hours of narcosis immediately following each day's dose. By day 50 of the study, 33% of rats in the 2500 mg/kg group and 47% of rats in the 5000 mg/kg group had died. The only finding in these animals upon gross necropsy was pulmonary congestion. The deaths were attributed by the researchers to repeated, protracted CNS depression, although it was noted that chronic murine pneumonia may also have contributed. According to the study protocol, the 2500 and 5000 mg/kg-day groups were housed together in a different isolation module than the 0 and 500 mg/kg-day groups. The study authors do not address whether chronic murine pneumonia may have been present in all four exposure groups. There was one death in the 500 mg/kg group that was due to gavage error. Body weights of the 2500 and 5000 mg/kg groups were significantly reduced for the time these animals were on study; the deficit on Day 51 was about 22% in both groups. Body weight of the 500 mg/kg group was slightly lower than controls throughout the entire study, but the difference was never statistically significant. Slight, 2-fold increases were seen in OCT activity in the 5000 mg/kg group throughout the 7 weeks these animals were on study; statistical significance was achieved on weeks 2 and 4. ALT activity was also slightly and significantly increased in the 5000 mg/kg group on weeks 2 and 4, but after 6 weeks was similar to controls. SDH activity was significantly greater than controls in all treated groups after 6 weeks, but comparisons to the values at 2 and 4 weeks and the lack of any apparent dose-response suggest that this reflects a low level in the controls at 6 weeks, rather than a treatment-related effect. No significant changes in serum enzyme level activities were

seen in the 500 mg/kg group throughout the remainder of the study, and no effects on absolute or relative liver weights or liver histopathology were found in this group after 13 weeks of exposure or after the 1-week recovery period (data not presented in the study report). The 500 mg/kg (357 mg/kg-day) dose is an apparent NOAEL in this study, although the liver was the only potential target systematically investigated. The 2500 mg/kg (1786 mg/kg-day) dose level is a LOAEL for gross CNS depression and associated mortality. The early accidental termination of the 2500 and 5000 mg/kg-day groups and incomplete reporting of methods and results limit the usefulness of this study.

A thirteen-week feeding study was conducted in rats and mice (NTP, 2000). Groups of 10 male and 10 female F344/N rats and B6C3F1 mice, 6-7 weeks old at the start of the study, were fed diets containing 0 (untreated feed), 0 (placebo microcapsules), 5000, 10,000, 20,000, 40,000, or 80,000 ppm of microencapsulated 1,1,1-trichloroethane (>99% pure) 7 days/week for 13 weeks. Average daily doses calculated by the researchers were 290, 600, 1200, 2400, and 4800 mg/kg in male rats; 310, 650, 1250, 2500, and 5000 mg/kg in female rats; 850, 1770, 3500, 7370, and 15,000 mg/kg in male mice; and 1340, 2820, 5600, 11,125, and 23,000 mg/kg in female mice. Clinical signs and body weight were recorded weekly. Feed consumption was recorded every 3-4 days. Urine was collected for analysis and measurement of 1,1,1-trichloroethane metabolites from 5 randomly selected male rats in the vehicle control, 5000, 20,000 and 80,000 ppm groups on days 28 and 84. Blood for hematology and clinical chemistry determinations was collected from all rats at the end of the study, and from satellite groups of 10 male and 10 female rats (exposed to the same concentrations as the main study groups) on days 3 and 23. Vaginal cytology (over 12 days prior to sacrifice) and sperm motility (at necropsy) evaluations were performed on all main study rats and mice in the vehicle control, 20,000, 40,000, and 80,000 ppm groups at the end of the study. All animals in the main study were necropsied; organs and tissues were examined for gross lesions, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Rats and mice in the untreated control, vehicle control, and 80,000 ppm groups in the main study received complete histopathological examinations. Rats in 5000, 10,000, 20,000 and 40,000 ppm main study groups were examined for renal histopathology only.

All rats survived to study termination and no clinical signs of toxicity were observed (NTP, 2000). Body weight gain over the course of the study was significantly reduced in the 80,000 ppm male rats in comparison to both the untreated and vehicle controls. Final body weight was 10% less than vehicle controls (statistically significant), but only 4% less than untreated controls (not significant). Because of the nutritional content of the vehicle used (i.e., microcapsules composed of 80% food grade modified corn starch and 20% sucrose), the vehicle control was considered the most appropriate comparison group. In the 80,000 ppm females,

body weight gain and final body weight were lower than vehicle and untreated controls, but only the difference in final body weight versus vehicle controls (4.2%) was statistically significant. Body weight changes in lower dose groups were unremarkable. Feed consumption was similar to controls in all groups. Hematology analyses revealed minimal increases in red blood cell count, hemoglobin, and hematocrit in male and female rats at 10,000 ppm and above. NTP considered these changes to indicate a minimal hemoconcentration effect likely due to physiological processes unrelated to 1,1,1-trichloroethane exposure. No toxicologically meaningful changes were found in clinical chemistry or urine analyses. Absolute and relative liver weights were significantly reduced in female rats treated with 80,000 ppm by about 15% and 11%, respectively, in comparison to both untreated and vehicle controls. In male rats treated with 80,000 ppm, absolute liver weight was significantly reduced by about 13% compared with vehicle controls, but did not differ from untreated controls, and relative liver weight was unaffected. Male rats treated with 20,000 ppm or above of 1,1,1-trichloroethane showed renal lesions considered by study investigators to be consistent with α_{2u}-globulin nephropathy, as indicated by significant, dose-related increases in incidence and/or severity of renal tubule hyaline degeneration, cast formation, and regeneration, and chronic interstitial inflammation of the kidney. Assays for the presence of α_{2u}-globulin were not conducted. No lesions in other tissues were observed in the males, and no lesions in any tissue were observed in the female rats. Treatment with 1,1,1-trichloroethane had no effect on vaginal cytology parameters in female rats. In males, epididymal spermatozoal concentration was significantly reduced by about 10% in the 80,000 ppm group compared with vehicle controls (untreated controls not tested), but no other associated changes were found. Renal changes associated with α_{2u}-globulin nephropathy in male rats are specific to this sex and species, and are not considered to be predictive for effects in humans (U.S. EPA, 1991c). Therefore, this study identified a LOAEL of 80,000 ppm (4800 mg/kg-day in males and 5000 mg/kg-day in females) and NOAEL of 40,000 ppm (2400 mg/kg-day in males and 2500 mg/kg-day in females), based on reduced liver weights in males and females and reduced epididymal spermatozoal concentration in males.

Mice also showed no clinical signs of toxicity from 1,1,1-trichloroethane ingestion, and suffered no mortality during the study (NTP, 2000). Significant, dose-related reductions in body weight gain and terminal body weight were observed in male mice treated with 5000 ppm or above and female mice treated with 10,000 ppm or above, in relation to both untreated and vehicle controls. Terminal body weights for mice relative to controls were as follows:

Table 12. Terminal Body Weights for Mice

Group	Final Body Weight					
	Male[1]			Female[2]		
	Final body weight (g)	Mean weight change (g) (±SE)	Wt. relative to vehicle control (%)	Final body weight (g)	Mean weight change (g) (±SE)	Wt. relative to vehicle control (%)
Untreated control	35.4±0.8	12.8±0.5		28.8±0.9	10.1±0.8	
Vehicle control	36.9±0.7	13.7±0.5		29.3±0.8	11.2±0.8	
5,000 ppm	33.6±0.7▲	11.2±0.5*▲	91	28.4±0.6	9.6±0.7	97
10,000 ppm	33.7±0.6▲	10.8±0.5**▲	91	27.2±0.8	8.7±0.6▲	93
20,000 ppm	32.7±0.5**▲	9.9±0.4**▲	88	26.0±0.8**▲	7.5±0.7**▲	89
40,000 ppm	33.1±0.5**▲	10.0±0.3**▲	90	25.8±0.7**▲	7.2±0.6**▲	88
80,000 ppm	31.3±0.4**▲	8.7±0.3**▲	85	24.5±0.5**▲	6.2±0.5**▲	84

[1] Corresponding doses, in mg/kg-day, for male mice were: 850, 1770, 3500, 7370, and 15,000 mg/kg-day.
[2] Corresponding doses, in mg/kg-day, for female mice were: 1340, 2820, 5600, 11,125, and 23,000 mg/kg-day.
* Significantly different (P≤0.05) from the untreated control group.
** Significantly different (P≤0.01) from the untreated control group.
▲ Significantly different (P≤0.01) from the vehicle control group.
Source: NTP, 2000

Feed consumption was generally greater in treated mice than in controls. Statistically significant changes in absolute and/or relative organ weights were seen in the heart, liver, and kidney in male mice and in the kidney in female mice. However, these changes were considered by the researchers to be secondary to the changes in body weight, and not toxicologically significant. No gross or microscopic lesions due to 1,1,1-trichloroethane were seen in male or female mice. Vaginal cytology parameters in treated female mice were similar to controls. Male mice in the 80,000 ppm group had a significant 20% reduction in epididymal spermatozoal concentration compared with vehicle controls (untreated controls not tested), but no other associated changes. Effects on body weight were the most sensitive indicators of 1,1,1-trichloroethane toxicity in both male and female mice. NTP (2000) estimated the dose of 10,000 ppm (1770 mg/kg-day) in male and female mice to be a NOAEL and 20,000 ppm (3500 mg/kg-day) to be a LOAEL based on decreases in terminal body weight greater than 10% of the control values.

In a study designed to investigate the effect of 1,1,1-trichloroethane on water palatability, groups of 32 male CD-1 mice were given 1,1,1-trichloroethane (97% pure, inhibited with 3% p-dioxane) in an Emulphor vehicle at concentrations of 0, 0.5 or 5.0 mg/ml (0, 103 or 1041 mg/kg-day, respectively, as estimated by the researchers) in the drinking water for 90 days (Kallman and Kaempf, 1984). Neither body weight nor fluid intake, the only two variables recorded, were influenced by exposure to 1,1,1-trichloroethane.

4.2.1.4. *Chronic Studies*

A chronic carcinogenesis bioassay was conducted in which technical grade 1,1,1-trichloroethane (≈95% pure containing 3% dioxane stabilizer and 2% minor impurities) was administered in corn oil by gavage to male and female Osborne-Mendel rats and B6C3F1 mice on 5 days/week for 78 weeks (NCI, 1977). Control and treated group sizes were 20/sex/species and 50/sex/species, respectively. Male and female rats were treated with doses of 750 or 1500 mg/kg-day for 78 weeks and observed for the next 32 weeks; untreated control rats were observed for 110 weeks. Low-dose male and female mice were sequentially treated with 2000 mg/kg-day for 10 weeks, 2500 mg/kg-day for 10 weeks and 3000 mg/kg-day for 58 weeks (TWA dose 2807 mg/kg-day), and observed for the following 12 weeks. High-dose male and female mice were sequentially treated with 4000 mg/kg-day for 10 weeks, 5000 mg/kg-day for 10 weeks and 6000 mg/kg-day for 58 weeks (TWA dose 5615 mg/kg-day), and observed for the following 12 weeks. Untreated male and female control mice were observed for 90 weeks. Study endpoints were limited to clinical observations, body weight, food consumption and histopathology. Effects in male and female rats included reduced survival (≈30-40% increased mortality compared to controls during the first year of the study), decreased body weight (≈10-15% in males, starting on week 20; up to ≈30% in females, starting on week 75), and urine staining of abdominal fur in both the low and high dose groups. No histopathological changes were observed. Effects occurred in mice in both dose groups, including reduced survival in females (13 and 35% increase in low- and high-dose group mortality during the first year) and ≈15-20% decreased body weight in both sexes. The reduced survival in rats and mice was considered compound-related by NCI (1977), although chronic murine pneumonia was a prevalent spontaneous lesion in all control and treated groups of both sexes and was a probable contributing factor in the early deaths. Based on reduced survival, the lowest doses tested, 750 mg/kg-day (536 mg/kg-day after adjustment for 5/7 day exposure) in rats and 2807 mg/kg-day (2005 mg/kg-day after adjustment for 5/7 day exposure) in mice, are LOAELs for chronic exposure. The incidence and type of neoplasms observed in treated rats and mice were similar to those observed in the untreated controls. Because of the high rate of early mortality in treated animals, NCI did not consider this study to be an adequate test of 1,1,1-trichloroethane carcinogenicity for either rats or mice.

In a screening level chronic carcinogenesis bioassay, Sprague-Dawley rats were administered 0 (50/sex) or 500 mg/kg (40/sex) 1,1,1-trichloroethane (technical grade containing 3.8% dioxane) by gavage in olive oil, 4-5 days/week for 104 weeks (Maltoni et al., 1986). Adjusting for partial weekly exposure yields an estimated average daily dose of 321 mg/kg-day. The experiment lasted 141 weeks, as animals that survived to the end of the treatment period

were allowed to live until spontaneous death. Body weight and survival were assessed throughout the study, and complete necropsies, including histopathological examinations, were performed on each animal. Survival of the treated and control animals over the course of the study appeared to be comparable, although no statistical analysis was performed. Average body weight was reduced in treated females after approximately 80 weeks of exposure; body weight in exposed females was ≈12% and ≈25% lower than controls at the end of the treatment and observation periods, respectively. Tumor incidences were not analyzed statistically by the researchers, but an apparent increase in the total incidence of leukemias occurred (13 in treated rats, 4 in controls). This increase was mainly due to an apparent increase in immunoblastic lymphosarcomas in the lungs of treated rats [7 in treated rats (5 male, 2 female) and 1 in controls (1 male)]. Increases for both total leukemias and for pulmonary immunoblastic lymphosarcomas in males and females combined were statistically significant ($p<0.05$) by Fisher Exact tests performed for the current evaluation; the increase in pulmonary immunoblastic lymphosarcomas in males was of marginal significance ($p=0.10$). The study did not include evaluation of non-neoplastic lesions. Based on reduction in body weight gain, this study identifies a chronic LOAEL of 321 mg/kg-day. Tumor findings are considered inconclusive because of inherent limitations of the experimental design (one dose, one species) and incomplete analysis and reporting of results.

4.2.2. Inhalation Exposure

4.2.2.1. *Acute Studies*

LC_{50} values ranged from 3911 ppm (21,350 mg/m^3) for a 2-hour exposure in mice (Horiguchi and Horiuchi, 1971) to 38,000 ppm (207,480 mg/m^3) for a 15-minute exposure in rats (Clark and Tinston, 1982). However, most studies estimated LC_{50} values between 10,000 and 30,000 ppm (54,600 and 163,800 mg/m^3) (for durations ranging from 10 minutes to 7 hours) (Adams et al., 1950; Siegel et al., 1971; Gradiski et al., 1978; Bonnet et al., 1980; Woolverton and Balster, 1981; Moser and Balster, 1985; Calhoun et al., 1988). There was a general trend for LC_{50} to decrease as the exposure duration increased. For example, Moser and Balster (1985) estimated LC_{50} values in male CD-1 mice after 10, 30 or 60 minute exposures to 1,1,1-trichloroethane and found corresponding LC_{50} values of 29,492, 20,616, and 18,358 ppm (161,030, 112,560, and 100,230 mg/m^3). There appears to be little difference in susceptibility between rats and mice. Researchers in one laboratory that tested both species obtained a 6-hour LC_{50} of 10,305 ppm (56,270 mg/m^3) in male rats and 13,414 ppm (73,240 mg/m^3) in female mice exposed by the same protocol (Gradiski et al., 1978; Bonnet et al., 1980).

1,1,1-Trichloroethane-associated lethality in these studies was generally preceded by increasingly serious signs of central nervous system depression, including initial excitability,

ataxia, loss of righting reflex, loss of movement, narcosis, and irregular and shallow respiration (Adams et al., 1950; Clark and Tinston, 1982; Moser and Balster, 1985; Lazarew, 1929; Gehring, 1968; Bonnet et al., 1980; Woolverton and Balster, 1981; Calhoun et al., 1988). Clark and Tinston (1982) estimated an EC_{50} in rats for CNS depression of 5000 ppm (27,300 mg/m^3) for 10 minute exposure. Studies designed specifically to investigate the effects of 1,1,1-trichloroethane on the central nervous system are discussed in Section 4.4.

When performed, gross necropsy failed to find tissue lesions associated with mortality (Bonnet et al., 1980; Calhoun et al. 1988). Death was generally attributed to cardiac or respiratory depression (Adams et al., 1950; Krantz et al., 1959; Woolverton and Balster, 1981; Clark and Tinston, 1982). Mechanistic studies have demonstrated that brief exposure to high concentrations of 1,1,1-trichloroethane can produce direct depression of both the respiratory center (Uchigasaki et al., 1998; Kobayashi et al., 1986, 1987a) and the heart (Uchigasaki et al., 1998; Herd et al. 1974; Belej et al., 1974; Taylor et al., 1976). Depression of myocardial function produces a concomitant reduction in blood pressure (Uchigasaki et al., 1998; Herd et al., 1974; Belej et al., 1974; Taylor et al., 1976), which can result in death if blood pressure drops too low (Herd et al., 1974; Krantz et al., 1959). Blood pressure is also reduced, to a lesser extent, at lower exposure concentrations. At levels below which myocardial function is depressed, the decrease in blood pressure appears to be due to a 1,1,1-trichloroethane-induced increase in peripheral vasodilation (Herd et al., 1974; Kobayashi et al., 1983, 1984; Aoki et al., 1997). The dose-response curve for effects on blood pressure was studied by Kobayashi et al. (1983). These researchers observed a concentration-related decrease in systemic blood pressure, with no effect at 3500 ppm (19,110 mg/m^3), slight decreases at 4500-6200 ppm (24,570-33,850 mg/m^3), and larger decreases at 15,000-28,000 ppm (81,900-152,880 mg/m^3) in anesthetized mongrel dogs (7-14 kg) of both sexes exposed to various concentrations of 1,1,1-trichloroethane vapor by tracheal tube for 2 minutes. The slight decreases at around 5000 ppm (27,300 mg/m^3) correspond to the threshold for decreased peripheral vascular resistance observed in a follow-up study by the same researchers (Kobayashi et al., 1984). The larger decreases at $\geq$15,000 ppm (81,900 mg/m^3) presumably correspond to decreases associated with depressed myocardial function, which occurred at these concentrations in the study by Herd et al. (1974). No gross or microscopic lesions in the heart were observed at any exposure level (Herd et al., 1974). It has been proposed that depression of respiration, blood pressure and myocardial function by 1,1,1-trichloroethane may result, in part, from effects on the autonomic nervous system (Kobayashi et al., 1986, 1987a,b, 1988).

Sensitization of the heart to epinephrine, resulting in the production of cardiac arrhythmias, is another potential cause of death from high-level 1,1,1-trichloroethane exposure (Rennick et al., 1949). Healthy male beagles were exposed by face mask to 2500, 5000 or

10,000 ppm (13,650, 27,300 or 54,600 mg/m^3) of 1,1,1-trichloroethane for 10 minutes following 7 minutes exposure to house air and injected with epinephrine twice (a control dose after 2 minutes of the air exposure and a challenge dose after 5 minutes of chemical exposure). Electrocardiographic signals were recorded. Arrhythmias were detected in 0/12 trials at 2500 ppm, 3/18 trials (17%) at 5000 ppm, and 12/12 trials (100%) at 10,000 ppm. Behavioral changes (excitement and struggling) were observed in dogs exposed to 10,000 ppm (Reinhardt et al., 1973). A similar study in which groups of 4-7 beagles were exposed by face mask to various concentrations of 1,1,1-trichloroethane for 5 minute periods with challenge and control adrenaline injections determined an EC_{50} of 7500 ppm (40,950 mg/m^3) (95% CI: 4000-11,000 ppm; 21,840-60,060 mg/m^3) for cardiac sensitization from this chemical (Clark and Tinston, 1973). Kobayashi et al. (1982) conducted a series of experiments in which anesthetized dogs were given epinephrine by i.v. drip until bigeminy (extrasystole) occurred with and without exposure to 1,1,1-trichloroethane vapor at concentrations of 1750 to 69,000 ppm (9560-376,740 mg/m^3) for periods ranging from 0.5 to 20 minutes. The ratio of epinephrine dose needed to produce arrhythmia with and without 1,1,1-trichloroethane exposure was used to measure the sensitizing effect of 1,1,1-trichloroethane. There were significant negative correlations between this ratio and the product of exposure concentration and time (C x T) and concentration alone when time was held constant, indicating that the sensitizing effect of 1,1,1-trichloroethane increased with exposure. For a 10-minute exposure, the threshold concentration for cardiac sensitization was between 4900 and 8500 ppm (26,750 and 46,410 mg/m^3).

Other studies of cardiac sensitization and arrhythmia in animals exposed to 1,1,1-trichloroethane found that: 1) dogs with experimentally-induced myocardial infarctions were no more likely to show cardiac sensitization to 1,1,1-trichloroethane than healthy dogs (Trochimowicz et al., 1974, 1976); 2) arrhythmias (premature ventricular contractions) occurred in response to epinephrine challenge in anesthetized rabbits exposed to 5600 ppm (30,580 mg/m^3) of 1,1,1-trichloroethane for 7.5 minutes to 1 hour and were enhanced by co-treatment with enzyme inhibitors (SKF-525A, Lilly 18947) that increased blood levels of parent compound and slightly diminished by co-treatment with the enzyme inducer phenobarbital, which slightly reduced the level of parent compound in the blood, suggesting that the cardiac sensitizing property of 1,1,1-trichloroethane is due to the parent compound (Carlson, 1981); and 3) 1,1,1-trichloroethane can produce arrhythmias without co-treatment with epinephrine at exceedingly high exposure levels (25,000-50,000 ppm [136,500-273,000 mg/m^3] for 5 minutes in anesthetized rhesus monkeys, and 400,000 ppm [2,184,000 mg/m^3] for 6 minutes in anesthetized Swiss mice) (Aviado and Belej, 1974; Belej et al., 1974). Although cardiac sensitization by 1,1,1-trichloroethane has been demonstrated repeatedly in a number of studies, not all studies have reported positive results. Egle et al. (1976) found no evidence of cardiac

sensitization in anesthetized beagles exposed for 30 minutes to 5000 or 10,000 ppm (27,300 or 54,600 mg/m^3) of 1,1,1-trichloroethane released from aerosols.

There is little evidence of damage to the liver or other tissues in acute inhalation studies of 1,1,1-trichloroethane. Adams et al. (1950) exposed rats (10-84 per group, males and females combined) to concentrations ranging from 5000 to 30,000 ppm (27,300 to 163,800 mg/m^3) for durations of 0.1-7 hours. Survivors generally recovered rapidly after the end of exposure and at 24 hours appeared normal and showed no effect on body weight. Internal examinations for organ weight and histopathology (lung, heart, liver, kidneys, testes) were performed 24 hours after exposure for groups of 3-5 rats exposed to 8000, 12,000, or 18,000 ppm (43,680, 65,520, or 98,280 mg/m^3) for 0.1-7 hours and 17 unexposed control rats. Rats exposed to 8000 ppm for 7 hours had significantly increased relative liver weight (12%) and slight histopathology (fatty change) in the liver. Rats exposed to 12,000 ppm for 7 hours had a larger increase in relative liver weight (27%) and slight-to-moderate liver lesions, including more marked fatty changes and, in some cases, congestion and hemorrhagic necrosis. A slight increase in relative kidney weight (8%) at this dose was not accompanied by histopathology in this organ. Rats exposed to 18,000 ppm were only exposed for up to 2 hours, and the only significant effect in this group was a small (11%) increase in relative kidney weight.

Studies with shorter exposure durations found no evidence of damage to the liver or other tissues due to 1,1,1-trichloroethane. Carlson (1973) exposed groups of 5 adult male albino rats to 11,600 or 13,070 ppm (63,340 or 71,360 mg/m^3) 1,1,1-trichloroethane for 2 hours and compared with unexposed controls. No effects were observed on relative liver weight, liver glucose-6-phosphatase activity, or serum levels of ALT and AST 22 hours after exposure termination, although rats pretreated with phenobarbital (but not 3-methylcholanthrene) did have significantly elevated enzyme levels (~4- to 7-fold). Cornish and Adefuin (1966) exposed male Sprague-Dawley rats to 5000 ppm (27,300 mg/m^3) for 6 hours, 10,000 ppm (54,600 mg/m^3) for 2 or 4 hours, or 15,000 ppm (81,900 mg/m^3) for 2 hours to reagent grade 1,1,1-trichloroethane. No differences from unexposed controls were found 24 or 48 hours after exposure for serum ALT, AST or isocitric dehydrogenase (ICD), or histopathology of the liver, kidney, adrenal, spleen or lung. Two of 14 rats died after exposure to 15,000 ppm. Gehring (1968) found that in female Swiss-Webster mice exposed to 13,500 ppm (73,710 mg/m^3), the exposure duration estimated to increase serum ALT (measured 24 hours after the start of exposure) in half of the mice (ET_{50}) could not be determined because it exceeded the estimate of time required to kill half of the mice ($LT_{50} \approx 10$ hours). Loizou et al. (1996) observed no evidence of liver toxicity, as assessed by serum SDH, LDH and GDH, 2 hours post-exposure in groups of 4-6 male Wistar rats exposed to 1,1,1-trichloroethane for 3 hours at concentrations of 0, 2000, 4000, 8000, 15,000 or 25,000 ppm (0, 10,920, 21,840, 43,680, 81,900 or 136,500 mg/m^3). There was no effect on liver function

(bromosulfalein retention test) in dogs anesthetized with 1,1,1-trichloroethane for 1 hour (Krantz et al., 1959). Takahara (1986b) measured serum ALT, liver and plasma triglyceride, and liver ATP at 0, 3, 11 and 23 hours in female mice (5/group) exposed to 800 ppm (4370 mg/m^3) 1,1,1-trichloroethane for 3 hours. Although there appeared to be some very mild changes over time, most notably an increase in liver triglyceride levels during exposure, the study did not include a concurrent control group and there was no statistical comparison of pre-exposure and post-exposure groups.

The effects of acute inhalation exposure to 1,1,1-trichloroethane on hematological parameters were studied in anesthetized dogs (Hobara et al., 1983, 1984). Groups of 5 cross-bred dogs (males and females, 2-5 years old) anesthetized with sodium pentobarbital were exposed to 200, 500, 700, 1000, 1500, or 2000 ppm (1090, 2730, 3820, 5460, 8190 or 10,920 mg/m^3) 1,1,1-trichloroethane for 1 hour or 700 ppm (3820 mg/m^3) for 4 hours. A control group of 15 dogs was sham-exposed to fresh air only. Blood samples were collected before exposure and 60 minutes after exposure in all groups, and more frequently in the two 700 ppm groups. No significant effect on erythrocyte count, hematocrit, or thrombocyte count was observed. After the one hour exposure, leukocyte count was markedly and statistically significantly reduced at 500 ppm and above (25-30% of control levels at 700 ppm and above). Investigators observed a trend to recovery after the end of exposure. During the 4-hour exposure, the minimum leukocyte count occurred in the first hour and the trend to recovery started after 2 hours, even though exposure continued. Differential counts in the 700 ppm studies showed marked decreases in neutrophils and increases in lymphocytes, with only slight changes in eosinophils and monocytes. The changes in differential followed the same time course as the overall decrease in leukocytes. The researchers suggested that these results could reflect temporary trapping of neutrophils from peripheral blood in the capillary beds of other tissues as 1,1,1-trichloroethane is taken up from the blood into the tissues. These findings, therefore, appear to indicate a temporary physiological response to 1,1,1-trichloroethane, rather than an adverse effect on the blood or hematopoietic tissues. Clotting time of blood from dogs anesthetized with 1,1,1-trichloroethane for 1 hour was not different from unexposed controls (Krantz et al., 1959).

Neuroendocrine effects were investigated in one study in rats. Groups of 8-12 male Sprague-Dawley rats were exposed to 3500 or 5000 ppm (19,110 or 27,300 mg/m^3) 1,1,1-trichloroethane (>99% pure) for 10 or 30 minutes, or air exposed for 20 minutes (Pise et al., 1998). Plasma corticosterone levels were statistically significantly decreased after 30 minutes at 3500 ppm and 10 or 30 minutes at 5000 ppm. Plasma adrenocorticotropic hormone (ACTH) levels were significantly reduced at 5000 ppm at both time points, but not at 3500 ppm at either time point. In the brain, no clear pattern of effect was seen on hypothalamic, hippocampal, or

cortical levels of ACTH or corticotropin-releasing factor.

The RD_{50} (concentration producing a 50% decrease in respiratory rate), a measure of respiratory irritation, was reported to be >1000 ppm (5460 mg/m^3) for 1,1,1-trichloroethane in a study in which pulmonary function was evaluated in male Swiss-Webster mice exposed to 1000 ppm of the chemical for 30 minutes (Stadler and Kennedy, 1996).

4.2.2.2. *Short-Term Studies*

Groups of 10 male and 10 female rats (strain not specified) were exposed to 0 or 1000 (0 or 5460 mg/m^3) ppm 1,1,1-trichloroethane from a stabilized commercial formulation 7 hours per day, 5 days per week for 4 weeks (22 exposures) (Dow Chemical Co., 1969). The animals were monitored daily for clinical signs and body weight. Blood was collected for hematological examination prior to exposure and on the 5th and 20th exposure days. Animals were sacrificed at the end of the study and the major organs were examined for gross and microscopic changes. The lung, liver, spleen, kidney, and gonad (males only) were weighed. No deaths were observed in exposed rats, and no differences from controls were seen for clinical signs, growth, hematology, relative organ weights, or gross or microscopic pathology. The study defined a free-standing NOAEL of 1000 ppm (5460 mg/m^3).

Other short-term inhalation studies were more restricted in the scope of endpoints investigated. Groups of 6 adult male Wistar rats were exposed to 0, 200, 400, or 800 ppm (0, 1090, 2180, or 4370 mg/m^3) 1,1,1-trichloroethane continuously for 10 days (Koizumi et al., 1983). Limited hematology (RBC, WBC) and serum chemistry (ALT) analyses were performed, and the liver was weighed and analyzed for enzyme activity. There was no effect on hematology or serum ALT at any concentration. Relative liver weight and liver mixed function oxidase activity were significantly increased in all treated groups. The increase in liver weight appears to reflect enzyme induction, rather than toxicity, in this study, making the high level of 800 ppm (4370 mg/m^3) a NOAEL. A 48-hour study of similar design found no effect of 1,1,1-trichloroethane on liver or red blood cell δ-aminolevulinic acid dehydratase (ALA-D) activity, inhibition of which is an early indicator for disruption of heme synthesis, at concentrations up to 800 ppm (4370 mg/m^3) (Koizumi et al., 1984). NMRI mice exposed to 625 ppm (3410 mg/m^3) 1,1,1-trichloroethane continuously for 30 days showed slight (8-12%), statistically significant increases in absolute liver and kidney weight in females and decreased absolute spleen weight in males (Kjellstrand et al., 1985a). Neither body weights nor relative organ weights were reported. These researchers also reported a slight significant decrease in plasma butyrylcholinesterase activity in females, but no effect in males, suggesting that 1,1,1-trichloroethane did not affect testosterone activity in these animals. Slight increases (15%) in absolute and relative liver weight were noted in male Sprague-Dawley rats exposed to 0 or 820 ppm (4480 mg/m^3) 1,1,1-

trichloroethane 6 hours/day, 5 days/week for 4 weeks (Toftgard et al., 1981). Rats given repeated anesthesia with 1,1,1-trichloroethane, one hour per day, for 3-9 days had no lesions in the kidney, brain, or spinal cord; 1/9 exposed animals had midzonal necrosis of the hepatic parenchyma in the liver (Krantz et al., 1959).

4.2.2.3. *Subchronic Studies*

Groups of 20 male and 20 female CDF rats (4-6 weeks old) and B6C3F1 mice (5-6 weeks old) were chamber-exposed to 0, 150, 500, 1000 or 2000 ppm (820, 2730, 5460 or 10,920 mg/m^3) of production grade 1,1,1-trichloroethane (≈94% pure) for 6 hours/day, 5 days/week for up to 94 days (Calhoun et al., 1981). This study was conducted in preparation for selecting exposure concentrations for the Quast et al. (1984, 1988) chronic study. An interim sacrifice of 10 animals/sex/concentration was performed after 30 (rats) or 29 (mice) exposures, and terminal sacrifice was conducted on the remaining 10 animals/sex/concentration after 62 (rats) or 63 (mice) exposures. Study endpoints included clinical signs, body weight, hematology, clinical chemistry, urinalysis, liver triglyceride level, body and organ weights, gross pathology and histopathology. Gross pathology was evaluated in all animals following the interim and terminal sacrifices. Histology was assessed as follows: liver and kidneys in all exposure groups at interim sacrifice; possible target organs (liver, kidney, lung, nasal turbinates, esophagus, trachea, thyroid, parathyroid and/or gall bladder) in the 150, 500 and 1000 ppm (820, 2730 and 5460 mg/m^3) groups at terminal sacrifice; and complete examinations in the 0 and 2000 ppm (10,920 mg/m^3) groups at terminal sacrifice. Histological changes were observed in the liver and nasal turbinates of both species at 2000 ppm. Hepatic changes occurred in only a few animals at 2000 ppm and were generally minimal, including decreased hepatocyte size with altered staining affinity suggestive of decreased glycogen content (3/10 female rats vs. 0/10 controls; 4/10 male mice vs. 1/10 controls) and slight centrilobular hepatocellular swelling (2/10 male rats vs. 0/10 controls; 2/10 male mice vs. 0/10 controls). These histopathological changes more likely represent an adaptive physiologic response (i.e., stimulation of the drug metabolizing enzyme system) and as such are not considered adverse. The investigators considered remaining microscopic findings not to be treatment-related. The histopathology summary tables, however, showed generalized hepatocellular atrophy in 2000 ppm male rats (3/10 vs. 0/10 controls and lower-exposure groups) and focal necrosis in 2000 ppm female mice (2/10 vs. 0/10 in controls and lower-exposure groups). These findings suggest adverse effects in the liver of 2000 ppm rats and mice. Mild olfactory epithelium degeneration and other nasal alterations were found in all male and female rats and approximately one-half of the male and female mice at 2000 ppm. The turbinate changes were degenerate in type and confined to the olfactory epithelial region. Microscopically, they were characterized by loss of epithelial cytoplasmic processes and

flattening of the epithelium. These olfactory epithelial findings were not confirmed in subsequent chronic studies by the same group of investigators (Quast et al., 1984, 1988). Reduced mean body weight was also observed in 2000 ppm male rats after 82 and 88 days of exposure (≈7% lower than control values, $p<0.05$). No effects attributable to exposure were found at 1000 ppm (5460 mg/m^3) or less, indicating that this level is a NOAEL for both rats and mice in this study. The LOAEL is 2000 ppm (10,920 mg/m^3) in both species based on the weight-of-evidence for mild liver effects and lesions of the nasal turbinates at this concentration.

