1,1,2,2-Tetrachloroethane; CASRN 79-34-5

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 1,1,2,2-Tetrachloroethane

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/2010
Inhalation RfC (I.B.)	qualitative discussion	09/30/2010
Carcinogenicity Assessment (II.)	yes	09/30/2010

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) FOR ORAL EXPOSURE

Substance Name — 1,1,2,2-Tetrachloroethane
CASRN — 79-34-5
Section I.A. Last Revised — 09/30/2010

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of

substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. SUBCHRONIC ORAL RfD

The subchronic RfD applies to exposures for more than 30 days, up to approximately 10% of the life span in humans (up to approximately 90 days in typically used laboratory animals species).

I.A.1.1. SUBCHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Subchronic RfD
Increased relative liver weight in rats **Subchronic dietary study** **NTP (2004)**	$BMDL_{1SD}$: 15 mg/kg-day	300	0.05 mg/kg-day

*Conversion Factors and Assumptions - A benchmark response (BMR) of 1 standard deviation (SD) of the control mean was considered appropriate for derivation of the RfD under the assumption that it represents a minimally biologically significant response level.

I.A.1.2. PRINCIPAL AND SUPPORTING STUDIES

The National Toxicology Program (NTP, 2004) exposed F344 rats (10/sex/group) to 0, 20, 40, 80, 170, or 320 mg/kg-day (both males and females) and $B6C3F_1$ mice (10/sex/group) to 0, 100, 200, 370, 700, or 1,360 mg/kg-day (males) and 0, 80, 160, 300, 600, or 1,400 mg/kg-day (females) in the diet for 14 weeks.

A statistically significant decrease in body weight gain (<10%) in both male and female rats at ≥80 mg/kg-day was observed. Low dose effects observed in the liver included statistically significantly increased relative liver weights in both male and female rats at ≥40 mg/kg-day. In addition, hepatocyte vacuolization was observed at ≥20 mg/kg-day in male rats and ≥40 mg/kg-day in female rats. The severity of vacuolization was reported to be minimal to mild. Serum enzyme activity levels of both male and female rats were also affected. For example, increases in serum alanine aminotransferase (ALT) and sorbitol dehydrogenase

(SDH) activity were observed at ≥80 mg/kg-day in male rats and ≥170 mg/kg-day in female rats. In addition, increased cholesterol levels and alkaline phosphatase (ALP) activity were observed in female rats at ≥80 and 170 mg/kg-day, respectively. Additional histopathology observed in the liver included a statistically significantly increased incidence of minimal to moderate hepatocyte hypertrophy at ≥170 mg/kg-day in females and ≥200 mg/kg-day in males. Also, increased incidence of necrosis and pigmentation were observed at ≥80 mg/kg-day, and hepatocellular mitotic alterations and foci of cellular alterations were observed at ≥80 and ≥170 mg/kg-day in male rats, respectively. In females, increased incidence of hepatocellular hypertrophy was observed at ≥80 mg/kg-day and necrosis, pigmentation, and foci of cellular alterations were reported at ≥170 mg/kg-day. Bile duct hyperplasia, increased bile acids, spleen pigmentation, and spleen atrophy were also observed in both male and female rats at the two highest doses.

Evidence of liver effects was also observed in mice by NTP (2004). A statistically significant increase in relative liver weights was observed in both male and female mice at ≥200 and 80 mg/kg-day, respectively. Increases in serum ALT and ALP activity, bile acid levels, and hepatic 5'-nucleotidase activity (males only) were observed in males and females at ≥370 and 160 mg/kg-day, respectively. The study authors also reported an increase in SDH activity at ≥200 and 80 mg/kg-day in male and female mice, respectively. Serum cholesterol levels were statistically significantly increased in female mice at ≥160 mg/kg-day. The incidence of hepatocellular necrosis was statistically significantly increased in male mice at ≥370 mg/kg-day and in female mice at ≥700 mg/kg-day. Hepatocellular hypertrophy was also reported in both genders at ≥160–200 mg/kg-day. A statistically significant increase in incidence of liver pigmentation and bile duct hyperplasia occurred at ≥300 mg/kg-day in females and ≥370 mg/kg-day in males.

