

Drinking Water Health Advisory for 1,1,2,2-Tetrachloroethane

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**Drinking Water Health Advisory
for 1,1,2,2-Trichloroethane**

Prepared by:

Health and Ecological Criteria Division
Office of Science and Technology
Office of Water
U.S. Environmental Protection Agency
Washington, DC 20460

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1,1,2,2-Tetrachloroethane

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1,1,2,2-Tetrachloroethane

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LIST OF ABBREVIATIONS

ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BV	bed volumes
bw	body weight
CAS	Chemical Abstracts Registry
CHO	Chinese hamster ovary (cells)
CSF	cancer slope factor
DCA	dichloroacetic acid
DNA	deoxyribonucleic acid
DW	drinking water
DWI	drinking water intake
DWEL	drinking water equivalent level
FDA	Food and Drug Administration
GAC	granular activated carbon
gd	gestation day
GGT+	γ -glutamyl transpeptidase-positive
HA	Health Advisory
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
kg	kilogram
Kow	octanol-water partition coefficient
L	liter
LD ₅₀	lethal dose for 50% of tested animals
LOAEL	lowest observed adverse effect level
m ³	cubic meters
mg	milligram
min	minute
mL	milliliter
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NIOSH	National Institute for Occupational Safety and Health
NPL	National Priorities List
NTP	National Toxicology Program
OW	Office of Water
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion

RCRA	Resources Conservation and Recovery Act
RfD	reference dose
RR	relative risk
RSC	relative source contribution
SDH	sorbitol dehydrogenase
TRI	Toxics Release Inventory
UF	uncertainty factor
USGS	U.S. Geological Survey
U.S. EPA	U.S. Environmental Protection Agency
VOC	volatile organic compound

1.0 INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water (OW), provides information on the, environmental properties, health effects, analytical methodologies, and treatment technologies for regulated and unregulated drinking water contaminants. HAs establish nonregulatory concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations (one-day, ten-days, several years, and a lifetime). HAs serve as informal technical guidance to assist Federal, State and local officials, and managers of public or community water systems in protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

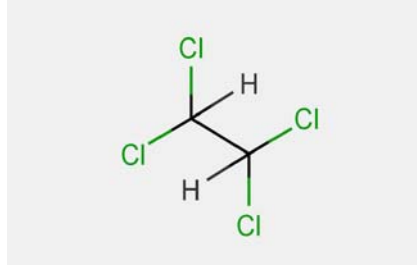
The Health Effects Support Document for 1,1,2,2-Tetrachloroethane (U.S. EPA, 2006) is the peer-reviewed, risk assessment that supports this HA. It can be accessed at http://www.epa.gov/ogwdw/ccl/pdfs/reg_determine2/healtheffects_ccl2-reg2_1122tetrachloroethane.pdf and will provide a more comprehensive summary of the available data. The less than lifetime HA values were independently peer reviewed by the Office of Water.

1,1,2,2-Tetrachloroethane

2.0 GENERAL INFORMATION AND PROPERTIES

2.1 Physical and Chemical Properties

1,1,2,2-tetrachloroethane is a chlorinated hydrocarbon that is occasionally found as a contaminant in treated drinking water. At room temperature the pure compound is a



1,1,2,2-Tetrachloroethane

Synonyms: Acetylene tetrachloride; sym-Tetrachloroethane; s-Tetrachloroethane

Registered Trade Names: Bonoform; Cellon; Westron

TABLE 1. Physical and Chemical Properties	
Property	Data
CAS Number	79-34-5
Chemical Formula	C ₂ H ₂ Cl ₄
Molecular Weight	167.85
Physical State	Liquid
Boiling Point	145.1 - 146.5°C
Melting Point	-43.8°C
Density (at 20°C)	1.59 g/mL
Vapor Pressure	4.62 mm Hg (25°C) 9 mm Hg (30°C)
Log Kow	2.39
Koc	46-240
Water Solubility at 20°C	2.87 g/L
Water Solubility at 25°C	2.86 g/L
Odor Threshold (water)	0.50 ppm

TABLE 1. Physical and Chemical Properties	
Property	Data
Odor Threshold (air)	1.5 ppm; 3-5 ppm; 2.9 ppm for 10 min
Taste Threshold	NA
Conversion Factors (at 25°C, 1 atm)	1 ppm= 6.98 mg/m ³ 1 mg/m ³ = 0.14 ppm

NA = Not available

Refs: ATSDR, 1996, 2006; HSDB, 2004; Lobo-Mendonca, 1963

2.2 Uses

Prior to the 1980's, 1,1,2,2-tetrachloroethane was a starting material for the production of other chlorinated hydrocarbons (Archer, 1979). It was used commercially as a metal degreaser; extractant for oils and fats; a component of paint removers, varnishes and lacquers; and in photographic films (Hawley, 1981). 1,1,2,2-Tetrachloroethane can still occur as a chemical intermediate in or as a byproduct from the production of a variety of other chlorinated organic compounds (ATSDR, 1996)

3.0 OCCURRENCE AND EXPOSURE

1,1,2,2-Tetrachloroethane is no longer produced as a commercial product in the United States, and importation is thought to be minimal (ATSDR, 2006). Toxics Release Inventory (TRI) data show that total releases to the environment have declined from about 50,000 pounds per year to about 5,000 pounds per year over the past ten years (U.S. EPA, 2004b).

3.1 Air

Much of the data on the concentrations of 1,1,2,2-tetrachloroethane in ambient and indoor air have come from sampling programs conducted in the 1980s or earlier. They may not be relevant now that production of 1,1,2,2-tetrachloroethane in the U.S. has ended (ATSDR, 1996). In the most recent studies, the median ambient air concentration was less than the detection limit, with most of the samples showing concentrations less than or equal to 10 ppt (Pratt et al., 2000; Shah and Heyerdahl, 1988). However, between 1996 and 2001, releases to air declined (14 to 3 thousand pounds per year) and accounted for the largest fraction (>50%) of the total releases reported to the TRI (U.S. EPA, 2004b).

