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Provisional Peer-Reviewed Toxicity Values for

1,1,1,2-Tetrachloroethane
(CASRN 630-20-6)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,1,1,2-TETRACHLOROETHANE (CASRN 630-20-6)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

A chronic RfD of 3×10^{-2} mg/kg-day is available for 1,1,1,2-tetrachloroethane (chemical structure shown in Figure 1) on IRIS (U.S. EPA, 1987a). The RfD, verified on 04/16/87, is based on a 125 mg/kg-day LOAEL for liver and kidney lesions in rats in a chronic National Toxicology Program (NTP, 1983) gavage study. The source document for the IRIS RfD assessment is a 1983 Health Hazard Profile on 1,1,1,2-tetrachloroethane (U.S. EPA, 1983). The same RfD is included in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006), where it is sourced to a Drinking Water Health Advisory (U.S. EPA, 1989). The HEAST (U.S. EPA, 1997) adopted the chronic RfD of 3×10^{-2} mg/kg-day as a subchronic RfD for 1,1,1,2-tetrachloroethane. No other U.S. EPA documents on 1,1,1,2-tetrachloroethane are included in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991a, 1994).

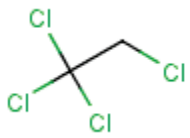

Figure 1. Chemical Structure of 1,1,1,2-Tetrachloroethane

No RfC for 1,1,1,2-tetrachloroethane is available on IRIS (U.S. EPA, 2009) or in the HEAST (U.S. EPA, 1997). The American Conference of Governmental Industrial Hygienists (ACGIH, 2008) does not list a threshold limit value for 1,1,1,2-tetrachloroethane, nor is the chemical listed by the Occupational Safety and Health Administration (OSHA, 2009). The National Institute for Occupational Safety and Health (NIOSH, 2005) does not list a Recommended Exposure Limit (REL) for 1,1,1,2-tetrachloroethane but advises caution when handling the chemical in the workplace to protect against CNS and liver effects and carcinogenicity associated with some other chloroethanes.

1,1,1,2-Tetrachloroethane is classified as Group C (Possible Human Carcinogen) on IRIS (U.S. EPA, 2009) based on increased incidences of liver tumors in female mice following chronic oral exposure (NTP, 1983) and inadequate evidence in humans. The mouse liver tumor data were used to derive an OSF of 2.6×10^{-2} per mg/kg-day; an IUR of 7.4×10^{-6} per ($\mu g/m^3$) was derived by extrapolation from the oral data. This assessment was first presented in U.S. EPA (1987b) and verified 05/04/88. The International Agency for Research on Cancer (IARC, 1999) classified the carcinogenicity of 1,1,1,2-tetrachloroethane as Group 3 (Not Classifiable as to its Carcinogenicity in Humans) based on limited evidence in animals and no data in humans. The chemical is not included in the NTP (2005) Report on Carcinogens.

The Agency for Toxic Substances Disease Registry (ATSDR, 2009), World Health Organization (WHO, 2009), and California Environmental Protection Agency (CalEPA, 2002, 2009a,b) have not evaluated the toxicity or carcinogenicity of 1,1,1,2-tetrachloroethane.

Literature searches were conducted from the 1960s through November 2008 for studies relevant to the derivation of provisional toxicity values for 1,1,1,2-tetrachloroethane. Databases searched include MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents (last 6 months). An updated search was conducted to May 2009.

REVIEW OF PERTINENT DATA

Human Studies

No information was located regarding the effects of oral or inhalation exposure to 1,1,1,2-tetrachloroethane in humans.

