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

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Reference Dose for Chronic Oral Exposure (RfD)



0265

1,1,1,2-Tetrachloroethane; CASRN 630-20-6

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 1,1,1,2-Tetrachloroethane

File First On-Line 09/30/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	12/01/1996*
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	01/01/1991*

*A comprehensive review of toxicological studies was completed (August 8, 2006) - please see sections I.A.6. and II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 1,1,1,2-Tetrachloroethane

CASRN — 630-20-6

Last Revised — 12/01/1996

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic

effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is 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. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this 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. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Mineralization of the kidneys in males, hepatic clear cell change in females	NOAEL: none LOAEL: 125 mg/kg/day (converted to 89.3 mg/kg/day)	3000	1	3E-2 mg/kg/day
Rat, Chronic Oral Gavage Study				
NTP, 1983				

*Conversion Factors -- Dose adjusted for gavage schedule (5\days/week).

__I.A.2. Principal and Supporting Studies (Oral RfD)

NTP (National Toxicology Program). 1983. Carcinogenesis studies of 1,1,1,2- tetrachloroethane in F344/N rats and B6C3F1 mice. NTP, Washington, DC.

The NTP (1983) treated groups of 50 male and 50 female F344/N rats by gavage with doses of 0, 125, or 250 mg/kg/day of technical grade 1,1,1,2- tetrachloroethane (>99% pure) in corn oil 5 days/week for 103 weeks. Mortality, body weights, and clinical signs were noted, and comprehensive histopathologic examinations were performed on rats from all groups.

Mean body weights of treated and control rats were similar throughout the study. During weeks 44-103, signs of CNS effects, inactivity, and incoordination were observed in high-dose rats of both sexes. A statistically significant reduction in survival in high-dose males occurred. Eleven control and 7 low-dose males apparently died from heat stress. In addition, 20 male rats (14 control, 3 low-dose, and 3 high-dose) and 15 female rats (2 control, 5 low-dose, and 8 high-dose) died from gavage error. Male rats showed treatment-related increased incidences of mineralization of the kidneys (control 12/48, low dose 19/50, high dose 26/48). Hepatic clear cell changes in female rats were also increased in a dose-related manner (0/48 control, 3/49 low dose, 9/44 high dose). The low dose, 125 mg/kg/day, was considered the LOAEL.

In the NTP (1983) study, groups of 50 male and 50 female B6C3F1 mice were treated by gavage with 0, 250, or 500 mg/kg/day of technical 1,1,1,2- tetrachloroethane (greater than 99% pure) in corn oil 5 days/week for 103 weeks (control and low-dose mice) or 65 weeks (high-dose mice). A statistically significant decrease in mean body weights was observed in high- dose mice. Beginning at week 34, CNS involvement was noted in high-dose mice. The mice appeared sluggish after treatment and by week 51 appeared uncoordinated and weak, and breathed rapidly after

treatment. A statistically significant reduction in survival occurred in high-dose mice of both sexes and low-dose female mice, as compared with controls. At week 65, surviving high-dose mice were sacrificed because they were moribund. Incidences of nonneoplastic alterations of the liver (inflammation, necrosis, fatty metamorphosis, and hepatocytomegaly) were greatly increased in high-dose mice, but not in low-dose groups.

___I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 3000 was used: 10 to extrapolate from a LOAEL, 10 for interspecies extrapolation and 10 to provide additional protection for unusually sensitive individuals, and an additional factor of 3 for lack of adequate supporting reproductive and chronic toxicity studies.

MF — None

___I.A.4. Additional Studies/Comments (Oral RfD)

The only oral reproductive study of 1,1,1,2-tetrachloroethane was part of a long-term oral study conducted by Truhaut et al. (1974). In this study, male and female rats were treated by gavage at 0 or 300 mg/kg/day, 5 days/week for up to 10 months. Treated females had reduced growth, and treated males and females had increased mortality. Reproductive function was not impaired, but all of the pups from treated rats died within 48 hours of birth. Hepatic fatty vacuolization was observed in adults and pups, and centrilobular necrosis was observed in adults.

1,1,1,2-Tetrachloroethane has not been tested for teratogenicity.

___I.A.5. Confidence in the Oral RfD

Study — Low

Database — Low

RfD — Low

Because a NOAEL in rats was not identified, confidence in the NTP (1983) study is low. Confidence in the database is low because, although two chronic and one reproductive bioassays are available, no NOAELs were established, the effects seen at the LOAELs were significant, and only a few doses were given. Low confidence in the RfD follows.

___I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 1983

Other EPA Documentation — None

Agency Work Group Review — 04/16/1987

Verification Date — 04/16/1987

A comprehensive review of toxicological studies published through August 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfD for 1,1,1,2-Tetrachloroethane and a change in the RfD is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

__I.A.7. EPA Contacts (Oral RfD)

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 (internet address).