1,1,2,2-Tetrachloroethane released to air gradually accumulates in the troposphere and degrades by photolysis with a half life of about 50 to 60 days. The remainder diffuses slowly into the stratosphere where it degrades by photolysis (ATSDR, 2006).

3.2 Food

1,1,2,2-Tetrachloroethane was not detected in any of the foods sampled during the recent FDA Total Diet Study monitoring of volatile organic chemicals in foods (Fleming-Jones and Smith, 2003; FDA, 2003). Bioaccumulation data were not identified for fish from waters contaminated with 1,1,2,2-tetrachlorethane, however, based on measured bioconcentration values in bluegill sunfish and fat head minnows, bioaccumulation in aquatic organisms is likely to be low (ATSDR, 2006).

3.3 Water

The U.S. EPA monitored for 1,1,2,2-tetrachloroethane in finished drinking water from 1988 to 1992 and again from 1993-1997. The decrease in detections of 1,1,2,2-tetrachlorethane over this timeframe coincides with the cessation of production in the US and the decline in use and discharge to the environment observed in the TRI data. The percent of samples with detections decreased from 0.16% to 0.02% and the 99th percentile concentration of detections decreased from 112 µg/L to 3.9 µg/L (U.S. EPA, 2006). During the 1993-1997 monitoring, 22 of 28,000 systems reported a detection of 1,1,2,2-tetrachloroethane at least once during the 5 year period. States with detections were evenly distributed across the United States.

The United States Geological Service Surveys did not detect 1,1,2,2-tetrachloroethane in ambient surface waters studied or in 204 urban or 1,267 rural wells at a detection level of 0.2 µg/L

(Delzer and Ivahnenko, 2003; Squillace et al., 1999). Data on TRI releases to surface water indicate that the levels dropped precipitously in 1995 from about 2,000 pounds per year to about a tenth or less of that amount in subsequent years (U.S. EPA, 2004b).

Levels of 1,1,2,2-tetrachloroethane in surface waters may be reduced through volatilization to the atmosphere and hydrolysis. The volatilization half-life was estimated to be 6.3 hr for a modeled flowing river and 6.1 days from a modeled lake (Thomas, 1982). The hydrolysis half-life in water is shorter at neutral to alkaline pHs (~ 600 days) than at neutral or acid pHs (30-40 days) (Haag and Mill, 1988)

3.4 Soil

Releases to soil can occur as a result of disposal in landfills or accidental spills of products or wastes containing the compound. Information on the Toxics Release Inventory (TRI) indicate that between 1994 and 2004 releases to landfills occurred in only three years, and the amounts were only 1, 1, and 66 pounds (U.S. EPA, 2004b). An analysis of test wells around RCRA disposal sites, determined that 25 of 479 sites had levels above the detection limit (Plumb, 1991). Based on ATSDR's HazDat database (HazDat, 1996), 1,1,2,2-tetrachloroethane was found in soil or sediment samples at 47 of 273 current or past NPL sites.

Chlorinated hydrocarbons such as 1,1,2,2-tetrachloroethane may be degraded in soil through biotic and abiotic processes that, in time, can reduce the concentration to below detection levels (O'Loughlin et al., 1999; 2003; Lorah et al., 2003).

3.5 Other Sources

In a survey of 1,159 common household products, 216 contained 1,1,2,2-tetrachloroethane (Sack et al., 1992). Trace amounts were commonly found in adhesives, oils, greases, and lubricants. Concentrations in these products were uniformly near the method detection limits (detection limits not reported). The presence of 1,1,2,2-tetrachloroethane in commercial products has most likely paralleled the decline in use and production over the past 15 years. A study by Bi et al. (2005) detected 1,1,2,2-tetrachloroethane in environmental tobacco smoke at levels of 3 to 6 µg/cigarette.

4.0 HEALTH EFFECTS DATA

4.1 Human Studies

4.1.1 Short-term Exposure

Lethal doses for humans range between 357 mg/kg (Lilliman, 1949) and $\geq 1,000$ mg/kg (Hepple, 1927; Mant, 1953). Death occurs between 3 to 20 hours after exposure. In a case report of a medical accident, doses of 70 to 117 mg/kg of undiluted 1,1,2,2-tetrachloroethane caused loss of consciousness, shallow breathing, and pronounced lowering of blood pressure in the orally exposed patients (Sherman, 1953; Ward, 1955). There were no fatalities and the reported effects disappeared about an hour after the exposure.

There are a number of occupational case reports where workers were exposed to 1,1,2,2-tetrachloroethane either alone or in combination with other chemicals by way of respiration and/or dermal contact. The majority of these reports lack information on exposure levels. Symptoms reported include tremors, dizziness, numbness, and drowsiness, fatigue, irritability, headache, and in severe cases, coma (Hamilton, 1917; Jeney et al., 1957; Lobo-Mendonca, 1963; Minot and Smith, 1921; Parmenter, 1921). Autopsy records from one fatal incident reported inflammation and cirrhosis of the liver, enlargement of the heart and spleen, and bleeding in the gastrointestinal tract (Coyer, 1944); the victim died 20 days after exposure.

4.1.2 Long-term Exposure

There are no well documented reports of adverse health effects from longer-term exposure to 1,1,2,2-tetrachloroethane. Existing records come from occupational situations and utilization of the data in the health assessment of 1,1,2,2-tetrachloroethane is confounded by co-exposures to other chemicals and a lack of quantitative exposure information. Effects that have been reported include loss of body weight, jaundice, hepatitis, an enlarged liver, slight anemia, increased mononuclear cells, white blood cells, and platelets (Horiguchi et al., 1964; Koelsch, 1915; Willcox et al., 1915; Jeney et al., 1957; Minot and Smith, 1921).

4.1.3 Reproductive and Developmental Effects

No data were identified that apply to developmental or reproductive effects in humans exposed to 1,1,2,2-tetrachloroethane.