Animal Studies

Oral Exposure

1,1,1,2-Tetrachloroethane was included in a 21-day study designed to screen a series of halogenated ethanes for ability to induce hyaline droplet (α_{2u}-globulin) nephropathy in male rats (NTP, 1996). Groups of five male F344/N rats were administered 1,1,1,2-tetrachloroethane in corn oil by gavage at doses of 0, 0.62, or 1.24 mmol/kg-day (0, 104, or 208 mg/kg-day) for 21 consecutive days. Groups of five female rats were similarly administered 0 or 208 mg/kg-day of 1,1,1,2-tetrachloroethane, with the treated females serving as negative controls for hyaline droplet nephropathy. Evaluations included clinical signs, body weight, urinalysis (volume, specific gravity, creatinine, glucose, total protein, aspartate aminotransferase, γ-glutamyl transpeptidase [GGT], and *N*-acetyl-β-D-glucosaminidase [NAG]), gross necropsy, selected organ weights (right kidney, liver, and right testis), selected histopathology (right kidney, left liver lobe, and gross lesions), and kidney cell proliferation analysis (PCNA [proliferating cell nuclear antigen] labeling index for proximal and distal tubule epithelial cells in S phase). Nephropathy was induced in the high-dose male rats, as shown by increased absolute and relative kidney weights, increased urinary protein output, and NAG activity, decreased urinary GGT activity, hyaline droplet accumulation, increased incidences of tubule regeneration and granular casts, and increased renal PCNA labeling index. There were no other changes in the high-dose males, and no effects were observed in the low-dose males or treated females. Although definitive immunological identification of the protein droplets as α_{2u}-globulin was not

conducted, NTP (1996) concluded that 1,1,1,2-tetrachloroethane has the capacity to induce hyaline droplet nephropathy in male rats. As discussed by U.S. EPA (1991b), the hyaline droplet nephropathy syndrome is specific to male rats and not relevant to humans.

Groups of 10 male and 10 female F344/N rats were administered 1,1,1,2-tetrachloroethane in corn oil by gavage at dose levels of 0, 5, 10, 50, 100, or 500 mg/kg-day on 5 days/week for 13 weeks (NTP, 1983). The purity of 1,1,1,2-tetrachloroethane in all NTP (1983) studies was >99.99%. Evaluations included mortality, clinical signs, body weight, and gross pathology in all dose groups and comprehensive histopathology at 0 and 500 mg/kg-day. Compound-related effects consisted of loss of equilibrium in females and reduced body-weight gain in both sexes (final body weights 7−8% less than controls) at 500 mg/kg-day; no histopathological changes in the liver, kidneys, or other tissues were observed. This study did not include the specific evaluations for hyaline droplet nephropathy. Based on clinical signs of neurotoxicity and reduced body-weight gain, this study identifies a LOAEL of 500 mg/kg-day and NOAEL of 100 mg/kg-day for subchronic toxicity in rats.

Groups of 50 male and 50 female F344/N rats were administered 1,1,1,2-tetrachloroethane in corn oil by gavage at dose levels of 0, 125, or 250 mg/kg-day on 5 days/week for 103 weeks (NTP, 1983). Evaluations included mortality, clinical signs, body weight, gross pathology, and comprehensive histopathology. Survival was statistically significantly reduced ($p = 0.001$) in the male rats at 250 mg/kg-day; at 104 weeks, survival of the 0-, 125-, and 250-mg/kg-day males was 29/50 (58%), 25/50 (50%), and 21/50 (42%), respectively. The reduction in survival began at approximately Week 45 (as indicated by survival curves) and coincided with the appearance of CNS effects (weakness, inactivity, and loss of coordination), which occurred in males as well as females beginning at Week 44. There was no effect on survival in females or on body weight in either sex. Liver lesions were observed in females, including clear-cell changes (0/48, 3/49, and 9/44) and fatty changes (3/48, 1/49, and 7/44) in the 0-, 125-, and 250-mg/kg-day groups, respectively. The increase in clear-cell changes in the 250 mg/kg-day group was statistically significant ($p < 0.05$, Fisher's Exact tests conducted for this evaluation). Mineralization of the kidney was seen in males; this effect was characterized by multifocal deposits of basophilic material and crystals in the tubules of the papilla, and occurred in 12/48 (25%), 19/50 (38%), and 26/48 (54%) males at 0, 125, and 250 mg/kg-day, respectively. The increase in the 250 mg/kg-day group was statistically significant ($p < 0.05$, Fisher's Exact tests conducted for this evaluation). It should be noted that the subsequently conducted NTP (1996) renal toxicity study summarized above indicates that the kidney mineralization in the male rats is likely to have been associated with hyaline droplet nephropathy. Based on the clinical signs of neurotoxicity and concurrent reduced survival beginning at Weeks 44−45 at the high dose, and the lack of statistically significant increases in liver lesions, relevant kidney lesions, or other effects at the low dose, this study identifies a frank effect level (FEL) of 250 mg/kg-day and NOAEL of 125 mg/kg-day for subchronic and chronic toxicity in rats. These effect levels differ from those in the 1987 evaluation of this study on IRIS, in which a LOAEL of 125 mg/kg-day and no NOAEL were identified based on increases in kidney mineralization in males and liver clear-cell changes in females at both dose levels. The difference in interpretation reflects the newer analysis of α_{2u}-globulin accumulation as a mode of action for kidney effects and additional information on the occurrence of kidney lesions (NTP, 1996) that was not available at the time of the IRIS assessment, as well as uncertainty associated with the increase in liver clear cell changes at the low dose. NTP (1996) evaluated the