__I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 1,1,1,2-Tetrachloroethane
CASRN — 630-20-6

Not available at this time.

__II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,1,1,2-Tetrachloroethane
CASRN — 630-20-6
Last Revised — 01/01/1991

Section II 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 exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen.

Basis — increased incidence of combined hepatocellular adenomas and carcinomas in female mice; inadequate evidence from human studies.

__II.A.2. Human Carcinogenicity Data

Inadequate. Norman et al. (1981) reported a study of the effects on military personnel of exposure to tetrachloroethane used as a solvent on clothing during World War II. It was not specified which isomer or mixture of isomers was used. One isomer, 1,1,2,2-tetrachloroethane, has been classified as C, possible human carcinogen. Of 3859 exposed men, 833 deaths were reported during the period 1946-1976 compared with 1821 deaths among 9396 nonexposed men. Results were reported by race; further analyses were restricted to white males. Risks for

leukemia, lymphoma, and cancers of the prostate and testis were shown to be slightly elevated among the exposed group, but these increases were not significant. It should be noted that there were possible concomitant exposures to dry cleaning solvents.

__II.A.3. Animal Carcinogenicity Data

Limited. One chronic study has been reported (NTP, 1983). 1,1,1,2- tetrachloroethane was administered in corn oil by gavage to 50 each male and female F344/N rats and B6C3F1 mice per dose group. Rats received 0, 125, or 250 mg/kg/day 5 days/week for 103 weeks, and mice were similarly treated with 0, 250, or 500 mg/kg/day. Primarily as a consequence of heat stress during week 62, 27 male rats died (14/50 controls, 10/50 low-dose group and 3/50 high-dose group) and were excluded from statistical analysis of survival. In addition, 15 female rats were accidentally killed during the study (2 control, 5 low-dose, and 8 high-dose). Cumulative toxic effects with signs of CNS involvement were noted from week 44. There were no significant increases in tumor incidence as a consequence of treatment in female rats. Mortality was significantly increased in high-dose male rats. Male rats were also observed to have a significant dose-related trend for only the combined incidence of neoplastic nodules and carcinomas of the liver in the life table test (0/49 controls; 1/49 low dose; 3/48 high dose). While NTP concluded that carcinogenicity was not demonstrated in F344 rats, an increased proportion of male rats with liver tumors that may have been associated with treatment was observed. Accidental killing of 27 male and 15 female rats decreased the sensitivity of this assay.

High-dose mice were sacrificed at 65 weeks as signs of CNS toxicity were observed. The low-dose and control mice were killed at 104-105 weeks. Increased incidences of hepatocellular adenomas and carcinomas were noted in female mice, and a dose-related trend was observed. A statistically significant dose-related increase in the incidence of hepatocellular adenomas occurred in male mice; a significant increase in hepatocellular carcinomas was not observed. Incidence of hepatocellular adenomas were 4/49, 8/46, and 24/48 in the control, low- and high-dose females and 6/48, 14/46, and 21/50 in the control, low- and high-dose males, respectively. Incidences of hepatocellular carcinomas were 1/49, 5/46, and 6/48 in the control, low-, and high-dose females and 12/48, 13/46, and 6/50 in the control, low-, and high-dose males, respectively.

The NTP study authors concluded that carcinogenicity was not demonstrated for rats, but that the sensitivity of the assay was compromised by the accidental killing of animals. They concluded that although the MTD for mice was exceeded at the high dose and survival was decreased, carcinogenicity was demonstrated for mice.

__II.A.4. Supporting Data for Carcinogenicity

1,1,1,2-Tetrachloroethane was not mutagenic for *Salmonella typhimurium* (Simmon et al., 1977) and was negative in a rat liver focus initiation/promotion assay (Story et al., 1986).

__II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

__II.B.1. Summary of Risk Estimates

Oral Slope Factor: 2.6E-2 per (mg/kg)/day

Drinking Water Unit Risk: 7.4E-7 per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+2 ug/L
E-5 (1 in 100,000)	1E+1 ug/L
E-6 (1 in 1,000,000)	1E+0 ug/L

__II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type: hepatocellular adenoma or carcinoma

Test animals: mouse/B6C3F1, female

Route: gavage

Reference: NTP, 1983

Administered Dose (mg/kg)/day	Human Equivalent Dose (mg/kg)/day	Tumor Incidence
0	0	5/49
250	14.8	13/46
500	27.6	30/48

__II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Human equivalent doses were calculated using animal body weights of 40 g for the control and low-dose groups and 32 g for the high-dose group. Although the high-dose animals were killed at 65 weeks, no adjustment was made for early termination of the high-dose group; animals were moribund; and currently accepted adjustments were inconsistent with the dose-response data.

The unit risk should not be used if the water concentration exceeds 1E+4 ug/L, since above this concentration the unit risk may not be appropriate.