MacEwen and Vernot (1974) exposed groups of 40 rats, 180 mice, 8 dogs, and 4 monkeys to 0, 250, or 1000 ppm (0, 1370, or 5460 mg/m^3) 1,1,1-trichloroethane vapor continuously for 100 days in Thomas domes. The findings of the mouse study were reported separately by McNutt et al. (1975), and are described below. Rats, dogs, and monkeys were weighed biweekly. Blood samples collected from dogs and monkeys at the time of weighing were used for hematology (red blood cell count, white blood cell count, hemoglobin, hematocrit, reticulocyte count) and serum chemistry (ALT, AST, AP, total bilirubin, triglycerides, BUN, creatinine, protein, glucose, and electrolytes) determinations. Rats were sacrificed at the end of the exposure period for organ weights, liver fat stains, and complete histopathology. No exposure-related effects were seen in dogs or monkeys. The only treatment-related effect reported in rats was a significant increase in relative liver weight at 1000 ppm (5460 mg/m^3) (no further information provided). Increased liver weight in the absence of pathology is not generally considered to be an adverse effect. Although limited by incomplete reporting, the 1000 ppm (5460 mg/m^3) level appears to have been a NOAEL in rats, dogs, and monkeys.

Mice were relatively more sensitive to 1,1,1-trichloroethane than rats, dogs and monkeys. Male CF-1 mice were chamber-exposed to 0, 250 or 1000 ppm (1370 or 5460 mg/m^3) technical grade 1,1,1-trichloroethane (94-97% pure, 2.4-3.0% dioxane, 0.12-0.30% butanol) continuously for up to 14 weeks (McNutt et al., 1975). Serial sacrifices were performed on 10 mice/concentration at weekly intervals during the exposure period and at postexposure weeks 2 and 4. Endpoints included clinical observations, food and water intake, liver weight, liver fat content (determined by oil red O staining in 3 mice/concentration and triglyceride analysis in remaining 7 mice/concentration), liver ultrastructure (3 mice/concentration) and histology (liver, kidney, pancreas, intestine, heart, lung and brain). Minimal changes, consisting of occasional mild liver ultrastructural variations after 10 weeks of exposure, were observed at 250 ppm (1370 mg/m^3). At 1000 ppm (5460 mg/m^3), hepatic ultrastructural changes were more pronounced, and accompanied by increases in relative liver weight, triglycerides and lesions visible by light microscopy. Relative liver weight and liver triglyceride values were 22% ($p<0.01$) and 237% ($p<0.01$) higher at 1000 ppm compared to controls at exposure week 14. Histopathological changes included centrilobular hepatocyte swelling, vacuolation, lipid

accumulation and, after 10 weeks, single-cell necrosis. By 12 weeks of exposure, necrosis of individual hepatocytes (associated with acute inflammatory infiltrate and hypertrophy of Kupffer cells) occurred in 40% of the mice exposed to 1000 ppm. Exposure-related effects in tissues other than liver were not found. The minimal ultrastructural changes observed at 250 ppm do not constitute clear evidence of an adverse effect. This study, therefore, identified a NOAEL of 250 ppm (1370 mg/m^3) and LOAEL of 1000 ppm (5460 mg/m^3) for liver effects in mice with continuous exposure.

In another study, groups of 15 Long-Evans or Sprague-Dawley rats, 15 Hartley guinea pigs, 3 New Zealand rabbits, 2 beagle dogs and 3 squirrel monkeys were continuously or intermittently exposed to commercial grade 1,1,1-trichloroethane vapor (Prendergast et al., 1967). In the continuous exposure study, the animals were exposed to 0, 140 or 380 ppm (760 or 2070 mg/m^3) for 90 days. In the intermittent exposure study, the animals were exposed to 2230 ppm (12,180 mg/m^3) 8 hours/day, 5 days/week for 6 weeks. Endpoints in both studies included clinical signs, body weight, and limited hematology (total and differential leukocyte counts, hemoglobin, hematocrit) and histology (heart, lung, liver, spleen and kidney). BUN was determined in treated and control guinea pigs. The only notable finding was reduced body weight gain in rabbits and dogs in the 380 ppm (2070 mg/m^3) continuous exposure and 2230 ppm (12,180 mg/m^3) intermittent exposure groups. Terminal body weights were not reported, but it can be inferred from the data on initial body weight and growth that terminal body weights were likely reduced by less than 5% in rabbits of both groups and intermittently exposed dogs and by about 17% in dogs exposed continuously to 380 ppm. A NOAEL of 140 ppm (760 mg/m^3) and LOAEL of 380 ppm (2070 mg/m^3) are identified based on the decreased body weight in dogs. Confidence in the LOAEL is low due to the small group sizes (2 dogs per group).

Torkelson et al. (1958) performed studies in which groups of 4-5 female guinea pigs and 4-5 male rats were exposed to $\geq$1000 ppm ($\geq$5460 mg/m^3) 1,1,1-trichloroethane for $\leq$3 hrs/day on 5 days/week for approximately 3 months. Toxicity endpoints were general appearance and behavior, survival, hematology, body and organ weights, and gross and histologic pathology of the major organs. The guinea pigs were exposed to 0 ppm (3 hrs/day), 1000 ppm (5460 mg/m^3) (0.3, 0.6, 1.2 or 3 hrs/day) or 2000 ppm (10,920 mg/m^3) (0.05, 0.1, 0.2 or 0.5 hrs/day) for a total of 69 times in 98 days. Exposure to 1000 ppm for 3 hrs/day or 2000 ppm for 0.5 hrs/day produced effects in the livers (fatty changes, increased organ weight) and lungs (irritation, inflammation) of guinea pigs. The rats were exposed to 0 ppm (1 hr/day) or 10,000 ppm (54,600 mg/m^3) (0.05, 0.1, 0.2, 0.5 or 1 hr/day) for a total of 70 times in 99 days. Effects were observed only in rats exposed for 1 hr/day; changes included various degrees of anesthesia and slightly increased liver weight. The findings of this study indicate that guinea pigs were more sensitive

than rats, and that 1000 ppm (5460 mg/m^3) is the LOAEL in guinea pigs for this study.

Adams et al. (1950) also found guinea pigs to be more sensitive than other species. Guinea pigs, rats, rabbits and a monkey were exposed to various concentrations of 1,1,1-trichloroethane (redistilled commercial product containing ≤1% dichloroethane) for 7 hours/day, 5 days/weeks for ≈1-3 months (Adams et al., 1950). Study endpoints included general appearance, body weight, blood urea nitrogen, and weight and histology of selected major organs (lungs, liver, kidneys, spleen and testes). Groups of 9-20 guinea pigs, divided evenly between the sexes, were exposed to 650, 1500, 3000, or 5000 ppm (3550, 8190, 16,380 or 27,300 mg/m^3) of 1,1,1-trichloroethane 5 days per week for 29 to 93 days. A concurrent control was run with each group. Similarly constituted groups of rats were exposed to 3000 or 5000 ppm (16,380 or 27,300 mg/m^3) for 44 to 67 days with concurrent controls by the same protocol. For rabbits, groups of 2 females were exposed to 0 or 5000 ppm (27,300 mg/m^3) 5 days/week for 44 days. A single female monkey was exposed to 3000 ppm (16,380 mg/m^3) 5 days/week for 74 days (no control tested for this species). Guinea pigs had slight, but significantly reduced body weight gain at all exposure levels; at 650 ppm (3550 mg/m^3), terminal body weights were reduced to 86-94% of control values. Other effects in guinea pigs occurred at higher levels of exposure, including slight fatty degeneration in liver at 3000 ppm (16,380 mg/m^3) (incidence not specified), slight to moderate fatty degeneration (not accompanied by necrosis) in liver at 5000 ppm (27,300 mg/m^3) (10/10), and varying degrees of testicular degeneration at 5000 ppm (incidence not specified). Effects in other species occurred at 5000 ppm, and included signs of anesthesia in rats and slightly decreased body weight gain in rabbits. Based on decreased body weight gain in guinea pigs, the low concentration of 650 ppm (3550 mg/m^3) is a LOAEL.

Truffert et al. (1977) exposed groups of 55 adult female Sprague-Dawley rats to 0 or 1100 mL/m^3 (1100 ppm or 6000 mg/m^3) of technical grade 1,1,1-trichloroethane 5 or 6 hours/day, 5 days/week for 15 weeks. Weight gain was monitored throughout the study. Periodic determinations were made for hepatic DNA synthesis 4 hours after injection of radiolabelled thymidine. Sacrifices were performed periodically during the study and at termination for hematology and pathological examination of the lungs, liver, kidneys, adrenals, ovaries, and uterus. The only effect found in treated rats was a 67% increase in hepatic DNA synthesis after 1 week of exposure that was not, however, seen at later time periods. There was no corresponding effect on liver weight or histopathology at any time. In light of the transitory nature of the observed change in DNA synthesis and the failure to find corresponding tissue damage, the toxicological significance of this finding is uncertain. The 1100 ppm (6000 mg/m^3) level is a NOAEL based on histopathology.

Groups of 20 male Wistar rats were exposed to 0 or 204 ppm (1110 mg/m^3) of 1,1,1-trichloroethane vapor 8 hours per day, 5 days per week for 14 weeks (Eben and Kimmerle,

1974). Animals were weighed weekly. At study termination, analyses were performed for hematology (including red blood cell count, hemoglobin, hematocrit, and white blood cell count and differential), blood glucose, and serum chemistry markers for hepatotoxicity (ALT, AST, SDH, total bilirubin) and nephrotoxicity (urea, creatinine). Animals were examined for gross lesions by necropsy and the heart, lungs, liver, kidneys, adrenals, testes and thyroid were weighed. The same organs (except the thyroid) and the spleen were examined for histopathology in 4 animals from each group. No treatment-related effects were seen. This study identified 204 ppm (1110 mg/m^3) as a free-standing NOAEL.

4.2.2.4. *Chronic Studies*

Quast et al. (1978, 1984, 1988) carried out two inhalation bioassays for 1,1,1-trichloroethane. In the first study, groups of 189, 94 and 92 Sprague-Dawley rats of each sex were exposed to 0, 875 or 1750 ppm (0, 4780 or 9560 mg/m^3) of 1,1,1-trichloroethane 6 hours/day, 5 days/week for 12 months (Quast et al., 1978). A commercial grade formulation was tested (≈96% 1,1,1-trichloroethane by weight; identity of the stabilizers and impurities was not provided). The animals were observed for 19 months after the exposure period, making the total length of study 31 months (923 days). Endpoints included clinical signs, body weight, hematology (7-10 rats/sex/group on study months 12 and 24), urinalysis (10 rats/sex/group after 24 months), serum indices (BUN, ALT and AP activities prior to terminal necropsy) and pathology, including organ weights and histology (all unscheduled deaths and moribund animals, 3 rats/sex/group at the end of the exposure period, remaining rats at the end of the observation period). The only histopathologic lesion considered by study investigators to be treatment related was an increased incidence of focal hepatocellular alterations in females at 1750 ppm (9560 mg/m^3) at the end of the observation period (data not presented in the study report). Because these effects were observed 19 months after exposure to 1,1,1-trichloroethane ceased and because other studies of 1,1,1-trichloroethane have generally not shown effects of 1,1,1-trichloroethane to progress even while exposure is occurring, it is questionable whether the focal hepatocellular alterations in high-exposure animals observed at 31 months can be considered related to treatment. Therefore, a NOAEL and LOAEL were not identified in this study. Exposure to 1,1,1-trichloroethane was not associated with an increased incidence of neoplastic lesions. However, exposure was substantially less than lifetime and the maximum tolerated dose (MTD) may not have been reached.

In the second study by Quast et al. (1984, 1988), groups of 80 male and 80 female F344 rats and B6C3F1 mice were exposed to 0, 150, 500 or 1500 ppm (0, 820, 2730 or 8190 mg/m^3) 1,1,1-trichloroethane vapor for 6 hours/day, 5 days/week for 2 years (516 total exposure days). A production grade 1,1,1-trichloroethane formulation was tested [≈94% pure, with 5%

stabilizers (butylene oxide, t-amyl alcohol, methyl butynol, nitroethane, nitromethane) and <1% minor impurities]. Ten rats and 10 mice of each sex from each exposure group were scheduled for interim sacrifices after 6, 12 and 18 months of exposure, and the remaining 50 rats and 50 mice/sex/group were scheduled for sacrifice after 24 months of exposure. Clinical signs of toxicity, mortality, hematology, serum chemistry, urinalysis endpoints (rats only), body weight, organ weights (liver, kidneys, brain, heart, testes), gross pathology and histopathology were comprehensively assessed. In rats, histologic examinations were performed on all (53) tissues, including the lung, trachea, larynx, and nasal turbinates, following exposure to 0 or 1500 ppm (0 or 8190 mg/m^3) for 6, 12, 18 or 24 months, liver following exposure to 150 or 500 ppm for 6, 12 or 18 months, and selected (12) tissues following exposure to 150 or 500 ppm for 24 months. In mice, histologic examinations included all tissues following exposure to 0 or 1500 ppm for 6, 12, 18 or 24 months, selected tissues following exposure to 150 or 500 ppm for 6, 12 or 18 months, and all tissues following exposure to 150 or 500 ppm for 24 months.

There was no statistically significant reduction in survival of treated rats or mice compared with their respective controls, and survival at the end of the study ranged from 40-70% (Quast et al., 1984, 1988). Female rats in both the 500 and 1500 ppm (2730 and 8190 mg/m^3) groups showed slight, statistically significant deficits in body weight throughout much of the study (≤7% less than controls, estimated from growth curves); the researchers considered the effect to be exposure-related at 1500 ppm (8190 mg/m^3). In rats, no exposure-related histopathologic changes were observed with the exception of histopathologic changes in the liver. Very slight microscopic hepatic changes ("accentuation of the normal hepatic lobular pattern"; "altered cytoplasmic staining in the cells surrounding the central vein"; and "hepatocytes in the portal region that appeared smaller in the exposed rats when compared with their respective controls") were described in both male and female rats of the 1500 ppm exposure group necropsied at 6 months (10/10 males and 10/10 females), 12 months (10/10 males and 10/10 females) and 18 months (7/10 males and 5/10 females); no difference from controls was seen in the animals after 2 years of exposure because of confounding geriatric changes. These histopathologic changes were not seen in any control or lower-dose animals at any time point. The histopathologic findings at 1500 ppm are consistent with a minimal hepatocellular hypertrophy, which is considered an adaptive physiologic response (i.e., stimulation of the drug metabolizing enzyme system) and not a measure of toxicity. No effects were observed in mice. In light of the adaptive physiologic nature of the liver findings in rats at the highest exposure concentration, this study identified a NOAEL of 1500 ppm (8190 mg/m^3) in rats and mice. A LOAEL was not identified.

Tumor findings were unremarkable. In rats, there was a statistically significant trend for increased incidence of bilateral benign testicular interstitial cell tumors in males (36/50, 30/50,

38/50 and 45/50 in the 0, 150, 500 and 1500 ppm groups, respectively) (Quast et al., 1984, 1988). There was no trend, however, for an increase in the overall (i.e., unilateral or bilateral) incidence of these tumors (43/50, 41/50, 41/50 and 49/50, respectively). In contrast to the oral bioassay by Maltoni et al. (1986), there were no increases in leukemias or any lymphoreticular proliferative processes. In mice, there was a statistically significant trend for increased adenoma or cystadenoma of the lacrimal/Hardarian gland in females (3/50, 1/50, 2/50 and 7/50, respectively). The authors stated that the incidence was within the historical range of spontaneous incidence for this strain of mouse; they did not consider the tumor to be treatment-related. This study found no clear evidence of a carcinogenic effect of 1,1,1-trichloroethane in either rats or mice. However, the MTD was not reached in mice and may not have been reached in rats, as the only toxic effects (described above) were a slight (≤7%) reduction in body weight gain in female rats and slight microscopic hepatic changes (suggestive of a physiologic response only) in male and female rats exposed to the high concentration (1500 ppm or 8190 mg/m^3).

The only other study of chronic duration was an older study reported by Torkelson et al. (1958). Groups of 20 male and 20 female rats, 8 male and 8 female guinea pigs, 2 male and 2 female rabbits and 2 female monkeys were exposed 126-130 times to 0 or 500 ppm (2730 mg/m^3) of 1,1,1-trichloroethane (94-97% pure, 2.4-3.0% dioxane, 0.12%-0.3% butanol) for 7 hours/day, 5 days/week for 6 months (Torkelson et al., 1958). Animal strains were not reported. Assessment of general appearance and behavior, survival, hematology, body and organ weights, gross pathology and histopathology showed no exposure-related effects. The scope of the histologic examinations was not specified, but may be the same as the organs that were weighed (lung, heart, liver, kidney, spleen and testes). The lack of effects indicates that 500 ppm (2730 mg/m^3) is a NOAEL for 6-month exposure in the rats, guinea pigs and other species.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES - ORAL AND INHALATION

4.3.1. Oral Exposure

Cardiac anomalies were associated with maternal exposure to 1,1,1-trichloroethane in an exploratory study of 1,1,1-trichloroethane developmental toxicity (Dapson et al., 1984a,b; Hutcheon et al., 1985). Groups of 2-3 male and 7-8 female Sprague-Dawley rats (225-250 g) were given drinking water containing 0 or 10 ppm of 1,1,1-trichloroethane (97% pure, inhibited with 3% 1,4-dioxane) in 0.05% Tween 80, starting before mating and continuing through pregnancy and lactation. Based on the U.S. EPA (1988a) reference allometric equation for water consumption and body weight data reported in the study, the dose is estimated to be 1.4 mg/kg-day. Rats in each group were mated until pregnant and then housed separately by sex. Pregnant females were allowed to deliver naturally and nurse their pups. Pups and dams were observed and weighed daily until weaning, when pups were sacrificed and necropsied. Hearts were

weighed and examined for gross structural abnormalities. Although not tested statistically, length of exposure prior to successful mating appeared to be longer in treated rats (avg = 20.4 days; range = 7 to 27 days) than in controls (avg = 14.7 days; range = 8 to 30 days). Given the small number of males (2 in the control group and 3 in the treated group) and the wide range in time to successful mating (7 to 30 days), no biological significance is ascribed to this finding. Gestation period, pup sex ratio, and litter size in treated rats were all similar to controls. Five litters (52 pups) were weaned and sacrificed in the treated group, as were 6 litters (70 pups) in the controls. Pup body weights at sacrifice were not affected by treatment. Pup mean absolute heart weight was 9% higher in treated rats than controls, although the difference was not statistically significant. The incidence of total gross cardiac anomalies (persistent ductus arteriosis, remnant ductus arteriosis, right atrial hypoplasia, right atrial displacement, other right atrial deformations [grooves, abnormal contour], left atrial hypoplasia, superior vena cava abnormalities, and other abnormalities [excessive fat, large amount of pericardium]) was increased in pups from the exposed group (32/52 = 62%) versus controls (3/70 = 4%). The most prominent individual anomaly was persistent ductus arteriosis, which was seen in 15/52 or 29% of treated group pups and 0/70 control pups. A comparison of cardiac anomalies based on number of affected litters was not performed. No malformations were seen outside of the cardiovascular system. Persistent ductus arteriosis was considered by the researchers to indicate delay of cardiac development. Confidence in the results was limited, however, by use of only a single dose level and incomplete analysis of the data (no litter-based comparisons of cardiac abnormalities).

In a postnatal developmental study designed to assess the reproducibility of the cardiovascular effects reported by Dapson et al. (1984a,b), Charles River CD rats were exposed to drinking water containing 0 (water-only control), 0 (water containing stabilizer and emulsifier), 3, 10 or 30 ppm of 1,1,1-trichloroethane (97% pure stabilized with 3% dioxane) in 0.05% Tween 80 emulsifying agent (George et al., 1989; NTP, 1988a). Groups of more than 30 males and 30 females (exact numbers not reported) were exposed for 14 days prior to cohabitation for up to an additional 13 days. Male breeders and sperm-negative females were killed after the cohabitation period was completed, and sperm-positive females (24-30 per group) continued to be exposed through lactation [postnatal day (PND) 21]. Reported average compound consumption during the premating period was 0.3, 0.9 and 2.6 mg/kg-day for exposed males and 0.3, 1.3 and 3.3 mg/kg-day for exposed females. Reported average maternal intake was 0.3, 1.2 and 3.5 mg/kg-day from gestational day 0 to parturition and 0.6, 2.0 and 5.9 mg/kg-day from PND 1 to PND 21. Evaluation of adult males and females included clinical signs, food and water consumption and body weight throughout the exposure period. Other endpoints included number of implantation sites, gestation length, litter size and pup weight and survival.

Litters containing >10 pups on PND 4 were culled to a litter size of 10 and the remaining pups were evaluated until PND 21. The culled pups (PND 4) and surviving pups (PND 21) were sacrificed and examined for visceral malformations with special attention given to the heart and surrounding vasculature. No treatment-related parental effects or changes in postnatal growth or development of offspring were observed. Percent mortality from implantation to PND 1 was significantly higher (224%, $p \leq 0.05$) in 30 ppm litters than in the vehicle control group, but this increase appeared to be primarily due to high mortality (61%) in one litter on PND 1 and was not accompanied by an effect on numbers of live pups/litter on PNDs 1 or 4. Of the pups found dead on PND 1, patent ductus arteriosis occurred in 10/28 treated pups (6 from 4 litters at 3 ppm, 1 at 10 ppm, 3 from 2 litters at 30 ppm) (no occurrence in either control group). Patent ductus arteriosis also occurred in 1 pup (3 ppm) culled on PND 4. Statistical analysis of incidence by litter indicated no significant effect of treatment, and there was no evidence of cardiac or other malformations in any dose group on PND 21, which was the time at which Dapson et al. (1984a,b) reported effects. In the discussion of their results, NTP (1988a) noted that functional closure of the ductus arteriosis (i.e., constriction of the smooth muscle wall) in rats occurs in the first 1 to 3 hours after birth and that at this stage constriction is reversible. The second stage of closure of the ductus arteriosis, which may take up to 5 days in the rat, involves permanent sealing of the lumen vessel. NTP stated that the observation of ductus arteriosis in animals found dead on PND 1 in the current study may have been a result of the absence of chemical (prostaglandin or oxygen) control of constriction of the vessel and did not consider the finding an indication of abnormal development. Accordingly, 3.5 mg/kg-day (highest tested dose) is considered a NOAEL for developmental toxicity.

A teratogenicity study of 1,1,1-trichloroethane (NTP, 1988b) was conducted in conjunction with the postnatal developmental evaluation summarized above (NTP, 1988a). Exposure and other aspects of the experimental design are essentially the same as in the postnatal study except that dams were sacrificed on gestational day 20 and comprehensive teratological examinations of fetuses were performed. Reported average compound consumption corresponding to the 3, 10 and 30 ppm drinking water concentrations were 0.3, 0.6 and 2.0 mg/kg-day for males during the premating period and 0.3, 0.8 and 2.4 mg/kg-day for females from premating to gestational day 20. No exposure-related maternal, embryotoxic, fetotoxic or developmental (external, visceral, skeletal or cardiovascular) abnormalities were found, indicating that 2.4 mg/kg-day (highest tested dose) is a developmental toxicity NOAEL.

An oral multigeneration reproduction study modified to include screening for teratogenic and dominant lethal effects of 1,1,1-trichloroethane was conducted in mice (Lane et al., 1982). Groups of 30 female and 10 male ICR Swiss mice (F_0 generation) were provided drinking water containing 1,1,1-trichloroethane (97% pure containing 3% p-dioxane inhibitor) in concentrations

of 0 (water-only control), 0 (vehicle control), 0.58, 1.75 or 5.83 mg/mL (reported nominal calculated doses of 100, 300 or 1000 mg/kg-day) for 5 weeks prior to mating and throughout gestation and lactation of the F_{1a} litters. At 2 weeks postweaning of the F_{1a} litters, the F_0 adults were remated to produce F_{1b} litters. At 2 weeks postweaning of the F_{1b} litters, the F_0 adults were remated for teratology and dominant lethal screening of female and male F_{1c} pups, respectively. The F_{1b} litters were culled to 30 females and 10 males at weaning and placed on test solutions until age 14 weeks when they were mated to produce the F_{2a} litters. At 2 weeks postweaning of the F_{2a} pups, the F_{1b} adults were remated for teratology and dominant lethal screening of female and male F_{2b} pups, respectively. Adult observations included body weight and water consumption, reproductive performance (fertility and gestation indices[3]), mortality and gross pathology (necropsies performed after week 24 or 25 of dosing). Offspring endpoints included litter size, body weight, viability and lactation indices, and gross pathology (necropsies performed on F_{1a} and F_{1b} pups at age 21 days). The teratology screenings involved sacrificing females on gestational day 18 for assessment of implantations, resorptions, fetal viability, gross malformations, visceral abnormalities (one-third of fetuses) and skeletal abnormalities (remaining fetuses). Dominant lethal reproductive indices were based on implantation, resorption and fetal viability data in untreated females that were mated with the exposed F_{1c} and F_{2b} males. No exposure-related effects on male or female reproductive function (as evaluated by fertility and gestation indices) or offspring development were found in this study, indicating that 1000 mg/kg-day, the highest dose tested, is a NOAEL for reproductive and developmental toxicity.

Maurissen et al. (1993, 1994) conducted a study to investigate 1,1,1-trichloroethane for neurodevelopmental effects. Groups of 50 (2 replicates of 25 each) mated sperm positive female Fisher 344 rats were treated by gavage with 1,1,1-trichloroethane (> 99.9% pure with <0.1% butylene oxide stabilizer) in corn oil at doses of 0, 75, 250 or 750 mg/kg-day from day 6 of gestation through day 10 of lactation. Dams were allowed to give birth naturally. From each replicate, 10 litters were selected for testing and 1 other as an alternate for each dose (i.e., there were a total of 20 litters and 2 alternates selected for each dose). Preference was given to larger litters (8 or more pups) with 4:4 or 5:3 sex ratios. Litters were culled to 8 pups (4 males and 4 females, if possible) on postnatal day 4. Dams were monitored for body weight and examined for neurobehavioral signs throughout gestation and lactation. All pups were monitored for mortality and body weight, and examined for neurobehavioral signs throughout lactation. Subsets of pups from each litter were evaluated periodically for physical maturation milestones

[3] Fertility index = (# females pregnant/# females mated) x 100; gestation index = (# females with live litters/# females pregnant) x 100.

(pinna detachment, incisor eruption, eye opening, and testes descent/vaginal opening), motor activity, auditory brainstem response, functional observational battery (hand-held and open field observations and grip performance test), learning and memory (delayed matching to position test), brain weight and size (days 28 and 62), or neuropathology (days 28 and 62). No treatment-related effects were seen in any parameter monitored in dams or pups, making 750 mg/kg-day a NOAEL for both dams and pups in this study.

4.3.2. Inhalation Exposure

Groups of 23 Sprague-Dawley rats and 13 Swiss Webster mice were exposed to 0 or 875 ppm (4780 mg/m^3) 1,1,1-trichloroethane (94.52% pure) by inhalation for 7 hours/day on days 6-15 of gestation (Schwetz et al., 1975). Maternal rats and mice were sacrificed on gestation day 21 and 18, respectively. Study parameters included maternal food consumption, body weight and liver weight; numbers of live, dead and resorbed fetuses and litters; fetal weight, length and sex ratio; and external (all fetuses), visceral (one half of fetuses) and skeletal (remaining fetuses) anomalies. A slight (5%) increase in absolute, but not relative, liver weight was reported in treated rat dams. No other effects were found in rat or mice dams or pups. The 875 ppm (4780 mg/m^3) level is a NOAEL for developmental effects.

York et al. (1982) exposed four groups of 30 Long-Evans hooded rats to 0 or 2100 ppm (11,470 mg/m^3) 1,1,1-trichloroethane (purity not reported) for 6 hours/day for 2 weeks prior to mating (5 days/week) and throughout pregnancy (7 days/week) until gestation day 20 in a 2 x 2 factorial design: 1) 1,1,1-trichloroethane before mating and during pregnancy, 2) 1,1,1-trichloroethane before mating only, 3) 1,1,1-trichloroethane during pregnancy only, and 4) filtered air before and during pregnancy. Half of the dams in each group were sacrificed on gestation day 21 and the remaining dams were used for postnatal evaluations. Study parameters included maternal food consumption, body weight and liver weight; numbers of live, dead and resorbed fetuses and litters; fetal weight and sex ratio; external (all fetuses from sacrificed dams), visceral (4 fetuses/litter) and skeletal (4 fetuses/litter) anomalies; postnatal body weights (litters at age 10 days and individual offspring at 20-day intervals from weaning to age 320 days) and gross pathology (dams after weaning, offspring at age 12 months); and offspring neurobehavior (open-field activity at age 21 days, running wheel activity at age 40-110 days and amphetamine challenge at age 110-120 days). No signs of maternal toxicity were observed in any group. A very slight (<5%), but statistically significant, reversible decrease in fetal body weight was found in groups 1 and 3, in comparison to groups 2 and 4 by ANOVA. There were no significant differences in pup weight at birth (6.0, 5.8, 5.9, and 5.8 g for groups 1, 2, 3 and 4, respectively). Overall incidences of skeletal and soft tissue anomalies were significantly increased in group 1 (see Table 13), but specific types of anomalies were not increased and the

anomalies seen were considered indicative of reversible developmental delay (e.g., delayed ossification). Postnatal evaluation revealed no effects on neurobehavioral development (as measured by open-field activity, running wheel activity, and amphetamine challenge) or gross lesions. The tested concentration of 2100 ppm (11,470 mg/m^3) is considered a NOAEL for both maternal and developmental toxicity in this study.

Table 13. Incidence of Anomalies in Fetal Rats After Maternal Exposure to 1,1,1-Trichloroethane

	Number of Affected Fetuses (number of affected litters)			
	Group 1	Group 2	Group 3	Group 4
Total skeletal anomalies	19 (8)[1]	8 (4)	1 (1)	5 (4)
Total soft tissue anomalies	6 (6)[2]	2 (2)	1 (1)	0 (0)

Group 1: exposure before mating and during pregnancy
2: exposure before mating only
3: exposure during pregnancy only
4: control

[1] statistically significant effect 1>2,3,4
[2] statistically significant effect 1>4

Source: York et al., 1982

Subsequent studies found evidence of mild fetotoxicity at higher levels producing overt effects in the dams. Groups of 30 timed-pregnant female Sprague-Dawley rats were exposed to 0, 1000, 3000 or 6000 ppm (0, 5460, 16,380, or 32,760 mg/m^3) 1,1,1-trichloroethane 6 hours per day on days 6-15 of gestation (BRRC, 1987a). The dams were observed daily for clinical signs and weighed and monitored for food and water consumption periodically during gestation. On gestation day 21, the dams were sacrificed for internal examination. All live fetuses were examined for external and skeletal malformations, while half from each litter were processed and examined for visceral malformations. No females died, delivered early, aborted, or were removed from the study. The pregnancy rate was similar in all groups, so that each group contained 22-25 litters. Maternal body weight gain over the entire gestation period was significantly reduced in all treated groups, but maternal body weight was statistically less than controls only in the 6000 ppm (32,760 mg/m^3) group and only during the post-exposure phase of gestation. Food intake was significantly reduced in all groups during exposure, and after the end of exposure in the 3000 and 6000 ppm (16,380 and 32,760 mg/m^3) groups. Water intake was significantly increased during and after exposure in the 6000 ppm group. The only clinical signs associated with treatment were perioral wetness and hypoactivity in the 6000 ppm (32,760 mg/m^3) dams. Necropsy revealed no treatment-related lesions in the dams. Gravid uterine weight was significantly reduced in both the 3000 and 6000 ppm (16,380 and 32,760 mg/m^3) groups. The decrease in gravid uterine weight in the 6000 ppm (32,760 mg/m^3)

dams was apparently responsible for the decrease in body weight in this group, as the corrected body weight (terminal body weight - gravid uterine weight) did not differ from controls. Absolute and relative liver weights were similar to controls in all groups. Gestational parameters were unremarkable; slight decreases in corpora lutea/dam, total implants/litter and viable implants in the 6000 ppm (32,760 mg/m^3) group were not considered treatment-related since ovulation occurred prior to the start of exposure and percent preimplantation loss, number of nonviable implants per litter (early or late resorptions or dead fetuses), and percent live fetuses were all unaffected. Fetal body weight was significantly reduced by 6% for female fetuses in the 6000 ppm (32,760 mg/m^3) group; decreases for male fetuses and all fetuses (about 4%) were not statistically significant. No increases in fetal malformations were associated with treatment, but significant increases (on a per litter basis) were seen for two fetal skeletal variations, unossified cervical centrum 6 and poorly ossified cervical centrum 7, in the 6000 ppm (32,760 mg/m^3) group, suggesting slight developmental delay at this concentration. This study identified a NOAEL of 3000 ppm (16,380 mg/m^3) and LOAEL of 6000 ppm (32,760 mg/m^3) for mild fetotoxicity manifested by delayed cervical ossification and decreased body weights of female fetuses. Maternal effects were also seen at the 6000 ppm level (32,760 mg/m^3), including hypoactivity and reductions in food consumption, body weight gain, body weight, and gravid uterine weight.

In a companion study in rabbits, groups of 24 timed-pregnant New Zealand white rabbits were exposed to 0, 1000, 3000 or 6000 ppm (0, 5460, 16,380, or 32,760 mg/m^3) of 1,1,1-trichloroethane 6 hours per day on days 6-18 of gestation (BRRC, 1987b). Sacrifice for internal examination occurred on day 29 of gestation. All live fetuses were examined for external and visceral malformations; half from each litter were also processed and examined for skeletal malformations. The pregnancy rate was high and not affected by treatment, so that 20-22 gravid females were available in all groups. Several litters from multiple groups (including 5 from the 1000 ppm [5460 mg/m^3] group), were completely resorbed before scheduled sacrifice, leaving 16-21 litters in all groups. Does in the 3000 and 6000 ppm (16,380 and 32,760 mg/m^3) groups lost weight during the exposure period and had reduced body weight gain for the gestation period as a whole, although body weights were not significantly affected at any time during the study. Clinical signs were unremarkable. Necropsy revealed no treatment-related lesions and there were no treatment-related changes in gravid uterine weight or absolute or relative liver weight. Gestational parameters were not altered by treatment. Slight, statistically significant decreases in total implants per litter and viable implants in the 6000 ppm (32,760 mg/m^3) group were due to a non-significant decrease in corpora lutea per doe, but were not accompanied by increases in preimplantation loss or non-viable implants (early or late resorptions or dead fetuses) or a decrease in percent live fetuses. Fetal body weights were similar in all groups. No

increases in fetal malformations were associated with treatment, but there was a statistically significant increase (on a per litter basis) in the incidence of extra 13th rib, a common skeletal variation, in the 6000 ppm (32,760 mg/m^3) group. This study identified a NOAEL of 3000 ppm (16,380 mg/m^3) and LOAEL of 6000 ppm (32,760 mg/m^3) for mild fetotoxicity manifested by increased incidence of extra 13th rib. Reduced maternal weight gain was also observed at the 6000 ppm (32,760 mg/m^3) level.