NTP (2004) also observed effects associated with reproduction in adult rats and mice following subchronic exposure to 1,1,2,2-tetrachloroethane at dose levels as low as 40 mg/kg-day. In male rats, sperm motility was decreased at ≥40 mg/kg-day, and higher doses resulted in decreased epididymis weight and increased atrophy of the preputial and prostate gland, seminal vesicle, and testicular germinal epithelium. In female rats, minimal to mild uterine atrophy was increased at ≥170 mg/kg-day, and clitoral gland atrophy and ovarian interstitial cell cytoplasmic alterations were increased at 320 mg/kg-day. Female F344 rats in the 170 mg/kg-day group also spent more time in diestrus compared to controls. Male mice had increased incidences of preputial gland atrophy at ≥100 mg/kg-day. Less sensitive effects included decreases in absolute testes weight (≥700 mg/kg-day), absolute epididymis, and cauda epididymis weights (1,360 mg/kg-day), and a decrease in epididymal spermatozoal motility (1,360 mg/kg-day). The only noted reproductive toxicity parameter in female mice affected was a significant increase in the length of the estrous cycle at a dose of 1,400 mg/kg-day.

BMD modeling was conducted using the EPA's benchmark dose software (BMDS, version 2.1.1.) to analyze the effects associated with subchronic exposure to 1,1,2,2-tetrachloro-ethane. The software was used to calculate potential PODs for deriving the subchronic RfD by estimating the effective dose at a specified level of response (BMD_x) and its 95% lower bound ($BMDL_x$). For all continuous endpoints, a benchmark response (BMR) of 1SD of the control mean was considered appropriate for derivation of the RfD under the assumption that it represents a minimally biologically significant response level. For the dichotomous data (i.e., the incidence of hepatocellular cytoplasmic vacuolization), a BMR of 10% extra risk was considered appropriate for derivation of the RfD under the assumption that it represents a minimally biologically significant response level. The effects modeled include liver weight changes, serum ALT and SDH, bile acids, hepatocellular cytoplasmic vacuolization, and rat fetal body weights.

I.A.1.3. UNCERTAINTY FACTORS

UF = 300

A default UF of 10 was selected to account for the interspecies variability in extrapolating from laboratory animals (rats) to humans (i.e., interspecies variability), because information was not available to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans for 1,1,2,2-tetrachloroethane.

A default UF of 10 was selected to account for interindividual variability (UF_H) in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1,1,2,2-tetrachloroethane in humans.

An UF of 3 was selected to account for deficiencies in the database. The NTP (2004) 14-week study provides comprehensive evaluations of systemic toxicity and neurotoxicity in two species. The NTP (2004) study provides information on effects on sperm, estrous cycle, and male and female reproductive tissues in rats and mice, but the database lacks a two-generation reproductive toxicity study. Available developmental toxicity studies provide information on embryo or fetotoxicity in orally exposed rats and mice (Gulati et al., 1991a, b), but the studies did not include skeletal and visceral examinations.

An UF for lowest-observed-adverse-effect level (LOAEL)-to- no-observed-adverse-effect level (NOAEL) extrapolation was not used because the current approach is to address this factor as one of the considerations in selecting a benchmark response (BMR) for BMD modeling. In this case, a BMR associated with a change of 1 standard deviation (SD) from the control mean was selected under an assumption that it represents a minimally, biologically significant change.

I.A.1.4. ADDITIONAL STUDIES/COMMENTS

Gulati et al. (1991a) exposed pregnant CD Sprague-Dawley rats to 0, 34, 98, 180, 278, or 330 mg/kg-day 1,1,2,2-tetrachloroethane from gestation days (GDs) 4 through 20. Small but statistically significant decreases were observed in maternal body weight and average fetal weight at ≥98 mg/kg-day. No other maternal or fetal effects were reported by the study authors. In a second study, Gulati et al. (1991b) exposed pregnant Swiss CD-1 mice to 0, 987, 2,120, 2,216, or 4,575 mg/kg-day 1,1,2,2-tetrachloroethane from GDs 4 through 17. All animals (9/9) in the high-dose group died prior to the end of the study, precluding calculation of the average dose in this exposure group. Maternal body weights were statistically significantly decreased compared to controls at ≥2,120 mg/kg-day beginning on study day 9. Gross hepatic effects such as pale or grey and/or enlarged livers and a prominent lobulated pattern were also reported in dams from all groups except at the low dose. Complete litter resorption occurred in 1/11, 0/9, 2/8, 1/1, and 1/2 dams in the 0, 987, 2,120, 2,216, and 4,575 mg/kg-day groups, respectively. No other developmental effects were reported.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.A.1.5. CONFIDENCE IN THE SUBCHRONIC ORAL RfD

Study – high
Data Base – medium
RfD – medium

The overall confidence in the subchronic RfD assessment is medium. Confidence in the principal study (NTP, 2004) is high. Confidence in the database is medium. Reflecting high confidence in the principal study and medium confidence in the database, confidence in the subchronic RfD is medium.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.2. CHRONIC ORAL RfD

Critical Effect	Point of Departure*	UF	Chronic RfD
Increased relative liver weight in rats	$BMDL_{1SD}$: 15 mg/kg-day	1,000	0.02 mg/kg-day

Critical Effect	Point of Departure*	UF	Chronic RfD
Subchronic dietary study **NTP (2004)**			

*Conversion Factors and Assumptions - A benchmark response (BMR) of 1 standard deviation (SD) of the control mean was considered appropriate for derivation of the RfD under the assumption that it represents a minimally biologically significant response level.