4.1.4 Carcinogenicity

There is one study that reports an increased relative risk of death due to genital cancers (relative risk [RR] =4.56), leukemia (RR=1.77), and other lymphatic cancers (RR=5.19) among a group of military personnel who were exposed to tetrachloroethane in field processing units where clothing was impregnated with N,N-dichlorohexachlorodiphenylurea in a tetrachloroethane solvent (Norman et al., 1981). None of these relative risk values were statistically significant

within 90% confidence bounds. The period between exposure and the epidemiology study was 31 years (1946-1976). Quantitative data on exposures to 1,1,2,2-tetrachloroethane and to other chemicals during military service and subsequent employment were lacking. Given the lack of statistical significance, poor exposure information, and co-exposure to other chemicals, confidence in the results of this study is low.

4.2 Animal Studies

4.2.1 Short-term Exposure

The oral LD₅₀ values for 1,1,2,2-tetrachloroethane in rats fall between 250 mg/kg and 330 mg/kg (Gohlke, et al., 1977; Schmidt et al., 1980; Smyth et al., 1969). The only available LD₅₀ value for mice is 1,476 mg/kg (Paolini, et al. 1992).

The available short term studies of 1,1,2,2-tetrachloroethane toxicity cover durations of 1 to 21 days. The liver appears to be the primary target organ in all studies. The single dose and 4 day studies are limited in that they evaluated only clinical signs and measures of hepatic toxicity.

A single oral dose of 100 mg/kg given to ten male Wister rats was associated with hepatic necrosis and fatty degeneration of the liver. No changes in relative liver weight or body weight were observed when the animals were sacrificed about 20 hours after exposure (Schmidt et al., 1980).

In another study, single doses of 143.5, 287, 574, or 1148 mg/kg were administered by gavage in corn oil to groups of 4-6 male Sprague-Dawley rats (Cottalasso et al. 1998). The animals were sacrificed 24 hours later and the liver excised for analysis. Levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity were significantly elevated at doses of ≥ 287 mg/kg. A significant increase in liver triglycerides was observed at ≥ 574 mg/kg. This study did not examine a full array of standard toxicological endpoints, and there was no control group. Based on the limited endpoints observed, the 143.5 mg/kg dose is a NOAEL and the 287 mg/kg dose a LOAEL.

Groups of 5-6 male Osborne-Mendel rats were exposed to doses of 0, 25, 75, 150, or 300 mg/kg/day by gavage in corn oil for 4 days in a study by Dow Chemical Company (1988). The animals in the highest dose group exhibited central nervous system depression, and frank signs of toxicity that lead to elimination of the fourth dose for this group. After sacrifice, enlargement of hepatic cells in the centrilobular region, increased glycogen deposits, hepatic mitosis and hyperplasia were seen at doses of 75 mg/kg/day and above. Body weight was significantly depressed at the highest dose. When groups of six male B6C3F1 mice were exposed under the same conditions, centrilobular swelling and a centrilobular hepatocyte swelling was noted at a dose of 75 mg/kg/day and hepatic mitosis was increased at the highest dose. The no observed adverse effect level (NOAEL) in this study was 25 mg/kg/day for both mice and rats and the lowest observed adverse effect level (LOAEL) was 75 mg/kg/day based on effects in the liver.

1,1,2,2-Tetrachloroethane

The NTP (2004) conducted a 15-day range finding study of 1,1,2,2-tetrachloroethane in groups of five/sex F344/N rats and B6C3F1 mice. The chemical was administered through microcapsules incorporated in the feed at levels of 0, 3325, 6650, 13300, 26600, or 53200 ppm (0, 300, 400, 500 mg/kg/day for the first 4 rat dose groups; doses were not provided by NTP for the highest two dose groups because they were sacrificed early). Due to excessive scattering of feed NTP did not determine doses for mice; however they were approximately 0, 600, 1200, 2400 mg/kg/day for the lowest 4 dose groups based on the conventions of EPA, 1988). As with the rats the highest two dose groups were sacrificed early. The animals were examined for clinical signs, body weights, and food intake. At termination, the animals were sacrificed; selected organs were weighed and the tissues were examined histologically. All rats except those in the lowest dose group lost weight during the study. At the lowest dose, relative liver and kidney weight were increased. Some of the liver lesions were observed in both the controls and treated animals. The LOAEL for the rats was identified by the authors as 300 mg/kg/day (3325 ppm); there was no NOAEL. The results in mice were similar to those in rats except that the liver damage in the exposed mice was more prominent and increased in severity with dose. Effects were seen in all dose groups of mice; however, the authors did not identify a dose for mice in association with the lowest feed concentration of 3325 ppm because excessive spilling of the feed prevented an accurate assessment of intake.

NTP (1996) examined 1,1,2,2-tetrachloroethane in a study of the renal toxicity of halogenated ethanes. Groups of five male F344/N rats received 0, 104 or 208 mg/kg/day tetrachloroethane by gavage for 21 days. All animals were examined for body weight, clinical signs, urinalysis, organ weights, and gross pathology. Histology was conducted on the liver and right kidney. The animals in the high dose group showed clinical signs of frank toxicity (i.e. death, respiratory difficulty, emaciation, diarrhea). In the low-dose group, absolute and relative liver weights were greater than those of the controls and mild to moderate hepatic cytoplasmic vacuolization was observed. The authors did not consider the cytoplasmic vacuolization to be an adverse effect. No effects on survival, body weight gain, urinalysis, absolute and relative kidney weight, or kidney histopathology were observed. The 104 mg/kg dose can be considered a marginal LOAEL based on the observed hepatic effects.

4.2.2 Long-term Exposure

A 2004 subchronic study by the National Toxicology Program (NTP) using groups of F-344 rats and B6C3F1 mice (10/dose/sex) provides the most comprehensive dose-response data on the noncancer effects of 1,1,2,2-tetrachloroethane. The study revealed that rats were more sensitive to the noncancer effects of 1,1,2,2-tetrachloroethane than mice. In the rat study, the animals were maintained for 14 weeks on diets containing 0, 268, 589, 1180, 2300, or 4600 ppm (0, 20, 40, 80, 170 or 320 mg/kg/day) microencapsulated 1,1,2,2-tetrachloroethane. They were examined for clinical signs daily; body weight and food consumption were recorded weekly. Blood samples were analyzed for hematological and serum biochemistry measurements. Complete histopathological examinations were conducted on animals in the high dose group and on the liver, spleen, bone, and bone marrow of animals in the lower dose groups; reproductive organs were analyzed for all animals.