Jones et al. (1996) used two different exposure protocols to study the effects of late gestational exposure to 1,1,1-trichloroethane. In the first, groups of 10 timed-pregnant CD-1 mice were exposed to 0 (both sham-exposed to air and untreated groups) or 2000 ppm (10,920 mg/m^3) 1,1,1-trichloroethane vapor, 17 hours/day, on gestation days (GD) 12-17. In the second, groups of 12 timed-pregnant CD-1 mice were exposed for 60 minutes, 3 times/day, to 0 (sham exposed) or 8000 ppm (43,680 mg/m^3) 1,1,1-trichloroethane on GD 12-17. Dams in the second experiment only were semiquantitatively scored on a subset of tests from a functional observational battery for neurobehavioral toxicity testing after the first exposure each day. Dams in both experiments were allowed to give birth. After litter data were collected, litters were culled to 4 of each sex (litters with less than 7 pups were discarded). Litters in the first experiment were fostered to surrogate mothers who had delivered within 24 hours of the experimental dams. Fostering was not employed in the second experiment. Pups in both experiments were observed for physical development and tested for reflex development (righting and rooting reflexes), forelimb grip strength, motor coordination (negative geotaxis and inverted screen tests), and spontaneous activity. Tests and observations were conducted through postnatal day 14 in the first experiment and 21 in the second experiment. Some pups in the second experiment were retained until 85 days of age and tested for learning and memory (one-trial passive avoidance conditioning).

Dams in the second experiment were nearly anesthetized during exposure, and the observational battery revealed both gait abnormalities (splayed hindlimbs, severe sway, ataxia) and clonic movements (mild tremors) that were not seen in controls (Jones et al., 1996). In neither experiment was there any effect on maternal weight gain, number of litters, gestation length, litter size, or number of live male or female pups per litter. Litter weight was about 15% lower than controls in both experiments, but the differences were not statistically significant. Pup body weight was significantly reduced throughout most of the postnatal observation period in both experiments, and in both, significant delays were seen for attainment of all 3 developmental landmarks monitored (pinnae detachment, incisor eruption, and eye opening). Behavioral test results were similar in both experiments, with statistically significant impaired performance in tests for righting reflex, rooting reflex (experiment 2 only), forelimb grip strength, negative geotaxis, and inverted screen climbing (experiment 1 only). Spontaneous

motor activity was not altered by treatment, and there was no effect in the passive avoidance conditioning test in experiment 2. This study found developmental delay and neurobehavioral deficits in offspring exposed to 2000 ppm (10,920 mg/m^3) for 17 hour/day, GD 12-17, a concentration that did not produce obvious maternal toxicity (although a systematic investigation of behavioral effects in these dams was not conducted).

Coleman et al. (1999) reported the results of a similar study in rats. Mated female Sprague-Dawley rats were exposed to 0 (sham air and untreated controls) or 7000 ppm (38,220 mg/m^3) 1,1,1-trichloroethane for 60 minutes, three times per day, on days 13-19 of gestation. There were 9 pregnant dams in the treated group, 10 in the air exposed controls, and 19 in the untreated controls, which also served as foster dams for the treated pups. Dams were monitored for body weight and food and water intake daily throughout gestation. After each exposure period, dams were scored on an abbreviated functional observational battery. Dams were allowed to litter. After litter data were collected (24 hours after birth), litters were culled to 5 of each sex. All litters were fostered to surrogate mothers from the untreated control group who had given birth within 24 hours of the treated dams. The exposed dams were sacrificed and their uteri inspected for implantation sites and resorptions. Pups were observed for physical development (body weight and dates of pinnae detachment, incisor eruption, and eye opening) and tested for righting reflex, coordination (negative geotaxis and inverted screen tests), muscle strength (vertical screen and forelimb grip tests) and spontaneous motor activity through postnatal day 21. Two pups from each litter were sacrificed on postnatal day 22 for determination of brain weights.

Maternal weight gain was significantly reduced during the exposure period in the treated group, but the difference from controls over the whole gestation period was not statistically significant (Coleman et al., 1999). There was also a trend for reduced food consumption in treated rats, although the difference from controls was not statistically significant. Water consumption was similar in the control and treated groups. The assessment of dam behavior immediately after exposure revealed salivation, lacrimation, and abnormal gait (ataxia, body dragging, splaying of hindlimbs) in the treated dams, none of which were observed in controls. Of the 9 treated dams, only 7 produced offspring, as 2 completely resorbed their litters. The treated group showed significant increases in gestation length, resorptions per litter (based on either all litters or live litters), and mortality index [(# stillbirths + # resorptions) / # implantation sites], and significant decreases in number of live pups per litter (total and for each sex, based on either all litters or live litters), and litter weight. Pup birth weight did not differ between the groups. Postnatal pup body weights were slightly reduced compared to controls on postnatal days 2-14, but not subsequently. Attainment of developmental milestones was not delayed in the treated rats. In the behavioral tests, the treated pups showed significant deficits in coordination

(both negative geotaxis and inverted screen tests) and muscle strength (both vertical screen and forelimb grip tests), and reduced spontaneous ambulatory activity. Righting reflex was not affected. Body weight was significantly lower in the treated rats used for brain weight measurements than in controls (13% deficit). Both absolute (31% deficit) and relative (21% deficit) brain weight were significantly reduced in the treated group, as was absolute cerebellar weight (25% deficit). This study found gross neurological effects in dams, increased resorptions and decreased live pups per litter, and pup neurobehavioral deficits, in rats exposed to 7000 ppm (38,220 mg/m^3) intermittently during the late gestational period.

4.4. OTHER ENDPOINT-SPECIFIC STUDIES

4.4.1. Neurological Effects

4.4.1.1. *Oral Exposure*

Limited information is available regarding neurological effects of 1,1,1-trichloroethane in animals following oral exposure. Rats that were treated with 705 mg/kg-day of 1,1,1-trichloroethane by gavage for 2 days did not show any changes in behavior or appearance that could be detected by a functional observational battery, although neurophysiological testing performed after exposure for 4 days showed some alterations (Spencer et al., 1990). Neurophysiological effects included marked flash-evoked potential (FEP) and EEG changes and smaller alterations in somatosensory-evoked potential (SEP), and were similar to effects observed after inhalation exposure to 2000 ppm for 4 days (see below). No significant changes in tissue levels of monoamine neurotransmitters and metabolites in the brain were found in rats given a single oral dose of 3250 mg/kg of 1,1,1-trichloroethane and sacrificed 2 hours later (Kanada et al., 1994).

4.4.1.2. *Inhalation Exposure*

The CNS depressant effects of inhaled 1,1,1-trichloroethane are well known. The effects range from subtle behavioral effects at relatively low concentrations to unconsciousness at very high concentrations. Human data regarding neurological effects of 1,1,1-trichloroethane were presented in Section 4.1. Animal studies support the results of the human studies.

Increasingly serious signs of central nervous system depression preceded 1,1,1-trichloroethane-associated lethality in acute animal inhalation studies. The progression of effects with increasing concentration and duration of exposure in rats was described by Adams et al. (1950). At 5000 ppm (27,300 mg/m^3), there was a decreased tendency to move about the chamber and a reduced resistance to handling within an hour. At 10,000 ppm (54,600 mg/m^3), effects progressed from a markedly reduced tendency to move about the chamber after a few minutes, to weakness and ataxia after 10 minutes, to irregular respiration and semi-consciousness

after 3 hours, and in some cases, death. Similar effects occurred more rapidly at higher concentrations. Clark and Tinston (1982) observed that death followed a progression from slight ataxia to loss of righting reflex, loss of movement, narcosis, and shallow respiration in rats. These researchers estimated an EC_{50} in rats for CNS depression of 5000 ppm (27,300 mg/m^3) for 10 minute exposure. Moser and Balster (1985) reported that signs of CNS depression in mice exposed to high concentrations in lethality studies progressed from excitability and hyperactivity to lethargy and complete cessation of activity, with shallow, rapid breathing indicating imminent death. Effects indicative of CNS depression were also found in other lethality studies (Lazarew, 1929; Gehring, 1968; Bonnet et al., 1980; Woolverton and Balster, 1981; Calhoun et al., 1988). Studies designed specifically to investigate the effects of 1,1,1-trichloroethane on the central nervous system are discussed below.

The neurobehavioral effects of 1,1,1-trichloroethane in laboratory animals have been studied extensively following acute inhalation exposure. Observed effects include increased motor activity (Horiguchi and Horiuchi, 1971; Kjellstrand et al., 1985b, 1990; Albee et al., 1990a; Bowen and Balster, 1996, 1998; Warren et al., 2000; Wiley et al., 2002), reduced response rate in operant behavior tests (Woolverton et al., 1982; Balster et al., 1982; Geller et al., 1982; Mullin and Krivanek, 1982; Moser et al., 1985; Moser and Balster, 1986; You et al., 1994; Warren et al., 1997, 1998; Bowen et al., 1998; Bowen and Balster, 1998), impaired performance in functional observational battery and similar tests (Woolverton and Balster, 1981; Mullin and Krivanek, 1982; DeCeaurriz et al., 1983; Moser and Balster, 1985; Bowen et al., 1996a,b; Balster et al., 1997; Paez-Martinez et al., 2001), effect on anxiety-like actions (burying behavior) (Paez-Martinez et al., 2003), and reduced response to induced seizures (DeCeaurriz et al., 1981; Frantik et al., 1994).

Increases in motor activity were observed at concentrations as low as 1000 ppm (5460 mg/m^3) in acute animal studies. Horiguchi and Horiuchi (1971) found increased wheel turning activity in male mice exposed to 1000 ppm (5460 mg/m^3) of 1,1,1-trichloroethane 2 hours/day, every other day, for 9 exposures, but did not test other concentrations. There was no effect on open-field activity of male Sprague-Dawley rats exposed to 500 ppm (2730 mg/m^3) of 1,1,1-trichloroethane vapor 6 hours per day for 4 consecutive days (recorded 1 and 17 hours after the 4-day exposure) (Savolainen et al., 1977). For a 1-hour exposure, Kjellstrand et al. (1985b) reported a slight increase in motor activity at 2000 ppm (10,920 mg/m^3) and no effect at 1300 ppm (7100 mg/m^3) in male mice. Bowen and Balster (1996) saw concentration-related increases in motor activity in male mice (30-minute exposure) that were statistically significant at 2500 ppm [13,650 mg/m^3] (NOAEL = 1250 ppm [6830 mg/m^3]) in a static exposure system and 1250 ppm [6830 mg/m^3] (NOAEL = 500 ppm [2730 mg/m^3]) in a dynamic exposure system. These researchers also found that motor activity decreased back towards or even under control

levels at very high concentrations (≥10,000 ppm [54,600 mg/m^3]). The biphasic nature of 1,1,1-trichloroethane's effect on motor activity was noted in other studies as well (Bowen and Balster, 1998; Warren et al., 2000; Wiley et al., 2002). A study that directly compared sensitivity of motor activity versus operant behavior as an endpoint for 1,1,1-trichloroethane toxicity found both endpoints to be equally sensitive in adult male mice exposed for 30 minutes (Bowen and Balster, 1998). In male mice exposed to 1,1,1-trichloroethane at 2000, 6000, 10,000, or 13,300 ppm (10,920, 32,760, 54,600, 72,620 mg/m^3), 0.5 hours/day for 15 consecutive days and tested using locomotor activity as well as functional observational battery (FOB), Bowen and Balster (2006) found that both tolerance and sensitization occurred with repeated exposure, with concentration primarily affecting the magnitude of the change and not whether tolerance or sensitization occurred.

The most sensitive measure of effect on operant behavior was obtained in baboons. Four juvenile male baboons trained in a match-to-sample discrimination task were exposed for 4 hours to 0, 700, 1400, 1800, or 2100 ppm (0, 3820, 7640, 9830, or 11,470 mg/m^3) of 1,1,1-trichloroethane (Geller et al., 1982). Although there was no effect on error rate at any concentration, there was a marked significant decrease in number of trials attempted and a significant increase in response time at ≥1800 ppm (9830 mg/m^3), with no difference from controls at 700 or 1400 ppm (3820 or 7640 mg/m^3). The same effects were seen at 1200 ppm (6550 mg/m^3) when the baboons were exposed at that concentration continuously for 7 days. No other concentrations were tested in the 7-day study. In rodent studies, the lowest level reported to produce decreases in operant task response rates was 2000 ppm (10,920 mg/m^3) for exposure durations ranging from 20-100 minutes (Balster et al., 1982, 1997; Warren et al., 1997, 1998; Bowen et al., 1998). The no-effect level was 1000 ppm (5460 mg/m^3) in all of these studies.

1,1,1-Trichloroethane impaired performance in various non-conditioned neurobehavioral tests at concentrations as low as 2000 ppm (10,920 mg/m^3). In the most sensitive of these, DeCeaurriz et al. (1983) reported significant, concentration-related decreases in the duration of immobility in male mice subjected to a 3-minute behavioral despair swimming test after 4 hour exposure to 2064-3569 ppm (11,270-19,490 mg/m^3). Lower concentrations were not tested. Bowen et al. (1996b) demonstrated significant increases in open arm entries in an elevated plus-maze by male mice exposed to ≥2500 ppm (13,650 mg/m^3) for 30 minutes. At higher concentrations, the time spent in open arms also increased. No lower concentrations were tested. Similar effects were reported by Paez-Martinez et al. (2001), although only concentrations greater than 4000 ppm (21,840 mg/m^3) were included in this study. Studies that included tests of both conditioned behavior and functional observation battery differed on the relative sensitivity of the assays. Mullin and Krivanek (1982) found no effects in a general behavior screen (functional observational battery) in male rats exposed to 1500 ppm (8190 mg/m^3) for 4 hours,

but increasing failures at concentrations of 3000 to 12,000 ppm (16,380 to 65,520 mg/m^3). This screen was more sensitive than the conditioned avoidance test performed in the same study, which found effects only at ≥6000 ppm (32,760 mg/m^3). This is in contrast to the results of Balster et al. (1997), who found effects on conditioned behavior at ≥2000 ppm (10,920 mg/m^3) and effects on functional observational battery only at ≥8000 ppm (43,680 mg/m^3).

The reduction in response to induced seizures may be more sensitive than other behavioral measures of effect for 1,1,1-trichloroethane. Frantik et al. (1994) measured neurophysiological response to electrical shock in male Wistar rats exposed for 4 hours and female H strain mice exposed for 2 hours to air or 1,1,1-trichloroethane at various concentrations. The concentrations estimated to produce a 30% depression in seizure discharge (specifically, duration of tonic extension of hindlimb in rats and velocity of tonic extension in mice) were 734 ppm (4000 mg/m^3) in rats and 1810 ppm (9880 mg/m^3) in mice. Effect on seizure response was considerably less sensitive as a measure of 1,1,1-trichloroethane effect in mice exposed to the chemical for 4 hours and given penetrazole to induce clonic convulsions (DeCeaurriz et al., 1981). The concentration estimated to produce a 50% increase in seizure threshold was 6644 ppm (36,280 mg/m^3).

The CNS depressant effects of 1,1,1-trichloroethane appear to be similar to those of several other known CNS depressant chemicals, including ethanol and pentobarbital. Studies in mice trained to lever press in response to exposure to pentobarbital, ethanol, diazepam, and phencyclidine show that mice do not discriminate between the effects of 1,1,1-trichloroethane and those of the former 3 chemicals, but do discriminate between 1,1,1-trichloroethane and phencyclidine. For example, Rees et al. (1987a,b) trained mice to press one lever in response to ethanol (or pentobarbital) and another in response to a saline injection. Following a 20-minute exposure to 1,1,1-trichloroethane, there was a concentration-dependent increase in the percentage of time mice pressed the ethanol (or pentobarbital) lever, indicating that mice were generalizing the effects of ethanol (or pentobarbital) to those of 1,1,1-trichloroethane. The EC_{50} was 850 ppm (4640 mg/m^3) for mice to generalize from 1,1,1-trichloroethane to ethanol (1 g/kg) and 2876 ppm (15,700 mg/m^3) to generalize to pentobarbital (15 mg/kg) (Rees et al., 1987a,b). 1,1,1-Trichloroethane partially substituted for diazepam (67% at the maximum concentration of 16,000 ppm [87,360 mg/m^3]), but did not substitute for phencyclidine at any concentration (Bowen et al., 1999). In contrast to some other CNS depressants, there is little evidence of animals developing tolerance to 1,1,1-trichloroethane with continued exposure. Moser et al. (1985) observed only slight attenuation of response suppression with repeated exposure to 1,1,1-trichloroethane (6000 ppm [32,760 mg/m^3], 20 minutes/day, 4 days/week for 4 weeks) in mice trained in an operant conditioning task. Kjellstrand et al. (1990) followed the time course of motor activity during exposure and found that the increase in motor activity induced by

5000 ppm (27,300 mg/m^3) 1,1,1-trichloroethane in mice remained relatively constant throughout a 3-hour exposure period, in contrast to some other solvents that produced an initial increase that subsequently returned to pre-exposure levels even while exposure continued. It has also been shown that withdrawal symptoms occur in mice exposed to 1,1,1-trichloroethane for a period of time and abruptly removed from exposure (Evans and Balster, 1993; Balster et al., 1997). Mice exposed continuously for 4 days to concentrations of 500, 1000, 2000 or 4000 ppm (2730, 5460, 10,920, or 21,840 mg/m^3) and then removed from exposure showed a concentration-related increase in incidence and severity of handling-induced convulsions at all concentrations through 24 hours post-exposure. No such convulsions were seen in controls at any time. The effects were mitigated by re-exposure to 1,1,1-trichloroethane or exposure to some other known depressants.

A few studies have investigated neurophysiological effects of 1,1,1-trichloroethane in laboratory animals. Electroencephalogram (EEG), flash evoked potential (FEP) and somatosensory evoked potential (SEP) were evaluated in Fischer 344 rats exposed to 0, 1000, or 2000 ppm (0, 5460, or 10,920 mg/m^3) of 1,1,1-trichloroethane for 6 hours per day on 4 consecutive days and tested before and immediately after exposure on the fourth day (Albee et al., 1990b). Significant differences from control in EEG, FEP, and SEP were produced by 1,1,1-trichloroethane at both exposure conditions in a dose-related fashion. Hougaard et al. (1984) also observed depression of EEG activity by 1,1,1-trichloroethane in anesthetized male Wistar rats exposed to 7400 ppm (40,400 mg/m^3) for 60 minutes. Other findings in these animals were decreased blood pressure and increased cerebral blood flow throughout the brain. These investigators also exposed unanesthetized rats to 0, 3500, 6000, or 7800 ppm (19,110, 32,760 or 42,590 mg/m^3) for up to 2 hours. They found no effects at 3500 ppm (19,110 mg/m^3); noticeable intoxication, increased cerebral blood flow throughout the brain, and decreased local glucose consumption in 10/24 brain regions at 6000 ppm (32,760 mg/m^3); and ataxia and decreased arterial blood pressure at 7800 ppm (42,590 mg/m^3).

1,1,1-Trichloroethane has been observed to have neurochemical effects. The most sensitive neurochemical change reported was decreased cGMP (cyclic guanosine monophosphate) in the cerebellum of male mice exposed to 100 ppm (550 mg/m^3) or more of 1,1,1-trichloroethane for 4 hours, with no effect at 70 ppm (380 mg/m^3) (Nilsson, 1986a). cGMP was also decreased in the cerebral cortex and brain stem at higher concentrations in this study. Large (>50%) significant decreases in cGMP in cerebellum and medulla oblongata, and smaller decreases in cerebral cortex, were seen in male CD-1 mice exposed for 40 or 100 minutes to 5000 ppm (27,300 mg/m^3) of 1,1,1-trichloroethane (You and Dallas, 2000). The same study also showed significant decreases in cGMP in cerebellum, cortex, and hypothalamus (but not medulla) in male Sprague-Dawley rats exposed by the same protocol. In contrast to these

results, no effect on cortical cGMP was seen in anesthetized male Wistar rats exposed to 8000 ppm (43,680 mg/m^3) of 1,1,1-trichloroethane for 5 or 60 minutes (Folbergrova et al., 1984). However, cAMP (cyclic adenosine monophosphate) in the cerebral cortex was slightly reduced at both time points in the Folbergrova et al. (1984) study. Nilsson (1986b) also observed a slight reduction in cortical cAMP, with no effect on cAMP in cerebellum or hippocampus, and a significant increase in cAMP in brain stem, in male mice exposed to 1010 ppm (5500 mg/m^3) or more for 4 hours. Cyclic nucleotides act as intracellular signal transducers in nerve cells, and a change in levels of these molecules presents a potential mechanism by which 1,1,1-trichloroethane could affect neurological function.

Other neurochemical changes were also noted in anesthetized male Wistar rats exposed to 8000 ppm (43,680 mg/m^3) of 1,1,1-trichloroethane for 5 or 60 minutes (Folbergrova et al., 1984), including significant, reversible increases in lactate (~46% over control) and pyruvate (20-40% over control) and citric acid cycle intermediates (all less than 2-fold increase over control) in the cerebral cortex (without corresponding changes in the blood). The researchers suggested these changes were consistent with stimulation of glycolysis (or possibly inhibition of pyruvate oxidation) and moderate tissue hypoxia. Continuous exposure to 1200 ppm (6550 mg/m^3) of 1,1,1-trichloroethane vapor in the air for 30 days had no effect on body or brain weight or lipid class composition of the cerebral cortex in male Sprague-Dawley rats, but did produce slight, statistically significant changes in the fatty acid pattern of cerebral cortex ethanolamine phosphoglyceride (Kyrklund and Haglid, 1990, 1991). The effect on fatty acid pattern was not seen at 320 ppm (1750 mg/m^3) (Kyrklund et al., 1988). The toxicological significance of the observed change in fatty acid pattern is unclear; the researchers considered it most likely to reflect an adaptive response to the altered local physio-chemical environment (Kyrklund and Haglid, 1991).

Several subchronic studies of 1,1,1-trichloroethane have specifically investigated neurologic endpoints in exposed animals (Rosengren et al., 1985; Karlsson et al., 1987; Mattsson et al., 1993). In the Rosengren et al. (1985) study, groups of 4 male and 4 female Mongolian gerbils were continuously exposed to 0, 70, 210 or 1000 ppm (380, 1150 or 5460 mg/m^3) of 1,1,1-trichloroethane for 3 months. The control animals were sex-matched littermates. All animals were sacrificed 4 months post-exposure for assessment of brain weight [total and cerebral cortex frontal, middle (sensorimotor) and dorsal (occipital) regions] and regional biochemical alterations in the cerebral cortex. Brain histology and neurobehavioral endpoints were not evaluated. The brain biochemical analyses consisted of determinations of total protein and two astroglial protein [S-100 protein and glial fibrillary acidic protein (GFPA)] concentrations. No deaths occurred during the study and no effects on body weight were found at the end of the exposure or post-exposure periods. Brain weight was significantly ($p \leq 0.01$)

reduced in the 1000 ppm (5460 mg/m^3) group, although the difference from controls was slight (2.5% reduction). Significantly increased concentrations of GFAP were found in the sensorimotor cerebral cortex following exposure to 210 ppm (1150 mg/m^3) (~ 33%, estimated from graph, $p \leq 0.01$) and 1000 ppm (5460 mg/m^3) (~ 38%, $p \leq 0.01$). GFAP levels were not increased in the frontal cerebral cortex or the occipital cerebral cortex. Brain S-100 protein concentrations were statistically significantly decreased (~9%) in the frontal cerebral cortex at 210 ppm, but not in any other brain regions or at other exposure concentrations, and total protein concentrations were statistically significantly decreased only in the sensorimotor cerebral cortex (~8%) at 210 ppm (1150 mg/m^3). GFAP is the main protein subunit of astroglial filaments and is used by neurobiologists as a marker for demonstrating formation of astroglial fibrils in response to brain injury. Increase in GFAP therefore is associated with astrogliosis and some insult to the CNS, and the findings of this study indicate that the sensorimotor cerebral cortex was affected by 1,1,1-trichloroethane. S-100 protein is also used as a marker for astroglial cell increase in response to brain injury, but is found in both protoplasmic and fibrillary astrocytes. The authors speculated that the failure to observe an increase in S-100 could have been due to a shift from protoplasmic to fibrillary astrocytes in response to 1,1,1-trichloroethane exposure, although other studies have shown that similar compounds (trichloroethylene and tetrachloroethylene) produced increases in S-100 as well as GFAP (Rosengren et al., 1985). Based on increased GFAP indicating brain astrogliosis in gerbils following continuous exposure, the NOAEL and LOAEL for CNS effects are 70 and 210 ppm (380 and 1150 mg/m^3), respectively.

A related study was conducted in which groups of 6 male and 6 female Mongolian gerbils were continuously exposed to 0 or 70 ppm (380 mg/m^3) of commercial grade 1,1,1-trichloroethane (containing 5% dioxane-free stabilizers) for 3 months, followed by a 4-month exposure-free period ending with sacrifice (Karlsson et al., 1987; Haglid et al., 1990). Study endpoints included body weight, and total and regional brain weight, brain protein and brain DNA concentrations; brain histology and neurobehavioral endpoints were not evaluated. DNA concentration was used as a measure of cell density. Exposure to 70 ppm significantly reduced DNA concentrations in 3 of 9 brain areas investigated (posterior cerebellar hemisphere, anterior cerebellar vermis and hippocampus), although not the sensorimotor cerebral cortex affected in the study by Rosengren et al. (1985). The reduction in DNA content in these areas could reflect a decrease in cell density, possibly as a result of cell death and/or inhibition of nonneuronal cell acquisition, although other interpretations are possible. Because the toxicological significance of reduced DNA content and reliability of it as a biomarker are unclear, the 70 ppm (380 mg/m^3) level is not characterized as a NOAEL or LOAEL.

Neurobehavioral effects of 1,1,1-trichloroethane (99.9% pure containing 0.1% butylene oxide stabilizer) were evaluated in groups of 14 male and 14 female F344 rats ($\approx$16 weeks old)

that were exposed to 0, 200, 630 or 2000 ppm (1090, 3440 and 10,920 mg/m^3) for 6 hours/day, 5 days/week for 13 weeks (Mattsson et al., 1993). This study was conducted in response to special neurotoxicity testing required by the U.S. EPA Interagency Testing Committee. Body weight was measured weekly, clinical observations were performed twice daily, and detailed physical examinations were performed weekly. Functional observational battery (FOB) and fore- and hindlimb grip performance testing were conducted on all rats prior to the start of exposure, monthly during the study, and 65 or more hours after the end of the 13-week exposure period. Behavioral testing during the study was conducted before the daily exposure period, and therefore, approximately 16 hours after the end of the previous exposure. An electrophysiological test battery was conducted on 12 rats/sex/exposure level after 13 weeks of exposure (tests conducted 65 or more hours after the end of exposure); this included flash evoked potential, cortical flicker response, auditory brainstem responses, sensory evoked potentials and caudal nerve action potentials. Following the electrophysiological testing, animals were necropsied for measurement of brain weight (5/sex/level) and neurohistopathology assessment (5 rats/sex in the 0 and 2000 ppm [10,920 mg/m^3] groups). The neurohistological examinations were comprehensive and included brain (10 areas), trigeminal ganglion and nerve, eyes, spinal cord and nerve roots, dorsal root ganglia and peripheral nerves and skeletal muscles. Tissues from rats exposed to 200 or 630 ppm (1090 or 3440 mg/m^3) were not examined due to lack of treatment-related histological findings at 2000 ppm (10,920 mg/m^3). The remaining rats were held for 7 weeks post-exposure and retested for grip performance and examined for histopathology of forelimb muscles and nerves.

The only notable findings were slight, statistically significant deficits in forelimb grip performance in both sexes (≈9% and ≈20% lower than controls in males and females, respectively) of the 2000 ppm (10,920 mg/m^3) group at exposure week 13 (but not before) in comparison to concurrent controls at the same time point (Mattsson et al., 1993). The deficits were not statistically significant in a more rigorous statistical treatment designed to take into account the observed changes over time in the control and treated groups. Forelimb grip performance in 2000 ppm rats was also significantly less than controls at post-exposure week 7 in comparison to concurrent controls, but this was due to an increase in control performance at this time point in comparison to pre-exposure values. Forelimb grip performance in 2000 ppm males and females at 7 weeks post-exposure was improved in comparison to exposure week 13, and roughly similar to pre-exposure performance levels. Hindlimb grip performance was not affected at any time point, and the histopathological, electrophysiological, and FOB studies found no supporting evidence consistent with a performance deficit in forelimb grip performance (e.g., forelimb neuropathy). The investigators hypothesized that sedative properties of 1,1,1-trichloroethane may have been responsible for the effect on forelimb grip performance, but this

is unlikely since the sedative effects of 1,1,1-trichloroethane wear off quickly and the grip tests were conducted well after the end of the previous exposure. This study, therefore, provides only weak evidence for a neurotoxic effect of 1,1,1-trichloroethane. Based on decreased forelimb grip performance, 2000 ppm (10,920 mg/m^3) is a LOAEL for CNS effects in rats; the NOAEL is 630 ppm (3440 mg/m^3).

4.4.2. Immunological Effects

There is no clear evidence for immunological effects produced by 1,1,1-trichloroethane in animal studies. Aranyi et al. (1986) found that exposure of mice to 350 ppm (1900 mg/m^3) of 1,1,1-trichloroethane for 3 hours per day on 1 or 5 days had no effect on mortality from respiratory infection due to streptococcal pneumonia introduced simultaneously with chemical exposure. These researchers found a slight significant increase in bactericidal activity of alveolar macrophages against introduced ^{35}S-*Klebsiella pneumonia* after single exposure, but not after repeated exposure, that the researchers did not consider to be treatment-related.

Two studies from the Russian literature (Shmuter, 1973, 1977), available in English only as an abstract, reported immunological effects (decreased summary titres of typhoid antibodies, increased electrophoretic mobility of the antibodies towards β- and α-globulin fractions, decreased response to sheep erythrocytes, increased spleen weight and cells in the spleen, and decreased number of antibody producing cells) in rabbits and/or rats exposed by inhalation to 2 or 18 ppm (10 or 100 mg/m^3) of trichloroethane for an unspecified period, but the reliability of this study could not be evaluated because of minimal reporting of study design and results. Furthermore, it could not be ascertained whether exposure was to the 1,1,1- or 1,1,2-isomer of trichloroethane. Therefore, these studies provide little useful information on the immunotoxic potential of 1,1,1-trichloroethane.

4.4.3. Effects by Dermal Exposure

The toxicity of 1,1,1-trichloroethane by dermal exposure has been the subject of limited investigation. Direct contact of the eyes and skin with 1,1,1-trichloroethane generally resulted in mild to moderate irritation with single or repeated application (Iyadomi et al., 2000; Wahlberg, 1984a,b; Kronevi et al., 1981; Duprat et al., 1976; Marzulli and Ruggles, 1973; Torkelson et al., 1958). Lethality by the dermal route is low. No rabbit or guinea pig deaths resulted from 24-hour occlusive dermal exposure to ≤7000 mg/kg, and even a dose of 16,000 mg/kg killed fewer than half the rabbits treated (Kinkead and Leahy, 1987; Wahlberg and Boman, 1979; Torkelson et al., 1958). Guinea pigs treated with 2 mL (≈7000 mg/kg) of 1,1,1-trichloroethane had significantly lower body weights than controls throughout a 35-day observation period following treatment (9% deficit at termination) (Wahlberg and Boman, 1979). Rabbits exposed to 2 mL/kg

(≈2700 mg/kg) had similar body weight to controls over a 14-day observation period after treatment (Kinkead and Leahy, 1987). Systemic effects from dermal exposure were studied by Torkelson et al. (1958) and Viola et al. (1981). Torkelson et al. (1958) found no effect on mortality, clinical signs, body weight, food intake, hematology, or gross and microscopic pathology and weights of the major organs in rabbits treated with up to 500 mg/kg-day of 1,1,1-trichloroethane dermally 5 days/week for 90 days. In rats, however, Viola et al. (1981) observed hepatocellular alterations (dark and granular cytoplasm, mitochondrial swelling, fatty degeneration, inflammatory cell infiltration, disrupted mitochondria and cytoplasmic organelles in some hepatocytes) and serum enzyme changes indicative of hepatotoxicity (increased AST, OCT, and GGT) in male Wistar rats treated dermally with 240-320 mg/kg-day on 16 of 22 days. Body weight gain was also significantly reduced, leading to about a 13% deficit in terminal body weight in the treated group. Renal and pancreatic histology were normal.

4.4.4. Effects by Parenteral Exposure

Parenteral studies are consistent with the characterization of 1,1,1-trichloroethane as a weak hepatotoxicant. The chemical produced evidence of hepatotoxicity, including increases in serum enzyme markers, altered liver function tests, and mild-to-moderate lesions, only at near-lethal doses (Plaa et al., 1958; Klaassen and Plaa, 1966, 1967; Gehring, 1968; Cornish et al., 1973; Traiger and Plaa, 1974; Priestly and Plaa, 1976; Kukongviriyapan et al., 1995), with little or no effect at lower doses (Cornish et al., 1973; Traiger and Plaa, 1974; DiVincenzo and Krasavage, 1974; Hanasono et al., 1975; Pollak and Harsas, 1982; Takahara, 1986b; Lundberg et al., 1986; Stacey, 1989; Charbonneau et al., 1991; Honma, 1990; Kukongviriyapan et al., 1995). Even near-lethal doses failed to produce changes in liver triglyceride levels, glucose-6-phosphatase activity, or lipid peroxides in rats (Klaassen and Plaa, 1969). The hepatotoxicity of 1,1,1-trichloroethane was not affected by pretreatment with phenobarbital (Cornish et al., 1973), ethanol (Klaassen and Plaa, 1966, 1967), isopropanol (Traiger and Plaa, 1974), acetone (Traiger and Plaa, 1974; Charbonneau et al., 1991), alloxan (Hanasono et al., 1975), or nicotine (Priestly and Plaa, 1976).

There is little evidence from parenteral studies of a nephrotoxic effect of 1,1,1-trichloroethane. Studies in mice, dogs, and female rats found no effect of this compound on renal function or the incidence of necrotic lesions, even at lethal doses (Plaa et al., 1958; Plaa and Larson, 1965; Klaassen and Plaa, 1966, 1967; Bernard et al., 1989). The only kidney effects observed were mild lesions at high doses: tubular swelling in mice (Plaa and Larson, 1965) and slight calcification of tubules in dogs (Klaassen and Plaa, 1967). Male rats were not tested for nephrotoxicity in parenteral studies, so these studies do not address the potential of the chemical to produce male-rat specific α_{2u}-globulin nephropathy, which has been reported following oral

exposure.

Intravenous injection of 1,1,1-trichloroethane resulted in a decrease in leukocyte count and alterations in differential in dogs that were similar to those seen after acute inhalation exposure; there were no effects on erythrocyte count, hematocrit, or thrombocytes (Hobara et al., 1983, 1984). Intratesticular injection of 1,1,1-trichloroethane produced a significant decrease in testicular DNA synthesis in male mice (Borzelleca and Carchman, 1982), but repeated intraperitoneal injections had no effect on the incidence of sperm head abnormalities in mice (Topham, 1980, 1981).