I.A.2.2. PRINCIPAL AND SUPPORTING STUDIES

Information on the chronic oral toxicity of 1,1,2,2-tetrachloroethane is available from a bioassay in rats and mice. The National Cancer Institute (NCI, 1978) exposed groups of 50 male and 50 female Osborne-Mendel rats and B6C3F_1 mice to 1,1,2,2-tetrachloroethane in corn oil via gavage 5 days/week for 78 weeks.

There were no clear effects on survival in the male rats. In female rats, survival in the vehicle control, low-dose, and high-dose groups at the end of the study was 70, 58, and 40%, respectively. The increased mortality was affected by the deaths of 10 high-dose females, 8 with pneumonia and 2 with no reported lesions, during the first 5 weeks of the study. A statistically significant association between mortality and dose was observed in male and female mice, as survival was markedly decreased in the high-dose mice. In rats, histopathological effects included a dose-related increased incidence of hepatic fatty metamorphosis in high-dose males. In mice, nonneoplastic lesions observed included hydronephrosis and chronic inflammation in the kidneys in high-dose females and chronic inflammation in the low- and high-dose males.

The 14-week dietary study in rats and mice (NTP, 2004) used to derive the subchronic RfD was also considered for the derivation of the chronic RfD. The subchronic NTP (2004) study appears to be a more sensitive assay than the chronic NCI (1978) bioassay. The NTP (2004) study also uses lower dose levels and a wider dose range than the NCI (1978) study, and thereby provides a better characterization of the dose-response curve in the low-dose region. Additionally, dietary exposure is a more relevant route of exposure for the general population exposed to 1,1,2,2-tetrachloroethane in the environment than is gavage exposure. For these reasons, the NTP (2004) subchronic study was selected as the principal study.

I.A.2.3. UNCERTAINTY FACTORS (UFs)

UF = 1,000

A default UF of 10 was selected to account for the interspecies variability in extrapolating from laboratory animals (rats) to humans, because information was not available to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans for 1,1,2,2-tetrachloroethane.

A default UF of 10 was selected to account for interindividual variability (UF_H) in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of 1,1,2,2-tetrachloroethane in humans.

An UF of 3 was selected to account for extrapolation from a subchronic exposure duration study to a chronic RfD. The study selected as the principal study was a 14-week study by NTP (2004), a study duration that is minimally past the standard subchronic (90-day) study and falls well short of a standard lifetime study. In addition, some data are available to inform the nature and extent of effects that would be observed with a longer duration of exposure to 1,1,2,2-tetrachloroethane. Specifically, the available chronic cancer bioassay data (NCI, 1978) suggest that liver damage observed in F344 rats following subchronic exposure to 1,1,2,2-tetrachloroethane (NTP, 2004) (e.g., increased liver weight and incidence of necrosis, and altered serum enzyme and bile acid levels) may not progress to more severe effects following chronic exposures. The chronic cancer bioassay was conducted in Osborne-Mendel rats and did not measure liver enzyme levels. However, NCI (1978) observed minimal alterations in liver pathology, including inflammation, fatty metamorphosis, focal cellular change, and angiectasis in rats, and organized thrombus and nodular hyperplasia in mice. NCI (1978) reported that the study authors performed complete histological analysis on the liver, but specific endpoints assessed were not included. The available database does not abrogate all concern associated with using a subchronic study as the basis of the RfD. For these reasons, a threefold UF was used to account for the extrapolation from subchronic to chronic exposure duration for the derivation of the chronic RfD.

A UF of 3 was selected to account for deficiencies in the database. The NTP (2004) 14-week study provides comprehensive evaluations of systemic toxicity and neurotoxicity in both rats and mice. However, the database is limited by the lack of a two-generation reproductive toxicity study. The NTP (2004) study provides information on effects on sperm, estrous cycle, and male and female reproductive tissues in rats and mice, but the database lacks a two-generation reproductive toxicity study. Available developmental toxicity studies provide information on embryo or fetotoxicity in orally exposed rats and mice (Gulati et al., 1991a, b), but the studies did not include skeletal and visceral examinations.

A UF for LOAEL-to-NOAEL extrapolation was not used because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In this case, a BMR associated with a change of 1 SD from the control mean was selected under an assumption that it represents a minimally biologically significant change.