data available for a number of haloethanes and determined that the observed nephrotoxicity in rats following exposure to 1,1,1,2-tetrachloroethane was likely due to α_{2u}-globulin accumulation, a male rat-specific effect. Although a detailed mode of action analysis has not been conducted in this assessment, EPA is relying on the NTP (1996) analysis, and as such, the kidney effects are not considered relevant to humans (U.S. EPA, 1991b).

Male and female Wistar rats were administered 0 or 0.30 g/kg (0 or 300 mg/kg-day) of 1,1,1,2-tetrachloride in olive oil by gavage on 5 days/week for 10 months in a briefly reported study published in French (Truhaut et al., 1974). The numbers of animals were not clearly reported but appear to be 20 (2 lots of 10) of each sex in the treated group and 10 of each sex in the control group. Effects in treated rats included reduced growth in females, increased mortality in both sexes (25% in treated males and 40% in treated females compared to 10% in controls) and hepatic histopathology in both sexes. The liver lesions included cytoplasmic granulation, microvacuolization, and centrilobular necrosis that varied in degree but were often severe, particularly in females. The study authors indicated that reproductive function was not impaired, but no details were provided. Due to incomplete reporting of methods and results, additional study information (e.g., incidence data) is not available. The apparently increased mortality in both sexes suggests that 300 mg/kg-day is a FEL for subchronic toxicity in rats, but confidence in this effect level is low due to the limitations of the available information.

Groups of 10 male and 10 female B6C3F1 mice (10/sex/dose) were administered 1,1,1,2-tetrachloroethane in corn oil by gavage at dose levels of 0, 5, 10, 50, 100, or 500 mg/kg-day, 5 days/week, for 13 weeks (NTP, 1983). Evaluations included survival, clinical signs, body weight, and gross pathology in all dose groups, and comprehensive histopathology at 0 and 500 mg/kg-day. There were no compound-related effects on any endpoint, indicating that a NOAEL of 500 mg/kg-day and no LOAEL were identified for subchronic toxicity in mice.

Groups of 50 male and 50 female B6C3F1 mice were administered 1,1,1,2-tetrachloroethane in corn oil by gavage at dose levels of 0, 250, or 500 mg/kg-day on 5 days/week for 65 weeks (high-dose mice) or 103 weeks (control and low-dose mice) (NTP, 1983). Mortality, clinical signs, body weight, gross pathology, and comprehensive histopathology were evaluated. Effects included clinical signs of neurotoxicity in both sexes (sluggishness beginning at Week 34 and weakness, incoordination, and rapid breathing beginning at Week 51) and reduced body-weight gain in both sexes (beginning at Week 20 in males and Week 40 in females) at 500 mg/kg-day. Survival was significantly ($p < 0.05$) reduced in females at ≥250 mg/kg-day and males at 500 mg/kg-day. The reduced survival in the 250 mg/kg-day females began at approximately 70 weeks of exposure (as indicated by a survival curve); after 104 weeks, survival in females at 250 mg/kg-day was 31/50 (62%) compared to 41/50 (82%) in controls. At 500 mg/kg-day, reduced survival began at approximately 40 weeks in males and 50 weeks in females, and all mice of both sexes were dead by Week 66.