Neurological effects are well known following inhalation exposure to 1,1,1-trichloroethane, but have not been widely studied by parenteral routes. 1,1,1-Trichloroethane was reported to have effects on electroretinogram and standing potential of the eye in monkeys given low intravenous doses (Jarkman et al., 1985) and also to produce vestibular disturbances, indicated by positional nystagmus (involuntary eye movements), but without nystagmus response to rotary acceleration, in rabbits at low intravenous doses (Larsby et al., 1978; Odkvist et al., 1979, 1980). In the brain, intraperitoneal injection of a sedating dose of 1,1,1-trichloroethane (2400 mg/kg) in mice produced no effect on calcium flux into synaptosomes (isolated nerve endings) from the cerebral cortex, while significantly decreasing calcium flux into cerebellar synaptosomes and increasing calcium flux into brain stem synaptosomes (Nilsson, 1987). The effect on voltage-dependent calcium channels could have ramifications for neurotransmitter release and cyclic nucleotide metabolism, and represents a potential mechanism by which 1,1,1-trichloroethane might produce neurological effects.

4.5. MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION

4.5.1. Mechanistic Data from *In Vitro* Studies

There is a body of evidence suggesting that the effects of 1,1,1-trichloroethane on the heart (Krantz et al., 1959; Herd and Martin, 1975) and the liver (Kukongviriyapan et al., 1990) may result, at least in part, from interference with energy generation within the cells. In isolated hepatocytes, uptake of 3 chemicals with different active transport systems (taurocholate, ouabain, 2-aminoisobutyric acid) was inhibited by sub-cytotoxic levels of 1,1,1-trichloroethane in a dose-related fashion, while passive uptake of other substances ($CdCl_2$, 3-*O*-methyl-D-glucose) was not affected (Kukongviriyapan et al., 1990). Cellular ATP and membrane ATPase activities were reduced, suggesting that the effect on active transport systems may reflect an energy deficit in the cells. Studies in isolated rat heart and liver mitochondria have demonstrated that 1,1,1-trichloroethane can uncouple oxidative phosphorylation, decreasing intracellular respiration and production of ATP (Herd and Martin, 1975; Ogata and Hasegawa, 1981; Takano

and Miyazaki, 1982). The effect of 1,1,1-trichloroethane on energy generation is apparently related to alterations in passive mitochondrial membrane permeability to calcium (Ca^{2+}) and H^{+}; Ca^{2+} binding and sequestration mechanisms appeared unaffected (Herd and Martin, 1975).

Altered permeability of cell membranes to calcium has also been implicated in the cardiac and nervous system effects of 1,1,1-trichloroethane. Reduced contractility of isolated cardiac myocytes exposed to 1,1,1-trichloroethane was shown to be due to an inhibitory action on influx of extracellular calcium into the cell (Toraason et al., 1990; Hoffmann et al., 1992, 1994). 1,1,1-Trichloroethane also changed calcium flux across cell membranes in isolated brain synaptosomes (Nilsson, 1987; Robinson et al., 2001) and dorsal root ganglion neurons (Okuda et al., 2001). Other studies found that 1,1,1-trichloroethane enhanced ligand-gated ion channel activity: GABA-mediated synaptic currents in hippocampal neurons and ligand-evoked currents of recombinant GABA and glycine receptors expressed in *Xenopus* oocytes (Beckstead et al., 2000, 2002). 1,1,1-Trichloroethane can produce effects on cell membranes by acting directly on membrane-bound proteins; the chemical produced concentration-related inhibition of acetylchlolinesterase and ATPase in both isolated human red blood cells and rat synaptosomes (Tahti and Korpela, 1986; Korpela and Tahti, 1986, 1987; Korpela, 1989). Incorporation into the membrane, leading to modification of the immediate environment of gap junctions, was hypothesized to explain the observed inhibition of gap junction intercellular communication in cardiac myocytes by 1,1,1-trichloroethane (Toraason et al., 1992). Inhibition of intercellular communication is thought to be related to the arrhythmogenic effects of 1,1,1-trichloroethane.

In studies using perfused rat liver and rat liver microsomes (Takano et al., 1985, 1988), 1,1,1-trichloroethane was also found to uncouple the cytochrome P-450 dependent mixed function oxidase system by binding to cytochrome P-450 (without undergoing significant metabolism - see Section 3.3), leading to futile oxygen consumption and high hydrogen peroxide production, although not peroxidation of membrane lipids. Although, 1,1,1-trichloroethane did not produce lipid peroxidation in the liver in this study or others (Klaassen and Plaa, 1969), the compound did produce evidence of lipid peroxidation in cultured arterial endothelial and aortic smooth muscle cells when low levels of iron were also present (Tse et al., 1990). It was hypothesized by these researchers that this interaction may explain toxic effects of 1,1,1-trichloroethane in tissues, such as vascular cells, with little cytochrome P-450 or metabolic capacity.

Studies of direct injection of chick embryos found reduced survival and increased malformations associated with injection of 1,1,1-trichloroethane (Elovaara et al., 1979; Gilani and Diaz, 1986). 1,1,1-Trichloroethane had no effect on interferon induction in mouse embryo fibroblasts (Sonnenfeld et al., 1983) or on the natural tumoricidal activity (natural killer, natural cytotoxic, natural P815 killer) of human liver immune cells (Wright et al., 1994). Inhibited

induction of interferon and inhibition of natural immune function have been associated with cancer produced by some chemicals.

4.5.2. Genotoxicity

The genotoxic effects of 1,1,1-trichloroethane have been studied extensively. The chemical has shown little capacity to produce genotoxic effects in bacteria or fungi, regardless of test system, use of metabolic activation, or measures to counter loss due to volatility. Results in mammalian test systems *in vitro* and *in vivo* were more mixed, although still predominantly negative for assays other than cell transformation. The chemical has been shown to interact weakly with DNA.

Results for the Ames *Salmonella* assay have been mostly negative, both with and without metabolic activation (Baker and Bonin, 1981; Brooks and Dean, 1981; Dow Chemical Co., 1980, 1983; Falck et al., 1985; Ichinotsubo et al., 1981; Legault et al., 1994; MacDonald, 1981; Martire et al., 1981; Mersch-Sundermann, 1989; Milman et al., 1988; Nagao and Takahashi, 1981; Nestmann et al., 1980; Quillardet et al., 1985; Richold and Jones, 1981; Rowland and Severn, 1981; Simmon and Shepherd, 1981; SRI, 1984; Suovaniemi et al., 1985; Trueman, 1981; Venitt and Crofton-Sleigh, 1981; Warner et al., 1988), although others were positive with and without metabolic activation (Gocke et al., 1981; IBM, 1982; Nestmann et al., 1980, 1984; Shimada et al., 1985; Simmon et al., 1977). The tests giving positive results were carried out in a desiccator to maximize exposure, but so were several of those giving negative results (Dow Chemical Co., 1980, 1983; Milman et al., 1988; SRI, 1984; Warner et al., 1988). Two studies have suggested that weakly positive results in the Ames *Salmonella* assay may be due to compounds included in commercial samples as stabilizers of 1,1,1-trichloroethane, rather than to 1,1,1-trichloroethane itself (Nestmann et al., 1984; Shimada et al., 1985). Other tests of microbial mutagenicity in *Salmonella typhimurium* and *Escherichia coli* were negative with or without metabolic activation (Gatehouse, 1981; Hubbard et al., 1981; Legault et al., 1994; Matsushima et al., 1981; Roldan-Arjona et al., 1991; Skopek et al., 1981). Tests for DNA damage in bacteria, assessed by SOS induction (Legault et al., 1994; Nakamura et al., 1987; Ono et al., 1991a,b; Quillardet et al., 1985; Thomson, 1981) or differential killing (Green, 1981; Kada, 1981; Tweats, 1981), were negative, except for a weak positive result with activation in a differential killing test in *E. coli* (Rosenkranz et al., 1981).

In the yeast *Saccharomyces cerevisiae*, 1,1,1-trichloroethane did not produce, with or without metabolic activation, reverse mutation (Mehta and von Borstel, 1981), mitotic crossing over (Kassinova et al., 1981), mitotic gene conversion (Jagannath et al., 1981; Sharp and Parry, 1981a; Zimmermann and Scheel, 1981), DNA damage (Sharp and Parry, 1981b), or chromosome loss (Parry and Sharp, 1981; Whittaker et al., 1990), but did produce weak positive results in a

test for induction of deletions via intrachromosomal recombination (tested without activation only) (Brennan and Schiestl, 1998). Results were negative for forward mutation in the yeast *Schizosaccharomyces pombe*, with or without activation (Loprieno, 1981). 1,1,1-Trichloroethane did not produce forward mutations, mitotic crossing over, or aneuploidy in the mold *Aspergillus nidulans*, tested without activation (Crebelli and Carere, 1987; Crebelli et al., 1988). In plants, 1,1,1-trichloroethane produced positive results for mutations in *Tradescantia* flowers (Schairer et al., 1983) and chromosomal aberrations in the onion *Allium cepa* (Rank and Nielsen, 1994).

Mixed results have been obtained for *in vitro* genotoxicity tests of mammalian cells. The L5178Y mouse lymphoma cell mutagenesis assay has given both negative (Caspary et al., 1988; Mitchell et al., 1988; Myhr and Caspary, 1988) and weakly positive results in different laboratories (Caspary et al., 1988). 1,1,1-Trichloroethane did not cause unscheduled DNA synthesis in HeLa cells (Martin and McDermid, 1981) or in rat hepatocytes (Althaus et al., 1982; Dow Chemical Co., 1983; Naylor Dana Institute, 1983; Shimada et al., 1985; Milman et al., 1988; Williams et al., 1989), but had a positive result in mouse hepatocytes (Naylor Dana Institute, 1983; Milman et al., 1988). An assay for degranulation of endoplasmic reticulum from rat hepatocytes was positive (Fey et al., 1981). 1,1,1-Trichloroethane has been both positive (Galloway et al., 1987) and negative (Sofuni et al., 1985) in tests for chromosome aberrations in cultured Chinese hamster cells. Assays for induction of micronuclei in cytochalasin B-induced binucleate cells of human lymphoblastoid cell lines of varying metabolic activity (AHH-1 with CYP1A1 activity, h2E1 with CYP2E1, and MCL-5 with multiple CYP activities) were all positive (Doherty et al., 1996). Tests for sister chromatid exchange in Chinese hamster ovary cells and human peripheral lymphocytes were negative (Galloway et al., 1987; Lindahl-Kiessling et al., 1989; Perry and Thomson, 1981). Cell transformation assays have been positive for BALBc/3T3 cells (Arthur D. Little, 1983; Milman et al., 1988; Tu et al., 1985), rat embryo cells (Price et al., 1978) and hamster embryo cells (Hatch et al., 1982, 1983), but have given both positive (Daniel and Dehnel, 1981) and negative (Styles, 1981) results with baby hamster kidney cells.

In vivo tests of 1,1,1-trichloroethane genotoxicity were predominantly negative. The *Drosophila* sex-linked recessive lethal assay has given negative results for injection (Gocke et al., 1981; SRI, 1985; U.S. EPA, 1987), and both negative and weakly positive results for feeding (U.S. EPA, 1987). An assay for interchromosomal mitotic recombination in *Drosophila* (white/white+ eye mosaic assay) was negative (Vogel and Nivard, 1993). The mouse micronucleus assay has given negative results (Gocke et al., 1981; ICI Central Toxicology Lab., 1990; Katz et al., 1981; Salamone et al., 1981; Tsuchimoto and Matter, 1981). A rat liver foci assay for tumor initiating and promoting activity was negative for both (Story et al., 1986;

Milman et al., 1988). 1,1,1-Trichloroethane did not bind to calf thymus DNA *in vitro* (DiRenzo et al., 1982), but *in vivo* binding of 1,1,1-trichloroethane to DNA, RNA and protein was found to be typical of very weak initiators (Turina et al., 1986; Prodi et al. 1988). Overall the highest level of binding was to RNA. There was a small increase associated with both RNA and DNA of the kidney compared to that of other organs, and binding was slightly higher in the mouse than in the rat. Milman et al. (1988) reported similar findings, with greater binding of 1,1,1-trichloroethane to mouse than to rat hepatic proteins. 1,1,1-Trichloroethane did not cause DNA damage (unwinding in fluorometric assay) in mouse liver (Taningher et al., 1991).

4.6. SYNTHESIS OF MAJOR NONCANCER EFFECTS

4.6.1. Oral

Tables 14 and 15 present summary noncancer results of the major studies for oral exposure to 1,1,1-trichloroethane in humans and experimental animals, respectively.

The primary target of 1,1,1-trichloroethane at high oral doses is the central nervous system. Gross CNS depression, as indicated by initial hyperexcitability followed by a period of prolonged narcosis (often leading to death), was observed in rats given 1,1,1-trichloroethane by gavage in corn oil at average doses of 3750 mg/kg-day or above for 12 days or 1786 mg/kg-day or above for 90 days (Bruckner et al., 2001). No gross CNS effects were seen following gavage doses of 375 mg/kg-day for 12 days or 357 mg/kg-day for 90 days (Bruckner et al., 2001). This study did not include systematic investigation of neurological endpoints, however, making it uncertain whether neurological effects more subtle than gross CNS depression may have gone undetected at these doses. NCI (1977) found no evidence of gross CNS depression in rats treated by gavage in corn oil at 536 or 1071 mg/kg-day for 78 weeks. Mice are apparently less susceptible than rats to CNS effects from 1,1,1-trichloroethane, as even TWA gavage doses of 4011 mg/kg-day for 78 weeks failed to elicit clinically evident CNS effects. The potency of 1,1,1-trichloroethane to induce CNS depression was clearly enhanced by bolus administration in the gavage studies. In contrast to the LOAEL of 1786 mg/kg-day identified in the 13-week gavage study by Bruckner et al. (2001), a 13-week feeding study in rats (NTP, 2000) reported no evidence of gross CNS effects at doses up to 4800-5000 mg/kg-day. Tests for more subtle neurological effects detected neurophysiological changes (EEG, FEP, SEP) in rats treated with 705 mg/kg-day of 1,1,1-trichloroethane by gavage for 4 days (Spencer et al., 1990). These investigators found no neurobehavioral effects at this same gavage dose (705 mg/kg-day). Similarly, neurobehavioral effects were not found in rats treated with 705 mg/kg-day by gavage for 2 days (Spencer et al., 1990) or in rat dams or pups of dams treated with up to 750 mg/kg-day from day 6 of gestation to day 10 of lactation (Maurissen et al., 1993, 1994). The only available human data come from a case report of an individual who swallowed a bolus dose of

approximately 600 mg/kg of 1,1,1-trichloroethane on a single occasion. No clinically evident CNS effects were reported, and thorough neurological examinations designed to detect more subtle CNS effects revealed no abnormalities. The neurological effects of 1,1,1-trichloroethane have been studied in more detail following inhalation exposure.

Evidence for the liver as a potential target of orally administered 1,1,1-trichloroethane is equivocal. Some, but not all, studies suggest that 1,1,1-trichloroethane may produce mild hepatotoxicity. An individual who swallowed one ounce of 1,1,1-trichloroethane (approximately 600 mg/kg), a dose that induced severe vomiting and diarrhea but no neurological effects, had only a slight increase in serum bilirubin and no changes in serum ALT or AST (Stewart and Andrews, 1966). In experimental animals, serum enzyme changes indicative of mild hepatotoxicity were seen in two single dose gavage studies (at 670 mg/kg in one study and 2500 mg/kg with a NOAEL of 1300 mg/kg in the other) (Xia and Yu, 1992; Tyson et al., 1983), and in a 13-week gavage study at a dose (3571 mg/kg-day) that was lethal to 50% of the rats tested (Bruckner et al., 2001). In these studies, the observed changes were slight, occurred in only 1 or 2 of multiple measures of hepatotoxicity examined, and were not accompanied by gross or microscopic liver lesions. NTP (2000) reported decreases in relative and/or absolute liver weight (12%) in female and male rats exposed to 4800-5000 mg/kg-day of 1,1,1-trichloroethane in the diet for 13 weeks (NOAEL = 2400-2500 mg/kg-day) (NTP, 2000). No histopathologic changes in the liver were observed. Increases in liver weight, rather than decreases, were found in most other studies that reported changes in liver weight, regardless of exposure route. These increases in liver weight were generally associated with induction of drug metabolizing enzymes by 1,1,1-trichloroethane. Dermal, parenteral, and inhalation studies support identification of 1,1,1-trichloroethane as a weak hepatotoxicant (e.g., Viola et al., 1981; Cornish et al., 1973; Kukongviriyapan et al., 1995; Adams et al., 1950; McNutt et al., 1975; Quast et al., 1984, 1988).

There is some evidence for the kidney as a target of 1,1,1-trichloroethane in male rats following oral exposure. Male rats exposed to 1200 mg/kg-day or more in the diet for 13 weeks showed renal lesions characteristic of α_{2u}-globulin nephropathy, as indicated by significant, dose-related increases in incidence and/or severity of renal tubule hyaline degeneration, cast formation, and regeneration, and chronic interstitial inflammation of the kidney (NTP, 2000), although specific analysis for α_{2u}-globulin was not conducted by NTP. Renal changes associated with α_{2u}-globulin nephropathy in male rats are specific to this sex and species, and are not considered to be predictive for effects in humans (U.S. EPA, 1991c). In a 21-day gavage study in rats designed specifically to examine renal toxicity of halogenated ethanes (NTP, 1996), no renal lesions, including hyaline droplet nephropathy, tubule regeneration, or granular casts, were seen at the high dose of 165 mg/kg-day. Increases in mean urine protein and AST were reported in the high dose group in this study, but may have been due to high levels in a single individual,

and therefore, may not have been related to treatment. Male rats treated dermally with 240-320 mg/kg-day for 3 weeks showed no evidence of renal lesions (Viola et al., 1981). Parenteral studies found little evidence of nephrotoxicity even at lethal dose levels (e.g., Plaa et al., 1958; Klaassen and Plaa, 1967; Bernard et al., 1989), but were not conducted in male rats. The kidneys were not adequately evaluated as a potential endpoint of toxicity in other subchronic or chronic oral studies. Inhalation studies, including studies of subchronic and chronic durations, did not show renal effects in male rats or other species tested. The overall weight of evidence does not show the kidney to be a sensitive target organ for 1,1,1-trichloroethane.

Epididymal spermatozoal concentration was reduced in high-dose male rats (4800 mg/kg-day) and mice (15,000 mg/kg-day) in the 13-week feeding study (NTP, 2000). The toxicological significance of these changes is uncertain, as the magnitude was relatively small (10-20%) and no associated changes in sperm motility or the weight or histopathology of the reproductive organs were seen in either species. The epididymis was not evaluated as a potential endpoint of toxicity in other oral studies, and was not identified as a target in inhalation studies. Intratesticular injection of 1,1,1-trichloroethane produced a significant decrease in testicular DNA synthesis in male mice (Borzelleca and Carchman, 1982), but repeated intraperitoneal injections had no effect on the incidence of sperm head abnormalities in mice (Topham, 1980, 1981). No effect on male or female reproductive function was seen in mice tested in a multigeneration oral study at doses up to 1000 mg/kg-day (Lane et al., 1982).

Significantly decreased body weight gain was the most sensitive effect in 13-week feeding studies in rats and mice (NTP, 2000). In the 90-day gavage study (Bruckner et al., 2001), low-dose rats had slightly non-significant reduced body weights (~95% of control) with no other reported effects. Reduced body weight gain was observed in the 104-week study by Maltoni et al. (1986) in the absence of effects on survival; non-neoplastic lesions were not further examined in this study. Reduced body weight gain has also been observed in inhalation studies in the absence of other toxicity (Prendergast et al., 1967; Adams et al., 1950) or at dose levels causing minimal liver histopathologic changes (some reflective of an adaptive physiologic response) (Calhoun et al., 1981; Quast et al., 1984, 1988).

One preliminary study reported cardiac abnormalities, especially persistent ductus arteriosis, in rat pups of parents exposed to a low dose (1.4 mg/kg-day) of 1,1,1-trichloroethane in drinking water (Dapson et al., 1984a,b). However, this study was limited by small group sizes, use of only a single exposure level, examination of few endpoints, and incomplete analysis of the data. Subsequent studies, designed to evaluate this observation and including large numbers of animals, found no evidence of any developmental effects at dose levels up to 3.5 mg/kg-day (George et al., 1989; NTP, 1988a,b). The multigeneration study by Lane et al. (1982) found no developmental effects in mice tested at doses up to 1000 mg/kg-day. A study designed

primarily to evaluate neurological endpoints in developing rat pups found no effects at doses up to 750 mg/kg-day (Maurissen et al., 1993, 1994). Overall, the database shows no evidence of developmental effects in rats or mice exposed to 1,1,1-trichloroethane by the oral route. However, all of these studies were conducted at relatively low doses that failed to elicit maternal toxicity. Inhalation studies in rodents found evidence for developmental delay in fetuses and delayed attainment of developmental milestones and neurodevelopmental effects in pups under certain exposure regimens, including an exposure regimen that did not produce observable effects in the dams (BRRC, 1987a,b; Jones et al., 1996; Coleman et al., 1999). Studies of direct injection of chick embryos found reduced survival and increased malformations associated with injection of 1,1,1-trichloroethane (Elovaara et al., 1979; Gilani and Diaz, 1986).

The available oral toxicity studies were not, in general, designed to examine whether the effects associated with 1,1,1-trichloroethane were reversible upon cessation of exposure or whether effects might manifest after some latency period. The CNS depressant effects of 1,1,1-trichloroethane, like those of other solvents, are generally considered to be readily reversible (Evans and Balster, 1991). The effects are thought to be related to presence of the parent compound in neural membranes, and to resolve as the parent compound is rapidly eliminated from the body following exposure. One 13-week oral toxicity study included a one-week post-exposure period; no effects were observed at either 13-weeks or one-week post-exposure.

Table 14. Summary Noncancer Results of Major Studies for Oral Exposure of Humans to 1,1,1-Trichloroethane

Study Population	Sex	Average Daily Dose (mg/kg-d)	Exposure Duration	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Responses at LOAEL	Comments	Reference
Acute Exposure								
One case	M	600	once	ND	600	Severe vomiting and diarrhea, slightly elevated serum bilirubin.	No gross CNS effects and no abnormalities in neurological examination.	Stewart and Andrews, 1966
Short-term Exposure								
No suitable short-term studies available								
Subchronic Exposure								
No suitable long-term studies available								
Chronic Exposure								
No suitable chronic studies available								

ND = Not Determined

Table 15. Summary Noncancer Results of Major Studies for Oral Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Average Daily Dose (mg/kg-d)	Exposure Duration	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Responses at LOAEL	Comments	Reference
Acute Exposure								
Rat	F	0 or 670 (g)	once	ND	670	Serum ALT increased 1.5 fold.	No effect on serum SDH or GDH, and no liver lesions detected. Study did not investigate other endpoints. Group sizes not specified.	Xia and Yu, 1992
Rat	M	0, 300, 1300, or 2500 (g)	once	1300	2500	Serum AST increased 2-fold.	No effect on serum ALT. Study did not investigate other endpoints. Small group sizes (3-5 per dose).	Tyson et al., 1983
Rat	M	0, 500, 1000, 2000, or 4000 (g)	once	4000	ND	None	No effect on serum ALT, SDH or OCT, or liver weight or histopathology. Study did not investigate other endpoints. Group sizes not specified.	Bruckner et al., 2001
Short-term Exposure								
Rat	M	0, 375, 3750, or 7500 (g)	12 d	375	3750	Death, narcosis, reduced body weight (20%).	No effect on serum ALT, SDH or OCT, or liver weight or histopathology. Study did not investigate other endpoints.	Bruckner et al., 2001
Rat	F	0 or 705 (g)	4 d	ND	705	Electrophysiological changes (marked changes in EEG and FEP; smaller changes in SEP).	No neurobehavioral effects (measured after 2 days of exposure)	Spencer et al., 1990

Table 15. Summary Noncancer Results of Major Studies for Oral Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Average Daily Dose (mg/kg-d)	Exposure Duration	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Responses at LOAEL	Comments	Reference
Rat	F	0, 75, 250, or 750 (g)	GD 6- LD 10	750	ND	None	No neurobehavioral effects in dams or neurodevelopmental effects in pups.	Maurissen et al., 1993, 1994
Subchronic Exposure								
Rat	M	0, 357, 1786, or 3571 (g)	13 wk	357	1786	Death, narcosis, reduced body weight.	Early accidental termination of the two high-dose groups. No effect on serum ALT, SDH or OCT, or liver weight or histopathology in the low-dose group. In the high-dose group, slight increases in ALT and OCT. Study did not investigate other endpoints.	Bruckner et al., 2001
Rat	M, F	M: 290, 600, 1200, 2400, or 4800 F: 310, 650, 1250, 2500, or 5000 (f)	13 wk	2400-2500	4800-5000	Reduced liver weights (11-17%) in males and females, and reduced epididymal spermatozoal concentration (~10%) in males.	Hyaline droplet nephropathy in male rats at 1200 mg/kg and above (not considered relevant to human health risk assessment). Broad array of endpoints assessed, including complete histopathology at high dose. Body weight decreased, but within 10% of control.	NTP, 2000

Table 15. Summary Noncancer Results of Major Studies for Oral Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Average Daily Dose (mg/kg-d)	Exposure Duration	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Responses at LOAEL	Comments	Reference
Mouse	M, F	M: 850, 1770, 3500, 7370, or 15,000 F: 1340, 2820, 5600, 11,125, or 23,000 (f)	13 wk	1770-2820	3500-5600	Decreased body weight gain in males and females (11-12%).	Decreased body weight gain at lower doses was within 10% of control values and considered to be of marginal biological significance. At high doses (15,000 mg/kg-d), epididymal spermatozoal concentration decreased in males (20%). Complete histopathology at high-dose.	NTP, 2000
Rat	M, F	0 or 1.4 (dw)	Before mating through lactation	ND	1.4	Increased cardiac abnormalities, especially persistent ductus arteriosis, in pups.	Small group sizes, few endpoints examined, incomplete analysis of data (no litter-based comparison of cardiac anomalies).	Dapson et al., 1984a,b
Rat	M, F	0, 0.3, 1.2, or 3.5 (dw)	Before mating through lactation	3.5	ND	None	No increase in persistent ductus arteriosis or other cardiac anomalies in pups. Large group sizes. Designed to evaluate Dapson et al. (1984a,b).	George et al., 1989; NTP, 1988a
Rat	M, F	0, 0.3, 0.8, or 2.4 (dw)	Before mating through Gd20	2.4	ND	None	No maternal, embryotoxic, fetotoxic or developmental (external, visceral, skeletal or cardiovascular) abnormalities were found.	NTP, 1988b
Mouse	M, F	0, 100, 300, or 1000 (dw)	Before mating through lactation; multi-gen.	1000	ND	None	No effects on male or female reproductive function or offspring development.	Lane et al., 1982

Table 15. Summary Noncancer Results of Major Studies for Oral Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Average Daily Dose (mg/kg-d)	Exposure Duration	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Responses at LOAEL	Comments	Reference
Chronic Exposure								
Rat	M, F	0, 536, or 1071 (g)	78 wk	ND	536	Increased early mortality and decreased body weight.	Cancer bioassay with limited investigation of noncancer endpoints.	NCI, 1977
Mouse	M, F	0, 2005, or 4011 (g)	78 wk	ND	2005	Increased early mortality and decreased body weight.	Cancer bioassay with limited investigation of noncancer endpoints.	NCI, 1977
Rat	M, F	0 or 321 (g)	104 wk	ND	321	Decreased body weight in females (by ~12 and 25% at end of treatment and observation periods, respectively).	No effect on survival. Cancer bioassay with limited investigation of noncancer endpoints.	Maltoni et al., 1986

ND = Not Determined

dw = drinking water; f = feed; g = gavage.

4.6.2. Inhalation

Tables 16 and 17 present summary noncancer results of the major studies for inhalation exposure to 1,1,1-trichloroethane in humans and experimental animals, respectively.

CNS depressant effects are the predominant signs of acute inhalation exposure to 1,1,1-trichloroethane in humans and in animals. Studies of subtle neurological effects in humans provide the most sensitive indications of 1,1,1-trichloroethane toxicity. In male volunteers, Gamberale and Hultengren (1973) found impaired performance in a number of neurobehavioral performance tests at concentrations of 350 ppm (1900 mg/m^3) and above (NOAEL = 250 ppm [1370 mg/m^3]) for a 30 minute exposure. Mackay et al. (1987) found similar effects at lower levels (LOAEL = 175 ppm [950 mg/m^3], NOAEL not determined) in male volunteers receiving a 3.5-hour exposure. Tests for reaction time appeared to be the most sensitive. Muttray et al. (2000) monitored the EEG of male volunteers with eyes closed, eyes open, and while performing a choice reaction time test before and during 4-hour exposure to 200 ppm (1090 mg/m^3) 1,1,1-trichloroethane and found changes consistent with increased drowsiness in the closed eye test. Subjectively, the volunteers also reported increased tiredness. Animal studies have not proved as sensitive as human studies for detection of neurological effects of acute 1,1,1-trichloroethane inhalation exposure. Neurological effects in animals were reported following acute 1,1,1-trichloroethane exposure at concentrations of around 700 ppm (4000 mg/m^3) and above. Narcosis associated with acute exposure was shown to be reversible (Adams et al., 1950). The most sensitive response reported in animal studies was depression of seizure discharge (specifically, duration of tonic extension of hindlimb in rats) in response to electrical shock. The concentration estimated to produce a 30% depression in seizure discharge for a 4-hour exposure was 734 ppm (4000 mg/m^3) (Frantik et al., 1994). Neurochemical changes have been reported at lower concentrations, for example decreased cGMP in the cerebellum of male mice exposed to 100 ppm (550 mg/m^3) for 4 hours (Nilsson, 1986a). While changes in levels of cyclic nucleotides, which act as secondary messengers in neural cells, could have functional effects on the nervous system, there is no evidence that the chemical changes observed in existing studies are indicative of such an effect.

Neurological effects have been observed at lower concentrations in animal studies with repeated exposure. Continuous exposure to 500 ppm (2730 mg/m^3) for 4 days resulted in a concentration-related increase in incidence and severity of handling-induced convulsions in mice through 24 hours post-exposure (Evans and Balster, 1993; Balster et al., 1997). No such convulsions were seen in controls at any time. The effects were mitigated by re-exposure to 1,1,1-trichloroethane or exposure to other known depressants, and were interpreted as symptoms of withdrawal by the researchers. In a subchronic study designed to investigate persistent

neurotoxic effects, exposure to 2000 ppm (10,920 mg/m^3) for 6 hours/day, 5 days/week (NOAEL = 630 ppm or 3440 mg/m^3) for 3 months (but not less) produced ambiguous evidence for a deficit in forelimb grip performance in rats of both sexes (Mattsson et al., 1993); some indication of a deficit was still present 7 weeks post-exposure. Continuous exposure to 210 ppm (1150 mg/m^3) or above for 3 months produced increased concentrations of GFAP, a marker for formation of astroglial fibrils in response to brain injury, in the sensorimotor cerebral cortex of exposed gerbils (evaluated 4 months after the end of exposure) (Rosengren et al., 1985). There was no effect on GFA protein at 70 ppm (380 mg/m^3), and no dose-related effect on the concentrations of S-100, another protein marker of astroglial cell increase, or total protein in regions of gerbil brain. Another study from the same researchers (Karlsson et al., 1987) found decreased concentration of DNA in 3 of 9 brain areas examined in gerbils exposed to 70 ppm (380 mg/m^3) for 3 months (also evaluated 4 months after the end of exposure), although not the sensorimotor cerebral cortex affected in the study by Rosengren et al. (1985). Although reduced DNA content in these areas could reflect a decrease in cell density, possibly as a result of cell death and/or inhibition of nonneuronal cell acquisition, it is not clear that the observed DNA changes constitute reliable evidence of an adverse effect. Chronic animal studies found no evidence of gross CNS depression at exposures up to 1500 ppm (8190 mg/m^3) for 6 hours/day, 5 days/week, but did not include investigation of more subtle neurological effects. A study of workers with chronic occupational exposure to 1,1,1-trichloroethane provided evidence of neurobehavioral effects in workers, but exposure levels were not determined (Kelafant et al., 1994). Some other occupational studies did not find effects, but included limited investigation of neurological endpoints (Kramer et al., 1978) or included a battery of neurological tests, but not tests for reaction time, which was shown to be especially sensitive to 1,1,1-trichloroethane in acute studies (Maroni et al., 1977).

Effects on respiration, blood pressure, and the heart have been associated with acute exposure to high levels of 1,1,1-trichloroethane (approximately 5000 ppm [27,300 mg/m^3] and above) in both humans and animals (e.g., Dornette and Jones, 1960; Herd et al., 1974; Reinhardt et al., 1973). These effects have not been observed at lower levels and do not constitute sensitive measures of toxicity for 1,1,1-trichloroethane.

There is some evidence to suggest that nasal tissue is a sensitive target for 1,1,1-trichloroethane by inhalation exposure, although such effects have not been widely reported. Muttray et al. (1999) found increased levels of proinflammatory cytokines in nasal secretions from human volunteers exposed to 200 ppm (1090 mg/m^3), indicating a slight irritant response characterized by subclinical inflammation in the nasal mucosa. In animals, minimal lesions of the nasal turbinates were observed in male and female rats and mice exposed to 2000 ppm (10,920 mg/m^3) for 6 hours/day, 5 days/week, but not lower concentrations, for 14 weeks

(Calhoun et al., 1981). However, it is not clear that these lesions were related to 1,1,1-trichloroethane exposure, as subsequent chronic studies by the same group of investigators, which included interim sacrifices at 6, 12 and 18 months in addition to terminal sacrifice at 24 months, did not find nasal lesions in rats and mice exposed on a similar schedule (1500 ppm [8190 mg/m^3] for up to 2 years (Quast et al., 1984, 1988).

The liver is not a sensitive target of 1,1,1-trichloroethane by acute inhalation exposure. Aside from a transitory increase in urinary urobilinogen in 2 of 4 subjects given 15-minute exposure to 2650 ppm (14,470 mg/m^3) (Stewart et al., 1961), controlled exposure studies in humans found no evidence for hepatotoxicity, as determined by liver function tests and serum chemistry, hematology and urinalysis measurements (Stewart et al., 1961, 1969; Torkelson et al., 1958; Dornette and Jones, 1960). In animals, Adams et al. (1950) reported increased relative liver weight (12%) and slight histopathology (fatty change) in the liver of rats exposed to 8000 ppm (43,680 mg/m^3) for 7 hours, and a larger increase in relative liver weight (27%) and slight-to-moderate liver lesions, including more marked fatty changes and, in some cases, congestion and hemorrhagic necrosis, in rats exposed to 12,000 ppm (65,520 mg/m^3) for 7 hours. Exposure for shorter durations, even to much higher concentrations, produced little evidence of hepatotoxicity in animal studies (Adams et al., 1950; Loizou et al., 1996; Carlson, 1973; Cornish and Adefuin, 1966; Gehring, 1968; Krantz et al., 1959). In prolonged, repeated exposure animal studies, however, the liver is a more sensitive target for 1,1,1-trichloroethane. Minimal liver effects were observed in rats and mice following inhalation of 1,1,1-trichloroethane at 2000 ppm (10,920 mg/m^3) for 6 hours/day, 5 days/week for three months (NOAEL = 1000 ppm [5460 mg/m^3]) (Calhoun et al., 1981). More marked liver lesions were found in mice continuously exposed to 1000 ppm (5460 mg/m^3) for 14 weeks (McNutt et al., 1975). Histopathologic changes in the liver suggestive of an adaptive physiologic response were observed in rats exposed to 1500 ppm (8190 mg/m^3) 6 hours/day, 5 days/week for 2 years (Quast et al., 1984, 1988). Serum enzyme changes indicative of hepatotoxicity were not found, however, in workers exposed to up to 150-249 ppm (820-1360 mg/m^3) of 1,1,1-trichloroethane for up to 6 years (Kramer et al., 1978).