I.A.2.4. ADDITIONAL STUDIES/COMMENTS

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.A.2.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study – high
Data Base – medium
RfD – medium

The overall confidence in this chronic RfD assessment is medium. Confidence in the principal study (NTP, 2004) is high. Confidence in the database is medium. Reflecting high confidence in the principal study and medium confidence in the database, confidence in the chronic RfD is medium.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.3. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document – U.S. EPA (2010)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 1,1,2,2-Tetrachloroethane* (U.S. EPA, 2010). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

Agency Completion Date — 09/30/2010

I.A.4. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR INHALATION EXPOSURE

Substance Name – 1,1,2,2-Tetrachloroethane
CASRN – 79-34-5
Section I.B. Last Revised – 09/30/2010

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. CHRONIC INHALATION RfC SUMMARY

The inhalation toxicity database lacks a well-conducted study that demonstrates a dose-related toxicological effect following subchronic and/or chronic exposure to 1,1,2,2-tetrachloroethane. Therefore, an inhalation RfC was not derived.

Information on the inhalation toxicity of 1,1,2,2-tetrachloroethane is limited. In the Truffert et al. (1977) study, rats were exposed to a presumed concentration of 560 ppm (3,909 mg/m^3) for a time-weighted average (TWA) duration of 5.1 hours/day, 5 days/week for 15 weeks. Findings included transient histological alterations in the liver, including granular appearance and cytoplasmic vacuolation, which were observed after 9 exposures and were no longer evident after 39 exposures. Because of the uncertainty regarding the actual exposure concentration for the single dose, and a lack of incidence and severity data, this report cannot be used to identify a NOAEL or LOAEL or for possible derivation of an RfC.

Horiuchi et al. (1962) observed fatty degeneration of the liver and splenic congestion in a single monkey exposed to a TWA of 1,974 ppm (15,560 mg/m^3) 1,1,2,2-tetrachloroethane 2 hours/day, 6 days/week for 9 months. The monkey was weak after approximately seven exposures and had diarrhea and anorexia between the 12th and 15th exposures. Beginning at the 15th exposure, the monkey was "almost completely unconscious falling upon his side" for 20–60 minutes after each exposure. Also, hematological parameters demonstrated sporadic changes in hematocrit and red blood cell and white blood cell counts, but the significance of these findings cannot be determined. This study cannot be utilized to identify a NOAEL or LOAEL due to the use of a single test animal with no control group.

Mellon Institute of Industrial Research (1947) observed an increased incidence of lung lesions and an increase in kidney weight in rats following a 6-month exposure to 200 ppm 1,1,2,2-tetrachloroethane, but these results were not evaluated because the control animals experienced a high degree of pathological effects in the kidney, liver, and lung, and because of the presence of an endemic lung infection in both controls and treated groups. Mellon Institute of Industrial Research (1947) also observed increased serum phosphatase levels and blood urea nitrogen levels in a dog exposed to 200 ppm 1,1,2,2-tetrachloroethane, compared to control values, along with cloudy swelling of the liver and the convoluted tubules of the kidney, and light congestion of the lungs. However, identification of a LOAEL or NOAEL is precluded by poor study reporting, high mortality and lung infection in the rats, and the use of a single treated animal in the dog study.

Kulinskaya and Verlinskaya (1972) observed inconsistent changes in acetylcholine levels in Chinchilla rabbits exposed to 10 mg/m^3 (1.5 ppm) 1,1,2,2-tetrachloroethane 3 hours/day, 6 days/week for 7–8.5 months. A NOAEL or LOAEL was not identified because the changes

in acetylcholine were not consistent across time and incompletely quantified, and the biological significance of the change is unclear.

Shmuter (1977) observed increases in antibody levels in Chinchilla rabbits at 2 mg/m^3 1,1,2,2-tetrachloroethane and decreases in antibody levels at 100 mg/m^3. Exposure to 100 mg/m^3 1,1,2,2-tetrachloroethane also resulted in a decrease in the relative content of antibodies in the γ-globulin fraction and an increase in the T and β fractions. This is a poorly reported study that provides inadequate data, including reporting limitations, toxicological uncertainty in the endpoints, and inconsistent patterns of response, which preclude the identification of a NOAEL or LOAEL.