Adverse effects indicative of frank toxicity were observed at the two highest doses. They included weight loss, hematological changes, increased biomarkers of liver damage, and hepatic necrosis. Less severe but statistically significant, dose-related effects on the liver (increased serum ALT and SDH activity, increased liver weight, hepatocyte vacuolization), decreased red blood cell measures indicative of possible anemia, and testicular effects were observed across the lowest three dose groups, especially for the males. There were no significant indications of neurotoxic effects in the three lowest dose groups (the only ones tested) as measured using a battery of tests specific for neurotoxicity. According to the study authors, 40 mg/kg/day was the LOAEL for systemic effects, however, hepatocyte cytoplasmic vacuolization of minimal severity occurring in the males in the lowest dose group might justify treating the 20 mg/kg/day dose level as a minimal LOAEL. The cytoplasmic vacuolization was present in all treated groups, but not in the controls, and increased in severity with increasing dose.

In the NTP (2004) study, similar changes in body weight, liver enzyme activity, and liver and kidney weights were observed in B6C3F1 mice given doses of 589, 1120, 2300, 4550 or 9100 ppm (These corresponded to doses of 0, 100, 200, 370, 700, and 1360 mg/kg/day for the males and 0, 80, 160, 300, 600, and 1400 mg/kg/day for the females based on data supplied by NTP). Dose levels of 160 mg/kg/day for females and 200 mg/kg/day for males (1120 ppm) were identified as the LOAELs. Dose levels of 80 mg/kg/day for females and 100 mg/kg/day for males (589 ppm) were the NOAELs. These levels are higher than the NOAEL and LOAEL in the rat studies.

4.2.3 Reproductive and Developmental Effects

Reproductive Effects. As part of the NTP (2004) subchronic study on rats, sperm motility, testicular weight, vaginal condition, and estrus cycle were evaluated. There was a dose-related decrease in sperm motility at concentrations of 40 mg/kg/day and greater. The left epididymis weight was decreased at dose of ≥ 80 mg/kg/day and the right epididymis at ≥ 170 mg/kg/day. Estrus cycles were altered in females only at frankly toxic dose levels.

No oral one- or two-generation studies of reproductive toxicity were identified. A limited one-generation inhalation study using a control and single dose (13.3 mg/m³) did not result in any effects on body weight, visual malformations, or survival at birth or over an 84 day postnatal observation period (Schmidt et al., 1972).

Developmental Effects. NTP (1991 a,b) conducted screening studies of developmental toxicity in Sprague-Dawley rats and Swiss CD-1 mice). The dams were evaluated for Food consumption, body weights and clinical signs during treatment. At termination live and dead pups, implantation sites, resorption sites, and fetal body weights were recorded. Neither study evaluated external, visceral or skeletal abnormalities. Accordingly, the data base for developmental and reproductive toxicity is limited.

In groups of 8-9 pregnant Sprague-Dawley rats receiving dietary doses of 0, 34, 98, 180, 278, or 330 mg/kg/day from gd 0 to gd 20, weight gain in the dams was significantly decreased in all but the lowest dose group as were the average fetal body weights (NTP, 1991a). Total pup resorption was seen in one animal from the 98 mg/kg/day dose group and 4 of 9 animals in the 330 mg/kg/day dose group. The NOAEL for the dams and pups was 34 mg/kg/day based on the parameters evaluated (live and dead pups, implantation sites, resorption sites, clinical signs, maternal and fetal body weights); the LOAEL was 98 mg/kg/day based on the decreased weight gain by the dams and the significantly lower body weight for the pups.

In a second developmental toxicity study, Swiss CD-1 mice, received target dietary doses of 0, 987, 2120, 2216, or 4575 mg/kg/day (NTP, 1991b). The 987 mg/kg dose was the LOAEL for the dams based on clinical signs of toxicity, effects on body weight, and liver histopathology. Total resorptions occurred in 2 of 8 dams in the 2120 mg/kg/day dose group, but not in any animals from the lowest dose group (987 mg/kg/day). All but one dam died in the 2216 mg/kg/day dose group as did all of the animals in the high dose group.

4.2.4 Genotoxicity

Predominantly negative results have been reported for the induction of bacterial gene mutations, with and without metabolic activation (Haworth et al., 1983; Milman et al., 1988; Nestmann et al., 1980; Warner et al., 1988) with a few exceptions (Brem et al., 1974; Mersch-Sundermann et al., 1989a). However, 1,1,2,2-Tetrachloroethane induced sister chromatid exchanges in CHO cells (Galloway et al., 1987) and in BALB/c3T3 mouse cells (Colacci et al., 1992) but did not cause chromosomal aberrations in the CHO cells. It did not induce DNA growth, repair and synthesis in mouse and rat hepatocytes (Williams, 1983; Milman et al., 1988) or cause unscheduled DNA synthesis in human embryonic intestinal cells (McGregor, 1980).

Results for *in vivo* cell transformation in mammalian cells have been mixed, with positive results (Colacci et al., 1992, 1993) and negative results (Little, 1983; Tu et al., 1985; Milman et al., 1988) reported. A dose-related increase in the number of micronucleated monochromatic erythrocytes per thousand cells was recorded in an *in vivo* mouse micronucleus test using doses of about 100 to 1400 mg/kg/day (NTP, 2004). The mouse micronucleus results, in conjunction

with the *in vitro* tests for sister chromatid exchange, indicate that 1,1,2,2-tetrachloroethane can have clastogenic effects.

4.2.5 Carcinogenicity

The key study for the evaluation of the carcinogenicity of 1,1,2,2-tetrachloroethane is an NCI (1978) bioassay in which groups of Osborne- Mendel rats and B6C3F1 mice (50 per sex per dose group) were given 1,1,2,2-tetrachloroethane in corn oil by gavage 5 days/ week for 78 weeks. The doses normalized for 7 days/week were 44 and 78 mg/kg/day for male rats, 31 and 55 mg/kg/day for female rats, and 101 and 202 mg/kg/day for both male and female mice. After cessation of dosing the rats were observed for 32 additional weeks and the mice for 12 weeks. Dosing occurred 5 days/week and the dose levels were adjusted (up then down) during the study and required normalization for the assessment. Vehicle controls (20/sex) received corn oil at the same rate as the high-dose animals; untreated controls were not intubated.