Developmental effects have been reported following gestational exposure to 1,1,1-trichloroethane vapor in animals. Mild fetotoxic effects (skeletal variations, reduced fetal weights) were observed at high concentrations (LOAEL = 6000 ppm [32,760 mg/m^3] for 6 hours/day, NOAEL = 3000 ppm [16,380 mg/m^3]) that also produced effects on maternal body weight and behavior in both rats and rabbits (BRRC, 1987a,b). Similar studies using lower concentrations found no developmental or maternal effects (Schwetz et al., 1975). Some investigators have shown neurobehavioral deficits in the pups of mice and rats following late gestational exposure to 1,1,1-trichloroethane (Jones et al., 1996; Coleman et al., 1999). In mice,

achievement of developmental milestones was also delayed, and in rats, there was also an increase in the number of resorptions and decrease in the number of live pups per litter. While these effects were produced at fairly high concentrations, they were not necessarily accompanied by maternal effects. The mouse study (Jones et al., 1996) was performed using two exposure protocols, both of which produced neurobehavioral performance deficits in the pups. In one, the dams were exposed to 8000 ppm (43,680 mg/m^3) 3 hr/d on days 12-17 of gestation, for an average daily exposure of 5460 mg/m^3. This protocol produced anesthesia, severe gait abnormalities and clonic movements in dams. In the other, the dams were exposed to a lower concentration for a longer period each day (2000 ppm [10,920 mg/m^3] 17 hr/d on days 12-17 of gestation), resulting in a higher daily average concentration (7720 mg/m^3), but no effects on the dams. These studies demonstrated that maternal exposure to 1,1,1-trichloroethane can produce neurodevelopmental effects in pups, and that this can occur at exposures that do not produce observable effects in the dams. Exposure of rats to a similar concentration (2100 ppm [11,470 mg/m^3]) for a shorter daily exposure period (6 hours) from before mating through gestation (average daily gestational exposure of 2870 mg/m^3) produced no effects on pup development or on the dams (York et al., 1982). Case control studies in humans found no evidence of an association between spontaneous abortion and 1,1,1-trichloroethane exposure (Lindbohm et al., 1990; Windham et al., 1991; Taskinen et al., 1989), but have little power to detect a relationship.

The available inhalation toxicity studies were not, in general, designed to examine whether the effects of 1,1,1-trichloroethane were reversible upon cessation of exposure or whether effects might manifest after some latency period. Investigations for neurochemical changes in the brain conducted by Rosengren et al. (1985) were performed 4 months after the exposure ended. It may be inferred, therefore, that changes observed in this study were not readily reversible. It should be noted, however, that brain tissue was not examined at the end of the exposure to which tissues at 4-months post-exposure could be compared, and the toxicological relevance of this finding is uncertain. The CNS depressant effects of 1,1,1-trichloroethane, like those of other solvents, are generally considered to be readily reversible (Evans and Balster, 1991). The effects are thought to be related to presence of the parent compound in neural membranes, and to dissipate as the parent compound is rapidly eliminated from the body following exposure.

Table 16. Summary Noncancer Results of Major Studies for Inhalation Exposure of Humans to 1,1,1-Trichloroethane

Study Population	Sex	Exposure Concentration (mg/m^3)	Exposure Duration	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses at LOAEL	Comments	Reference
Acute Exposure								
12 adult volunteers	M	0, 1370, 1900, 2450 and 3000	30 min	1370	1900	Impaired performance in tests of manual dexterity (wire spiral), perceptual speed (identical number and spokes tests), and simple and choice reaction time.	All subjects progressively exposed to all concentrations on 1 day and control conditions another day. Tests conducted during exposure.	Gamberale and Hultengren, 1973
12 adult volunteers	M	0, 950, and 1900	3.5 hr	ND	950	Impaired performance in tests of simple reaction time, choice reaction time, and tracking ability.	All subjects exposed to each concentration on a different day. Tests conducted before and during exposure.	Mackay et al., 1987
6 university students	M	0 and 2450	8 hr	ND	2450	Transient eye irritation and slight dizziness.	All subjects exposed to both exposure conditions on different days. Tests conducted before and during exposure. No effect in tests for complex reaction time, manual dexterity, perception with tachistoscopic presentation, and Wechsler memory scale.	Salvini et al., 1971
9 adult volunteers	M	0, 1090 and 2180	4 hr	2180	ND	No effect in tests for simple reaction time, hand tapping speed, critical flicker fusion threshold, gaze deviation nystagmus and body sway.	All subjects exposed to each concentration on a different day. Tests conducted before and during exposure.	Savolainen et al., 1981, 1982a,b

Table 16. Summary Noncancer Results of Major Studies for Inhalation Exposure of Humans to 1,1,1-Trichloroethane

Study Population	Sex	Exposure Concentration (mg/m^3)	Exposure Duration	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses at LOAEL	Comments	Reference
9 volunteers, divided into 3 groups of 3	M	0, 1090 (steady) or 1090 (variable)	3.67 hr	1090	ND	No significant effects on subjective symptoms, EEG, visual evoked potentials, or equilibrium. No signs of respiratory irritation.	Subjects exercised on a stationary bicycle for 10 minutes at the start of exposure. Tests conducted before, during, and after exposure.	Laine et al., 1996
12 volunteers	M	120 (control) and 1090	4 hr	ND	1090	Subtle neurological effects (tiredness and EEG changes) and slight nasal irritant response (increased levels of proinflammatory cytokines in nasal secretions).	All subjects exposed to both exposure conditions on different days. Tests conducted before and during exposure.	Muttray et al., 1999, 2000
Short-term Exposure								
No suitable short-term studies available								
Subchronic Exposure								
No suitable subchronic studies available								
Chronic Exposure								
28 workers from a single factory	NS	NS	10 yr	ND	ND	Impaired performance in tests of balance, memory, intermediate memory, rhythm and speed.	Exposure levels unknown; workers had been reporting symptoms for an avg of 3 yr.	Kelafant et al., 1994

Table 16. Summary Noncancer Results of Major Studies for Inhalation Exposure of Humans to 1,1,1-Trichloroethane

Study Population	Sex	Exposure Concentration (mg/m^3)	Exposure Duration	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses at LOAEL	Comments	Reference
Groups of 7-8 workers from the same factory	F	0, 600, 760-870 and 1090-5400	6.7 yr avg	1090	ND	No effect on subjective symptoms, general physical examination, neurophysiological examination or psychological test battery (23 variables including intelligence, psychomotor ability and memory tests).	Reaction time, shown to sensitive in acute studies, was not evaluated.	Maroni et al., 1977
151 employees split into 5 groups and matched with unexposed workers from a second factory	NS	0, <81, 81-269, 270-540, 550-810, and 820-1360	≤6 yr	820	ND	No effect on health histories or physical examinations (blood pressure, heart rate, spirometric parameters, electrocardiogram, urinalysis, hematology, and serum chemistry).	Neurological investigation limited to Romberg test	Kramer et al., 1978

ND = Not Determined

Table 17. Summary Noncancer Results of Major Studies for Inhalation Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Exposure Concentration[1] (mg/m^3)	Exposure Duration	NOAEL[1] (mg/m^3)	LOAEL[1] (mg/m^3)	Responses at LOAEL	Comments	Reference
Acute Exposure								
Rat	M, F	0, 43,680, or 65,520	7 hr	ND	43,680	Increased relative liver weight (12%) and slight histopathology (fatty change) in the liver.	More severe changes, including necrotic lesions at the higher exposure level. No liver effect after 2 hr exposure to 98,280.	Adams et al., 1950
Rat	M	0, 10,920, 21,840, 43,680, 81,900, or 136,500	3 hr	136,500	ND	No effect on serum SDH, LDH, or GDH.		Loizou et al., 1996
Baboon	M	0, 3820, 7640, 9830, or 11,470	4 hr	7640	9830	Impaired performance in match-to-sample discrimination task.		Geller et al., 1982
Rat	M	NS	4 hr	ND	4000	30% depression in duration of tonic extension of hindlimb in response to electrical shock.	Calculated EC_{30}	Frantik et al., 1994
Mouse	F	NS	2 hr	ND	9880	30% depression in velocity of tonic extension of hindlimb in response to electrical shock.	Calculated EC_{30}	Frantik et al., 1994
Mouse	M	11,270 - 19,490	4 hr	ND	11,270	Decreased duration of immobility in behavioral despair swimming test.		DeCeaurriz et al., 1983
Mouse	M	0, 7100, or 10,920	1 hr	7100	10,920	Increased motor activity.		Kjellstrand et al., 1985b

Table 17. Summary Noncancer Results of Major Studies for Inhalation Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Exposure Concentration[1] (mg/m^3)	Exposure Duration	NOAEL[1] (mg/m^3)	LOAEL[1] (mg/m^3)	Responses at LOAEL	Comments	Reference
Mouse	M	0, 2730, 6825, 13,650, 27,300, 40,950, or 54,600	30 min	2730	6830	Increased motor activity.	Results for dynamic exposure system. Effects at higher levels in static exposure system.	Bowen and Balster, 1996
Short-term Exposure								
Rat	M, F	0 or 1140 (0 or 5460 7 hr/d, 5 d/wk)	4 wk	1140 (5460 7 hr/d, 5 d/wk)	ND	None.	Wide array of endpoints investigated, including histopathology.	Dow Chemical Co., 1969
Rat	F	0 or 1390 (0 or 4780 7 hr/d)	GD 6-15	1390 (4780 7 hr/d)	ND	No maternal or developmental effects.	Sacrifice on GD 21.	Schwetz et al., 1975
Mouse	F	0 or 1390 (0 or 4780 7 hr/d)	GD 6-15	1390 (4780 7 hr/d)	ND	No maternal or developmental effects.	Sacrifice on GD 18.	Schwetz et al., 1975
Rat	F	0, 1370, 4090, or 8190 (0, 5460, 16,380, or 32,760 6 hr/d)	GD 6-15	4090 (16,380 6 hr/d)	8190 (32,760 6 hr/d)	Mild fetotoxicity manifested by delayed cervical ossification and decreased (~6%) body weights of female fetuses. Hypoactivity and reductions in food consumption, body weight gain, body weight, and gravid uterine weight in dams.	Sacrifice on GD 21. Developmental effects only at same level as overt maternal effects.	BRRC, 1987a

Table 17. Summary Noncancer Results of Major Studies for Inhalation Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Exposure Concentration[1] (mg/m^3)	Exposure Duration	NOAEL[1] (mg/m^3)	LOAEL[1] (mg/m^3)	Responses at LOAEL	Comments	Reference
Rabbit	F	0, 1370, 4090, or 8190 (0, 5460, 16,380, or 32,760 6 hr/d)	GD 6-18	4090 (16,380 6 hr/d)	8190 (32,760 6 hr/d)	Mild fetotoxicity manifested by increased incidence of extra 13th rib. Reduced maternal weight gain in does.	Sacrifice on GD 29. Developmental effects only at same level as overt maternal effects.	BRRC, 1987b
Mouse	F	0 or 7740 (0 or 10,920 17 hr/d)	GD 12-17	ND	7740 (10,920 17 hr/d)	No overt maternal effects. Developmental delay and neurobehavioral deficits in offspring.	Dams allowed to give birth. Developmental effects without maternal effects.	Jones et al., 1996
Mouse	F	0 or 5460 (0 or 43,680 3 hr/d)	GD 12-17	ND	5460 (43,680 3 hr/d)	Anesthesia, gait abnormalities (splayed hindlimbs, severe sway, ataxia) and clonic movements in dams. Developmental delay and neurobehavioral deficits in offspring.	Dams allowed to give birth. Developmental effects from an exposure that also produced obvious maternal toxicity.	Jones et al., 1996
Rat	F	0 or 4780 (0 or 38,220 3 hr/d)	GD 13-19	ND	4780 (38,220 3 hr/d)	Gross neurological effects in dams. Increased resorptions and decreased live pups per litter. Pup neurobehavioral deficits.	Dams allowed to give birth. Developmental effects from an exposure that also produced obvious maternal toxicity.	Coleman et al., 1999
Baboon	M	0 or 6550 (continuous)	7 d	ND	6550	Impaired performance in match-to-sample discrimination task.		Geller et al., 1982
Mouse	M	0, 2730, 5460, 10,920, or 21,840 (continuous)	4 d	ND	2730	Handling-induced convulsions after exposure.	Convulsions mitigated by re-exposure to 1,1,1-trichloroethane or other known depressants. Interpreted by researchers as symptom of withdrawal.	Evans and Balster, 1993; Balster et al., 1997
Rat	NS	0, 1360 or 2730	4 d	ND	1360	Significant differences from		

Table 17. Summary Noncancer Results of Major Studies for Inhalation Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Exposure Concentration[1] (mg/m^3)	Exposure Duration	NOAEL[1] (mg/m^3)	LOAEL[1] (mg/m^3)	Responses at LOAEL	Comments	Reference
		(0, 5460, or 10,920 6 hr/d)			(5460 6 hr/d)	control in EEG, FEP, and SEP.		Albee et al., 1990b
Mouse	M	0, 10,920, 32,760, 54,600, 72,620 0.5 h/d	15 d	ND	10,920 0.5 h/d, 15 d	Tolerance or sensitization, depending on the behavioral measure tested.	Mice were tested using locomotor activity and FOB. Because exposures represented repeated acute exposures, exposures were not adjusted to continuous exposure (see footnote 1).	Bowen and Balster, 2006
Subchronic Exposure								
Rat	M	0 or 260 (0 or 1110 8 hr/d, 5 d/wk)	14 wk	260 (1110 8 hr/d, 5 d/wk)	ND	None.	Wide array of endpoints investigated, including histopathology.	Eben and Kimmerle, 1974
Rat	M, F	0, 150, 490, 980, or 1950 (0, 820, 2730, 5460 or 10,920 6 hr/d, 5 d/wk)	94 d	980 (5460 6 hr/d, 5 d/wk)	1950 (10,920 6 hr/d, 5 d/wk)	Decreased (7%) body weight in males. Minimal lesions in the liver and nasal turbinates of males and females.	Wide array of endpoints investigated, including histopathology.	Calhoun et al., 1981
Mouse	M, F	0, 150, 490, 980, or 1950 (0, 820, 2730, 5460 or 10,920 6 hr/d, 5 d/wk)	94 d	980 (5460 6 hr/d, 5 d/wk)	1950 (10,920 6 hr/d, 5 d/wk)	Minimal lesions in the liver and nasal turbinates of males and females.	Wide array of endpoints investigated, including histopathology.	Calhoun et al., 1981

Table 17. Summary Noncancer Results of Major Studies for Inhalation Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Exposure Concentration[1] (mg/m^3)	Exposure Duration	NOAEL[1] (mg/m^3)	LOAEL[1] (mg/m^3)	Responses at LOAEL	Comments	Reference
Mouse	M	0, 1370 or 5460 (continuous)	14 wk	1370	5460	Fatty change and necrosis in hepatocytes.	Minimal ultrastructural liver changes in low-dose group.	McNutt et al., 1975
Rat	F	0 or 2050-2870 (0 or 11,470 6 hr/d, 5 d/wk before mating and 7 d/wk during gestation)	Before mating and/or GD 1-20	2870 (11,470 6 hr/d, 5-7 d/wk)	ND	No maternal or developmental effects.	Half of the dams in each group were sacrificed on day 21 and the remaining dams were used for postnatal evaluations.	York et al., 1982
Gerbil	M, F	0, 380, 1150 or 5460 (continuous)	3 mo	380	1150	Increased GFAP indicating brain astrogliosis.	Animals examined 4 mo after the end of exposure.	Rosengren et al., 1985
Rat	M, F	0, 195, 610, or 1950 (0, 1090, 3440 or 10,920 6 hr/d, 5 d/wk)	13 wk	610 (3440 6 hr/d, 5 d/wk)	1950 (10,920 6 hr/d, 5 d/wk)	Impaired forelimb grip performance after 13 weeks, but not earlier.	Ambiguous evidence of effect. No support from tests of hindlimb grip performance or other behavioral, electrophysiological, or histopathological evaluations.	Mattsson et al., 1993
<u>Chronic Exposure</u>								
Rat	M, F	0 or 570 (0 or 2730 7 hr/d, 5 d/wk)	6 mo	570 (2730 7 hr/d, 5 d/wk)	ND	None.	Wide array of endpoints investigated, including histopathology.	Torkelson et al., 1958

Table 17. Summary Noncancer Results of Major Studies for Inhalation Exposure of Experimental Animals to 1,1,1-Trichloroethane

Species	Sex	Exposure Concentration[1] (mg/m^3)	Exposure Duration	NOAEL[1] (mg/m^3)	LOAEL[1] (mg/m^3)	Responses at LOAEL	Comments	Reference
Rat	M, F	0, 850, or 1710 (0, 4780, or 9560 6 hr/d, 5 d/wk)	12 mo	ND	ND	Focal hepatocellular alterations in females after 19 mo observation period (i.e., study month 31). Questionable as to whether effects could be attributed to treatment.	Wide array of endpoints, but few animals examined for histopathology at end of exposure period.	Quast et al., 1978
Rat	M, F	0, 150, 490, or 1460 (0, 820, 2730 or 8190 6 hr/d, 5 d/wk)	2 yr	1460 (8190 6 hr/d, 5 d/wk)	ND	Slight microscopic hepatic changes in males and females at 6-18 mo (confounding geriatric changes at 24 mo) considered to be adaptive physiologic changes and not adverse. Slight (≤7%) decrease in body weight in females.	Comprehensive study.	Quast et al., 1984, 1988
Mouse	M, F	0, 150, 490, or 1460 (0, 820, 2730 or 8190 6 hr/d, 5 d/wk)	2 yr	1460 (8190 6 hr/d, 5 d/wk)	ND	None.	Comprehensive study.	Quast et al., 1984, 1988

[1] Actual exposure levels are presented for acute studies. For short-term, subchronic and chronic studies, intermittent exposures (e.g., 6 hr/day, 5 days/wk) were adjusted to continuous (average daily) exposures. For example, intermittent exposure to 820 mg/m^3 for 6 hr/d, 5 d/wk yields an adjusted (continuous) exposure concentration of 820 mg/m^3 x 6/24 x 5/7 = 146 mg/m^3. Actual (unadjusted) exposures are shown in parentheses.

The dosimetric adjustment factor for 1,1,1-trichloroethane used to derive a human equivalent concentration (HEC) is 1 (see Table 21). Therefore, the NOAEL and LOAEL values presented in this table are equivalent to HEC values.

ND = Not Determined

4.6.3. Mode of Action Information

1,1,1-Trichloroethane is rapidly and extensively absorbed via oral or inhalation exposure. Following absorption, the chemical is rapidly distributed throughout the body, with preferential accumulation in fat. Most of the absorbed 1,1,1-trichloroethane is rapidly eliminated from the body unchanged in the expired air. A small amount is metabolized in the liver. The initial step of metabolism is oxidation to trichloroethanol by ethanol- and phenobarbital-inducible cytochrome P450 isozymes. The major urinary metabolites are trichloroethanol glucuronide and trichloroacetic acid produced from further oxidation of trichloroethanol. Carbon dioxide, released by metabolism of trichloroacetic acid and exhaled in the breath, is the other major metabolite.

Because 1,1,1-trichloroethane is not metabolized to a large extent, the parent compound is suspected to be the proximal toxicant for depressive effects on the CNS, respiratory center, and the heart, which are evident almost immediately upon exposure under some conditions. Direct evidence for involvement specifically of the parent compound is limited. Studies in mice and rats have demonstrated that 1,1,1-trichloroethane enters the brain and may reach concentrations similar to those in blood, and also that 1,1,1-trichloroethane is eliminated more slowly from the brain than from blood. One rat study analyzed specifically for metabolites in the brain, and did not detect them (Westerberg and Larsson, 1982). No other comparable studies were located. It is possible that the metabolite trichloroethanol may contribute to the neurological effects. Trichloroethanol has been hypothesized to be the active agent responsible for the pharmacological effects of the sedative/hypnotic drug chloral hydrate (U.S. EPA, 2000f). At the clinically recommended dose of chloral hydrate (i.e., the dose causing clinical sedation), the blood concentration of trichloroethanol is estimated to be ~5 mg/L (U.S. EPA, 2000f). Nolan et al. (1984) found that a 6-hour exposure of humans to 350 ppm (1900 mg/m^3) 1,1,1-trichloroethane resulted in a peak blood trichloroethanol concentration of approximately 0.4 mg/L, and Monster et al. (1979) found that exposure to 145 ppm (790 mg/m^3) 1,1,1-trichloroethane for 4 hours resulted in a blood trichloroethanol concentration 2 hours after exposure of 0.2 mg/L. The 1,1,1-trichloroethane exposure concentration used by Nolan et al. and Monster et al. are in the range associated with only minimal neurobehavioral effects, and produced blood trichloroethanol levels 10- to 25-fold lower than a blood level associated with clinical sedation. It is plausible that higher 1,1,1-trichloroethane exposure concentrations could produce blood trichloroethanol concentrations sufficient to cause sedation, although data are not available to confirm this hypothesis.

The arrhythmogenic effects of 1,1,1-trichloroethane are also thought to be produced by the parent compound. Animal studies have shown that the arrhythmias are not caused directly by 1,1,1-trichloroethane, but result from its sensitization of the heart to epinephrine. For this

effect, there is direct evidence that the parent compound, rather than metabolites, is responsible: arrhythmias in response to epinephrine challenge in 1,1,1-trichloroethane-exposed rabbits were enhanced by co-treatment with enzyme inhibitors (SKF-525A, Lilly 18947) that increased blood levels of parent compound and slightly diminished by co-treatment with the enzyme inducer phenobarbital, which slightly reduced the level of parent compound in the blood (Carlson, 1981).

It is uncertain whether the hepatotoxic effects of 1,1,1-trichloroethane are due to the parent compound or are mediated by metabolites (such as trichloroacetic acid and/or reactive intermediates). For several other chlorinated hydrocarbons, it is well documented that liver damage may be caused by reactive (free radical) intermediates generated during the oxidative and/or reductive metabolism by microsomal cytochrome P450 (Klaassen et al., 1996). However, there are mechanisms by which the parent chlorinated hydrocarbon can produce liver effects as well. In support of the involvement of metabolites in the hepatotoxicity of 1,1,1-trichloroethane, Carlson (1973) found that rats pretreated with phenobarbital exhibited liver effects (increased serum levels of ALT and AST) at an exposure concentration that did not produce such effects without phenobarbital pretreatment. Other studies, however, found that the hepatotoxicity of 1,1,1-trichloroethane was not affected by pretreatment with phenobarbital (Cornish et al., 1973) or other inducers of CYP enzymes involved in metabolism of 1,1,1-trichloroethane: ethanol (Klaassen and Plaa, 1966, 1967), isopropanol (Traiger and Plaa, 1974) or acetone (Traiger and Plaa, 1974; Charbonneau et al., 1991).

The CNS depressant effects of 1,1,1-trichloroethane are thought to involve interactions of the parent compound with lipids and/or proteins in neural membranes (Evans and Balster, 1991). In general, the highly lipophilic nature of chlorinated hydrocarbons, such as 1,1,1-trichloroethane, allows them to cross the blood-brain barrier readily and partition into lipids in neuronal membranes. This property allows them to interfere with neural membrane function, bringing about CNS depression, behavioral changes and anesthesia (Klaassen et al., 1996). Effects of the 1,1,1-trichloroethane parent compound on the heart and liver also appear to involve altered function of cellular and mitochondrial membranes. Supporting evidence that 1,1,1-trichloroethane can interact with proteinaceous components of membranes comes from experiments showing that the chemical can inhibit the activity of membrane-bound integral enzymes (acetylcholinesterase and magnesium-activated ATPase) in human red blood cells and rat synaptosomes (Tahti and Korpela, 1986; Korpela and Tahti, 1986, 1987; Korpela, 1989). Possibly as a result of interactions with membrane proteins, 1,1,1-trichloroethane can alter membrane permeability to calcium. This ability has been demonstrated in brain synaptosomes (Nilsson, 1987; Robinson et al., 2001) and dorsal root ganglion neurons (Okuda et al., 2001), cardiac myocytes (Toraason et al., 1990; Hoffmann et al., 1992, 1994), and rat heart and liver mitochondria (Herd and Martin, 1975). Demonstrated consequences of altered calcium

permeability include reduced contractility of cardiac myocytes (Toraason et al., 1990; Hoffmann et al., 1992, 1994) and uncoupled oxidative phosphorylation leading to reduced cellular respiration and ATP production in rat heart and liver mitochondria (Herd and Martin, 1975; Ogata and Hasegawa, 1981; Takano and Miyazaki, 1982). Reduced cellular energy generation was apparently responsible for inhibition of active transport systems in rat hepatocytes by 1,1,1-trichloroethane (Kukongviriyapan et al., 1990).

In addition to the depressive effect on the heart, membrane alterations are also thought to play an important role in the occurrence of arrhythmogenic effects by 1,1,1-trichloroethane. Incorporation of 1,1,1-trichloroethane into the membrane of cardiac myocytes in the region of the gap junction has been hypothesized to explain the observed inhibition by 1,1,1-trichloroethane of gap junction intercellular communication in cardiac myocytes (Toraason et al., 1992). Inhibition of intercellular communication is thought to be related to the arrhythmogenic effects of 1,1,1-trichloroethane.

4.7. EVALUATION OF CARCINOGENICITY

4.7.1. Summary of Overall Weight-of-Evidence

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for 1,1,1-trichloroethane provides *inadequate information to assess carcinogenic potential*. Epidemiologic studies of humans chronically exposed to 1,1,1-trichloroethane are inconclusive. A two-year inhalation bioassay showed no treatment-related increase in tumors in rats and mice at an exposure concentration below the maximum tolerated dose. The two available oral cancer bioassays in rats and mice are considered inadequate for evaluation of carcinogenic potential. 1,1,1-Trichloroethane has been tested extensively for genotoxic potential. The chemical has shown little capacity to produce genotoxic effects in bacteria or fungi. Results in mammalian test systems *in vitro* and *in vivo* were more mixed, but still predominantly negative for assays other than cell transformation. The chemical has been shown to interact weakly with DNA.

The previous IRIS assessment (1987) classified 1,1,1-trichloroethane as Group D *(not classifiable as to human carcinogenicity*) under the 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986c) based on a lack of data on the carcinogenicity of 1,1,1-trichloroethane in humans and inadequate evidence of carcinogenicity in animals.

4.7.2. Synthesis of Human, Animal, and Other Supporting Evidence

The potential carcinogenicity of 1,1,1-trichloroethane was examined in two occupational cohort studies and several case-control and environmental studies. Finnish workers (male and female combined) exposed to 1,1,1-trichloroethane had statistically significantly increased standardized incidence ratios for cancer of the nervous system (SIR = 6.05; 95% CI: 1.25-17.7)

and multiple myeloma (SIR = 15.98; 95% CI: 1.93-57.7) (Anttila et al., 1995). The results are based on only 3 cases of nervous system tumors and 2 cases (both females) of multiple myeloma among 1,1,1-trichloroethane-exposed workers. The large confidence intervals reveal the low statistical power of these findings. An increased risk of multiple myeloma was also observed in female workers exposed to 1,1,1-trichloroethane at an aircraft maintenance facility in Utah (SMR = 56.6; 95% CI: 6.85-204.45) (Spirtas et al., 1991). This result was also based on only 2 observed cases. No cases of multiple myeloma were seen in men. In both studies, workers were exposed to multiple solvents, and in neither case was it possible to isolate the effects of 1,1,1-trichloroethane from those of other solvents. Case-control and environmental studies did not find statistically significant associations between tumors of various types (including astrocytic brain cancer) and 1,1,1-trichloroethane exposure (Infante-Rivard et al., 2005; Dosemeci et al., 1999; Kernan et al., 1999; Mulla, 1996; Heineman et al., 1994; Garland, 1987; Garabrant, 1986; Isacson et al., 1985); however, the power of such studies to find an association is low.

1,1,1-Trichloroethane has been tested for carcinogenicity in rats and mice by the oral route in two studies (NCI, 1977; Maltoni et al., 1986) and by the inhalation route in one study (Quast et al., 1984, 1988). Maltoni et al. (1986) found a small increase in the incidence of leukemias, primarily pulmonary immunoblastic lymphosarcomas, in rats (male and female combined) treated with 1,1,1-trichloroethane by gavage in oil for 104 weeks. These results were considered inconclusive, however, because of the marginal nature of the findings, inherent limitations of the experimental design (one dose level, one species), and incomplete analysis and reporting of results. Oral studies by NCI (1977) in rats and mice conducted at higher doses did not find tumor increases associated with 1,1,1-trichloroethane exposure, but were not adequate tests due to high early mortality in all groups of treated animals (due, at least in part, to intercurrent chronic murine pneumonia) that left few animals at risk for development of late-appearing tumors. Inhalation studies by Quast et al. (1984, 1988) found no evidence of a carcinogenic effect of 1,1,1-trichloroethane in either rats or mice. In these studies, however, it appears that exposure levels were too low. The MTD was not reached in mice (no adverse effects observed in either sex) and may not have been reached in rats, as the only toxic effects noted were a slight reduction in body weight gain in female rats and slight microscopic hepatic changes in male and female rats exposed to the high concentration of 1500 ppm (8190 mg/m^3). Therefore, the possibility of tumors occurring at higher inhalation exposures cannot be ruled out.

Supporting studies provide mixed evidence regarding the carcinogenic potential of 1,1,1-trichloroethane. A rat liver foci assay for tumor initiating and promoting activity was negative for both (Story et al., 1986; Milman et al., 1988). *In vitro* studies for effects associated with carcinogens (inhibition of interferon induction in mouse embryo fibroblasts and inhibition of the natural tumoricidal activity of human liver immune cells) were also negative (Sonnenfeld et al.,

1983; Wright et al., 1994). Although genotoxicity data were also primarily negative, positive results were found in some tests, including 6 of 7 reported cell transformation assays (Arthur D. Little, 1983; Milman et al., 1988; Tu et al., 1985; Price et al., 1978; Hatch et al., 1982, 1983; Daniel and Dehnel, 1981; Styles, 1981). It has also been shown that 1,1,1-trichloroethane has the ability to bind DNA, at least weakly, *in vivo* (Milman et al., 1988; Prodi et al. 1988; Turina et al., 1986).

A potential complicating factor in interpreting the results of cancer bioassays of 1,1,1-trichloroethane is the frequent addition of stabilizing chemicals to commercial formulations of this compound (Henschler et al., 1980). Several of these stabilizers have produced positive responses in cancer bioassays with rats and mice, e.g., 1,4-dioxane, 1,2-epoxybutane and nitromethane. This is a potential confounding factor for many studies of exposure to 1,1,1-trichloroethane, but has been addressed in relatively few studies (Nestmann et al., 1984; Shimada et al., 1985). The situation is complicated by the fact that not all formulations of 1,1,1-trichloroethane contain the same stabilizers. For instance, the 1,1,1-trichloroethane formulations used in the three animal cancer bioassays described above (Maltoni et al., 1986; NCI, 1977; Quast et al., 1984, 1988) contained different stabilizing chemicals. Anttila et al. (1995) reported that small amounts of 1,4-dioxane (<1-5%) were used as stabilizer in the 1,1,1-trichloroethane to which the workers in their study were exposed. However, these researchers did not consider this small exposure to 1,4-dioxane to be responsible for the increased cancer risks observed in workers exposed to 1,1,1-trichloroethane in their study.

One of the metabolites of 1,1,1-trichloroethane, trichloroacetic acid, has been reported to cause hepatocellular tumors in mice (U.S. EPA, 2004). Trichloroacetic acid is also a metabolite of trichloroethylene, and has been implicated as one of the active agents involved in the production of liver tumors in mice treated with trichloroethylene (Bull, 2000). However, metabolism of 1,1,1-trichloroethane is slight (<5% of the absorbed dose - see Section 3.3) and far less extensive than that of trichloroethylene (40-75% of the absorbed dose - ATSDR, 1997). The limited extent of metabolism of 1,1,1-trichloroethane (and resulting low production of trichloroacetic acid) may explain, at least in part, the apparent inability of 1,1,1-trichloroethane to produce liver tumors in mice, despite the production of mouse liver tumors by the metabolite trichloroacetic acid and the qualitatively similarly metabolized compound trichloroethylene.

A more definitive carcinogenicity assessment of 1,1,1-trichloroethane would be supported by additional bioassay data, including an oral cancer bioassay that incorporates several dose levels, sufficient group sizes, and more than one species. While Quast et al. (1988) was generally a well-conducted inhalation cancer bioassay, the inhalation database would be enhanced by a follow-up inhalation study incorporating higher exposure concentrations (i.e., concentrations that clearly reached the MTD).

4.8. SUSCEPTIBLE POPULATIONS AND LIFE STAGES

4.8.1. Possible Childhood Susceptibility

Exposure of the fetus or neonate (via lactation) to 1,1,1-trichloroethane is possible; however, pharmacokinetic data and the majority of developmental toxicity data indicate no particular susceptibility of the fetus or neonate. Danielsson et al. (1986) exposed pregnant mice (gestation day 17) to ^{14}C-labeled 1,1,1-trichloroethane by inhalation and found concentrations in fetal and placental tissues to be about 10-fold lower than concentrations in tissue samples from the dams immediately after exposure. By 24 hours after exposure, maternal and fetal/placental tissue levels were all low. A PBPK model for a lactating woman (Fisher et al., 1997) predicted that partitioning to milk (and excretion via the milk during nursing) was a minor physiological fate of inhaled 1,1,1-trichloroethane in a lactating woman exposed under a plausible occupational scenario (see also Section 3.5.). Thus, pharmacokinetic data indicate no fetal/neonatal susceptibility as a result of elevated exposure. In general, developmental toxicity has been observed in developing animals only at exposure concentrations also toxic to the dam, suggesting no particular susceptibility of the fetus to 1,1,1-trichloroethane. In only one inhalation developmental study in mice (Jones et al., 1996) did exposure of the dams to 2000 ppm 1,1,1-trichloroethane produce developmental delays in offspring at a concentration that did not produce obvious maternal toxicity. The relative sensitivity of dams and fetuses to 1,1,1-trichloroethane cannot be characterized with certainty based on this study, however, because the study design did not include systematic investigation of behavioral effects in dams and because the same exposure concentration has produced CNS effects in other rodent studies.

