

Trichloroethylene (TCE) | 2019

Substance Overview

Trichloroethylene (TCE) is an organic solvent that has been primarily used as a degreaser to clean metal parts and machinery.^{1,2} It is a human-made chemical that does not occur naturally in the environment. TCE is produced in large volumes for commercial use and is found in home products, such as paints, spot removers, metal cleaners, and varnishes. Before 1960, TCE was heavily used in the dry cleaning industry. TCE can enter groundwater and surface water from industrial discharge or from improper disposal.

Recommendations

The current NR140 Groundwater Quality Public Health Enforcement Standard of 5 micrograms per liter ($\mu\text{g/L}$) for TCE is based on United States Environmental Protection Agency's (EPA's) maximum contaminant level from the 1980s.

DHS recommends lowering the enforcement standard for TCE to $0.5 \mu\text{g/L}$. The recommended standard is based on the EPA's drinking water concentration based on a cancer risk level determination. A concentration of $0.5 \mu\text{g/L}$ corresponds with a lifetime cancer risk level of 1 in 1,000,000.

DHS recommends setting the NR140 Groundwater Quality Public Health Preventive Action Limit for TCE at 10% of the enforcement standard because it has been shown to have carcinogenic, mutagenic, and teratogenic effects.

Health Effects

Known health effects from TCE come from animal studies and from studies of people who have come into contact with TCE in their environments. High levels of TCE in drinking water may cause nausea, convulsions, liver and kidney damage, impaired heart function, coma, or even death.^{1,2} There is strong evidence that TCE can cause kidney cancer in people and some evidence that it can cause liver cancer and malignant lymphoma. Lifetime exposure to TCE resulted in increased liver cancer in mice and increased kidney cancer and testicular cancer in rats. Additional animal studies indicate there may be an association between maternal exposure to TCE and specific heart defects in offspring. There is some evidence that human exposure to TCE while pregnant may be associated with similar effects.

The EPA and the International Agency for Research on Cancer (IARC) have classified trichloroethylene as a human carcinogen by all routes of exposure.^{1,3} TCE has been shown to cause carcinogenic, mutagenic, and teratogenic effects.¹ TCE has not been shown to cause interactive effects.¹

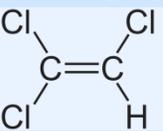
Current Standards

Enforcement Standard:	5 $\mu\text{g/L}$
Preventive Action Limit:	0.5 $\mu\text{g/L}$
Year:	2011

Recommended Standards

Enforcement Standard:	0.5 $\mu\text{g/L}$
Preventive Action Limit:	0.05 $\mu\text{g/L}$

Chemical Profile

Trichloroethylene	
Structure:	
CAS Number:	79-01-6
Formula:	C ₂ HCl ₃
Molar Mass:	131.38 g/mol
Synonyms:	Algylen, Anamenth, Benzinol, Caswell, Ethylene trichloride, Trichloroethene, Trilene

Exposure Routes

People can come in contact with TCE from contaminated air, water, or soil.¹ Drinking TCE-contaminated water is one of the most likely exposure routes for humans. Contaminated groundwater often occurs at or near hazardous waste sites where TCE has been improperly discarded and near industrial sites where it is used or produced in high volumes. Additional routes of exposure come from breathing in TCE vapors and absorption of TCE through the skin.

In the environment, TCE typically volatilizes into the air, but can also get into the soil and groundwater.¹ In soil and groundwater, TCE does not easily break down and can stay in the environment for long periods of time (months to years).

Current Standard

The current groundwater standard of 5 µg/L for TCE is based on the EPA's Maximum Contaminant Level (MCL).⁴ This regulation went into effect in 1989 and is required to receive a periodic review. Because TCE has shown to cause carcinogenic and mutagenic effects, the current preventive action limit is set at 10% of the enforcement standard.