No statistically significant increase in the incidence of neoplasms was observed in rats but there were two males with hepatocellular carcinomas and one with a hepatic preneoplastic nodule in the high dose group leading NCI to classify the results in males as equivocal because these tumors are rare in Osborne Mendel rats. There was a highly significant dose-related increase in the incidence of hepatocellular carcinomas in both male (3/36, 13/50, 44/49) and female (1/40, 30/48, 43/47) mice. The reported values for the control group are the combination of the untreated and vehicle treated controls).

4.3 Proposed Mode of Action

1,1,2,2-Tetrachloroethane is almost completely absorbed from the gastrointestinal tract (Dow, 1988; Mitoma et al., 1985). Data on tissue distribution are limited, but autoradiography after iv dosing and adverse effects in the liver, kidney and testes after oral dosing demonstrate distribution to these organs (Eriksson and Brittebo, 1991; NTP, 1996, 2004). Dichloroacetic acid (DCA) appears to be the major metabolite of 1,1,2,2-tetrachloroethane after single intraperitoneal doses ranging from 160 to 320 mg/kg ¹⁴C labeled compound (Yllner, 1971). Other metabolites identified in the urine of treated rats by Yllner (1971) were trichloroethanol, trichloroacetic acid, oxalate and glycolate; the latter two are metabolites of DCA. Excretion of the chlorine from 1,1,2,2-trichloroethane occurs primarily through metabolites in the urine; a substantial portion of the carbon is completely metabolized to carbon dioxide and excreted in exhaled air based on single dose studies. Some unmetabolized 1,1,2,2-tetrachloroethane is also removed from the body with exhaled air. Lack of multiple dose studies is a weakness of the 1,1,2,2-tetrachloroethane database because DCA, the principle metabolite inhibits its own metabolism. Therefore, in multiple dose studies the distribution of metabolites might well have differed from that observed in the single dose studies.

4.3.1 Noncancer Effects

The hepatic toxicity of 1,1,2,2-tetrachloroethane is thought to be due to the formation of free radical intermediates and/or toxic metabolites such as DCA, trichloroethanol or trichloroacetic acid (ATSDR, 1996, Paolini et al., 1992; Tomasi et al., 1984. Yllner, 1971) DCA is an important metabolite of 1,1,2,2-tetrachloroethane and shares some common manifestations of toxicity such as hepatic necrosis, increased liver weight, glycogen accumulation, testicular toxicity, and neurotoxicity in rats and mice (U.S. EPA, 2003). 1,1,2,2-Tetrachloroethane has also been implicated in the impairment of heme synthesis in the liver of treated animals, an effect which may account for the decrease in hemoglobin or hematocrit levels seen in several short term toxicity studies (NTP, 2004; Minot and Smith, 1921).

4.3.2 Cancer Effects

Haseman (1984) has reported that an increased incidence of hepatocellular carcinomas in B6C3F1 mice after exposure to 1,1,2,2-tetrachloroethane is not unusual because many chemicals increase the spontaneous rate of such tumors in this strain, however, DCA, the main metabolite of 1,1,2,2-tetrachloroethane, also causes liver tumors in both B6C3F1 mice and F-344 rats (U.S. EPA, 2003).

There have been numerous studies of the possible mechanisms through which DCA may cause the development of liver tumors. Like, 1,1,2,2-tetrachloroethane, DCA is a weak mutagen, inducing mutations and chromosome damage in *in vitro* and *in vivo* assays predominantly at high concentrations (U.S. EPA, 2003). Peroxisome proliferation, reparative hyperplasia, DNA hypomethylation, tumor promotion, impaired intracellular communication, and abnormal cell signaling have all been investigated as possible mechanisms leading to liver tumors after DCA exposure (U.S. EPA, 2003). A clear mode of action for DCA tumorigenicity has yet to be defined. A study of liver tissues from DCA treated rats concluded that based on observed patterns of lesion frequency and their progression across the time- and dose-range evaluated there might be three distinct routes to the development of malignant tumors (Carter et al., 2003). Tumors in the liver appeared to develop from eosinophilic, dysplastic and basophilic/clear cells. The majority of the tumors seemed to develop from the basophilic/clear cells.

Few studies of possible mechanisms for 1,1,2,2-tetrachloroethane carcinogenicity, have been conducted. Studies of initiation and promotion using the production of GGT + foci in the livers of male Osborne-Mendel rats and an *in vitro* two-stage BALB/c3T3 cell transformation assay in athymic CD1/BR mice indicate that 1,1,2,2-tetrachloroethane is a weak initiator that also can function as a tumor promoter (Story et al., 1986; Colacci et al., 1992, 1993).

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5.0 QUANTIFICATION OF TOXICOLOGICAL EFFECTS

HAs describe nonregulatory concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations. HAs are developed for both short-term and long-term (Longer-term and Lifetime) exposure periods based on data describing noncarcinogenic endpoints of toxicity.

Short Term exposures can include One-day and Ten-day exposure periods. One-day and Ten-day HAs use parameters that reflect exposures and effects for a 10 kg child consuming 1 liter of water per day.

A Longer-term HA covers an exposure period of approximately 7 years, or 10 percent of an individual's lifetime. Longer-term HAs can incorporate parameters for either a child (10 kg body weight consuming 1 liter per day water) or an adult (70 kg body weight consuming 2 liters per day water) parameters.

A Lifetime HA covers an individual's lifetime, approximately 70 years. A lifetime HA considers a 70 kg adult consuming 2 Liters of water per day. The lifetime HA is considered protective of non-carcinogenic adverse health effects over a lifetime exposure. A relative source contribution from water is also factored into the lifetime HA calculation to account for contaminant exposures from other sources (air, food, soil, etc) of the contaminant. For those substances that are *Carcinogenic to Humans, Likely To be Carcinogenic to Humans* (U.S. EPA, 2005), known (Group A), or probable (Groups B₁ and B₂) human carcinogens (U.S. EPA, 1986a), the development of a Lifetime Health Advisory is not usually recommended. A Lifetime HA can be calculated for substances that are possible carcinogens (U.S. EPA, 1986) or provide "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human carcinogenic Potential" (U.S. EPA 2005).