Effects following the chronic inhalation toxicity of 1,1,2,2-tetrachloroethane included hematological alterations and increased liver fat content in rats exposed to 1.9 ppm (13.3 mg/m^3) 4 hours/day for 265 days (Schmidt et al., 1972). Statistically significant changes included increased leukocyte (89%) and β1-globulin (12%) levels compared to controls after 110 days, and an increased percentage of segmented nucleated neutrophils (36%), decreased percentage of lymphocytes (17%), and increased liver total fat content (34%) after 265 days. A statistically significant decrease in γ-globulin levels (32%) at 60 days postexposure and a decrease in adrenal ascorbic acid content (a measure of pituitary ACTH activity) were observed at all three time periods (64, 21, and 13%, respectively). This study is insufficient for identification of a NOAEL or LOAEL for systemic toxicity because most of the observed effects occurred at a single dose or time point, or there was a reversal of the effect at the next dose or time point. A reproductive assessment in the Schmidt et al. (1972) study was sufficient for identification of a NOAEL for the single dose tested, 1.9 ppm (13.3 mg/m^3), for reproductive effects in male rats, including percentage of mated females having offspring, littering interval, time to 50% littered, total number of pups, pups per litter, average birth weight, postnatal survival on days 1, 2, 7, 14, 21, and 84, sex ratio, and average body weight on postnatal day 84. However, macroscopic malformations or significant group differences in the other indices were not observed at 13.3 mg/m^3. The lack of information on the reproductive toxicity precludes utilizing the selected NOAEL in the derivation of the RfC.

In addition, effects of chronic exposure to 1,1,2,2-tetrachloroethane included alterations in serum acetylcholinesterase activity in rabbits exposed to 1.5 ppm (10 mg/m^3) 1,1,2,2-tetrachloroethane 3 hours/day, 6 days/week for 7–8.5 months (Kulinskaya and Verlinskaya, 1972) and immunological alterations in rabbits exposed to 0.3–14.6 ppm (2–100 mg/m^3) 3 hours/day, 6 days/week, for 8–10 months (Shmuter, 1977). These studies are inadequate for identification of NOAELs or LOAELs for systemic toxicity due to inadequate study reporting.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES

Not applicable.

I.B.3. UNCERTAINTY FACTORS

Not applicable.

I.B.4. ADDITIONAL STUDIES/COMMENTS

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document – U.S. EPA (2010)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 1,1,2,2-Tetrachloroethane* (U.S. EPA, 2010). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

Agency Completion Date — 09/30/2010

I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name – 1,1,2,2-Tetrachloroethane
CASRN – 79-34-5
Section II. Last Revised – 09/30/2010

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The 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 a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). 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.

In the previous IRIS assessment, posted to the IRIS database in 1987, 1,1,2,2-tetrachloro-ethane was characterized as "Classification — C; possible human carcinogen" based on the increased incidence of hepatocellular carcinomas in mice observed in the NCI (1978) bioassay (U.S. EPA, 1987). An oral slope factor of 0.2 $(mg/kg\text{-}day)^{-1}$ was derived using the increased incidence of hepatocellular carcinomas in female mice (NCI, 1978) and a linearized multistage procedure.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) 1,1,2,2-tetrachloroethane is "likely to be carcinogenic to humans" based on data from an oral cancer bioassay in male and female Osborne-Mendel rats and $B6C3F_1$ mice (NCI, 1978). In $B6C3F_1$ mice, a statistically significant increase in the incidence of hepatocellular carcinomas in both genders was observed at doses of 142 and 284 mg/kg-day. A decrease in the time to tumor in both genders of mice was also observed. In this same bioassay, male Osborne-Mendel rats exhibited an increased incidence of hepatocellular carcinomas, a rare tumor in this strain (NCI, 1978), at the high dose only, although this increased incidence was not statistically significant. An untreated female control rat also developed a hepatocellular carcinoma.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

II.A.2. HUMAN CARCINOGENICITY DATA

Norman et al. (1981) evaluated groups of clothing-treatment workers employed during World War II in which some workers used 1,1,2,2 tetrachloroethane and some used water. Inhalation exposure concentrations and durations were not reported, and dermal exposures were likely. In addition, coexposures to dry-cleaning chemicals occurred. No differences in standard mortality ratios were seen between the 1,1,2,2 tetrachloroethane and water groups for total mortality, cardiovascular disease, cirrhosis of the liver, or cancer of the digestive and respiratory systems. The mortality ratio for lymphatic cancers in the 1,1,2,2 tetrachloroethane group was increased relative to controls and the water group, although the number of deaths was small (4 cases observed compared to 0.85 cases expected). No other information was located regarding the carcinogenicity of 1,1,2,2 tetrachloroethane in humans.