Standard Development

Federal Numbers

Maximum Contaminant Level:	5 µg/L	(2010)
Health Advisory:	N/A	
Drinking Water Concentration (Cancer Risk):	50 µg/L	(2011)
	5 µg/L	
	0.5 µg/L	

State Drinking Water Standard

NR809 Maximum Contaminant Level:	5 µg/L	(2016)
----------------------------------	--------	--------

Acceptable Daily Intake

EPA Oral Reference Dose:	0.0005 mg/kg-d	(2011)
--------------------------	----------------	--------

Oncogenic Potential

EPA Cancer Slope Factor:	0.0464 (mg/kg-d) ⁻¹	(2011)
--------------------------	--------------------------------	--------

Guidance Values

ATSDR Chronic Oral Minimum Risk Level:	0.0005 mg/kg-d	(2014)
--	----------------	--------

Literature Search

Search Dates:	2014 – 2019
Total studies evaluated:	Approximately 60
Key studies found?	Yes

Federal Numbers

Chapter 160, Wis. Stats., requires that DHS use the most recent federal number as the recommended enforcement standard unless one does not exist or there is significant technical information that was not considered when the federal number was established and that indicates a different number should be used.

Maximum Contaminant Level

The EPA has a maximum contaminant level of 5 µg/L for TCE.⁵ This regulation went into effect in 1989 and is subject to a periodic review. The EPA reviewed the MCL for TCE in 2010 and 2016 as part of their Six-Year Review. In 2010, the EPA determined that the MCL for TCE was a candidate for revision. They specified that the health assessment was in process but that new analytical feasibility and treatment technology information may justify revising the limit.⁶ In 2016, the EPA determined that the MCL for TCE was not appropriate for revision at the time due to recently completed, ongoing, or pending regulatory action.⁷

Health Advisory

The EPA has not established a health advisory for TCE.⁸

Drinking Water Concentrations at Specified Cancer Risk Levels

In 2011, the EPA established the drinking water concentrations at specified cancer risk levels for TCE based on the cancer slope factor (described in more detail below), an average body weight of 70 kilograms (kg), and water consumption rate of 2 liters per day (L/d).¹

Cancer Risk Level	Water Concentration
1 in 10,000	50 µg/L
1 in 100,000	5 µg/L
1 in 1,000,000	0.5 µg/L

State Drinking Water Standard

Chapter 160, Wis. Stats., requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

As of March 2016, Wisconsin has a maximum contaminant level of 5 µg/L for TCE.⁹ This drinking water standard is based on the EPA's maximum contaminant level.

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation. Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. The EPA provides ADIs, termed oral reference doses, as part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Assessment System (IRIS) program.

EPA Oral Reference Dose

In 2011, the EPA established an oral reference dose of 0.0005 milligrams per kilogram body weight per day (mg/kg-day) for TCE.¹ The EPA selected this value because it was a midpoint among three other similar reference doses: 0.00048 mg/kg-day for decreased thymus weight in mice; 0.00037 mg/kg-day for developmental immunotoxicity in mice; and 0.00051 mg/kg-day for fetal heart malformations in rats.

Oncogenic Potential

Chapter 160, Wis. Stats., requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard. If we determine that something is carcinogenic and there is no federal number or ADI from the EPA, DHS must set the standard at a level that would result in a cancer risk equivalent to 1 case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than 1 in 1,000,000.

To evaluate the oncogenic potential of TCE, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of TCE. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

The EPA has classified TCE as a human carcinogen by all routes of exposure.¹

The International Agency for Research on Cancer (IARC) has also classified TCE as a human carcinogen by all routes of exposure.³

EPA Cancer Slope Factor

In 2011, the EPA established a cancer slope factor of $0.0464 \text{ (mg/kg-d)}^{-1}$ for TCE as part of their Integrated Risk Assessment System (IRIS) review.¹ The EPA did this by converting from the inhalation unit risk to water concentration using an exposure model to protect from kidney cancer, non-Hodgkin's lymphoma, and liver cancer.