The histopathology evaluations identified the liver as the major target organ for toxicity as well as carcinogenicity (NTP, 1983). Nonneoplastic liver lesions, including inflammation, necrosis, fatty metamorphosis, and hepatomegaly, were statistically significantly ($p < 0.05$) increased in males and females at 500 mg/kg-day; incidences of these lesions were similar in both sexes, ranging from 30−80% at 500 mg/kg-day compared to 0−17% in controls and 2−7% at 250 mg/kg-day. For liver tumors, significant ($p < 0.05$) increases were observed for hepatocellular adenomas in males at ≥250 mg/kg-day and females at 500 mg/kg-day,

hepatocelluar carcinomas in females at 500 mg/kg-day and combined hepatocellular adenomas and carcinomas in both sexes at ≥250 mg/kg-day. The findings suggested to NTP (1983) that the increased mortality was caused by toxicity and not due to hepatocellular tumors. Based on the reduced body-weight gain from Week 20 and clinical signs of neurotoxicity from Week 34, this study identifies a NOAEL of 250 mg/kg-day and LOAEL of 500 mg/kg-day for subchronic toxicity in mice. Chronic effect levels for mice were not noted in the U.S. EPA evaluation of this study on IRIS. Based on the reduced survival from approximately Week 70, the study identifies a FEL of 250 mg/kg-day and no NOAEL for chronic toxicity in mice.

Inhalation Exposure

An unpublished short-term inhalation study was conducted in which groups of six male Sprague Dawley rats were exposed to 1,000 ppm of 1,1,1,2-tetrachloroethane vapor for 4 or 7 hours/day, on 4 days/week regimen, for 2 weeks (Dow Chemical Company, 1969). A group of 6 control rats was similarly exposed to untreated air for 7 hours/day. Evaluations included clinical signs, body weight, serum alanine aminotransferase (ALT) and alkaline phosphatase activities, organ weights (liver, kidneys, spleen, heart, brain, and testes), and complete gross and histological examinations. Ataxia was observed in rats exposed for 4 or 7 hours/day beginning approximately 1 hour after the beginning of each exposure, with recovery occurring approximately 1 hour following exposure. Body-weight gain was reduced in rats exposed for 4 or 7 hours/day, with weight loss occurring during the first 3 days with the 7 hours/day exposures. Rats exposed for 4 or 7 hours/day also had statistically significant increases in serum ALT (57 and 105% higher than controls) and absolute kidney weight (relative weight not reported), as well as gross pathology in the kidneys (pale appearance) and histopathology in the kidneys (moderate to severe hyaline droplet formation in the convoluted tubules) and liver (minimal-to-moderate central fatty metamorphosis). This study identifies a freestanding LOAEL of 1,000 ppm for CNS, liver, and other systemic effects of short-term inhalation exposure in rats.

Limited information is available on the subchronic inhalation toxicity of 1,1,1,2-tetrachloroethane in a briefly reported study published in French (Truhaut et al., 1974). Male and female Wistar rats were exposed to 0 or 500 mL/m^3 (0 or 500 ppm) of 1,1,1,2-tetrachloroethane vapor for 4 hours/day, 5 days/week, for 12 months. The numbers of exposed rats were not clearly reported but appear to be 20 (2 lots of 10) of each sex; there is no indication of the sizes of the rat control groups. Rabbits (two males and two females) were similarly exposed to 500 mL/m^3 (500 ppm) of 1,1,1,2-tetrachloroethane for 6 months apparently without controls. There were no exposure-related effects on survival, body weight, or hematology in either species. Histopathological examinations showed congested and hemorrhagic lungs and degenerative changes in the liver (cytoplasmic granulation, microvacuolization, and centrilobular necrosis) in both rats and rabbits. The authors indicated that reproductive function was not impaired in the rabbits, but also that embryos of the treated females accumulated the chemical through the placenta and died within 2 days of exposure (no details provided). Due to incomplete reporting of methods and results, additional study information (e.g., incidence data) is not available. These results suggest that 500 ppm is a freestanding LOAEL for subchronic toxicity in rats and rabbits, but confidence in this effect level is low due to limitations of the available information.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 1,1,1,2-TETRACHLOROETHANE