II.A.3. ANIMAL CARCINOGENICITY DATA

Male and female Osborne-Mendel rats were exposed to TWA doses of 0, 62, or 108 mg/kg-day (males) or 0, 43, or 76 mg/kg-day (females) 5 days/week for 78 weeks, followed by a 32-week observation period during which the rats were not exposed (NCI, 1978). No statistically significant increases in tumor incidences were observed in rats. However, two hepatocellular carcinomas, which were characterized by NCI (1978) as rare in Osborne-Mendel rats, and one

neoplastic nodule were observed in the high-dose male rats. A hepatocellular carcinoma was also observed in a female rat in the control group. NCI (1978) characterized the carcinogenic results in male rats as "equivocal." Male and female $B6C3F_1$ mice were exposed to TWA doses of 0, 142, or 284 mg/kg-day 5 days/week for 78 weeks, followed by a 12-week observation period during which the mice were not exposed. Statistically significant, dose-related increases in the incidence of hepatocellular carcinoma were observed in males (3/36, 13/50, and 44/49 in the control, low-, and high-dose groups, respectively) and females (1/40, 30/48, and 43/47, respectively). In addition, a decrease in the time to tumor for the hepatocellular carcinomas was also evident in both genders of mice. Lymphomas were also seen in the male and female mice, but the incidences were not found to be statistically significant. Limitations in the study included increased mortality in male and female mice, the variable doses given to the mice over the course of the 78-week exposure period, and the exposure duration of the study (78 weeks) was less than the standard 104 week chronic exposure duration. In the high-dose male mice, acute toxic tubular nephrosis was characterized as the cause of death in the mice that died prior to study termination, although hepatocellular carcinomas were observed in most of these mice.

The only other available study observed pulmonary adenomas in female Strain A/St mice given 99 mg/kg intraperitoneal injections 3 times/week for 8 weeks (Maronpot et al., 1986).

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

The predominant proposed metabolic pathway for 1,1,2,2-tetrachloroethane involves production of dichloroacetic acid (Casciola and Ivanetich, 1984; Halpert and Neal, 1981; Yllner, 1971). Dichloroacetic acid was identified as the major urinary metabolite in mice treated with 1,1,2,2-tetrachloroethane by intraperitoneal injection (Yllner et al., 1971) and in in vitro systems with rat liver microsomal and nuclear cytochrome P450 (Casciola and Ivanetich, 1984; Halpert, 1982; Halpert and Neal, 1981). Other pathways may involve the formation of trichloroethylene via dehydrochlorination or tetrachloroethylene via oxidation as initial metabolites (Mitoma et al., 1985; Ikeda and Ohtsuji, 1972; Yllner et al., 1971). 1,1,2,2-Tetrachloroethane may also form free radicals by undergoing reductive dechlorination (ATSDR, 1996).

Dichloroacetic acid induces hepatocellular carcinomas in both genders of F344 rats and $B6C3F_1$ mice (DeAngelo et al., 1999; DeAngelo et al., 1996; Pereira, 1996; Pereira and Phelps, 1996; Ferreira-Gonzalez et al., 1995; Richmond et al., 1995; Daniel et al., 1992; DeAngelo et al., 1991; U.S. EPA, 1991b; Bull et al., 1990; Herren-Freund et al., 1987). Trichloroethylene, also a metabolite of 1,1,2,2-tetrachloroethane, has been shown to produce hepatocellular carcinomas and hepatocellular adenomas in male and female $B6C3F_1$ mice, respectively, but did not demonstrate carcinogenicity in Osborne-Mendel or Sprague-

Dawley rats (NTP, 1990; NCI, 1976). Tetrachloroethylene, another metabolite of 1,1,2,2-tetrachloroethane, was characterized by NCI (1977) as a liver carcinogen in $B6C3F_1$ mice, but an evaluation of carcinogenicity in Osborne-Mendel rats was inadequate due to early mortality. In a study by NTP (1986), tetrachloroethylene demonstrated evidence of carcinogenicity in F344 rats, as shown by increased incidences of mononuclear cell leukemia, and in $B6C3F_1$ mice, as shown by increased incidences of hepatocellular adenomas and carcinomas in males and carcinomas in females.

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1. SUMMARY OF RISK ESTIMATES

II.B.1.1. Oral Slope Factor - 0.2 per mg/kg-day

The oral slope factor is derived from the LED_{10}, the 95% lower bound on the exposure associated with an 10% extra cancer risk, by dividing the risk (as a fraction) by the LED_{10}, and represents an upper bound, continuous lifetime exposure risk estimate:

LED_{10}, lower 95% bound on exposure at 10% extra risk – 0.65 mg/kg-day
ED_{10}, central estimate of exposure at 10% extra risk – 0.81 mg/kg-day

The slope of the linear extrapolation from the central estimate ED_x is 0.1/(0.81 mg/kg-day) = 0.1 per mg/kg-day.