4.8.2. Possible Gender Differences

The NTP (2000) subchronic feeding study demonstrated the occurrence of renal lesions in male, but not female, rats. The lesions included renal tubule hyaline degeneration, cast formation, and regeneration, and chronic interstitial inflammation of the kidney. The sex-specific pattern of occurrence in rats, type of lesions observed, and absence of renal lesions in mice of either sex in the same study are all consistent with the occurrence of α_{2u}-globulin nephropathy in the male rats, although α_{2u}-globulin was not specifically identified. This sex- and species-specific condition is not considered to be predictive of effects in humans (U.S. EPA, 1991c).

4.8.3. Other Potentially Susceptible Populations

1,1,1-Trichloroethane can induce the activity of microsomal enzymes, particularly CYP2E1 and CYP2B1/2 (Bruckner et al., 2001; Fuller et al., 1970; Lal and Shah, 1970; Shah and Lal, 1976). As a result, 1,1,1-trichloroethane could potentially enhance the toxicity of other chemicals, such as carbon tetrachloride and 1,1-dichloroethylene, that are metabolized by these CYP isozymes to reactive intermediates. 1,1,1-Trichloroethane has also been shown to deplete liver glutathione (Loizou et al., 1996). Binding of reactive metabolites by glutathione is an important detoxification pathway for many chemicals. Given the modest reduction in liver glutathione (23 to 42%) even at relatively high exposure concentrations (4000 to 25,000 ppm [21,840 to 136,500 mg/m^3] 1,1,1-trichloroethane), it is not clear that depletion of glutathione stores in the liver by 1,1,1-trichloroethane would likely enhance the toxicity of chemicals for which the detoxification pathway includes conjugation with glutathione.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Acute Oral RfD

The acute oral data for 1,1,1-trichloroethane are inadequate to support derivation of an acute oral RfD, a reference value intended for use with exposures up to 24 hours. Human data are limited to the results of a single accidental exposure incident. Acute animal studies are limited to the following: a handful of studies that investigated only hepatic endpoints and found conflicting results as to the potency of 1,1,1-trichloroethane by acute oral exposure in rats (Xia and Yu, 1992; Tyson et al., 1983; Bruckner et al., 2001), a study that found no significant changes in levels of neurotransmitters in the brains of rats dosed with 3250 mg/kg of 1,1,1-trichloroethane by gavage (Kanada et al., 1994), and some LD_{50} determinations. Data clearly establishing sensitive targets and associated dose-response relationships for acute oral exposure were not located.

5.1.2. Short-term Oral RfD

The short-term oral data for 1,1,1-trichloroethane are inadequate to support derivation of a short-term oral RfD, a reference value intended for use with exposures for more than 24 hours, up to 30 days. No short-term human data are available. Short-term animal studies identified dose levels associated with gross CNS depression and death by gavage exposure (Bruckner et al., 2001), but failed to conclusively identify targets or effect levels not associated with frank toxicity (Bruckner et al., 2001; Maurissen et al., 1993, 1994; Spencer et al., 1990; NTP, 1996; Platt and Cockrill, 1969). Spencer et al. (1990) observed neurophysiological changes at a relatively low dose level (705 mg/kg-day), but a threshold for these changes was not identified (only one dose level was tested) and the toxicological significance of these changes is uncertain, as other neurotoxicological endpoints were unaffected at similar doses (Spencer et al., 1990; Maurissen et al., 1993, 1994).

5.1.3. Subchronic Oral RfD

The subchronic oral RfD is intended for use with exposures for more than 30 days, up to approximately 10% of the lifespan in humans (or up to approximately 90 days in typically used laboratory animal species).

5.1.3.1. *Choice of Principal Study and Critical Effect—with Rationale and Justification*

No human data involving exposures of subchronic duration are available. Subchronic

animal studies include studies of developmental and reproductive toxicity, which did not conclusively demonstrate the occurrence of effects due to 1,1,1-trichloroethane (Dapson et al., 1984a,b; NTP, 1988a,b; George et al., 1989; Lane et al., 1982), and studies of systemic toxicity by gavage (Bruckner et al., 2001) and dietary (NTP, 2000) exposure.

Bruckner et al. (2001) reported a LOAEL of 2500 mg/kg (1786 mg/kg-day when adjusted for exposure 5 days per week) for gross CNS depression and death in rats exposed by gavage. Investigation of systemic endpoints was limited to the liver; only mild hepatic changes were found and only at lethal doses. Sensitive neurological endpoints were not monitored. In the feeding study, NTP (2000) observed no gross CNS effects or deaths at doses up to about 5000 mg/kg-day in rats or 23,000 mg/kg-day in mice. Dose-related decreases in body weight gain and terminal body weight were observed; terminal body weights were 10% lower than the vehicle control at a dose of ~4800 mg/kg-day in the male rat and 11-12% lower than the vehicle control at 3500 or 5600 mg/kg-day in the male and female mouse, respectively. Target organ effects found in this study were of uncertain toxicological significance. Renal lesions were reported in male rats at ≥1200 mg/kg-day. NTP (2000) considered the types of lesions observed and their occurrence only in male rats to be consistent with development of α_{2u}-globulin nephropathy, a nephropathy specific to male rats and not considered relevant to human health risk assessment (U.S. EPA, 1991c; NTP, 2000). Assays to confirm the presence of α_{2u}-globulin itself, however, were not conducted. Similar renal effects have not been reported in any other studies in the 1,1,1-trichloroethane database, including a short-term NTP (1996) study designed specifically to look for this effect. NTP (2000) also reported slight (10-20%) reductions in epididymal spermatozoal concentrations in high-dose male rats and mice at dose levels accompanied by reduced body weight gain (4800 mg/kg-day in rats and 15,000 mg/kg-day in mice). NTP (2000) considered this slight reduction in epididymal sperm count to be treatment related, probably affecting the epididymus. There were, however, no weight or histopathologic changes in this organ, and the absence of reproductive effects in other studies does not support effects on reproductive tissues as a sensitive target. The NTP (2000) study did not include investigation of sensitive neurological endpoints in either rats or mice. There were no clinical findings or histopathologic changes in the brain related to chemical exposure.

The differences in the findings of the Bruckner et al. (2001) and NTP (2000) studies can be attributed to the bolus dosing employed by Bruckner et al. (2001). In comparison to relatively steady intake throughout the day via dietary administration, bolus dosing will produce much higher peak blood levels as the entire daily dose is rapidly absorbed all at once. The gross CNS effects and mortality observed by Bruckner et al. (2001) are likely a reflection of the high peak blood levels by this mode of administration. This is particularly apparent by comparing survival in the male rats in the 13-week rat studies involving gavage administration (Bruckner et al.,

2001) and dietary administration (NTP, 2000) (see Table 18).

Table 18. Comparison of Survival in Rats Administered 1,1,1-Trichloroethane by Gavage and in the Diet

Study / Method of Administration	Survival (%)							
	290 mg/kg-d	357 mg/kg-d	600 mg/kg-d	1200 mg/kg-d	1790 mg/kg-d	2400 mg/kg-d	3570 mg/kg-d	4800 mg/kg-d
NTP (2000) [Diet]	100	–	100	100	–	100	–	100
Bruckner et al. (2001) [Gavage]	–	93	–	–	67	–	53	–

The findings from bolus exposure to 1,1,1-trichloroethane are considered less relevant to subchronic or chronic exposure conditions in humans. Accordingly, the 90-day dietary study in rats and mice (NTP, 2000) was selected as the basis for the subchronic oral RfD, and treatment-related decrements in body weight gain in mice as the critical effect.

Decreased body weight appears to be a sensitive effect in other subchronic and chronic studies by oral or inhalation routes of exposure, either in the absence of other toxicity (Bruckner et al., 2001; Prendergast et al., 1967; Adams et al., 1950) or at doses causing minimal liver changes (possibly physiologic changes) (Quast et al., 1984, 1988; Calhoun et al., 1981). Reduced body weight has also been observed at levels causing reduced survival without clear indication of any target organ toxicity (Bruckner et al., 2001; NCI, 1977).

5.1.3.2. *Methods of Analysis*

The subchronic RfD was derived using benchmark dose analysis of body weight data from male and female mice exposed to 1,1,1-trichloroethane for 90 days (NTP, 2000). These data were presented previously in Section 4.2.1.3 (Table 12).

Continuous data models (linear, polynomial, power, and Hill) with a constant variance were fit to the data using U.S. EPA Benchmark Dose Software (version 1.4). The software was used to calculate potential points of departure for deriving the subchronic RfD by estimating the effective dose at a specified level of response (BMD_x) and its 95% lower bound ($BMDL_x$). A 10% change in mean terminal body weight relative to the control mean was selected as the benchmark response (BMR) level for this continuous data set. A 10% change in body weight is the minimal level of change generally considered to be biologically significant (U.S. EPA, 2000c).

The BMDS outputs for mouse body weight data are summarized in Table 19. All models provided an adequate fit of the female body weight data based on the goodness-of-fit statistic (p-value $\geq$0.1). The Hill model provided the best fit of the data for the female mouse (based on the

lowest AIC); the detailed BMD modeling output for the Hill model is presented in Appendix B.

Table 19. Benchmark Dose Modeling Results using Terminal Body Weight Data for Mice

Model	GOFP	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Female mouse				
Linear	0.1428	159.4	15,024.6	11,256.5
Polynomial	0.1428	159.4	15,024.6	11,256.5
Power	0.1428	159.4	15,024.6	11,256.5
Hill	0.6893	157.2	5064.4	2155.2
Male mouse				
Hill	0.1417	139.2	1943.1	594.3

GOFP = goodness-of-fit p-value for chi-square
AIC = Akaike's Information Criterion
BMD_{10} = Benchmark dose calculated by BMDS associated with a 10% decrease in mean body weight relative to the control mean
$BMDL_{10}$ = 95% lower confidence limit on the BMD_{10} as calculated by BMDS
Source: NTP, 2000

With the exception of the Hill model, the continuous data models did not provide an adequate fit of the body weight data for the male mouse (i.e., goodness-of-fit p-value < 0.1). The Hill model provided an adequate fit of the male mouse data (see Table 19); the detailed BMD modeling output is presented in Appendix B.

Visual inspection of plots of body weight data for the male and female mouse (Appendix B) reveals that the female data set provides a much better relationship of dose and response than does the male data set. In the case of the male data set, the first four dose groups show a flat dose-response relationship; in the dose range between 850 and 7370 mg/kg-day, the body weight decrease (relative to controls) approaches 10%, but male mouse body weights appears to be relatively insensitive to increasing doses of 1,1,1-trichloroethane. A decrease in body weight relative to the control appears to exceed 10% only in the high-dose (15,000 mg/kg-day) male mice. Although the Hill model provided an adequate fit of the male mouse data, the resulting $BMDL_{10}$ of 594 mg/kg-day is not consistent with the data that shows no relationship between dose and reduction in body weight gain at a dose as high as 7370 mg/kg-day. NTP (2000) noted that feed consumption and estimates of average daily dose were determined by the disappearance of feed from the feeder and may not accurately represent intake. It is possible that imprecision in dose estimates may have contributed to the observed dose-response relationship in male mice.

Because male and female mice generally responded similarly to 1,1,1-trichloroethane in the diet (i.e., the decrease in body weight was similar, with terminal body weights in high-dose male and female mice 84 to 85% of controls) and because the female body weight data showed a clearer relationship between dose and response, the female mouse data were used as the basis for

the subchronic RfD. The $BMDL_{10}$ for female body weight data based on the Hill model of 2155 mg/kg-day was selected as the point of departure for the subchronic RfD.

5.1.3.3. *Subchronic RfD Derivation—Including Application of Uncertainty Factors (UFs)*

The $BMDL_{10}$ of 2155 mg/kg-day was used as the point of departure for calculating the subchronic RfD. This point of departure is associated with a 10% change in the mean terminal body weight relative to the control mean. A composite uncertainty factor (UF) of 300 was applied to this point of departure: 10 for extrapolation from animals to humans, 10 for intraspecies variation (human variability), and 3 for database deficiencies.

- A 10-fold UF was used to account for laboratory animal-to-human interspecies differences. This default UF accounts for differences in the toxicokinetics and toxicodynamics between the model species and humans.

- A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

- An UF to extrapolate from a LOAEL to a NOAEL was not necessary because BMD modeling was used to determine the point of departure.

- An UF to extrapolate from a shorter to a longer duration was not necessary because the subchronic RfD was derived from a study of subchronic duration.

- A 3-fold UF was used to account for deficiencies in the available 1,1,1-trichloroethane database. Oral reproductive and developmental toxicity studies include a multigeneration study in mice, drinking water developmental toxicity studies in rats, and a study of developmental neurotoxicity in rats, none of which clearly demonstrated any effects. The principal study, a 13-week NTP (2000) toxicity study, was conducted under an interagency agreement with the Agency for Toxic Substances and Disease Registry to fill data gaps identified during the ATSDR's 1995 review of 1,1,1-trichloroethane (ATSDR, 1995). Specifically, ATSDR identified the need for data from intermediate-duration oral exposure studies to provide information that would help determine the NOAELs and LOAELs for systemic, neurological, reproductive and developmental effects. NTP (2000) was a well-conducted repeat-dose oral study, but did not examine the potential for subtle neurotoxicity. Acute neurotoxicity was observed by the oral route following bolus dosing (e.g., hyperexcitability and narcosis reported by Bruckner et al., 2001) and by the inhalation route, where signs of central nervous system depression have been extensively documented. As discussed more thoroughly in the justification of the database uncertainty factor used in the derivation of the subchronic RfC, some uncertainty exists with respect to the neurotoxicity database for 1,1,1-trichloroethane, notably associated with findings from the epidemiological literature and from the Rosengren et al. study in gerbils.

Thus, lack of endpoints for subtle neurotoxic potential following repeated exposure is considered a deficiency in the oral database for this chemical in light of evidence of its acute neurotoxicity and uncertainties in the inhalation neurotoxicity database.

The subchronic RfD for 1,1,1-trichloroethane was calculated as follows:

Subchronic RfD = $BMDL_{10}$ ÷ UF
= 2155 mg/kg-day ÷ 300
= 7 mg/kg-day

5.1.4. Chronic Oral RfD

The chronic oral RfD is intended for use with exposures for more than approximately 10% of the lifespan in humans (or more than approximately 90 days to two years in typically used laboratory animal species).

5.1.4.1. *Choice of Principal Study and Critical Effect—with Rationale and Justification*

No chronic human data for 1,1,1-trichloroethane are available. Chronic oral animal studies consist of two cancer bioassays (NCI, 1977; Maltoni et al., 1986). NCI (1977) exposed male and female rats and mice to 1,1,1-trichloroethane by oral gavage for 78 weeks. In rats, effects included reduced survival, decreased body weight, but no clinical observations or histopathological changes. Effects in mice consisted of reduced survival and decreased body weight. Chronic murine pneumonia was a probable contributing factor in the early deaths. Because of the high rate of early mortality, NCI did not consider this to be an adequate test of 1,1,1-trichloroethane carcinogenicity (and by extension, noncancer toxicity). Body weight data from the study was provided in graphical format only without error bars, and a consistent dose-response relationship was not apparent.

Maltoni et al. (1986) administered 1,1,1-trichloroethane to rats by gavage at a single dose level for 104 weeks in a screening level carcinogenicity bioassay. The study did not include an evaluation of non-neoplastic lesions. A treatment-related reduction in body weight was observed in female rats but not males. Body weight data were reported graphically only and without error bars.

Both NCI (1977) and Maltoni et al. (1986) were designed as cancer bioassays and included only limited investigation of noncancer endpoints. Decreased body weight gain was the only noncancer effect reported and in the case of NCI (1977) was confounded by poor survival. In both studies, body weight data were provided graphically only. Finally, both NCI (1977) and Maltoni et al. (1986) used gavage administration. As discussed in Section 5.1.3.1., gavage

administration produces toxicity that likely reflects the high peak blood levels associated with bolus dosing and is considered less relevant that the toxicity associated with dietary administration. Therefore, these studies did not provide data suitable for reference value derivation.

In the absence of adequate chronic toxicity data, the 90-day toxicity study conducted by NTP (2000) was used as a basis for deriving the chronic oral RfD.

5.1.4.2. *Methods of Analysis*

The point of departure of 2155 mg/kg-day was derived from decreased terminal body weight in female mice relative to the control from NTP (2000) and application of BMD modeling methods as described in Section 5.1.3.2. for the subchronic oral RfD. This point of departure represents a 10% change in mean terminal body weight relative to the control mean.

5.1.4.3. *RfD Derivation—Including Application of Uncertainty Factors (UFs)*

A composite UF of 1000 was applied to the point of departure (POD) of 2155 mg/kg-day: 10 for extrapolation from animals to humans, 10 for intraspecies variation (human variability), 3 for extrapolation from subchronic to chronic exposure duration, and 3 for database deficiencies.

- A 10-fold UF was used to account for laboratory animal-to-human interspecies differences. This default UF accounts for differences in the toxicokinetics and toxicodynamics between the model species and humans.

- A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

- An UF to extrapolate from a LOAEL to a NOAEL was not necessary because BMD modeling was used to determine the point of departure.

- A 3-fold UF was used to extrapolate from subchronic to chronic exposure duration. The available body weight data from chronic toxicity studies suggest that body weight effects did not become more pronounced with duration of exposure. In the NCI (1976) cancer bioassay, body weight data are presented in graphic format only. Visual inspection of these graphs for rats shows reduction in mean body weight in treated animals in year one (beginning between weeks 10 and 20) to be similar to the weight reduction in year two (with the exception of low-dose females, where elevated mortality confounded body weight results). Similarly for mice, the treatment-related mean body weight reduction in year one (beginning between weeks 10 and 20) was similar to year two for male mice; for females, the differences in mean body weight were slightly higher in year two.

  The inhalation study by Quast et al. (1984, 1988) similarly revealed no

progression in any 1,1,1-trichloroethane associated effects with length of exposure. Mean body weight reduction in female rats versus controls was similar in year one and two (1,1,1-trichloroethane did not produce statistically significant effects on body weight in male rats or male and female mice). Histopathologic changes of the liver in rats – the only other exposure-related effect in this study – showed no progression in incidence or severity from the first interim sacrifice (6 months) to study termination (2 years). For these reasons, a partial UF of 3 is used for extrapolation from subchronic to chronic exposure duration.

- A 3-fold UF was used to account for deficiencies in the available 1,1,1-trichloroethane database. Oral reproductive and developmental toxicity studies include a multigeneration study in mice, drinking water developmental toxicity studies in rats, and a study of developmental neurotoxicity in rats, none of which clearly demonstrated any effects. Chronic oral animal studies (NCI, 1977; Maltoni et al., 1986) are available, but were designed as cancer bioassays with only limited investigation of noncancer endpoints. Neither the available chronic studies nor the 13-week NTP study included investigation of sensitive neurological endpoints. As noted in the discussion of the subchronic database UF, the principal study, a 13-week NTP (2000) toxicity study, was conducted under an interagency agreement with the Agency for Toxic Substances and Disease Registry to fill data gaps identified during the ATSDR's 1995 review of 1,1,1-trichloroethane (ATSDR, 1995). Specifically, ATSDR identified the need for data from intermediate-duration oral exposure studies to provide information that would help determine the NOAELs and LOAELs for systemic, neurological, reproductive and developmental effects. NTP (2000) was a well-conducted repeat-dose oral study, but did not examine the potential for subtle neurotoxicity. Acute neurotoxicity was observed by the oral route following bolus dosing (e.g., hyperexcitability and narcosis reported by Bruckner et al., 2001) and by the inhalation route, where signs of central nervous system depression have been extensively documented. As discussed more thoroughly in the justification of the database uncertainty factor used in the derivation of the chronic RfC, some uncertainty exists with respect to the neurotoxicity database for 1,1,1-trichloroethane, notably associated with findings from the epidemiological literature and from the Rosengren et al. study in gerbils. Lack of endpoints for subtle neurotoxic potential following repeated exposure is considered a deficiency in the oral database for this chemical in light of evidence for acute neurotoxicity and uncertainty in the inhalation database.

The chronic RfD for 1,1,1-trichloroethane was calculated as follows:

$$\begin{aligned} \text{Chronic RfD} &= \text{BMDL}_{10} \div \text{UF} \\ &= 2155 \text{ mg/kg-day} \div 1000 \\ &= 2 \text{ mg/kg-day} \end{aligned}$$

5.1.4.4. *Previous Oral Assessment*

A chronic oral assessment for 1,1,1-trichloroethane was previously included on the IRIS database but was withdrawn in 1991.

5.1.5. RfD Derivation Using Route-to-Route Extrapolation

Consideration was also given to the derivation of oral RfDs for 1,1,1-trichloroethane using relevant inhalation data and route-to-route extrapolation with the aid of a PBPK model. Several factors support the use of route-to-route extrapolation for 1,1,1-trichloroethane. 1,1,1-Trichloroethane is well absorbed by all pathways of exposure and is largely excreted unchanged by the lungs in the expired air, whether administration is by oral or inhalation exposure. Evidence suggests that the metabolism of 1,1,1-trichloroethane following oral and inhalation exposure are similar (see Section 3).

PBPK modeling was conducted for the U.S. EPA by Yang (2006) using the Reitz et al. (1988) model (see Section 3.5.). Application of the model is more fully described in Yang (2006).

5.1.5.1. *Acute Duration*

Yang (2006) explored the use of available PBPK models, and in particular the Reitz et al. (1988) model, to carry out route-to-route extrapolation of findings from acute inhalation studies to the oral route. Reitz et al. (1988) reported that their model did not provide an adequate simulation of experimentally-derived oral gavage rat data from their own laboratory, nor did the Reitz et al. model simulate well the oral gavage data of Bruckner (Yang, 2006; personal communication). It was concluded that the use of a PBPK model to extrapolate from acute inhalation data to the oral route was not supported.

5.1.5.2. *Subchronic and Chronic Durations*

Consideration was given to the derivation of subchronic and chronic oral RfDs by extrapolation of the inhalation RfC. As described more fully in Sections 5.2.3.1. and 5.2.4.1., the repeat-dose studies used for the evaluation of subchronic and chronic inhalation exposure were the two-year bioassay in rats by Quast et al. (1984, 1988) and 14-week study in mice by McNutt et al. (1975), where the target organ for 1,1,1-trichloroethane was the liver. As discussed in Section 4.6.1., evidence for the liver as a potential target following oral administration of 1,1,1-trichloroethane is equivocal; some, but not all, studies suggest that 1,1,1-trichloroethane may produce mild hepatotoxicity following oral exposure. The most comprehensive study of 1,1,1-trichloroethane oral toxicity – the subchronic toxicity study by NTP (2000) – reported no changes in liver histopathology or clinical chemistry that would suggest the liver to be a

sensitive target organ in rats or mice. Similarly, Bruckner et al. (2001) found only small and transient elevations in liver enzymes at gavage doses of 1,1,1-trichloroethane high enough to cause increased mortality. Thus, given the apparent differences in relative hepatotoxicity of 1,1,1-trichloroethane by the oral and inhalation routes, a route-to-route extrapolation approach to derive the subchronic or chronic oral RfD was not considered appropriate.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

5.2.1. Acute Inhalation RfC

The acute inhalation RfC is intended for use with exposures up to 24 hours.

5.2.1.1. *Choice of Principal Study and Critical Effect—with Rationale and Justification*

The acute inhalation toxicity database for 1,1,1-trichloroethane is extensive. The most sensitive target following acute inhalation exposure has been shown to be the CNS. Selected studies that examined CNS effects after acute inhalation exposure, some considered candidates for RfC derivation, are presented in Figures 2a and 2b (exposure-response array) and Table 20. Figure 2a presents an array of inhalation studies over a range of HEC concentrations up to 22,000 mg/m^3. To provide better resolution of study information in the low end of the exposure range, Figure 2b presents the same array of studies, but over a more narrow range of exposure concentrations (up to 5000 mg/m^3).

Figure 2a. Exposure-Response Array for 1,1,1-Trichloroethane

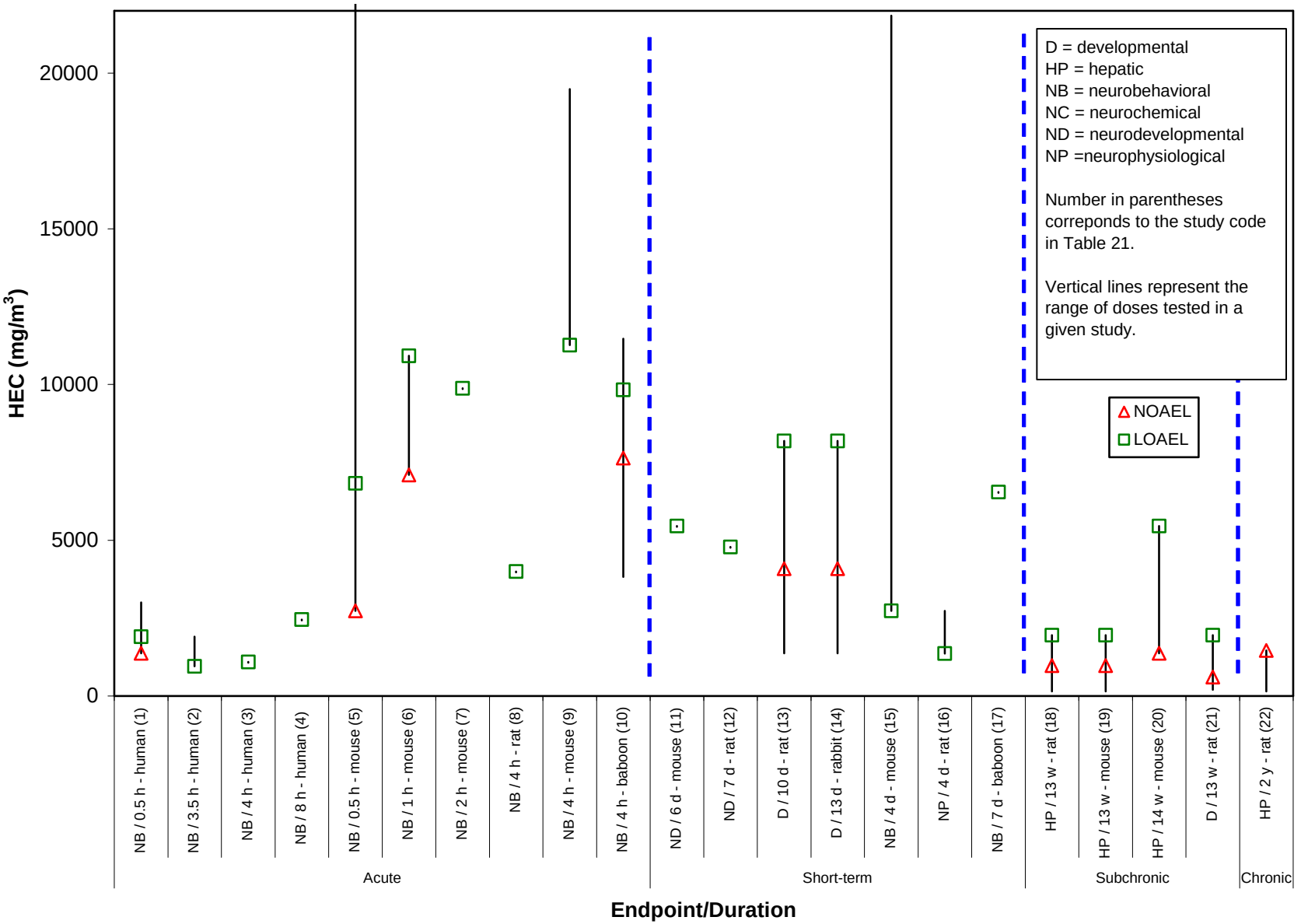


Figure 2b. Exposure-Response Array for 1,1,1-Trichloroethane

(range on the y-axis restricted to 5000 mg/m^3 to improve the resolution at the low-exposure region)

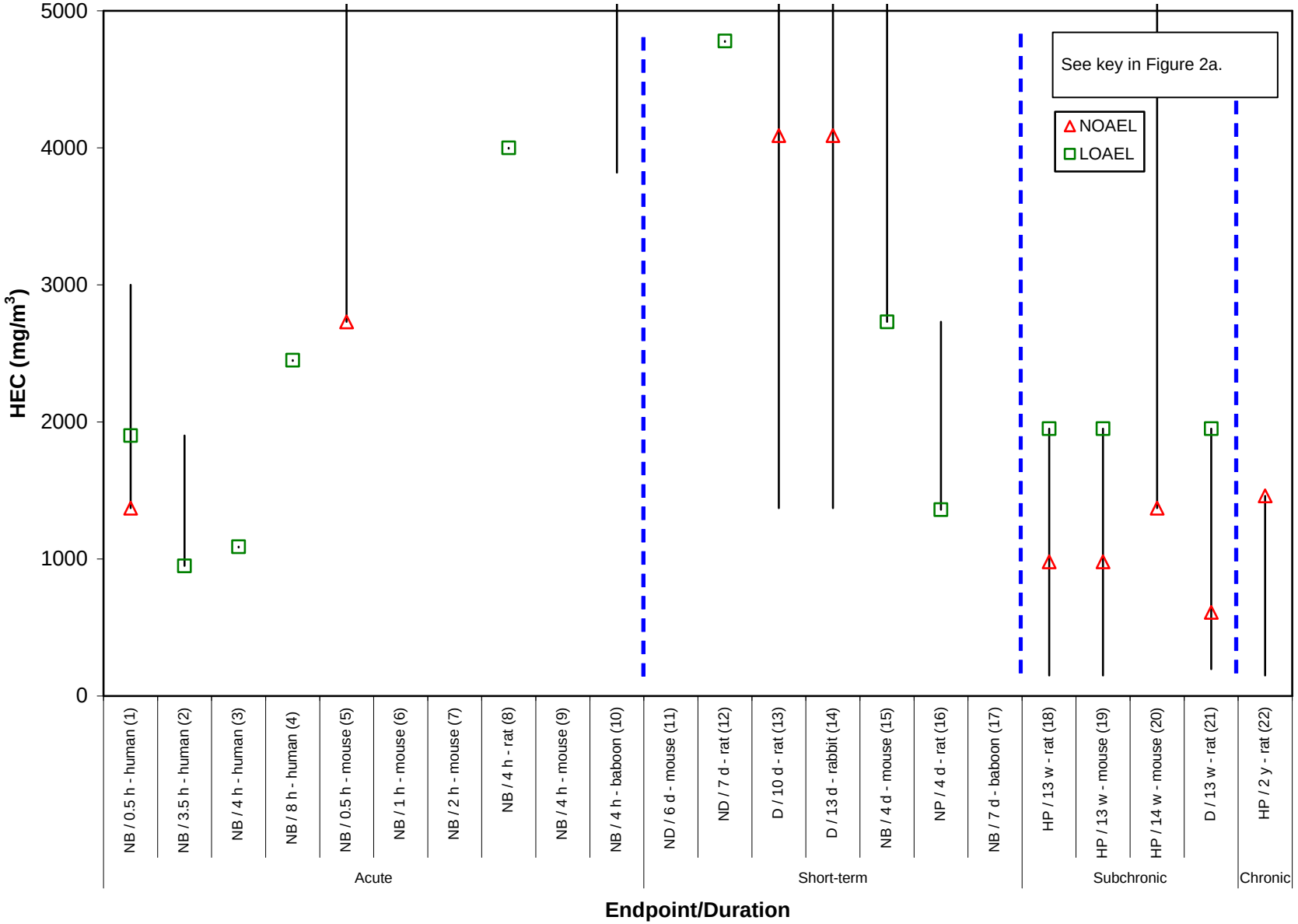


Table 20. Summary Description of Studies Plotted in Figures 2a and 2b

Reference Value Category	Citation	Figure 2a & 2b Identifier	Exposure Duration	HEC[a] (mg/m^3)	Species	Type of Effect[b]
Acute	Gamberale and Hultengren (1973)	1	0.5 hr	1370 N[c]	human	NB
	Mackay et al. (1987)	2	3.5 hr	950 L[c]	human	NB
	Muttray et al. (2000)	3	4 hr	1090 L[c]	human	NB
	Salvini et al. (1971)	4	8 hr	2450 L[c]	human	NB
	Bowen and Balster (1996)	5	0.5 hr	2730 N[c]	mouse	NB
	Kjellstrand et al. (1985b)	6	1 hr	7100 N[c]	mouse	NB
	Frantik et al. (1994)	7	2 hr	9880 L[c]	mouse	NB
	Frantik et al. (1994)	8	4 hr	4000 L[c]	rat	NB
	DeCearriz et al. (1983)	9	4 hr	11,270 L[c]	mouse	NB
	Geller et al. (1982)	10	4 hr	7640 N[c]	baboon	NB
Short-term	Jones et al. (1996)	11	GD 12-17, 3 hr/d	5460 L	mouse	ND
	Coleman et al. (1999)	12	GD 13-19, 3 hr/d	4780 L	rat	ND
	BBRC (1987a)	13	GD 6-15, 6 hr/d	4090 N	rat	D
	BBRC (1987b)	14	GD 6-18, 6 hr/d	4090 N	rabbit	D
	Evans and Balster (1993); Balster et al. (1997)	15	4 d, continuous	2730 L	mouse	NB
	Albee et al. (1990b)	16	4 d, 6 hr/d	1360 L	rat	NP
	Geller et al. (1982)	17	7 d, continuous	6550 L	baboon	ND
Subchronic	Calhoun et al. (1981)	18	94 d, 5 d/wk, 6 hr/d	980 N	rat	HP
	Calhoun et al. (1981)	19	94 d, 5 d/wk, 6 hr/d	980 N	mouse	HP
	McNutt et al. (1975)	20	14 wk	1370 N	mouse	HP

Table 20. Summary Description of Studies Plotted in Figures 2a and 2b

Reference Value Category	Citation	Figure 2a & 2b Identifier	Exposure Duration	HEC[a] (mg/m^3)	Species	Type of Effect[b]
	Mattsson et al. (1993)	21	90 d, 5 d/wk, 6 hr/d	610 N	rat	D
Chronic	Quast et al. (1984, 1988)	22	2 yr, 5 d/wk, 6 hr/d	1460 N	rat	HP

[a] HECs calculated assuming extrarespiratory effects for a category 3 gas (U.S. EPA, 1994b; U.S. EPA, 2000e). The default procedure for category 3 gases involves adjustment of the experimental exposure concentration by a dosimetric adjustment factor (DAF), which is calculated as the ratio of the blood:gas (air) partition coefficient ($H_{b/g}$) for the laboratory species to the $H_{b/g}$ for humans. According to Table 6, the $H_{b/g}$ for the rat and mouse is 5.76 and 10.8, respectively, and for humans is 2.53. The reference concentration (RfC) methodology stipulates that where the animal coefficient is greater than the human coefficient, or where $H_{b/g}$ values are unknown, a value of one is used for the ratio (U.S. EPA, 1994b). The RfC Methodology (U.S. EPA, 1994b) was developed specifically for deriving chronic reference values, i.e., for use with long-term repeated exposures under which steady-state conditions are likely to be attained. Because 1,1,1-trichloroethane reaches steady state relatively quickly (see Section 3), U.S. EPA's RfC methodology is considered applicable to short-term and subchronic RfC values as well as chronic. For developing acute inhalation RfCs for category 3 gases, U.S. EPA's draft ARE Methodology (U.S. EPA, 2000e) recommends that the ratio of animal/human $H_{b/g}$ also be used as the default for HEC derivation. Therefore, the dosimetric adjustment factor (DAF) applied to the duration adjusted concentrations for studies involving all exposure durations is 1 (see Table 17).