The One-day, Ten-day, or Longer-term HA is derived using the following formula:

$$HA = \frac{NOAEL \text{ or } LOAEL \times BW}{UF \times DWI}$$

Where:

NOAEL or LOAEL	=	No- or Lowest-Observed-Adverse-Effect Level (in mg/kg bw/day) from a study of an appropriate duration
BW	=	Assumed body weight of a child (10 kg) or an adult (70 kg).
UF	=	Uncertainty factor in accordance with EPA guidelines
DWI	=	Assumed human daily consumption for a child (1 L/day) or an adult (2 L/day)

The Lifetime HA is calculated in a three-step process:

Step 1: Adopt a pre-existing Reference Dose (RfD) or calculate an RfD using the following equation:

$$\text{RfD} = \frac{\text{NOAEL, LOAEL or BMDL}}{\text{UF}}$$

Where:

NOAEL or LOAEL	=	No- or Lowest-Observed-Adverse-Effect Level (in mg/kg bw/day).
BMDL	=	Lower confidence bound on the Bench Mark Dose (BMD). The BMD and BMDL are obtained through modeling of the dose-response relationship.
UF	=	Uncertainty factor established in accordance with EPA guidelines.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily human exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose with uncertainty factors generally applied to reflect limitations in the data used.

Step 2: Calculate a Drinking Water Equivalent Level (DWEL) from the RfD. The DWEL assumes that 100% of the exposure comes from drinking water.

$$\text{DWEL} = \frac{\text{RfD} \times \text{BW}}{\text{DWI}}$$

Where:

RfD	=	Reference Dose (in mg/kg bw/day).
BW	=	Assumed body weight of an adult (70 kg).
DWI	=	Assumed human daily consumption for an adult (2 L/day)

Step 3: The Lifetime HA is calculated by factoring in other sources of exposure (such as air, food, soil) in addition to drinking water using the relative source contribution (RSC) for the drinking water.

$$\text{Lifetime HA} = \text{DWEL} \times \text{RSC}$$

Where:

DWEL	=	Drinking Water Equivalent Level (calculated from step 2)
RSC	=	Relative source contribution

Note. The procedure for establishing the RSC is described in U.S. EPA (2000) Human Health Methodology (pages 4-5 to 4-17). The methodology can be accessed at: <http://www.epa.gov/waterscience/criteria/humanhealth/method/complete.pdf>

5.1 One-day Health Advisory

The study by Dow (1988) was selected for use in the derivation of the One-day HA because it provided the lowest LOAEL among the short term-studies with an appropriate duration. Several endpoints related to liver toxicity were evaluated. The single dose studies of Schmidt et al. (1980) and Cottalasso et al. (1998) and the 14 day and 21 day studies of NTP (1996, 2004) also identify the liver as a major target organ for short-term 1,1,2,2-tetrachloroethane exposures. The animal data are supported by the limited clinical information identifying the liver as a target organ in humans.

In the Dow (1988) study, enlargement of hepatic cells in the centrilobular region, glycogen deposits, hepatic mitosis and hyperplasia were seen in Osborne Mendel rats at a dose of 75 mg/kg/day (LOAEL) and centrilobular hepatic swelling was observed in B6C3F1 mice at the same dose. The NOAEL was 25 mg/kg/day. The LOAEL in the Schmidt et al. (1980) single dose study using male Wistar rats was 100 mg/kg/day based on hepatic necrosis and fatty degeneration of the liver. There was no NOAEL. Cottalasso et al. (1998) observed increased serum ALT and AST activity (biomarkers for liver damage) in groups of Sprague-Dawley rats at a LOAEL of 287 mg/kg/day and a NOAEL of 143.5 mg/kg/day.

Each of these studies has its limitations because of the small number of animals evaluated (4 to 10/dose group), the use of a single sex, and the less-than-complete evaluation of toxicological endpoints. However, the three studies provide data on two species, three strains of rats, and show a common impact on the liver which is supported by the longer-term, more-comprehensive studies. These factors justify the use of the NOAEL from the Dow (1988) study as the basis of the One-day HA.

The One-day HA for a 10-kg child is calculated as follows:

$$\text{One Day HA} = \frac{25 \text{ mg/kg/day} \times 10 \text{ kg}}{100 \times 1 \text{ L/day}} = 2.5 \text{ mg/L (rounded to 3 mg/L)}$$

Where:

25 mg/kg/day	=	NOAEL for hepatotoxicity in rats (Dow, 1988).
10 kg	=	Assumed body weight of a child
100	=	Uncertainty factor, chosen for interspecies (10) and intraspecies (10) differences
1 L	=	Assumed daily water consumption of a child.

5.2 Ten-day Health Advisory

The studies by Dow Chemical corporation (1988), NTP (1996) and NTP (2004) were selected to serve as the basis for the Ten-day HA for 1,1,2,2-tetrachloroethane. The NTP (1996) study in rats used a 3-week (21-day) exposure duration and identified a lower LOAEL (104 mg/kg/day) than did the 2-week NTP (2004) study in rats (300 mg/kg/day). There was no NOAEL in either study. The DOW Chemical Corporation study (1988) provided a NOAEL (25 mg/kg/day) as

well as a LOAEL. All three studies identified the liver as the target organ for 1,1,2,2-tetrachloroethane and the observed impacts on the liver were consistent across the studies. The histological changes effects seen at the LOAEL in the NTP (1996) study were classified as mild to moderate centrilobular vacuolization and were not considered as adverse by the authors. The LOAEL (104 mg/kg/day) in the NTP (1996) study is roughly comparable to the LOAEL in the 4-day Dow Chemical Corporation study (75 mg/kg/day).

The advantage of using the Dow (1988) study for quantification of the ten day HA is the fact that it identified a NOAEL of 25 mg/kg/day for liver effects and the LOAEL is lower than the LOAELS from the other two studies. Accordingly the ten-day HA calculation is based in the NOAEL from the Dow (1988) study and the same as that for one-day HA. Accordingly the ten-day Ha is 3 mg/L.