Additional Technical Information

Chapter 160, Wis. Stats., allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For TCE, we searched for values that been published since 2011 when the EPA published their latest IRIS review. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Chronic Oral Minimum Risk Level

In 2014, the ATSDR established a chronic oral minimum risk level for TCE.² For this level, they used EPA's chronic reference dose of 0.005 mg/kg-d (see *EPA Oral Reference Dose* section above for more details).

Literature Search

The most recent federal number for TCE was established by the EPA in 2011 and the most recent federal literature review occurred with the ATSDR Toxicological Profile for TCE in 2014. Thus, in addition to reviewing these federal reviews, our literature review focused on the scientific literature published after the review by ATSDR in 2014.

A search on the National Institutes of Health's PubMed resource for relevant articles published from 2014 to September 2018 was carried out for studies related to TCE toxicity or TCE effects on a disease state in which information on exposure or dose was included as part of the study.¹ Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

¹ The following search terms were used in the literature review:
Title/Abstract: Trichloroethylene
Subject area: toxicology OR cancer
Language: English

Approximately 60 studies were returned by the search engine. We excluded studies on non-oral exposure routes, non-mammalian species, and acute poisonings from further review. After applying these exclusion criteria, we located four key studies (Table A-1 contains a summary of these studies). To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.² None of the key studies met the requirements to be considered a critical study (see Table A-2 for details on the evaluation).

Standard Selection

DHS recommends an enforcement standard of 0.5 µg/L for TCE.

There are two federal numbers for TCE: the maximum contaminant concentration and EPA’s drinking water concentrations based on a cancer risk level determination. The drinking water concentrations at various cancer risk levels are based on the latest scientific information for TCE. While the EPA has reviewed the MCL for TCE as part of their six year reviews, they have not taken action to update the MCL because of other ongoing regulatory actions. Based on the latest scientific information for TCE, DHS recommends adopting the drinking water concentrations based on a cancer risk level determination as the enforcement standard.

Basis for Enforcement Standard

- Federal Number
- Cancer Potential
- EPA Acceptable Daily Intake
- Technical information

When calculating an acceptable daily intake from cancer risk, Chapter 160 requires that DHS used a cancer risk of 1 in 1,000,000. To be consistent with this requirement, we recommend using EPA’s drinking water concentration at a cancer risk level of 1 in 1,000,000 as the enforcement standard for TCE. In our review of recent information, we did not find any significant technical information that a different enforcement standard is appropriate.

DHS recommends a preventive action limit of 0.05 µg/L for TCE.

DHS recommends setting the preventive action limit for TCE at 10% of the enforcement standard because TCE has been shown to cause carcinogenic, mutagenic, and teratogenic effects.¹ TCE has not been shown to cause interactive effects.¹

² Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect, and the BMD is an estimation of the dose that would cause a specific level of response (typically 5 or 10%).¹⁰

Prepared by Michael Metcalf and Sarah Yang, Ph.D.

Wisconsin Department of Health Services

References

1. USEPA. Toxicological Review of Trichloroethylene. In: (IRIS) IRIS, ed. Vol EPA/635/R-09/011F2011.
2. ATSDR. Draft Toxicological Profile for Trichloroethylene. In: Registry AFTSaD, ed2011.
3. IARC. List of Classification, Volumes 1-123. 2018; <https://monographs.iarc.fr/list-of-classifications-volumes/>. Accessed May 17, 2019.
4. WIDNR. Groundwater Quality. In: Resources WDoN, ed. *Chapter NR 140*2017.
5. USEPA. National Primary Drinking Water Regulations. 2018; <https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations>.
6. USEPA. Six-Year Review 2 of Drinking Water Standards. 2010; <https://www.epa.gov/dwsixyearreview/six-year-review-2-drinking-water-standards>. Accessed June 5th, 2019.
7. USEPA. Six-Year Review 3 of Drinking Water Standards. 2016; <https://www.epa.gov/dwsixyearreview/six-year-review-3-drinking-water-standards>. Accessed June 5th, 2019.
8. USEPA. Drinking Water Contaminant Human Health Effects Information. 2019; <https://www.epa.gov/dwstandardsregulations/drinking-water-contaminant-human-health-effects-information#hh1>.
9. WIDNR. Safe Drinking Water In: Resources WDoN, ed. *Chapter NR 809*2018.
10. USEPA. A Review of the Reference Dose and Reference Concentration Processes. 2002(EPA/630/P-02/002F).