Subchronic p-RfD

Information relevant to the derivation of a subchronic p-RfD for 1,1,1,2-tetrachloroethane is available from 13-week and 2-year studies in rats and mice (NTP, 1983) and a 10-month study in rats (Truhaut et al., 1974). Compound administration in all studies was by gavage given 5 days/week. Based on evaluations that were limited to mortality, clinical signs, body weight, gross pathology, and histopathology in all studies.

As summarized in Table 1, subchronic effect levels in the rats include a NOAEL of 100 mg/kg-day and LOAEL of 500 mg/kg-day from the 13-week study based on clinical signs of neurotoxicity and reduced body-weight gain. Results of the 10-month and 2-year studies indicate that extended subchronic exposures caused cumulative toxicity in rats resulting in reduced survival and neurotoxicity at doses lower than the 13-week LOAEL of 500 mg/kg-day for neurotoxicity without mortality. In particular, 300 mg/kg-day was a freestanding FEL for reduced survival in the 10-month rat study, and 250 mg/kg-day was a FEL for reduced survival and clinical signs of neurotoxicity beginning at Weeks 44−45 in the 2-year rat study. The 2-year study identifies a NOAEL of 125 mg/kg-day, with no effects on survival, clinical signs, histopathology, or any other study endpoint.

Key subchronic effect levels in the mice are a NOAEL of 500 mg/kg-day and no LOAEL for 13 weeks, and a NOAEL of 250 mg/kg-day and LOAEL of 500 mg/kg-day based on reduced body-weight gain beginning at Week 20 and clinical signs of neurotoxicity beginning at Week 34 in the 2-year study. These results indicate a cumulative toxicity consistent with that observed in the rats. Because the mice were less sensitive than the rats (i.e., 250 mg/kg-day was a NOAEL in mice but a FEL in rats), the 125 mg/kg-day NOAEL in rats is a better basis for subchronic p-RfD derivation. BMD analysis was not performed due to problems with the NTP (1983) study (heat stress deaths, gavage errors).

The rat NOAEL of 125 mg/kg-day was adjusted from an intermittent (5 days/week) dose to an equivalent continuous daily dose of 89.3 mg/kg-day, and divided by a composite UF of 1,000 to derive a **subchronic p-RfD** as follows:

$$\begin{aligned} NOAEL_{ADJ} &= NOAEL \times 5 \text{ days}/7 \text{ days} \\ &= 125 \text{ mg/kg-day} \times 5/7 \\ &= 89.3 \text{ mg/kg-day} \end{aligned}$$

Table 1. Summary of Effect Levels from Key Oral Toxicity Studies of 1,1,1,2-Tetrachlorethane

Species	Exposure Duration[a]	NOAEL[b]	LOAEL[b]	FEL[b]	Effects	Reference
Rat	13 weeks	100	500	ND	Clinical signs of neurotoxicity and reduced body-weight gain in both sexes.	NTP, 1983
Rat	103 weeks	125	ND	250	Reduced survival in males and clinical signs of neurotoxicity in both sexes beginning at Weeks 44−45.	NTP, 1983
Rat	10 months	ND	ND	300	Increased mortality and degenerative liver lesions in both sexes, but confidence in study is low due to poor reporting.	Truhaut et al., 1974
Mouse	13 weeks	500	ND	ND	No effects on survival, clinical signs, body weight, gross pathology, or histopathology.	NTP, 1983
Mouse	103 weeks	ND	ND	250	Reduced survival in females beginning at Week 70. Clinical signs of neurotoxicity from Week 34 and reduced body-weight gain from Weeks 20−40 occurred in both sexes.	NTP, 1983

[a]Exposure was by gavage on a 5-days/week schedule in all studies.
[b]mg/kg-day.