The slope factor for 1,1,2,2-tetrachloroethane should not be used with exposures exceeding the point of departure (0.65 mg/kg-day), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of 1,1,2,2-tetrachloroethane.

II.B.1.2. Drinking Water Unit Risk* - 6×10^{-6} per µg/L

Drinking Water Concentrations at Specified Risk Levels

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	17 µg/L
E-5 (1 in 100,000)	1.7 µg/L
E-6 (1 in 1,000,000)	0.17 µg/L

*The unit risk and concentration estimates assume water consumption of 2 L/day by a 70 kg human.

II.B.1.3. Extrapolation Method

Multistage model with linear extrapolation from the point of departure (LED_{10}).

II.B.2. DOSE-RESPONSE DATA

Tumor Type — hepatocellular carcinomas
Test Species — female B6C3F_1 mice
Route — oral
References — NCI, 1978

Incidences of hepatocellular carcinomas in female B6C3F_1 mice used for dose-response assessment of 1,1,2,2-tetra-chloro-ethane			
Sex	**Dose (mg/kg-d)**		
	0	**142**	**284**
Female	1/40	30/48	43/47

Summary of human equivalent BMDs and BMDLs based on hepatocellular carcinoma incidence data in female B6C3F_1 mice			
	BMR (% extra risk)	**BMD_{HED} (mg/kg-d)**	**$BMDL_{HED/10}$mg/kg-d)**
Female mice	10	0.81	0.65

II.B.3. ADDITIONAL COMMENTS

II.B.4. DISCUSSION OF CONFIDENCE

Choice of low-dose extrapolation approach. The mode of action is a key consideration in clarifying how risks at low-dose exposures should be estimated. A linear low-dose extrapolation approach was used to estimate human carcinogenic risk associated with 1,1,2,2-tetrachloroethane exposure due to the unavailability of data that supports any specific mode of carcinogenic action for 1,1,2,2-tetrachloroethane. The extent to which the overall uncertainty in low-dose risk estimation could be reduced if the mode of action for

1,1,2,2-tetrachloroethane were known is of interest, but data on the mode of action of 1,1,2,2-tetrachloroethane are not available.

Dose metric. 1,1,2,2-Tetrachloroethane is metabolized to intermediates with carcinogenic potential. Dichloroacetic acid is recognized as hepatocarcinogenic in male B6C3F$_1$ mice and F344 rats (U.S. EPA, 2003). However, it is unknown whether a metabolite or some combination of parent compound and metabolites is responsible for the observed toxicity. If the actual carcinogenic moiety is proportional to administered exposure, then use of administered exposure as the dose metric is the least biased choice. On the other hand, if this is not the correct dose metric, then the impact on the slope factor is unknown.

Cross-species scaling. An adjustment for cross-species scaling ($BW^{3/4}$) was applied to address toxicological equivalence of internal doses between the rodent species and humans, consistent with the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). It is assumed that equal risks result from equivalent constant lifetime exposures.

Statistical uncertainty at the point of departure (POD). Parameter or probabilistic uncertainty can be assessed through confidence intervals. Each description of parameter uncertainty assumes that the underlying model and associated assumptions are valid. For the multistage cancer model applied to the female mice data, there is a reasonably small degree of uncertainty at a 10% increase in tumor incidence (the POD for linear low-dose extrapolation).

Bioassay selection. The study by NCI (1978) was used for development of an oral slope factor. This study was conducted in both sexes in two species with an adequate number of animals per dose group, with examination of appropriate toxicological endpoints in both sexes of rats and mice. Alternative bioassays were unavailable. Both genders of mice exhibited liver tumors. Uncertainties associated with the use of this study in the derivation of the oral slope factor arise primarily from the study design. The dose levels used in the study were poorly selected and were modified over the exposure duration, and the exposure duration of the study (78 weeks) was less than the standard 104-week chronic exposure duration. In addition, the bolus nature of the 1,1,2,2-tetrachloroethane gavage exposures in NCI (1978), as well as the use of corn oil as the gavage vehicle, may lead to more pronounced irritation, inflammation, cell death, and an eventual increase in tumor incidence at portals of entry; however, chemical-specific data demonstrating this progression is not available. There was also an increased incidence of endemic chronic murine pneumonia in male and female rats and mice, and while interpretation of this study is complicated by the chronic murine pneumonia, it is unlikely to have contributed to the carcinogenicity results observed in male and female rats.

Choice of species/gender. The oral slope factor for 1,1,2,2-tetrachloroethane was quantified using the tumor incidence data for female mice. The hepatocellular carcinoma data in male mice demonstrated tumorigenicity, but the data in male mice did not achieve adequate model fit for any of the dichotomous models when BMD modeled. The male and female rat tumor incidence data were not suitable for deriving low-dose quantitative risk estimates, and NCI described the rat strain as relatively insensitive to the carcinogenic effects of chlorinated organic compounds.