Appendix A. Toxicity Data

Table A-I. TCE Epidemiology Study from Literature Review

Study Type	Population	Time period	Exposure	Outcomes	Results	Variables not accounted for	Acronyms	Reference
Cross sectional	Infants born at Camp Lejeune	1968-1985	Estimated contaminant levels in drinking water at residences from historical reconstruction models	Small for gestational age (SGA) Mean birth weight (MWB)	SGA OR:1.5 (95%CI: 1.2-1.9) in >=90 th percentile exposure group (>=9.8 ppb) MBW – significant differences at all exposure levels (>0 ppb)	Maternal smoking, alcohol use, other factors not included on birth certificate	OR: Odds Ratio 95% CI: 95% confidence interval	Ruckart, 2014 (7)

Table A-2. TCE Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Development	Mouse	GD 0 – PND 0	10 µg/mL (2.96 mg/kg-d) 100 µg/mL (26.56 mg/kg-d)	Water	Enhanced immune response	LOAEL: 2.96	Blossom, 2017 (8)
Development	Mouse	GD 0 - PND 254	0.05 µg/mL (0.0074-0.0155) 500 µg/mL (about 30-150)	Water	Early life exposure to TCE at low concentration (0.05 µg/ml) triggered autoimmune hepatitis.	LOAEL: 0.0074	Gilbert, 2017 (9)
Development	Mouse	GD 0 - PND 254	0.05 µg/mL (0.0074-0.0155) 500 µg/mL (about 30-150)	Water	Altered gut microbiome	LOAEL: 0.0074	Khare, 2018 (10)

Table A-3. Critical Study Selection

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity value identifiable?	Critical study?
Gilbert,2017	✓	see Note A	✓	2	✓	No
Blossom, 2017	✓	See Note A	✓	2	✓	No
Khare, 2018	✓	See Note B	See Note B	2	✓	No
Ruckart, 2014	✓	✓	✓	⊖	⊖	No

To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.

- A. These are the first studies to evaluate these effects at these levels and as such are not consistent with other studies at this time. These two studies are both from the same research group.
- B. This is an emerging area of science which was conducted from the same research group.

Tetrachloroethylene (PCE) | 2019

Substance Overview

Tetrachloroethylene (PCE) is an organic solvent that has been primarily used as a degreaser to clean metal parts and machinery.^{1,2} It is a human-made chemical that does not occur naturally in the environment. PCE is produced in large volumes for commercial use and is used for dry cleaning, metalworking, textile processing, and fluorocarbons manufacturing.

Recommendations

The current NR140 Groundwater Quality Public Health Enforcement Standard of 5 micrograms per liter ($\mu\text{g/L}$) for PCE is based on the United States Environmental Protection Agency's (EPA's) maximum contaminant level from the 1990s.

DHS recommends raising the enforcement standard to 20 $\mu\text{g/L}$. The recommended standard is based on the United States Environmental Protection Agency's (EPA's) drinking water concentration based on a cancer risk level determination. A concentration of 20 $\mu\text{g/L}$ corresponds with a lifetime cancer risk level of 1 in 1,000,000.

DHS recommends setting the NR140 Groundwater Quality Public Health Preventive Action Limit for PCE at 10% of the enforcement standard because it has been shown to have carcinogenic, mutagenic, and teratogenic effects.