5.3 Longer-term Health Advisory

The study by NTP (2004) was selected to serve as the basis for the Longer-term HA for 1,1,2,2-tetrachloroethane. In this study, the LOAEL for changes in hepatocyte vacuolization, relative liver weight, and increased activity of serum liver enzymes (ALT, SDH) in F-344 male rats following dietary exposure for 14 weeks was 40 mg/kg/day. Male rats were more sensitive to the effects of 1,1,2,2-tetrachloroethane than the females and F-344 rats were more sensitive than B6C3F1 mice (NTP, 2004). This study was selected because it was of high quality, used an appropriate duration, and was conducted in an appropriate species for the evaluation of noncancer effects.

From the NTP (2004) data set, U.S. EPA (2006) derived a Benchmark Dose (BMD) of 13.08 mg/kg/day and a lower bound limit on the Benchmark Dose (BMDL) of 10.71 mg/kg/day for a one standard deviation increase in the relative liver weight compared to controls. In addition to relative liver weights, the changes in serum ALT and SDH, hemoglobin concentrations, and sperm motility were also modeled. Adequate fit was achieved for all but the sperm motility data and the lowest BMD/BMDL values were those for relative liver weight. The BMD analysis in the Health Effects Support Document is located on pages 8-3 to 8-6.

For a 10 kg child, the Longer-term HA is calculated as follows:

$$\text{Longer-term HA} = \frac{10.71 \text{ mg/kg/day} \times 10 \text{ Kg}}{300 \times 1 \text{ L/day}} = 0.36 \text{ mg/L (rounded to 0.4 mg/L)}$$

Where:

10.71 mg/kg/day	=	BMDL, Benchmark Dose, lower-bound confidence bound for a one standard deviation increase in relative liver weight compared to controls (NTP, 2004)
10 kg	=	Assumed body weight of a child
300	=	Uncertainty factor, chosen for interspecies (10) and intraspecies (10) differences and an incomplete database (3)
1 L	=	Assumed daily water consumption of a child.

For an adult, the Longer-term HA is calculated as follows:

$$\text{Longer-term HA} = \frac{10.71 \text{ mg/kg/day} \times 70 \text{ Kg}}{300 \times 2 \text{ L/day}} = 1.25 \text{ mg/L (rounded to 1 mg/L)}$$

Where:

10.71 mg/kg/day	=	BMDL, Benchmark Dose, lower-bound confidence bound for a one standard deviation increase in relative liver weight compared to controls (NTP, 2004)
70 kg	=	Assumed body weight of an adult
300	=	Uncertainty factor, chosen for interspecies (10) and intraspecies (10) differences and an incomplete database (3)
2L	=	Assumed daily water consumption of an adult.

Note: The 3-fold database UF is based on the need for a multigenerational study of reproductive toxicity and additional studies of developmental toxicity that examine the fetus for visceral and skeletal abnormalities. The available NTP developmental screening assays do not examine these endpoints.

5.4 Lifetime Health Advisory

The subchronic study by NTP was selected as the basis of the oral RfD of 0.02 mg/kg/day (U.S. EPA, 2006). As described above, the LOAEL for male F-344 rats in this study was 40 mg/kg/day based on hepatocyte vacuolization, increased relative liver weights, and increased activity liver enzymes (ALT, SDH) in serum following dietary exposure for 14 weeks was 40 mg/kg/day. Male rats were more sensitive to the effects of 1,1,2,2-tetrachloroethane than the females and F-344 rats were more sensitive than B6C3F1 mice (NTP, 2004). This study was selected because it was of high quality, provided a thorough evaluation of noncancer endpoints and included more doses than the NCI chronic cancer study.

The RfD was derived from the lower-bound limit based on the dose associated with a one standard deviation increase in relative liver weight (10.71 mg/kg/day) in animals exposed to 1,1,2,2-tetrachloroethane in their diet for 14 weeks. The change in relative liver weight was accompanied by hepatocyte vacuolization and increased activity levels of liver enzymes (ALT and SDH) in the serum. The activities of the liver enzymes were also modeled. The BMDL₁₀ for a one standard deviation change in ALT was 29.13 mg/kg/day and that for SDH was 31.69 mg/kg/day. The BMDL for the increases in liver weight was chosen as the point of departure for the RfD because 7 of 10 male mice showed histological evidence of hepatocyte cytoplasmic vacuolization at the lowest dose tested (20 mg/kg/day), a factor which justified choosing the lowest BMDL from the modeled responses. The BMD analysis in the Health Effects Support Document is found on pages 8-3 to 8-6. The RfD is calculated from the BMDL as follows:

$$\text{RfD} = \frac{10.71 \text{ mg/kg/day}}{1000} = 0.0107 \text{ mg/kg/day (rounded to 0.01 mg/kg/day)}$$

Where:

- 10.71 mg/kg/day = BMDL, Benchmark Dose, lower-bound confidence bound for a one standard deviation increase in relative liver weight compared to controls (NTP, 2004)
- 1000 = Uncertainty factor, chosen for interspecies (10) and intraspecies (10) differences, the less than chronic duration of the study (3), and an incomplete database (3)

Note: The application of a 3-fold uncertainty factor for extrapolation from a subchronic to a chronic duration was justified based on the fact that the NCI (1978) study in Osborn Mendel rats, using higher dose levels than the BMDL did not identify cirrhosis or other major histological liver problems. However, the NCI (1978) study did not monitor for serum biochemistry or hematological effects. Accordingly, a UF of 3 was selected because of the differences in the rat strains used in the subchronic and chronic studies and the limited monitoring of effects other than tumors in the chronic study. The justification for the 3-fold database deficiency adjustment is provided under the Longer-term HA discussion above.

A Drinking Water Equivalent Level (DWEL) can be derived from the oral RfD as follows:

$$\text{DWEL} = \frac{0.01 \text{ mg/kg/day} \times 70 \text{ Kg}}{2 \text{ L/day}} = 0.35 \text{ mg/L (rounded to 0.4 mg/L)}$$

Where:

- 0.01 mg/kg/day = Oral Reference Dose
- 70 Kg = Assumed body weight of an adult
- 2L/day = Assumed daily water consumption of an adult.