ND = not determined.

$$\textbf{Subchronic p-RfD} = NOAEL_{ADJ} \div UF$$
$$= 89.3 \text{ mg/kg-day} \div 1{,}000$$
$$= \mathbf{0.09 \text{ or } 9 \times 10^{-2} \text{ mg/kg-day}}$$

The composite UF of 1,000 is composed of the following UFs:

- UF_H: A factor of 10 is applied to account fro potential human variability.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies toxicodynamic and toxicokinetic differences are not available.
- A factor of 10 is applied for database inadequacies. The database lacks a developmental toxicity study and adequate reproductive toxicity data.

Confidence in the principal study (NTP, 1983) is low because limited evaluations were performed in the subchronic studies in rats and mice and the studies are not reported in detail. In-life observations during the first year of the chronic studies supported and enhanced the findings of the subchronic studies, but they were limited to survival, clinical signs, and body

weight. Confidence in the database is low. Aside from the NTP studies, there is only one other relevant study in the database. This study provides supporting information for the derivation of the subchronic p-RfD, but methods and results are only briefly and incompletely reported. Reproductive and developmental toxicity have not been studied. Overall confidence in the subchronic p-RfD is low.

Chronic p-RfD

A chronic RfD of 0.03 mg/kg-day is available on IRIS (U.S. EPA, 2009) based on the 2-year oral study in rats (NTP, 1983). The RfD is calculated from a LOAEL of 125 mg/kg-day (adjusted to 89.3 mg/kg-day) for liver and kidney lesions and a composite UF of 3,000 (10 for extrapolation from rats to humans, 10 for protection of sensitive individuals, 10 for extrapolation from LOAEL, and 3 for lack of adequate supporting reproductive and chronic toxicity data). As indicated earlier, the kidney lesions were considered to be related to hyaline droplet nephropathy as determined by NTP (1996). For this PPRTV assessment, EPA has followed the recommendations of NTP and considers the nephropathy in male rats to not be relevant to humans.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 1,1,1,2-TETRACHLOROETHANE

Subchronic p-RfC

Information relevant to the subchronic inhalation toxicity of 1,1,1,2-tetrachloroethane is available from limited studies of rats exposed for 2 weeks (Dow Chemical Company, 1969) or 12 months (Truhaut et al., 1974) and rabbits exposed for 6 months (Truhaut et al., 1974). The 2-week study in rats identifies a freestanding LOAEL of 1,000 ppm for effects that included clinical signs of neurotoxicity (ataxia), reduced body-weight gain, and liver toxicity (increased serum ALT and fatty degeneration). The 6-month rabbit and 12-month rat studies appear to identify a freestanding LOAEL of 500 ppm in both species based on histopathology in the lungs (congestion and hemorrhages) and liver (degenerative changes including centrilobular necrosis), and possible embryotoxic effects, as well. However, the data are inadequate for subchronic p-RfC derivation due to limitations that include one study of short duration (2 weeks), a single exposure level that is not a NOAEL in all studies, a small number of rabbits (and possibly no controls) in the 6-month study, and poor reporting of the 6- and 12-month studies.

Chronic p-RfC

Derivation of a chronic p-RfC for 1,1,1,2-tetrachloroethane is precluded by a lack of chronic inhalation data and the insufficiencies of the 6-month rabbit and 12-month rat studies (Truhaut et al., 1974) as summarized above.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,1,1,2-TETRACHLOROETHANE

A cancer assessment for 1,1,1,2-tetrachloroethane is available on IRIS (U.S. EPA, 2009). 1,1,1,2-Tetrachloroethane was given a weight-of-evidence cancer classification of Group C (possible human carcinogen) using the U.S. EPA (1986) carcinogen risk assessment guidelines,

and an OSF of 2.6×10^{-2} per (mg/kg-day) was estimated based on hepatocellular adenoma or carcinoma (combined) in female mice treated by gavage for up to 103 weeks (NTP, 1983). An IUR of 7.4×10^{-6} per $\mu g/m^3$ was derived by extrapolation from the oral data.

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