Health Effects

Current knowledge about the health effects of PCE comes from studies in laboratory animals, workers, poisoning exposure reports, and epidemiological studies involving exposed communities, such as contaminated military bases.^{1,2} Short-term effects of PCE exposure in both humans and animals include liver and kidney damage and central nervous system effects. Longer-term PCE exposure causes changes in mood, memory, attention, reaction time, or vision. Long-term PCE exposure animal studies have also shown liver and kidney effects, as well as changes in brain chemistry. PCE may also have adverse effects on pregnancy and fetal development; problems such as miscarriage, birth defects, and slowed fetal growth have been observed in animal studies.

The EPA has classified PCE as a likely human carcinogen.² PCE has been shown not to be teratogenic, but it has been shown to have mutagenic effects and interactive effects with mixtures of trichloroethylene (TCE) and methylchloroform.^{1,2}

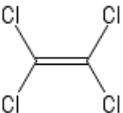
Current Standards

Enforcement Standard:	5 $\mu\text{g/L}$
Preventive Action Limit:	0.5 $\mu\text{g/L}$
Year:	2011

Recommended Standards

Enforcement Standard:	20 $\mu\text{g/L}$
Preventive Action Limit:	2 $\mu\text{g/L}$

Chemical Profile

Tetrachloroethylene	
Structure:	
CAS Number:	127-18-4
Formula:	C ₂ Cl ₄
Molar Mass:	165.8 g/mol
Synonyms:	1,1,2,2-tetrachloroethylene, perchloroethylene, PERC

Exposure Routes

The main way that people are exposed to PCE from groundwater are through breathing in water vapor (like when showering) or by drinking water.^{1,2} Contaminated groundwater often occurs at or near hazardous waste sites where PCE has been improperly discarded and near industrial sites where it is used or produced in high volumes.

In the environment, PCE typically volatiles into the air, but can also get into the soil and groundwater.^{1,2} In soil and groundwater, PCE does not easily break down and can stay in the environment for long periods of time (months to years).

Current Standard

The current groundwater standard of 5 µg/L for PCE is based on the EPA's Maximum Contaminant Level (MCL).³ This regulation went into effect in 1992 and is required to receive a periodic review. Because PCE has shown to cause carcinogenic and mutagenic effects, the current preventive action limit is set at 10% of the enforcement standard.

Standard Development

Federal Numbers

Maximum Contaminant Level:	5 µg/L	(2010)
Health Advisory:	N/A	
Drinking Water Concentration (Cancer Risk):	2,000 µg/L 200 µg/L 20 µg/L	(2012)

State Drinking Water Standard

NR809 Maximum Contaminant Level:	5 µg/L	(2016)
----------------------------------	--------	--------

Acceptable Daily Intake

EPA Oral Reference Dose:	0.006 mg/kg-d	(2012)
--------------------------	---------------	--------

Oncogenic Potential

EPA Cancer Slope Factor:	0.0021 (mg/kg-d) ⁻¹	(2012)
--------------------------	--------------------------------	--------

Guidance Values

ATSDR Chronic Oral Minimum Risk Level:	0.0005 mg/kg-d	(2014)
--	----------------	--------

Literature Search

Search Dates:	2014 – 2019
Total studies evaluated:	Approximately 640
Key studies found?	Yes

Federal Numbers

Chapter 160, Wis. Stats., requires that DHS use the most recent federal number as the recommended enforcement standard unless one does not exist or there is significant technical information that was not considered when the federal number was established and that indicates a different number should be used.