1,1,2,2-tetrachloroethane has been classified as *likely to be carcinogenic to humans* (U.S. EPA, 2006). Therefore, the development of a Lifetime Health Advisory is not recommended. The cancer risk at the DWEL is 1×10^{-3} (See section 5.5).

5.5 Evaluation of Carcinogenic Potential

The HA evaluation of carcinogenic potential includes the U.S. EPA descriptors for the weight of evidence of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed, as well as a quantitative estimate of cancer potency (slope factor), where available. The Cancer Slope Factor (CSF) is the result of the application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day of the contaminant. In cases where a CSF has been derived, HAs include the drinking water concentrations equivalent to an upper-bound excess lifetime cancer risk of one-in-ten-thousand (1×10^{-4}), one-in-one-hundred-thousand (1×10^{-5}), to one-in-one-million (1×10^{-6}).

Cancer assessments conducted before 1996 used the five-category, alpha-numeric system for classifying carcinogens established by the Guidelines for Carcinogen Risk Assessment (U.S.

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EPA, 1986a). The EPA currently requires that all new cancer risk assessments comply with the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005) or, if conducted between 1996 and 2005, comply with the draft versions of the 2005 Cancer guidelines.

The OW has classified 1,1,2,2-tetrachloroethane as *likely to be carcinogenic to humans* (U.S. EPA, 2006) following the 2005 Cancer Guidelines. The current IRIS cancer classification for 1,1,2,2-tetrachloroethane is Group C: a possible human carcinogen (U.S. EPA, 1986b). The International Agency for Research on Cancer (IARC, 1999) classifies 1,1,2,2-tetrachloroethane in Group 3; data in humans inadequate and limited evidence in experimental animals. The principal 1,1,2,2-tetrachloroethane metabolite, DCA, is classified as *likely to be carcinogenic to humans* (U.S. EPA, 2003).

Using the Benchmark Dose approach and the linear multistage model, the OW determined a CSF of $8.5 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$ using the data for female mice from the NCI (1978) study following the procedures of the 2005 Cancer Guidelines. The data for the male mice did not provide an adequate fit with the multistage model. The quantitative cancer assessment in the Health Effects Support Document is on pages 8-10 to 8-13". The concentration in drinking water corresponding to a 10^{-6} risk is 4×10^{-4} mg/L, that for a 10^{-5} risk is 4×10^{-3} mg/L and that for a 10^{-4} risk is 4×10^{-2} mg/L.

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6.0 OTHER CRITERIA, GUIDANCE, AND STANDARDS

The OW Human Health Ambient Water Quality Criterion (AWQC) for 1,1,2,2-tetrachloroethane is 0.17 µg/L. The AWQC is used by states in establishing regulatory limits for ambient water and in developing fish advisories.

Six states have established regulatory or guidance values for 1,1,2,2-tetrachloroethane in drinking water (HSDB, 2004). California and New Jersey have Standards of 1 µg/L. Arizona has a guideline value of 0.17 µg/L; Wisconsin and Minnesota a value of 0.2 µg/L and Florida a value of 1 µg/L. Three States (Connecticut, Delaware, and Oregon) have standards of 0.17 µg/L 1,1,2,2-tetrachloroethane for ambient water and fish ingestion (ATSDR, 1996).

ATSDR (2006) has established an intermediate-duration oral Minimal Risk Level (MRL) for 1,1,2,2-tetrachloroethane of 0.5 mg/kg/day based on a BMDL₁₀ of 53.88 mg/kg/day for hepatic necrosis for the rats in the NTP (2004) 14-week study using a total UF of 100. An intermediate duration value applies to exposures ranging from 15 to 364 days.

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7.0 ANALYTICAL METHODS

Two analytical methods are available for detecting 1,1,2,2-tetrachloroethane in drinking water. EPA Methods 502.2 and 524.2 rely on purge and trap gas chromatography (GC) followed by either electrolytic conductivity detection (ELCD) or mass spectrometry (MS). The method detection limit (MDL) for Method 502.2 is reported to range from 0.01 to 0.02 $\mu\text{g/L}$, and the average recovery is reported to range from 99 to 100 percent (U.S. EPA, 1995a). The MDL for Method 524.2 is reported to range from 0.04 to 0.2 $\mu\text{g/L}$, and the average recovery is reported to range from 91 to 100 percent (U.S. EPA, 1995b).

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8.0 TREATMENT TECHNOLOGIES

Potential treatment technologies for removing 1,1,2,2-tetrachloroethane from water include air stripping and activated carbon. Air stripping involves the continuous contact of air with the water being treated, allowing dissolved volatile contaminants to transfer from the source water to the air. Compounds that have a Henry's Law Constant above that for dibromochloropropane (0.003 mol/mol) or that for ethylene dibromide (0.013 mol/mol) are considered to be amenable to air stripping (Speth et al., 2001). The Henry's Law Constants for 1,1,2,2-tetrachloroethane have been reported to be 0.012 mol/mol and 0.016 mol/mol (Speth et al., 2001). Granular activated carbon (GAC) treatment removes contaminants via the physical and chemical process of sorption: the contaminants attach to the carbon surface as water passes through the carbon bed. Contaminants with an adsorption capacity, expressed as the Freundlich isotherm constant (K), above $200 \mu\text{g/g (L/\mu\text{g})}^{1/n}$ are considered to be amenable to GAC treatment (Speth et al., 2001). Speth and Adams (1993 as cited in Speth et al., 2001) report that the Freundlich (K) value for 1,1,2,2-tetrachloroethane is $823 \mu\text{g/g (L/\mu\text{g})}^{1/n}$.

Home drinking water treatment units have varying abilities to remove contaminants from tap water. The following site allows the user to identify treatment units according to the contaminants they can remove: <http://www.nsf.org/Certified/DWTU/>. At this time there are no units identified that have been evaluated for removal of 1,1,2,2-tetrachloroethane (see reduction claim type) but units that are certified as effective for removal of other chlorinated ethanes are identified.

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