__II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Adequate numbers of mice were treated, and low-dose animals only were observed for a period approximating their natural life span. Since the high-dose animals were terminated at 65 weeks, the incidence of carcinomas that may have been developed in a lifetime study is not known, but the adenoma incidence was statistically increased and was dose related in both males and females.

__II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure**__II.C.1. Summary of Risk Estimates**

Inhalation Unit Risk: 7.4E-6 per (ug/cu.m)

Extrapolation Method — Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+1 ug/cu.m
E-5 (1 in 100,000)	1 ug/cu.m
E-6 (1 in 1,000,000)	1E-1 ug/cu.m

__II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

This inhalation risk estimate was derived from oral data presented in II.B.2.

__II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The unit risk should not be used if the air concentration exceeds 1E+3 ug/cu.m, since above this concentration the unit risk may not be appropriate.

__II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

See II.B.4.

__II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

Source Document — U.S. EPA, 1987

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 02/24/1988, 03/23/1988, 05/04/1988, 10/19/1988

Verification Date — 05/04/1988

A comprehensive review of toxicological studies published through August 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for 1,1,1,2-Tetrachloroethane and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

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 (internet address).

__III. [reserved]

__IV. [reserved]

__V. [reserved]

__VI. Bibliography

Substance Name — 1,1,1,2-Tetrachloroethane

CASRN — 630-20-6

Last Revised — 08/01/1991

_VI.A. Oral RfD References

NTP (National Toxicology Program). 1983. Carcinogenesis studies of 1,1,1,2- tetrachloroethane (CAS No. 630-20-6) in F344/N rats and B6C3F1 mice (gavage studies). NTP-81-53; NIH Publ. No. 83-1793; NTP Technical Report Series No. 237. NTIS, Springfield, VA.

Truhaut, R., N.P. Lich, H. Dutertre-Catella, G. Molas and V.N. Huyen. 1974. Contribution to the toxicological study of 1,1,1,2-tetrachloroethane. Arch. Mal. Prof. Med. Trav. Secur. Soc. 35(6): 593-608.

U.S. EPA. 1983. Health Hazard Profile on 1,1,1,2-Tetrachloroethane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

_VI.B. Inhalation RfD References

None

_VI.C. Carcinogenicity Assessment References

Norman, J.E., Jr., C.D. Robinette and J.F. Fraumeni, Jr. 1981. The mortality experience of army World War II chemical processing companies. J. Occup. Med. 23(12): 818-822.

NTP (National Toxicology Program). 1983. Carcinogenesis studies of 1,1,1,2- tetrachloroethane (CAS No. 630-20-6) in F344/N rats and B6C3F1 mice (gavage studies). NTP-81-53; NIH Publ. No. 83-1793; NTP Technical Report Series No. 237. NTIS, Springfield, VA.

Simmon, V.F., K. Kauhanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. Second International Conference on Environmental Mutagens. Edinburgh, Scotland, July, 1977. Develop. Toxicol. Environ. Sci. 2: 249-258.

Story, D.L., E.F. Meierhenry, C.A. Tyson and H.A. Milman. 1986. Differences in rat liver enzyme-altered foci produced by chlorinated aliphatics and phenobarbital. Toxicol. Ind. Health. 2(4): 351-362.

U.S. EPA. 1987. Evaluation of the Potential Carcinogenicity of 1,1,1,2- tetrachloroethane (630-20-6) in support of Reportable Quantity Adjustments Pursuant to CERCLA Section 102. Prepared by the Office of Emergency and Remedial Response and the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment, Carcinogenic Assessment Group, Washington, DC. OHEA-C-073-174.

_VII. Revision History

Substance Name — 1,1,1,2-Tetrachloroethane

CASRN — 630-20-6

Date	Section	Description
03/01/1989	II.A.	Carcinogen summary on-line
01/01/1990	VI.	Bibliography on-line
08/01/1990	I.A.	Text edited
08/01/1990	II.	Text edited
08/01/1990	III.A.	Health Advisory on-line
08/01/1990	IV.F.1.	EPA contact changed
08/01/1990	VI.D.	Health Advisory references added
01/01/1991	II.	Text edited
01/01/1991	II.C.1.	Inhalation slope factor removed (global change)
08/01/1991	VI.A.	Truhaut et al. 1974 reference clarified
01/01/1992	I.A.7.	Secondary contact changed
01/01/1992	IV.	Regulatory actions updated
12/01/1996	I.A.7.	Secondary contact removed
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
09/28/2006	I.A.6, II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

_VIII. Synonyms

Substance Name — 1,1,1,2-Tetrachloroethane

CASRN — 630-20-6

Last Revised — 09/30/1987

- 630-20-6
- ETHANE, 1,1,1,2-TETRACHLORO-
- Ethane, 1,1,1,2-tetrachloro- (8CI)(9CI)
- HSDB 4148
- NCI-C52459
- RCRA WASTE NUMBER U208
- 1,1,1,2-Tetrachloroethane
- Tetrachloroethane, 1,1,1,2-

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