Unless flagged (with a superscript c), the exposure concentration was adjusted to a continuous exposure (e.g., a 6 hr/day exposure concentration was adjusted by 6/24).

N = NOAEL; L = LOAEL

NOAELs or LOAELs were used as the point of departure for all of the data sets presented in this table. Benchmark dose (BMD) methods were considered. The data sets were not amenable to BMD methods, however, for one or more of the following reasons: use of only one exposure concentration, presentation of results in graphical format only or as a mean without standard deviations or standard errors, elevated incidence in the high-dose group only, or a measured response not amenable to BMD methods (e.g., biphasic response, response presented as a numerical score).

[b] D = developmental; HP = hepatic; NB = neurobehavioral; NC = neurochemical; ND = neurodevelopmental; NP = neurophysiological.

[c] The HEC was not extrapolated to an equivalent 24-hour concentration for data sets where the exposure duration was less than 24 hours. In these cases, the HEC represents the actual exposure concentration.

As Figures 2a and 2b show, studies of controlled exposure to 1,1,1-trichloroethane in humans provide the most sensitive measure of effect for this chemical. In particular, the studies of neurobehavioral performance by Mackay et al. (1987), Muttray et al. (1999, 2000), and Gamberale and Hultengren (1973) identified the lowest effect levels among the available human studies. Mackay et al. (1987) reported exposure-related impaired performance in tests of simple reaction time, choice reaction time, and digital step-input tracking at 175 and 350 ppm (950 and 1900 mg/m^3). Exposures in this study were conducted for 3.5 hours with neurobehavioral performance evaluated at four time periods during the exposure. Gamberale and Hultengren (1973) observed performance deficits in tests of simple and choice reaction time, manual dexterity, and perceptual speed at 350 ppm (1900 mg/m^3) following a 30-minute exposure. These researchers found no effect at 250 ppm (1370 mg/m^3). Muttray et al. (1999, 2000) found EEG changes consistent with increased drowsiness, as well as subjectively reported tiredness, in volunteers performing a choice reaction time test with eyes closed during 4-hour exposure to 200 ppm (1090 mg/m^3) 1,1,1-trichloroethane. The lower exposure level of 22 ppm (120 mg/m^3) served as the control in this study. Overall, these studies suggest a slight effect on neurobehavioral performance at exposure concentrations in the range of ~200 to 400 ppm (~1000 to 2000 mg/m^3) for up to 4 hours of exposure.

Collectively, the human intentional dosing studies provide some insight into the duration of exposure to 1,1,1-trichloroethane before adverse effects on neurobehavioral performance are observed. Mackay et al. (1987) measured psychomotor performance deficits beginning 20, 60, 120 and 180 minutes after exposure began. Changes in test performance were observed at an exposure concentration of 950 mg/m^3 as early as 20 minutes in some tests (e.g., tracking time on target, tracking RMS (room mean square) error, and simple reaction time), but in other tests impaired performance at 20 minutes was minimal and increased with exposure duration (e.g., tracking time outside target, four-choice reaction time, and Stroop test). It is unclear to what extent the changes observed at the earliest testing interval were biologically significant. Other investigators did not similarly observe deficits in performance after only 20 minutes of exposure. As shown in Table 9, simple and choice reaction times were assessed by Mackay et al. (1987), Savolainen et al. (1981, 1982a,b), and Gamberale and Hultengren (1973). After 4 hours of continuous exposure to a concentration of 400 ppm (2180 mg/m^3), Savolainen et al. (1981, 1982a,b) found no significant changes in simple reaction time in exposed volunteers. Gamberale and Hultengren (1973) reported no significant changes in tests of simple and choice reaction time following 30 minutes of exposure to 250 ppm (1370 mg/m^3) 1,1,1-trichloroethane but did see changes after 1 hour to a time-weighted average concentration of 300 ppm ([1640 mg/m^3]; 250 ppm for 30 minutes followed by 350 ppm for 30 minutes). Thus, the Salvolainen et al. (1981, 1982a,b) and Gamberale and Hultengren (1973) studies do not confirm a finding of

neurobehavioral effects following 20 minutes of exposure; however, the Gamberale and Hultengren (1973) findings suggest that changes in neurobehavioral performance may occur after 60 minutes of exposure to an exposure concentration of 300 ppm, generally consistent with the findings for Mackay et al. (1987) also at 60 minutes of exposure. Therefore, based on evidence from human intentional dosing studies as a whole, it appears that exposure to 950 mg/m^3 1,1,1-trichloroethane for 60 minutes represents a LOAEL.

There is extensive supporting evidence from the experimental animal literature that the central nervous system is a sensitive target for 1,1,1-trichloroethane. Neurological effects have been widely demonstrated in acute animal studies, and have been shown to be by far the most sensitive endpoints in these studies. In comparison to the human data, however, neurological effects in animals have been reported only at considerably higher concentrations ($\geq$700 ppm [$\geq$4000 mg/m^3] for effects of toxicological significance in acute studies).

Developmental effects have been reported in experimental animals following gestational exposure to 1,1,1-trichloroethane, including neurobehavioral deficits in pups (mice and rats) following late gestational exposure of the dams (Jones et al., 1996; Coleman et al., 1999). Although the developmental toxicity studies for 1,1,1-trichloroethane involved repeated (6 to 7 day) exposures during gestation, it is a plausible assumption for developmental toxic effects that "a single exposure at a critical time in development may produce an adverse developmental effect, i.e., repeated exposure is not a necessary prerequisite for developmental toxicity to be manifested" as discussed in U.S. EPA's Guidelines for Development Toxicity Risk Assessment (U.S. EPA, 1991a). To that end, the results of these studies are considered relevant to an acute exposure.

Reported neurodevelopmental effects occurred, however, at average daily exposure concentrations considerably higher than the levels at which neurobehavioral effects have been observed in human controlled exposure studies. For example, BRRC (1987a,b) reported an effect level for fetotoxicity in the rat and rabbit of 32,760 mg/m^3, 6 hours/day, on GD 6-15 or 6-18, respectively. Three other developmental toxicity studies (Schwetz et al., 1975; Jones et al., 1996; Coleman et al., 1999) reported either no developmental toxicity or effect levels well above the levels at which neurobehavioral effects were observed in human controlled exposure studies; further, because these three studies included only a single exposure concentration, they were not considered an appropriate basis for acute RfC development.

Consideration of human and experimental animal data support the use of data on the neurological effects of 1,1,1-trichloroethane in humans as the most sensitive and appropriate basis for derivation of the acute inhalation RfC. Mackay et al. (1987) was selected as the principal study for derivation of the acute RfC, with Gamberale and Hultengren (1973) and Muttray et al. (1999, 2000) providing support for effects on neurobehavioral performance.

5.2.1.2. *Methods of Analysis*

The use of benchmark dose methods was considered in analyzing the data set from Mackay et al. (1987). This study included two exposure levels and controls, and found statistically significant concentration-related effects on several variables; however, only mean changes were presented, without standard deviations or standard errors. Further, the finding of performance deficits associated with 1,1,1-trichloroethane exposure in this study is based on the pattern of performance changes in a battery of behavioral tests, rather than on the results of a single test. For these reasons, the data were not considered amenable to BMD analysis. Therefore, the LOAEL of 950 mg/m^3 following one hour of exposure was used as the point of departure for derivation of the acute RfC.

Because acute exposure durations are defined as 24 hours or less, there is interest in deriving RfCs for durations of 1, 4, 8, and 24 hours. The Reitz et al. (1988) PBPK model was used with data from Mackay et al. (1987) to predict effect levels at other acute exposure durations between 1 and 24 hours (Yang, 2006). As discussed in Section 3.5.2., the Reitz et al. (1988) model was evaluated using three human pharmacokinetic data sets (all involving inhalation exposure), and acceptably predicted the experimental data sets. Data points (blood 1,1,1-trichloroethane concentration versus time) from the graphic presentation of results in Mackay et al. (1987) were extracted using DigiMatic software (Yang et al., 2006).

Consideration was given to whether the area under the concentration vs. time curve (AUC) or the momentary concentration in the blood at the time of testing (Ct) constitutes the better internal dose metric in the case of the Mackay et al. (1987) study. Because Mackay et al. (1987) had actual measurements of blood concentration at the time of neurobehavioral testing (20, 60, 120 and 180 minutes), Ct was already available. Ct was determined to be the more appropriate dose metric as supported by the following:

- Several laboratory animals studies of 1,1,1-trichloroethane have shown a correlation between blood and brain 1,1,1-trichloroethane concentration and certain neurological deficits. Warren et al. (1998, 2000) found that blood and brain concentrations at the time of testing, as well as blood and brain Cmax and AUC values, were strongly correlated with operant performance in the rat receiving acute inhalation exposures to 1,1,1-trichloroethane for up to 100 minutes and with locomotor activity in the mouse at acute inhalation exposures up to 30 minutes in duration. In both studies, the investigators noted that all three values were suitable for predicting 1,1,1-trichloroethane-induced response rate changes. These investigators also reported that the assumption that all equivalent products of concentration and time (C x T) result in the same degree of toxicity (Haber's Rule) was not valid under the given exposure conditions.

- Studies of related solvents show momentary blood concentration to be the more appropriate dose metric. Specifically, studies of trichloroethylene (TCE) have shown that acute neurological deficits in rats (as measured by changes in performance of a behavioral signal detection task or changes in visual evoked potentials) are related to the momentary concentrations of TCE in blood or brain at the time of the neurobehavioral assessment and not to the total amount of TCE exposure expressed as AUC. Preliminary evidence suggests a similar relationship exists for toluene (Boyes et al., 2003, 2005, Bushnell et al., 2005). Boyes et al. (2000, 2005) reported that Haber's Rule did not accurately predict outcome for different combinations of C x T for TCE.

- While the brain is the target of toxicity following acute inhalation exposure, brain concentrations of 1,1,1-trichloroethane cannot be collected in human subjects. Animal studies show that blood and brain concentrations are strongly correlated (Warren et al., 1998, 2000), and, therefore, that blood concentrations are an effective surrogate for target tissue (brain) concentrations.

Based on data from Mackay et al. (1987), Yang (2006) estimated the internal dose (CV) in humans exposed to 950 mg/m^3 1,1,1-trichloroethane for one hour (1.33 mg/L). The model was then used to predict the exposure concentration required to achieve the same target internal dose (1.33 mg/L) after 4, 8, and 24 hours of exposure using continuous exposure assumptions. These exposure concentrations are provided in column 2 of Table 21 below:

Table 21. Predicted Exposure Concentrations at Different Exposure Durations for the Target Internal Dose

Exposure Duration (hr)	1,1,1-Trichloroethane Exposure Concentration (mg/m^3) for CV=1.33 mg/L[a]	UF	Acute RfC (mg/m^3)
1	950	100	9
4	715.3	100	7
8	693.4	100	7
24	649.8	100	6

[a] Target internal dose CV = 1.33 mg/L (or 9.97 μM).
Source: Yang (2006)

5.2.1.3. *Acute RfC Derivation—Including Application of Uncertainty Factors (UFs)*

The acute human LOAEL for 1 hour and predicted LOAELs for 4, 8, and 24 hours served as the points of departure for the acute RfC values at different durations. A composite UF of 100 was applied to these points of departure: 10 to extrapolate from a LOAEL to a NOAEL and 10 for intraspecies variation (human variability).

- A default 10-fold UF for intraspecies differences was used to account for

potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

- An interspecies UF was not necessary because the critical effect is based on human data.

- A default 10-fold UF for extrapolation from a LOAEL to a NOAEL was used because the lowest exposure concentration examined in the principal study was associated with a measurable deficit in a neurobehavioral test.

- A UF to extrapolate from a shorter to a longer exposure duration was not necessary because the acute RfC was derived from a study using an acute exposure protocol; a PBPK model was used to extrapolate to other acute exposure durations.

- A database UF was not applied because the database for this chemical was considered relatively complete. The inhalation database includes extensive testing for acute toxicity and inhalation developmental toxicity studies in three species. The neurobehavioral effects of 1,1,1-trichloroethane, the most sensitive effect following acute inhalation exposure, has been investigated in both animals and humans.

The acute RfC values for 1,1,1-trichloroethane were calculated as follows:

Acute RfC = LOAEL / UF

and are presented in column 4 of Table 21 above.

5.2.2. Short-term Inhalation RfC

The short-term inhalation RfC is intended for use with exposures for more than 24 hours, up to 30 days.

5.2.2.1. *Choice of Principal Study and Critical Effect—with Rationale and Justification*

No useful short-term inhalation studies in humans were located. Short-term studies in animals include investigations of neurological and developmental effects. The most sensitive effects in the animal studies were neurological: 1) development of withdrawal symptoms (handling-induced convulsions mitigated by re-exposure to 1,1,1-trichloroethane or exposure to some other known depressants) in mice exposed to 500 ppm (2730 mg/m^3) or more of 1,1,1-trichloroethane continuously for 4 days and abruptly removed from exposure (Evans and Balster, 1993; Balster et al., 1997), and 2) neurophysiological changes in rats following exposure to 1000 ppm (5460 mg/m^3) 6 hours/day for 4 days (adjusted concentration of 250 ppm

[1360 mg/m^3]) (Albee et al., 1990b). Developmental effects were found only at higher concentrations (adjusted concentrations 875 ppm [≥4780 mg/m^3]).

The LOAEL of 175 ppm (950 mg/m^3) for neurobehavioral effects in humans with acute exposure to 1,1,1-trichloroethane (Mackay et al., 1987) is below the effect level from any of the available short-term animal studies. This would suggest that protecting against acute neurobehavioral effects observed in human controlled-exposure studies will protect against the effects reported in short-term, repeat-exposure studies in animals. Consideration of the protectiveness of acute exposure data for repeat exposure situations requires consideration of (1) the influence of exposure duration on neurobehavioral toxicity and (2) the duration extrapolation.

Influence of exposure duration on neurobehavioral toxicity. Short-term human data are not available to directly establish whether 1,1,1-trichloroethane would produce neurobehavioral effects at lower levels with repeated exposure than with acute exposure. Human subject data from Mackay et al. (1987) suggest that neurobehavioral effects are correlated with momentary blood levels of 1,1,1-trichloroethane for time points up to 3.5 hours, but not longer exposure durations. Available toxicokinetic data, in combination with toxicity data from animals, inform the relationship between exposure duration and expression of neurobehavioral toxicity.

Toxicokinetic data from humans and animals suggest that 1,1,1-trichloroethane will preferentially partition to fat but is unlikely to accumulate in body tissues. Following single inhalation exposure, 1,1,1-trichloreothane is rapidly cleared from fat, with 1,1,1-trichloroethane partitioning back into blood and then being exhaled from the body (Schumann et al., 1982a). As discussed in Section 3.4, Schumann et al. (1982b) compared disposition and elimination of 1,1,1-trichloroethane in rats and mice exposed to 1500 ppm 1,1,1-trichloroethane for 6 hours/day, 5 days/week for 16 months, with the last day of exposure to radiolabeled compound, to age-matched controls exposed once to radiolabeled compound. Concentrations of radiolabel in fat and other tissues at 0 and 72 hours after exposure to the radiolabeled compound were comparable in animals receiving a single 6-hour exposure and in animals that had been exposed for 16 months. The results showed no significant effect of repeated exposure to 1,1,1-trichloroethane on the disposition of radiolabled compound compared to single exposure. Nolan et al. (1984) simulated repeated 8-hour daily exposure of humans based on a three compartment pharmacokinetic model and predicted that 12 daily exposures would be required to reach 95% of steady state concentrations of 1,1,1-trichloroethane in the body. At steady state, Nolan et al. (1984) predicted that the body would contain 3.6 times the amount of 1,1,1-trichloroethane as after a single 8-hour exposure and that ~70% of this would be in the fat. Rats and mice receiving a single oral exposure (1000 mg/kg) of radiolabeled 1,1,1-trichloroethane had 53-62% of the 1,1,1-trichloroethane deposited in tissues present in the fat 1 to 2 hours after exposure, a range

similar to that predicted by Nolan et al. (1984) at steady state. On balance, the available data suggest that 1,1,1-trichloroethane preferentially distributes to fat following both acute and repeated exposure to a similar extent, that partitioning to fat is at equilibrium with blood concentration, and that once exposure ceases, 1,1,1-trichloroethane is cleared from the fat.

Toxicity data in animals provide limited information related to the potential for effects to occur at lower concentrations with repeated versus acute exposure. For the most part, the specific neurological endpoints examined in acute studies differ from those examined in repeat-dose studies. In addition, dose spacing in acute and repeat dose studies differs, so that the proximity of NOAELs or LOAELs from acute and repeat dose studies to their respective thresholds is uncertain. Therefore, a comparison of the lowest acute effect level in Table 20 (4000 mg/m^3) with the lowest short-term effect level (2730 mg/m^3 for continuous exposure) provides only limited insights into whether duration of exposure influences the exposure concentration at which neurological effects occur.

Some data from animal studies allow a direct comparison of the same endpoint for acute and short-term exposure durations. Baboons displayed impaired performance in a match-to-sample discrimination task at a concentration of 1200 ppm (6550 mg/m^3) with continuous exposure for 7 days, while the NOAEL and LOAEL for this effect were 1400 and 1800 ppm (7640 and 9830 mg/m^3), respectively, with 4-hour exposure (Geller et al., 1982). This result suggests a reduction of the threshold for a behavioral effect from 7640 mg/m^3 to < 6550 mg/m^3 as the exposure duration increased from 4 hours to 7 days. The magnitude of the change is unknown because only a single concentration was tested in the 7-day experiment, precluding identification of a threshold for this duration.

On the other hand, mice exposed repeatedly to 6000 ppm (32,760 mg/m^3) 1,1,1-trichloroethane for 20 minutes per day, 4 days per week, over a 4 week period all maintained baseline performance in a fixed-ratio responding task during initial air exposures of each daily session and all recovered each day after solvent exposure, indicating no residual effect of the chemical with repeated exposures (Moser et al., 1985). Furthermore, suppression of responding by 1,1,1-trichloroethane changed only slightly over the course of the study (slight statistically significant increase in responding over the first two weeks of the study and significant decrease in latency for recovery of responding after the daily exposure terminated). These investigators also exposed mice to increasing concentrations of 1,1,1-trichloroethane (1000, 2000, 4000, and 8000 ppm [5460, 10,920, 21,840 and 43,680 mg/m^3]) in consecutive 8 minute sessions once per week over the 4 weeks of the study. Comparison of the resulting exposure-response curves and EC_{50} values showed no significant shifts in either direction with increasing number of exposure sessions. These results show no evidence for a reduced threshold for neurobehavioral effects with repeated versus acute exposure. They also show development of only minimal tolerance to

1,1,1-trichloroethane with repeated exposure.

Concentration x time adjustment of exposure concentration. As discussed previously, results from studies of 1,1,1-trichloroethane and related solvents in animal models demonstrate that Haber's Rule is not an accurate predictor of acute CNS toxicity (e.g., Boyes et al., 2000, 2005; Warren et al., 1998, 2000). Accordingly, acute neurobehavioral data from Mackay et al. (1987) were not adjusted for an exposure duration less than 24 hours. For exposures of longer duration and for endpoints other than CNS, exposures were adjusted to continuous exposure (i.e., Haber's Rule was assumed to apply) as a conservative estimate of exposure.

Selection of the point of departure. The comparison of points of departure from studies of short-term duration (1360 mg/m^3 and above; see Figures 2a and 2b and Table 20) with the acute LOAEL from the controlled human study report by Mackay et al. (1987) (950 mg/m^3) suggests that results from short-term animal studies are not necessarily protective of acute neurobehavioral effects seen in human intentional dosing studies. Accordingly, the results from Mackay et al. (1987) were further analyzed as the basis for a more health protective point of departure for the short-term RfC.

5.2.2.2. *Methods of Analysis*

PBPK modeling was used with data from Mackay et al. (1987) to predict effect levels at short-term exposure durations as described in Section 5.2.1.2. As described in Section 5.2.1.2. (for the acute RfC), Yang (2006) identified the internal dose of 1,1,1-trichloroethane (i.e., concentration in venous blood, CV) in humans associated with exposure to 950 mg/m^3 for 1 hour (i.e., the exposure considered to be associated with biologically significant changes in neurobehavioral performance). Yang (2006) used the Reitz et al. (1988) model to predict the exposure concentration required to achieve the same target internal dose once steady state had been reached at 336 hours (14 days).[4] This exposure concentration was predicted to be 526 mg/m^3.

5.2.2.3. *Short-term RfC Derivation—Including Application of Uncertainty Factors (UFs)*

The short-term inhalation RfC was estimated from the point of departure of 526 mg/m^3 derived from Mackay et al. (1987) and use of PBPK modeling to predict steady state conditions. This point of departure was divided by a composite UF of 100: 10 for intraspecies variation (human variability) and 10 to extrapolate from a LOAEL to a NOAEL.

- A default 10-fold UF for intraspecies differences was used to account for

4 Near steady state venous blood concentrations were achieved considerably sooner than 336 hours. 1,1,1-trichloroethane concentrations were at 87% of steady state at 48 hours, at 94% at 96 hours, and 98% of steady state at 168 hours.

potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

- An interspecies UF was not necessary because the critical effect is based on human data.

- A default 10-fold UF for extrapolation from a LOAEL to a NOAEL was used because the lowest exposure concentration examined in the principal study was associated with a measurable deficit in a neurobehavioral test.

- A PBPK model was used to predict the exposure concentration that would produce 1,1,1-trichloroethane levels associated with biologically significant changes in neurobehavioral performance when steady state had been achieved (14 days). Therefore, an UF for duration extrapolation was not considered necessary.

- A database UF was not applied because the short-term inhalation database was considered relatively complete. The database includes inhalation developmental toxicity studies in three species as well as several studies that investigated neurobehavioral effects of 1,1,1-trichloroethane following short-term exposure. The short-term RfC is based on a study of human neuropsychomotor performance (Mackay et al. 1987) extrapolated to short-term steady-state conditions. The acute literature suggests that the human model is more sensitive to neurobehavioral toxicity of 1,1,1-trichloroethane than the animal models tested, and thus Mackay et al. (1987) is an appropriate and sensitive data set for derivation of the short-term RfC. Further, the available data suggest that repeated exposure to 1,1,1-trichloroethane should not result in an appreciable reduction in the threshold for neurobehavioral effects. This is supported by chronic animal studies, in which no overt neurobehavioral effects were observed even after two years exposure of rats and mice to concentrations as high as 8190 mg/m^3 for 6 hours/day, 5 days/week.

The short-term RfC was calculated as follows:

Short-term RfC = Point of departure / UF
= 526 mg/m^3 / 100
= 5 mg/m^3

5.2.3. Subchronic Inhalation RfC

The subchronic inhalation RfC is intended for use with exposures for more than 30 days, up to approximately 10% of the lifespan in humans (or up to approximately 90 days in typically used laboratory animal species).

5.2.3.1. *Choice of Principal Study and Critical Effect—with Rationale and Justification*

No useful subchronic studies in humans were located. The lowest effect level identified in animals in subchronic studies was increased GFAP, potentially indicating formation of astroglial fibrils in response to brain injury, in the sensorimotor cerebral cortex of gerbils exposed continuously to 210 ppm (1150 mg/m^3) for 3 months, and evaluated 4 months after the end of exposure (Rosengren et al., 1985). There is some uncertainty, however, regarding the toxicological significance of this finding. Acute responses to severe chemical-induced injury to localized regions of the brain have been associated with several fold increases in GFAP. In addition to neuronal injury, however, other non-pathological conditions, such as intense stimulation, can also be associated with detectable increases in GFAP, although such increases are typically of a much smaller magnitude.

The increases observed by Rosengren et al. (1985), estimated from graphs, are ~33% above control values for 210 ppm (1150 mg/m^3) and ~40% for 1000 ppm (5460 mg/m^3). This effect appears to be treatment-related but not dose-dependent. Changes were observed in protein concentration and S-100 in other brain regions, only in the group exposed to the 210-ppm and not in the 1000-ppm group. These latter changes are therefore not considered treatment-related. S-100 protein, another marker for astrogliosis, was not increased in this study; studies of other compounds (ethanol, trichloroethylene and tetrachloroethylene) by the same researchers found increases in both GFAP and S-100 protein. Overall, the data do not provide compelling evidence for a dose-related effect on neurochemical parameters.

The reliable measurement of GFAP in specific brain regions requires consistent dissection, since different brain regions normally have significantly different levels of GFAP. For example, the concentration of GFAP in the hippocampus is dramatically greater than that in overlying sensorimotor cortex. Retention of fragments of hippocampus with the overlying cortex during dissection, or inclusion of varying amounts of white matter, could result in anomalous values. The description of the sample collection by Rosengren et al. is not adequate to determine if safeguards were undertaken to avoid the possibility of systematic errors of this type.

The increased GFAP levels observed in the 210- and 1000-ppm groups could reflect subtle but persistent alterations in 1,1,1-trichloroethane-exposed animals or other treatment-related alterations in other aspects of brain homeostasis; however; the neurochemical findings

reported by Rosengren et al. are equivocal. Furthermore, there are no other findings from pathological, physiological or neurochemical studies that provide additional support for a biological basis for the significance of a region-specific, treatment-related effect on the sensorimotor cortex. Specifically, comprehensive neurohistopathology assessment found no evidence of brain injury in rats exposed to 2000 ppm (10,920 mg/m^3) 1,1,1-trichloroethane intermittently for 3 months (duration adjusted concentration of 1950 mg/m^3) (Mattsson et al., 1993). Studies using standard techniques also failed to detect histological evidence of brain damage in rats or mice, most notably following intermittent exposure to 1500 ppm (8190 mg/m^3) (duration adjusted concentration of 1440 mg/m^3) for 2 years (Quast et al., 1984, 1988). Consequently, the GFAP findings of Rosengren were not considered to be adequate to establish a critical effect for subchronic exposure to 1,1,1-trichloroethane.

Other subchronic studies in animals found ambiguous evidence for impaired forelimb grip strength and minimal lesions of the nasal turbinates with exposure to 2000 ppm (10,900 mg/m^3) (duration adjusted concentration of 1939 mg/m^3) for 13 weeks (Calhoun et al., 1981; Mattsson et al., 1993). The deficits in forelimb grip strength reported in Mattsson et al. (1993) were not statistically significant using a statistical treatment designed to take into account the observed changes over time in the control and treated group, and were not confirmed by histopathological, electrophysiological, or FOB tests in the same study (see Section 4.4.1.2.). Lesions of the nasal turbinates observed by Calhoun et al. (1981) were not confirmed in subsequent chronic studies by the same group of investigators (Quast et al., 1984, 1988). Therefore, neither effect was considered appropriate as the basis for an inhalation reference value.

More consistent is the finding of histopathologic changes in the liver associated with 1,1,1-trichloroethane exposure. Quast et al. (1984, 1988) exposed rats and mice to 1,1,1-trichloroethane for up to two years, with interim sacrifices at 6, 12, and 18 months, and found minor histopathological changes in the liver in rats exposed to 1500 ppm (8190 mg/m^3), 6 hours/day, 5 days/week (duration adjusted concentration = 1460 mg/m^3). These changes (including altered staining around the central vein and smaller appearance of hepatocytes in the portal region) suggest a physiologic response of centrilobular hepatocytes (i.e., hypertrophy) that is not considered adverse. No differences from controls were discernable after 2 years of exposure because of confounding geriatric changes. The hepatic changes were not seen in control or lower-exposure animals at any time point. Because interim sacrifices were performed at 6, 12, and 18 months, the study provides information relevant to both subchronic and chronic exposure durations. In a 13-week range-finding study, Calhoun et al. (1981) reported effects in rats and mice exposed to 2000 ppm 6 hours/day, 5 days/week [duration adjusted concentration = 1950 mg/m^3] similar to those observed in rats by Quast et al. (1984, 1988), i.e., decreased

hepatocyte size with altered staining affinity and slight centrilobular hepatocellular swelling, but also reported low incidences of generalized hepatocellular atrophy in male rats and focal necrosis in female mice at this concentration. Treatment-related effects were not reported at the lower concentrations. More substantial liver lesions, including fatty change and necrosis, were reported in mice exposed continuously to 1000 ppm (5460 mg/m^3) for 14 weeks (McNutt et al., 1975). In mice exposed to the lower exposure concentration (250 ppm [1360 mg/m^3]) continuously for 14 weeks, minimal ultrastructural changes were observed that were generally consistent with those reported by Quast et al. (1984, 1988) and not considered adverse.

Thus, the experimental literature suggests that subchronic exposure to 1,1,1-trichloroethane induces hepatocellular hypertrophy at concentrations (adjusted for continuous exposure) of 1370 to 1460 mg/m^3 (Quast et al., 1984, 1988; McNutt et al., 1975); these effects do not appear to progress in severity or incidence with exposure duration (Quast et al., 1984, 1988) and are considered a physiologic rather than adverse response. At a duration-adjusted exposure concentration of 1950 mg/m^3, the histopathologic findings from a 13-week range-finding study indicated liver toxicity in rats and mice (Calhoun et al., 1981). Because the study was designed as a range-finding study, however, the findings cannot be considered definitive. At an exposure concentration of 5460 mg/m^3 [about 4-fold higher than the NOAELs from McNutt et al. (1975) and Quast et al. (1984, 1988)], clear hepatotoxicity was observed (McNutt et al., 1975), with effects including increased relative liver weight and triglyceride levels, increased lipid content, and necrosis.

Quast et al. (1984, 1988) and McNutt et al. (1975) together can be used to establish a NOAEL and LOAEL for effects on the liver in rodents. The highest tested concentration in Quast et al. of 1460 mg/m^3 (duration adjusted) is considered a NOAEL, and the concentration in the McNutt et al. (1975) study associated with clear hepatotoxic effects (5460 mg/m^3) is a LOAEL. The data from these studies were used for dose-response analysis. Quast et al. (1984, 1988) was selected as a co-principal study because it is the most comprehensive repeat-dose inhalation study of 1,1,1-trichloroethane, and McNutt et al. (1975) because it establishes a clear adverse effect level whereas the treatment-related effects in Quast et al. (1984, 1888) are not considered adverse.

5.2.3.2. *Methods of Analysis*

The use of benchmark dose (BMD) methods was considered in analyzing the data sets from Quast et al. (1984, 1988) and McNutt et al. (1975). Because the treatment-related response at the highest concentration tested in Quast et al. was not considered adverse, and because McNutt et al. did not provide incidence data, neither data set was considered amenable to BMD methods. The NOAEL (8190 mg/m^3, 6 hours/day, 5 days/week [duration adjusted = 1460

mg/m^3]) was used as the point of departure.

Yang (2006) used the Reitz et al. (1988) PBPK model to extrapolate from the animal NOAEL from Quast et al. (1984, 1988) to humans. The model was run for 6 months of exposure (time to first sacrifice). [The TWA AUC did not change with exposures longer than 6 months, indicating steady state had been achieved.]

Yang (2006) estimated the TWA liver 1,1,1-trichloroethane AUC resulting from inhalation exposure at various values for the NOAEL. Both liver and venous blood AUCs were considered as possible dose metrics; however, the TWA AUC-liver was considered the more appropriate dose metric because the liver is the target organ of 1,1,1-trichloroethane toxicity. The predicted TWA AUC-liver at steady state derived from the PBPK analysis of Yang (2006) is shown in Table 22. The calculated human inhalation exposure concentration (assuming continuous exposure) corresponding to the TWA AUC is also shown in this table.

Table 22. Calculation of Human Equivalent Concentration using PBPK Modeling (Using Liver Concentration as Dose Metric)

Rat Exposure Concentration -- NOAEL from Quast et al. (1984, 1988)	8190 mg/m^3, 6 hr/day, 5 days/week
Predicted AUC[a]	57,826 mg × hr/L
Predicted TWA AUC[a]	317 mg/L-day
Calculated Human Inhalation Exposure Concentration[b]	1553 mg/m^3

[a] At t = 4380 hours (6 months). The TWA AUC did not change with exposures longer than 6 months, indicating steady state had been achieved.

[b] Calculated based on TWA AUC-liver in humans equivalent to the rat internal dose under continuous infusion conditions up to 4380 hours.

Based on Yang (2006). Yang (2006) examined the relationship between exposure concentration and internal dose for exposure concentrations ranging over 5 orders of magnitude. The human exposure concentration (for continuous exposure) was calculated based on the TWA AUC in humans equivalent to the respective rat internal dose under inhalation exposure concentrations ranging from 27.3 to 273,000 mg/m^3. The relation (on a log scale) was shown to be linear over this range of concentrations. Using liver as the dose metric, the calculated human exposure concentration was lower than the rat exposure concentration yielding the same internal dose by a factor of 5.27. The values in this table are interpolated using the relationship presented in Yang (2006).

5.2.3.3. *Subchronic RfC Derivation—Including Application of Uncertainty Factors (UFs)*

The calculated human inhalation exposure of 1553 mg/m^3 corresponding to the NOAEL from Quast et al. (1984, 1988) was used as the point of departure for calculating a subchronic RfC. A composite UF of 100 was applied to the point of departure (3 for extrapolation from animals to humans, 10 for intraspecies variation (human variability), and 3 for database deficiencies), as follows:

- A 3-fold UF was used to account for pharmacodynamic uncertainty in extrapolating from laboratory animals to humans. Use of a PBPK model accounts for differences in the toxicokinetics between rats and humans.

- A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

- An UF to extrapolate from a LOAEL to a NOAEL was not necessary because a NOAEL was used to determine the point of departure.

- An UF to extrapolate from a shorter to a longer duration was not necessary because the NOAEL came from a two-year chronic study with interim sacrifices at 6, 12 and 18 months; no progression in liver histopathological findings were observed after 6 months.