Relevance to humans. The oral slope factor is derived from the incidence of hepatocellular carcinomas in female mice. Using liver tumors in $B6C3F_1$ mice as the model for human carcinogenesis is a potential concern because of the prevalence of and susceptibility to developing liver tumors in this strain of mice. If this strain of mice is excessively sensitive to the development of hepatocellular tumors, use of this species and strain may result in the derivation of an oral slope factor that is overly conservative in relation to human risk assessment.

Hasemen et al. (1998) reported a combined adenoma and carcinoma rate of 42 and 24% for male and female $B6C3F_1$ mice, respectively, from NTP carcinogenicity feeding bioassays. The $B6C3F_1$ mouse was also used in the NCI (1978) study, although only hepatocellular carcinomas were observed. Haseman et al. (1998) reported lower spontaneous rates of 17.9 and 8.4% for liver carcinomas in males and females, respectively, compared with adenomas and carcinomas combined. Even though the $B6C3F_1$ mouse is associated with a high spontaneous cancer incidence, the incidence in the control mice in NCI (1978) was rather low. In the vehicle controls the incidence was 1/18 in the males and 0/20 in the females, and 3/36 and 1/40 in the pooled male and female vehicle controls, respectively; suggesting that the mice exposed to 1,1,2,2-tetrachloroethane in NCI (1978) were not particularly susceptible to developing liver tumors.

Additional interspecies uncertainty may arise from the rate of metabolism across species. Reitz et al. (1996) demonstrated that mice possessed a greater relative ability to metabolize tetrachloroethylene than rats and humans, and, although data are not available, a similar situation may exist for 1,1,2,2-tetrachloroethane.

In addition, the genotoxicity and mutagenicity studies provide limited evidence of a mutagenic mode of action, with 1,1,2,2-tetrachloroethane displaying equivocal results of mutagenic activity. There are inadequate data to support any mode of action hypothesis.

Human population variability. The extent of interindividual variability in animals for 1,1,2,2-tetrachloroethane metabolism has not been characterized. A separate issue is that the human variability in response to 1,1,2,2-tetrachloroethane is also unknown. This lack of

understanding about potential differences in metabolism and susceptibility across exposed animal and human populations, thus, represents a source of uncertainty.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

In the absence of any data on the carcinogenicity of 1,1,2,2 tetrachloroethane via the inhalation route, an inhalation unit risk has not been derived in this evaluation.

II.C.2. DOSE-RESPONSE DATA

Not applicable.

II.C.3. ADDITIONAL COMMENTS

Not applicable.

II.C.4. DISCUSSION OF CONFIDENCE

Not applicable.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATIONs

Source Document – U.S. EPA (2010)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the

Toxicological Review of 1,1,2,2-Tetrachloroethane (U.S. EPA, 2010). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

II.D.2. EPA REVIEW

Agency Completion Date — 09/30/2010

II.D.3. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. BIBLIOGRAPHY

Substance Name – 1,1,2,2-Tetrachloroethane
CASRN – 79-34-5

VI.A. ORAL RfD REFERENCES

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VII. Revision History

Substance Name — 1,1,2,2-Tetrachloroethane
CASRN — 79-34-5
File First On-Line – 03/31/1987

Date	Section	Description
12/03/2002	II.D.2.	Screening-Level Literature Review Findings message has been added.
09/30/2010	I., II., VI.	RfD and cancer assessment updated; RfC discussion added; Screening-Level Literature Review Findings message removed.

VIII. SYNONYMS

Substance Name – 1,1,2,2-Tetrachloroethane
CASRN -- 79-34-5
Section VIII. Last Revised -- 09/30/2010

- ACETYLENE TETRACHLORIDE
- BONOFORM
- CELLON
- 1,1,2,2-CZTEROCHLOROETAN
- 1,1-DICHLORO-2,2-DICHLOROETHANE
- ETHANE, 1,1,2,2-TETRACHLORO-
- NCI-C03554
- RCRA WASTE NUMBER U209
- TCE
- 1,1,2,2-TETRACHLOORETHAAN
- 1,1,2,2-TETRACHLORAETHAN
- TETRACHLORETHANE
- 1,1,2,2-TETRACHLORETHANE
- 1,1,2,2-Tetrachloroethane
- Tetrachloroethane, 1,1,2,2-
- sym-TETRACHLOROETHANE
- TETRACHLORURE D'ACETYLENE
- 1,1,2,2-TETRACLOROETANO
- UN 1702
- WESTRON