- A database uncertainty factor of 3 was applied to account for deficiencies in the subchronic database for 1,1,1-trichloroethane. Although the database for 1,1,1-trichloroethane following subchronic durations is relatively complete, there exists some uncertainty related to the potential neurotoxicity of 1,1,1-trichloroethane following repeated exposure. The inhalation database includes several multi-dose studies that examined a range of endpoints, inhalation developmental toxicity studies in three species, and a single generation reproductive/developmental toxicity study that included exposure prior to mating. Although an inhalation multigeneration study has not been conducted, a multigeneration reproductive study of 1,1,1-trichloroethane by the oral route (Lane et al., 1982), that found no evidence of reproductive toxicity, is available. In addition, an oral developmental neurotoxicity study (Maurisien et al., 1993, 1994), sponsored by the Halogenated Solvents Industry Alliance under a 1,1,1-trichloroethane Testing Consent Order with the U.S. EPA, is available. Because pharmacokinetic data for 1,1,1-trichloroethane do not suggest route-specific differences in target organs, the findings from these oral studies can inform an evaluation of reproductive and neurodevelopmental toxicity following inhalation exposures. Limited information exists regarding the immunotoxicity of 1,1,1-trichloroethane by any route of exposure, although the limited information provides no clear evidence of immunotoxic potential. Aranyi et al. (1986) found no evidence of immunotoxicity in an in vivo study in mice involving acute inhalation exposure to 1,1,1-trichloroethane, and in repeat dose studies no effects were reported on spleen weight or histopathology (Adams et al., 1950; Calhoun et al., 1981; Prendergast et al., 1967; Torkelson et al., 1958) or spleen or thymus histopathology (Quast et al., 1984, 1988).

  The neurotoxicity of 1,1,1-trichloroethane in humans and animals following acute exposure has been extensively documented; in animal models, acute 1,1,1-trichloroethane exposure has caused CNS depression and effects on motor activity and cognitive function. On balance, the available animal data suggest that repeated exposure to 1,1,1-trichloroethane does not cause overt effects on the

CNS. Concern about the potential for 1,1,1-trichloroethane to effect the nervous system following prolonged exposure is raised by epidemiological findings and the findings of Rosengren et al. (1985) in gerbils. In a study of 28 workers exposed occupationally to 1,1,1-trichloreothane, Kelafant et al. (1994) reported increased sway in the Romberg test and statistically significant deficits for memory, intermediate memory, rhythm and speed in a neuropsychological test battery. Workplace exposures were not measured, the number of workers in the study was small, and Kelafant et al. findings were not confirmed in other limited studies of worker populations (Maroni et al., 1977; Cherry et al., 1983). Nevertheless, the qualitative findings from Kelafant et al. raise some concern about potential neurotoxic outcomes following prolonged 1,1,1-trichloroethane exposure. A limited number of experimental animal studies examined neurotoxic endpoints following repeated exposure. In a test of schedule-controlled operant behavior (fixed-ratio responding task), Moser et al. (1985) found that mice exposed repeatedly to high levels of 1,1,1-trichloroethane for 20 minutes per day, 4 days per week, over a 4-week period recovered each day after solvent exposure, indicating no residual effect of the chemical with repeated exposures; however, no similar study involving subchronic exposure is available. Mattsson et al. (1993) reported slight but statistically significant deficits in forelimb grip performance in rats exposed for 13 weeks; investigators considered the deficit possibly attributable to the sedative properties of 1,1,1-trichloroethane. No other deficits indicative of neurotoxicity were observed (the study included a functional observational battery, evaluations of visual, auditory, somatosensory, and caudal nerve-evoked potentials, and histopathologic examination), although evaluation for cognitive deficits was not performed. In light of the qualitative findings from the epidemiological literature, additional evaluation of cognitive endpoints for subchronic durations would reduce uncertainty in the database.

Rosengren et al. (1985) reported a small but statistically significant increase in regional brain levels of GFAP, a biomarker of glial hypertrophy in response to neuronal injury, in gerbils exposed to 1,1,1-trichloroethane for 3 months. Questions were raised about the reliability of these findings, and they were not supported by pathological, physiological or neurochemical findings from other studies (see Section 5.2.3.1.); however, the findings raise a potential concern for effects on the CNS in the absence of an adequately conducted confirmatory study. On balance, issues raised by neurotoxicity findings for 1,1,1-trichloroethane support a database UF for the subchronic RfC of 3.

The subchronic RfC for 1,1,1-trichloroethane of 16 mg/m^3 based on data from Quast et al. (1984, 1988) was calculated as follows:

Subchronic RfC = Point of Departure ÷ UF
= 1553 mg/m^3 ÷ 100
= 16 mg/m^3

Comparison to Shorter Duration RfCs and Final Subchronic RfC Derivation. The value of the subchronic RfC of 16 mg/m^3 derived from Quast et al. (1984, 1988) turns out to be larger than the acute and short-term RfCs for 1,1,1-trichloroethane, which range from 5 to 9 mg/m^3. It is generally anticipated, however, that acute (or short-term) RfCs would be higher in absolute value than the subchronic or chronic RfC for that chemical since the acute (or short-term) exposure durations are greatly reduced compared to exposures of subchronic or chronic duration. In the case of 1,1,1-trichloroethane, the effect levels for acute/short-term and subchronic inhalation exposures might not necessarily be expected to follow a continuum from higher to lower for a number of reasons.

- The point of departure for the acute (and short-term) exposure duration is based on central nervous system (CNS) effects in humans, whereas the point of departure for subchronic and chronic exposure durations is based on liver effects in rats and mice. Thus, the target organ for acute/short-term exposure durations differs from that for subchronic/chronic exposure durations. Although the modes of action for the CNS and liver effects of 1,1,1-trichloroethane have not been established, it is likely that the modes of action at the two sites of toxicity are different.

- The endpoints examined following acute exposure to 1,1,1-trichloroethane differ from those examined following subchronic or chronic exposure. In particular, sensitive neurobehavioral testing in humans is available for evaluating 1,1,1-trichloroethane acute toxicity. In fact, human test batteries proved to be more sensitive than animal models of acute neurobehavioral toxicity. Sensitive testing for neurobehavioral effects in either humans or animals is unavailable following repeated exposure.

- The acute/short-term RfCs are based on analysis of peak exposure, whereas subchronic/chronic RfCs are based on area-under-the-curve (AUC) exposure.

For 1,1,1-trichloroethane, the short-term RfC of 5 mg/m^3 is clearly protective of health effects associated with subchronic exposure. Accordingly, the subchronic RfC is set at 5 mg/m^3 so as not to exceed the limiting reference value derived for short-term exposure.

5.2.4. Chronic Inhalation RfC

The chronic oral RfC is intended for use with exposures for more than approximately 10% of the lifespan in humans (or more than approximately 90 days to two years in typically used laboratory animal species).

5.2.4.1. *Choice of Principal Study and Critical Effect—with Rationale and Justification*

Studies of workers with chronic occupational exposure to 1,1,1-trichloroethane provide

only limited data for use in dose-response assessment. Kelafant et al. (1994) found evidence of neurobehavioral effects in a group of workers exposed to high concentrations of 1,1,1-trichloroethane over a 10-year period, but exposures were not quantified. Maroni et al. (1977) did not find neurological effects in another group of workers, but exposures (110-345 ppm [600-1880 mg/m^3] for most workers) were estimated based on very limited data, group sizes were small (7-8 per group), and the neurological tests did not include reaction time, which was found to be the most sensitive endpoint in the controlled exposure studies. Kramer et al. (1978) conducted a larger study, but included only limited investigation of neurological endpoints (Romberg test).

Animal studies of chronic duration were limited to studies by Quast et al. (1984, 1988) in rats and mice. As discussed in Section 5.2.3.1., Quast et al. found only minor histopathological changes in the liver in rats at interim sacrifice at a concentration of 1500 ppm (8190 mg/m^3) (duration adjusted concentrations = 1460 mg/m^3). These findings appeared to reflect a physiologic response of centrilobular hepatocytes and were not considered adverse. Further, because of confounding geriatric changes, no treatment related effects were discernible at the final 2-year sacrifice. As discussed in Section 5.2.3.1. for the subchronic RfC, A LOAEL for liver effects can be estimated from the McNutt et al. (1975) study, where clearly adverse effects on the liver were reported in mice following continuous exposure to 1000 ppm (5460 mg/m^3) for 14 weeks. Quast et al. (1984, 1988) and McNutt et al. (1975) are used as co-principal studies to define the NOAEL and LOAEL. Although McNutt et al. (1975) was a subchronic study, the findings from Quast et al. (1984, 1988) suggest a lack of progression of effects, at least at the NOAEL, from subchronic to chronic exposure durations.

5.2.4.2. *Methods of Analysis*

The methods used to derive the chronic RfC for 1,1,1-trichloroethane are the same as those used to derive the subchronic RfC. As described in Section 5.2.3.2, the NOAEL from the Quast et al. (1984, 1988) study (8190 mg/m^3, 6 hours/day, 5 days/week) was used as the point of departure. PBPK modeling was performed to predict the human exposure concentration (assuming continuous inhalation exposure) of 1553 mg/m^3 (using the TWA AUC liver as the dose metric) (see Table 22).

5.2.4.3. *Chronic RfC Derivation—Including Application of Uncertainty Factors (UFs)*

The calculated human inhalation exposure of 1553 mg/m^3 corresponding to the NOAEL from Quast et al. (1984, 1988) was used as the point of departure for calculating a chronic RfD. A TWA AUC-liver was used as the dose metric because the liver is the target organ of 1,1,1-trichloroethane toxicity. A composite UF of 100 was applied to the point of departure (3 for

extrapolation from animals to humans, 10 for intraspecies variation (human variability), and 3 for database deficiencies), as follows:

- A 3-fold UF was used to account for pharmacodynamic uncertainty in extrapolating from laboratory animals to humans. Use of a PBPK model accounts for differences in the toxicokinetics between rats and humans.

- A default 10-fold UF for intraspecies differences was used to account for potentially susceptible individuals in the absence of information on the variability of response to 1,1,1-trichloroethane in the human population.

- An UF to extrapolate from a LOAEL to a NOAEL was not necessary because a NOAEL was used to determine the point of departure.

- An UF to extrapolate from a shorter to a longer duration was not necessary because the NOAEL came from a two-year chronic study with interim sacrifices at 6, 12 and 18 months; no progression in liver histopathological findings were observed after 6 months.

- A database uncertainty factor of 3 was applied to account for deficiencies in the chronic database for 1,1,1-trichloroethane. Although the database for 1,1,1-trichloroethane is relatively complete, there exists some uncertainty related to the potential neurotoxicity of 1,1,1-trichloroethane following repeated exposure. The inhalation database includes 2-year chronic inhalation bioassays in rats and mice, inhalation developmental toxicity studies in three species, and a single generation reproductive/developmental toxicity study that included exposure prior to mating. Although an inhalation multigeneration study has not been conducted, a multigeneration reproductive study of 1,1,1-trichloroethane by the oral route (Lane et al., 1982), that found no evidence of reproductive toxicity, is available. In addition, an oral developmental neurotoxicity study (Maurisien et al., 1993, 1994), sponsored by the Halogenated Solvents Industry Alliance under a 1,1,1-trichloroethane Testing Consent Order with the U.S. EPA, is available. Because pharmacokinetic data for 1,1,1-trichloroethane do not suggest route-specific differences in target organs, the findings from these oral studies can inform an evaluation of reproductive and neurodevelopmental toxicity following inhalation exposures. Limited information exists regarding the immunotoxicity of 1,1,1-trichloroethane by any route of exposure, although the limited information provides no clear evidence of immunotoxic potential. Aranyi et al. (1986) found no evidence of immunotoxicity in an in vivo study in mice involving acute inhalation exposure to 1,1,1-trichloroethane, and in repeat dose studies no effects were reported on spleen weight or histopathology (Adams et al., 1950; Calhoun et al., 1981; Prendergast et al., 1967; Torkelson et al., 1958) or spleen or thymus histopathology (Quast et al., 1984, 1988).

  The neurotoxicity of 1,1,1-trichloroethane in humans and animals following acute exposure has been extensively documented; in animal models, acute 1,1,1-

trichloroethane exposure has caused CNS depression and effects on motor activity and cognitive function. On balance, the available animal data suggest that repeated exposure to 1,1,1-trichloroethane does not cause overt effects on the CNS. Concern about the potential for 1,1,1-trichloroethane to effect the nervous system following prolonged exposure is raised by epidemiological findings and the subchronic findings of Rosengren et al. (1985) in gerbils. In a study of 28 workers exposed occupationally to 1,1,1-trichloreothane, Kelafant et al. (1994) reported increased sway in the Romberg test and statistically significant deficits for memory, intermediate memory, rhythm and speed in a neuropsychological test battery. Workplace exposures were not measured, the number of workers in the study was small, and Kelafant et al. findings were not confirmed in other limited studies of worker populations (Maroni et al., 1977; Cherry et al., 1983). Nevertheless, the qualitative findings from Kelafant et al. raise some concern about potential neurotoxic outcomes following prolonged 1,1,1-trichloroethane exposure. A limited number of experimental animal studies examined neurotoxic endpoints following repeated exposure. In a test of schedule-controlled operant behavior (fixed-ratio responding task), Moser et al. (1985) found that mice exposed repeatedly to high levels of 1,1,1-trichloroethane for 20 minutes per day, 4 days per week, over a 4-week period recovered each day after solvent exposure, indicating no residual effect of the chemical with repeated exposures; however, no similar study involving subchronic or chronic exposure is available. Mattsson et al. (1993) reported slight but statistically significant deficits in forelimb grip performance in rats exposure for 13 weeks; investigators considered the deficit possibly attributable to the sedative properties of 1,1,1-trichloroethane. No other deficits indicative of neurotoxicity were observed (the study included a functional observational battery, evaluations of visual, auditory, somatosensory, and caudal nerve-evoked potentials, and histopathologic examination), although evaluation for cognitive deficits was not performed. In light of the qualitative findings from the epidemiological literature, additional evaluation of cognitive endpoints for subchronic or chronic durations would reduce uncertainty in the database.

Rosengren et al. (1985) reported a small but statistically significant increase in regional brain levels of GFAP, a biomarker of glial hypertrophy in response to neuronal injury, in gerbils exposed to 1,1,1-trichloroethane for 3 months. Questions were raised about the reliability of these findings, and they were not supported by pathological, physiological or neurochemical findings from other studies (see Section 5.2.3.1.); however, the findings raise a potential concern for effects on the CNS in the absence of an adequately conducted confirmatory study. On balance, issues raised by neurotoxicity findings for 1,1,1-trichloroethane support a database UF for the chronic RfC of 3.

The chronic RfC for 1,1,1-trichloroethane of 16 mg/m^3 based on data from Quast et al. (1984, 1988) was calculated as follows:

Chronic RfC = Point of Departure ÷ UF
= 1553 mg/m^3 ÷ 100
= 16 mg/m^3

Comparison to Shorter Duration RfCs and Final Chronic RfC Derivation. The value of the chronic RfC of 16 mg/m^3 derived from Quast et al. (1984, 1988) turns out to be larger than the acute and short-term RfCs for 1,1,1-trichloroethane, which range from 5 to 9 mg/m^3. It is generally anticipated, however, that acute (or short-term) RfCs would be higher in absolute value than the subchronic or chronic RfC for that chemical since the acute (or short-term) exposure durations are greatly reduced compared to exposures of subchronic or chronic duration. In the case of 1,1,1-trichloroethane, the effect levels for acute/short-term and chronic inhalation exposures might not necessarily be expected to follow a continuum from higher to lower for a number of reasons.

- The point of departure for the acute (and short-term) exposure duration is based on central nervous system (CNS) effects in humans, whereas the point of departure for subchronic and chronic exposure durations is based on liver effects in rats and mice. Thus, the target organ for acute/short-term exposure durations differs from that for subchronic/chronic exposure durations. Although the modes of action for the CNS and liver effects of 1,1,1-trichloroethane have not been established, it is likely that the modes of action at the two sites of toxicity are different.

- The endpoints examined following acute exposure to 1,1,1-trichloroethane differ from those examined following subchronic or chronic exposure. In particular, sensitive neurobehavioral testing in humans is available for evaluating 1,1,1-trichloroethane acute toxicity. In fact, human test batteries proved to be more sensitive than animal models of acute neurobehavioral toxicity. Sensitive testing for neurobehavioral effects in either humans or animals is unavailable following repeated exposure.

- The acute/short-term RfCs are based on analysis of peak exposure, whereas subchronic/chronic RfCs are based on area-under-the-curve (AUC) exposure.

For 1,1,1-trichloroethane, the short-term RfC of 5 mg/m^3 is clearly protective of health effects associated with chronic exposure. Accordingly, the chronic RfC is set at 5 mg/m^3 so as not to exceed the limiting reference value derived for short-term exposure.

5.2.5. Previous Inhalation Assessment

No inhalation assessment for 1,1,1-trichloroethane was previously included in the IRIS database.

5.3. CANCER ASSESSMENT

As discussed in Section 4.7, some human epidemiological studies of 1,1,1-trichloroethane have found statistically increased incidences of cancer, but these studies are limited by the number of subjects in the cohort, the low number of cases reported, and confounding exposures to other solvents. 1,1,1-Trichloroethane has been tested for carcinogenicity in rats and mice by the oral route in two studies (NCI, 1977; Maltoni et al., 1986) and by the inhalation route in one study (Quast et al., 1984, 1988). These bioassays either showed no treatment-related increase in tumors or are considered inadequate for evaluation of carcinogenic potential. 1,1,1-Trichloroethane has been tested extensively for genotoxic potential; results are predominantly negative. The chemical has been shown to interact weakly with DNA.

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for 1,1,1-trichloroethane provides *inadequate information to assess carcinogenic potential.* This characterization is based on inadequate evidence of carcinogenicity in humans and animals. Accordingly, the development of quantitative assessments of the carcinogenicity of 1,1,1-trichloroethane is not supported.

5.3.1. Oral Exposure

Not applicable.

5.3.2. Inhalation Exposure

Not applicable.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HUMAN HAZARD POTENTIAL

1,1,1-Trichloroethane is a widely used industrial solvent. The chemical is well absorbed following oral, inhalation and dermal exposure. Blood levels approach steady-state after approximately 2 hours of inhalation exposure. 1,1,1-Trichloroethane is rapidly distributed throughout the body. The highest concentrations are found in fatty tissues. Most of the absorbed 1,1,1-trichloroethane is rapidly eliminated from the body unchanged in the expired air. A small amount is metabolized in the liver to trichloroethanol and trichloroacetic acid, which are excreted in the urine. 1,1,1-Trichloroethane and its metabolites have been shown not to accumulate to a large extent with repeated exposure.

The CNS is the most sensitive target for 1,1,1-trichloroethane following inhalation exposure. Deficits in neurobehavioral performance tests have been widely reported in humans and animals with acute exposure. Neurodevelopmental effects and neurochemical evidence of gliosis have been reported in inhalation animal studies of longer duration. Gross CNS depression is seen after exposure (by inhalation or oral gavage) to high levels. High levels have also been found to produce depression of respiration and blood pressure, and to produce cardiac arrhythmia by sensitizing the heart to endogenous epinephrine. Animal studies have also shown 1,1,1-trichloroethane to be a weak hepatotoxicant, producing mild effects on the liver at relatively high levels.

Most of the effects of 1,1,1-trichloroethane are thought to be produced by the parent compound, primarily by interfering with the function of mitochondrial and cellular membranes. Although produced only in low quantities, the metabolites trichloroethanol and trichloroacetic acid are known to have effects on the nervous system and liver, respectively, and may contribute to the observed effects on these targets.

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for 1,1,1-trichloroethane provides inadequate information to assess carcinogenic potential. This characterization is based on inadequate evidence of carcinogenicity in humans and animals.

6.2. DOSE RESPONSE

6.2.1. Noncancer/Oral

Acute and Short-term RfD. Oral data for 1,1,1-trichloroethane are inadequate to support dose-response assessment for acute and short-term exposure durations.

Subchronic and Chronic RfD. The NTP (2000) subchronic study was used as the basis

for the RfD. Decreased body weight gain was observed in male and female exposed mice relative to the control, which was not due to reduced feed consumption. The data were analyzed with BMD methods to derive a point of departure of 2155 mg/kg-day (associated with a 10% change in mean terminal body weight in female mice relative to the control mean). The subchronic oral RfD of 7 mg/kg-day was derived from this point of departure and application of a composite UF of 300 (10 for extrapolation from animals to humans, 10 for extrapolation to the most susceptible humans, and 3 for database deficiencies). The chronic oral RfD of 2 mg/kg-day was derived from the same point of departure and application of a composite UF of 1000 (10 for extrapolation from animals to humans, 10 for extrapolation to the most susceptible humans, 3 for extrapolation from subchronic to chronic exposure duration, and 3 for database deficiencies).

Confidence in the principal study, NTP (2000), is high. The 90-day feeding study is a recently-conducted, peer-reviewed study performed using standard protocols for NTP toxicity studies. 1,1,1-Trichloroethane was microencapsulated and administered in the diet to avoid chemical loss due to volatilization and to avoid toxicity that can occur when administered in a bolus dose. Confidence in the oral database is medium. Chronic oral animal studies were designed as cancer bioassays with only limited investigation of noncancer endpoints. Oral reproductive and developmental toxicity studies include a multigeneration study in mice, drinking water developmental toxicity studies in rats, and a study of developmental neurotoxicity in rats. Repeat-dose studies, including NTP (2000), did not include investigation of sensitive neurological endpoints; the neurological endpoints in repeat-dose oral studies were limited to clinical observations and brain histopathology. Overall confidence in both the subchronic and chronic RfDs is medium.

6.2.2. Noncancer/Inhalation

Acute inhalation RfC. The most sensitive endpoint for dose-response assessment is the effect of acute exposure on performance in neurobehavioral tests conducted by Mackay et al. (1987) in human volunteers. The data in this study were not presented in a manner amenable to benchmark dose modeling, so the LOAEL of 950 mg/m^3 following exposure for 1 hour was used as the point of departure for the dose-response assessment (a NOAEL was not identified). PBPK modeling was used for duration extrapolation (i.e., to derive acute RfC values for other exposure durations between 1 and 24 hours). Based on the assumption that CNS effects are correlated with blood 1,1,1-trichloroethane levels, the 1,1,1-trichloroethane level in blood associated with a 1-hour exposure to 950 mg/m^3 was determined. A PBPK model (Reitz et al., 1988) was used to estimate the ambient (external) exposure concentration required to achieve the same blood (internal) concentration following exposures of 4, 8, and 24 hours. The external concentrations were 715, 693 and 650 mg/m^3, respectively. Acute RfC values of 9, 7, 7, and 6 mg/m^3 for 1, 4,

8, and 24 hours, respectively, were derived by applying a composite UF of 100 (10 for use of a LOAEL and 10 for extrapolation to the most susceptible humans).

Short-term RfC. The acute neurobehavioral LOAEL of 950 mg/m^3 (following a 1-hour exposure) from the Mackay et al. (1987) study was observed to be lower than the LOAEL for any endpoint in studies of short-term duration. A PBPK model (Reitz et al., 1988) was used to estimate the external exposure concentration (526 mg/m^3) required to achieve the same blood (internal) concentration once steady state was reached at 14 days. Use of the acute inhalation data for longer exposures is supported by toxicokinetic evidence that 1,1,1-trichloroethane and its metabolites do not accumulate in blood to any appreciable extent, if at all, with repeated exposure. The weight of evidence of the animal toxicity data suggests there is no lowering of the threshold for neurobehavioral effects with repeated versus acute exposure, although such evidence is limited. The short-term RfC of 5 mg/m^3 was derived by applying an UF of 100 (10 for extrapolation to the most susceptible humans and 10 for extrapolation from a LOAEL to a NOAEL) to the point of departure of 526 mg/m^3.

Subchronic and Chronic RfC. The most appropriate repeat-dose studies for derivation of the subchronic and chronic RfCs are the 2-year inhalation bioassay in rats and mice by Quast et al. (1984, 1988) and the 14-week inhalation study in mice by McNutt et al. (1975). The highest concentration tested in Quast et al. (1984, 1988) caused treatment-related effects in the liver of rats considered to be adaptive physiological changes and not adverse (designated a NOAEL); the highest concentration tested in the McNutt et al. (1975) study, which was 3.7-folder higher than the NOAEL in Quast et al. (when both concentrations were adjusted for continuous exposure), caused clearly adverse effects on the liver in the mouse. PBPK modeling was used to estimate the human equivalent concentration at the NOAEL (1553 mg/m^3, based on a TWA AUC concentration in liver as the dose metric). A composite UF of 100 (3 for extrapolation from animals to humans, 10 for extrapolation to the most susceptible humans, and 3 for database deficiencies) was applied to obtain an RfC of 16 mg/m^3. Because the histopathologic findings in Quast et al. (1984, 1988) were observed at the 6-month sacrifice and did not progress in incidence or severity at later interim sacrifices, the RfC could apply to both subchronic and chronic durations. This value of the subchronic RfC (16 mg/m^3) derived from a repeat-dose inhalation study turns out to be larger than the acute and short-term RfCs for 1,1,1-trichloroethane, which range from 5 to 9 mg/m^3. It is generally anticipated that acute (or short-term) RfCs would be higher in absolute value than the subchronic or chronic RfC for that chemical since the acute (or short-term) exposure durations are greatly reduced compared to exposures of subchronic or chronic duration. In the case of 1,1,1-trichloroethane, clearly the short-term RfC of 5 mg/m^3 is protective of health effects associated with subchronic and chronic exposure. Accordingly, the subchronic and chronic RfCs are set at 5 mg/m^3 so as not to exceed

the limiting reference value derived for short-term exposure.

Overall confidence in the acute inhalation RfC is medium. Confidence in the principal study (Mackay et al., 1987) is medium. The study included a battery of neurobehavioral tests and correlated test outcomes with blood 1,1,1-trichloroethane levels. The number of volunteers was relatively small (12), and standard deviation/standard errors were not reported. Confidence in the acute inhalation database is high. The acute inhalation database is extensive, including both human and animal studies focused on the most sensitive endpoint, neurotoxicity. The inhalation database also includes inhalation developmental toxicity studies in three species.

Overall confidence in the short-term inhalation RfC is medium. Confidence in the principal study, Mackay et al. (1987) and in the short-term database is medium. Several animal studies of short-term exposure duration are available. Although most are limited in the scope of the endpoints investigated, these studies focused on endpoints expected to be the most sensitive following acute/short-term exposure.

Overall confidence in the subchronic and chronic RfCs is medium. Confidence in Quast et al. (1984, 1988), one of the co-principal studies, is high. This study was well conducted, using two species, adequate numbers of animals, and interim sacrifices. Failure to use an exposure concentration high enough to produce treatment-related effects in this study was off-set by the McNutt et al. (1975) study, which included an exposure concentration that resulted in clearly adverse hepatotoxic effects. Confidence in the database is medium. The database includes a two-year chronic inhalation bioassay in rats and mice, inhalation developmental toxicity studies in three species, and a single generation reproductive/developmental toxicity study that included exposure prior to mating. Although an inhalation multigeneration study has not been conducted, a multigeneration reproductive study by the oral route is available. While the available repeat-dose studies do not provide evidence of overt neurobehavioral effects, most repeat-dose studies did not include examination of subtle CNS toxicity.

6.2.3. Cancer/Oral and Inhalation

Under the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a), the database for 1,1,1-trichloroethane is inadequate to assess human carcinogenic potential. Accordingly, a quantitative assessment of carcinogenic potential was not performed.

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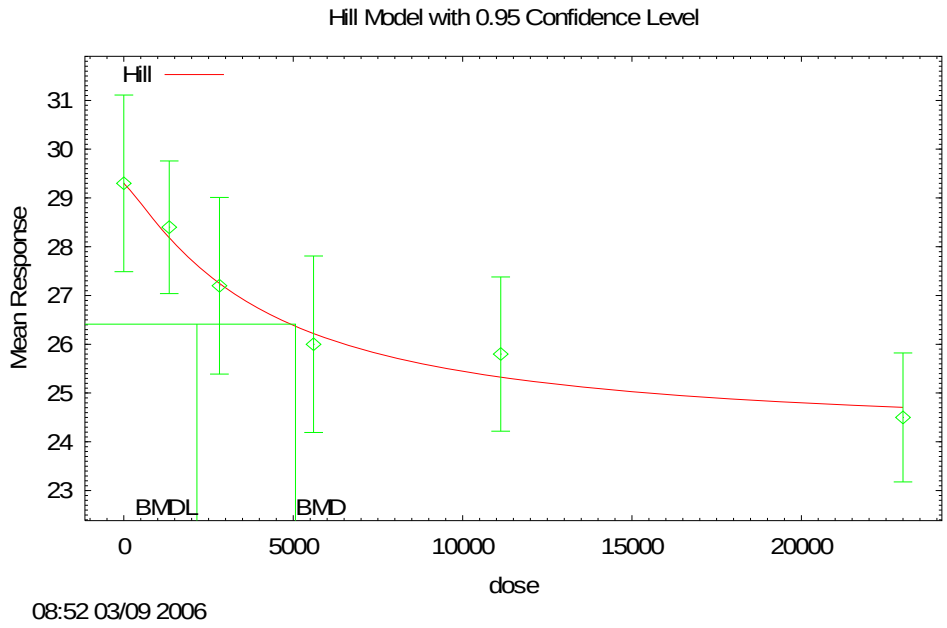
APPENDIX A
Summary of External Peer Review and Public Comments and Disposition

To be added after external peer review of this assessment has been completed.

APPENDIX B
Benchmark Dose Modeling Results and Output

Terminal Body Weight in Female Mice (NTP, 2000) – Hill Model

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  Hill Model. (Version: 2.5;  Date: 10/21/2005)
  Input Data File: FMOUSEBW_6DOSEGRPS.(d)
  Wed Mar 08 10:37:20 2006
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 BMDS MODEL RUN
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   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = MEAN
   Independent variable = DoseMg-Kg-D
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 6
   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 =      4.75395
                            rho =            0   Specified
                      intercept =         29.3
                              v =         -4.8
                              n =      1.30346
                              k =         3515


                              Parameter Estimates
                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
          alpha          4.65846            1.156            2.39274             6.92417
      intercept          29.3467                0            29.3467             29.3467
              v         -5.20438          3.52852           -12.1202              1.7114
              n          1.17137          1.94501           -2.64078             4.98353
```

k	4066.88	2.54568	4061.89	4071.87

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	n	k
alpha	1	-1.9e-007	-1.9e-007	-1.4e-007	2.7e-007
intercept	-1.9e-007	1	-0.37	-0.25	-0.13
v	-1.9e-007	-0.37	1	0.92	-0.84
n	-1.4e-007	-0.25	0.92	1	-0.81
k	2.7e-007	-0.13	-0.84	-0.81	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	29.3	29.3	2.53	2.16	-0.0684
1340	10	28.4	28.2	1.9	2.16	0.245
2820	10	27.2	27.3	2.53	2.16	-0.138
5600	10	26	26.3	2.53	2.16	-0.385
1.113e+004	10	25.8	25.4	2.21	2.16	0.635
2.3e+004	8	24.5	24.7	1.58	2.16	-0.323

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 A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = alpha*(Mu(i))^rho

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

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-73.249763	7	160.499525
A2	-71.686303	12	167.372607
A3	-73.249763	7	160.499525
fitted	-73.621836	5	157.243673
R	-86.493978	2	176.987956

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	29.6153	10	0.0009899
Test 2	3.12692	5	0.6804
Test 3	3.12692	5	0.6804
Test 4	0.744147	2	0.6893

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 .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.1

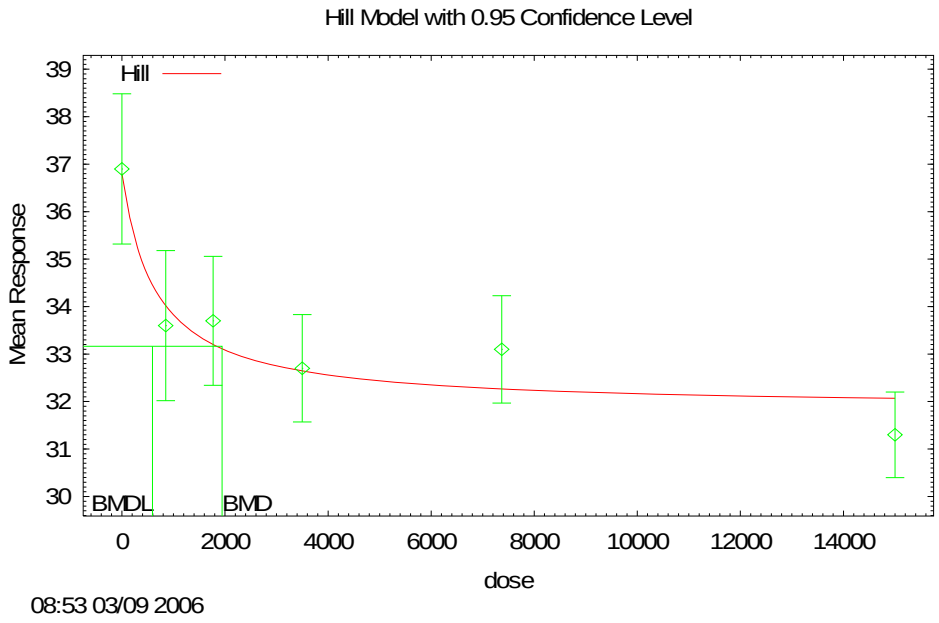
Risk Type = Relative risk

Confidence level = 0.95

BMD = 5064.36

BMDL = 2155.2

Terminal Body Weight in Male Mice (NTP, 2000) – Hill Model

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  Input Data File: MMOUSEBW_6DOSEGRPS.(d)
  Wed Mar 08 11:55:56 2006
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 BMDS MODEL RUN
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   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = MEAN
   Independent variable = DoseMg-Kg-D
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 6
   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 =      3.07899
                            rho =            0   Specified
                      intercept =         36.9
                              v =         -5.6
                              n =     0.883666
                              k =      721.212


                           Parameter Estimates

                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         alpha           3.2784           1.6707          0.00389591             6.55291
     intercept          36.8476                0             36.8476             36.8476
             v         -4.93548           4.27804            -13.3203             3.44932
             n                1                NA
```

k	659.541	3.18029	653.308	665.775

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	6.4e-007	-1.5e-007	-3.7e-007
intercept	6.4e-007	1	-0.69	-0.4
v	-1.5e-007	-0.69	1	-0.26
k	-3.7e-007	-0.4	-0.26	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	10	36.9	36.8	2.21	1.81	0.0916
850	10	33.6	34.1	2.21	1.81	-0.818
1770	10	33.7	33.3	1.9	1.81	0.783
3500	10	32.7	32.7	1.58	1.81	0.00934
7370	10	33.1	32.3	1.58	1.81	1.37
1.5e+004	10	31.3	32.1	1.26	1.81	-1.43

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 A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = alpha*(Mu(i))^rho

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

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-62.896204	7	139.792409
A2	-60.577188	12	145.154376
A3	-62.896204	7	139.792409
fitted	-65.620708	4	139.241416
R	-83.580886	2	171.161772

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	46.0074	10	<.0001
Test 2	4.63803	5	0.4616
Test 3	4.63803	5	0.4616

```
   Test 4              5.44901          3          0.1417

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 .1.  A homogeneous variance model appears to be
appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems to adequately describe the
data


        Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =     Relative risk

Confidence level =           0.95

             BMD =        1943.08

            BMDL =        594.296
```