Maximum Contaminant Level

The EPA has a maximum contaminant level (MCL) of 5 µg/L for PCE.⁴ This regulation went into effect in 1992 and is subject to a periodic review. The EPA reviewed the MCL for PCE in 2010 and 2016 as part of their Six-Year Review. In 2010, the EPA determined that the MCL for PCE was a candidate for revision. They specified that the health assessment was in process but that new analytical feasibility and treatment technology information may justify revising the limit.⁵ In 2016, the EPA determined that the MCL for PCE was not appropriate for revision at the time due to recently completed, ongoing, or pending regulatory action.⁶

Health Advisory

The EPA has not established a health advisory for PCE.⁷

Drinking Water Concentrations at Specified Cancer Risk Levels

In 2012, the EPA established the drinking water concentrations at specified cancer risk levels for PCE based on the cancer slope factor (described in more detail below), an average body weight of 70 kilograms (kg), and water consumption rate of 2 liters per day (L/d).²

Cancer Risk Level	Water Concentration
1 in 10,000	2,000 µg/L
1 in 100,000	200 µg/L
1 in 1,000,000	20 µg/L

State Drinking Water Standard

Chapter 160, Wis. Stats., requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

As of March 2016, Wisconsin has a maximum contaminant level of 5 µg/L for PCE.⁸ This drinking water standard is based on the EPA's maximum contaminant level.

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation. Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. The EPA provides ADIs, termed oral reference doses, as part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Assessment System (IRIS) program.

EPA Oral Reference Dose

In 2012, EPA established an oral reference dose of 0.006 mg/kg-d for PCE.² The EPA derived this value by taking an average of candidate reference doses for neurological endpoints from two studies in workers.^{9,10} The EPA used a model to convert air concentrations to oral exposure equivalents. They applied a total uncertainty factor of 1000 to account for differences among people (10), using a LOAEL instead of a NOAEL (10), and the limited availability of data (10).

Oncogenic Potential

Chapter 160, Wis. Stats., requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard. If we determine that something is carcinogenic and there is no federal number or ADI from the EPA, DHS must set the standard at a level that would result in a cancer risk equivalent to 1 case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than 1 in 1,000,000.

To evaluate the oncogenic potential of PCE, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of PCE. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

The EPA has classified PCE as a human carcinogen by all routes of exposure.²

The International Agency for Research on Cancer (IARC) has also classified PCE as a human carcinogen by all routes of exposure.¹¹

EPA Cancer Slope Factor

In 2012, the EPA established a cancer slope factor of $0.0021 \text{ (mg/kg-d)}^{-1}$ for PCE as part of their IRIS review.² The EPA did this by converting from the inhalation unit risk to water concentration using an exposure model to protect from non-Hodgkin's lymphoma and liver cancer.

Additional Technical Information

Chapter 160 of Wisconsin Statute allows DHS to recommend a value other than a federal number or acceptable daily intake for the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For PCE, we searched for values that been published since 2012 when the EPA published their latest IRIS review. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Chronic Oral Minimum Risk Level

In 2014, the ATSDR recommended a chronic oral minimum risk level of 0.006 mg/kg-d for PCE.¹ This value is equivalent to EPA's oral reference dose and is based on the same data as the EPA oral reference dose.

Literature Search

Our literature review focused on the scientific literature published after the review by the ATSDR in 2014. We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from 2014 to September 2018 for studies related to PCE toxicity or PCE effects on a disease state in which information on exposure or dose was included as part of the study.^a Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

Approximately 60 studies were returned by the search engine. We excluded studies on non-oral exposure routes, non-mammalian species and acute poisonings from further review. After applying these exclusion criteria, we located one key study (Table A-1 contains a summary of this study). To be

a The following search terms were used in the literature review:
Title/Abstract: Tetrachloroethylene
Subject area: toxicology OR cancer
Language: English

considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.^b The key study did not meet the requirements to be considered a critical study (see Table A-2 for details on the evaluation).

Standard Selection

DHS recommends an enforcement standard of 20 µg/L for PCE.

There are two federal numbers for PCE: the maximum contaminant concentration and EPA's drinking water concentrations based on a cancer risk level determination. The drinking water concentrations at various cancer risk levels are based on the latest scientific information for PCE. While the EPA has reviewed the MCL for PCE as part of their six year reviews, they have not taken action to update the MCL because of other ongoing regulatory actions. Based on the latest scientific information for PCE, DHS recommends adopting the drinking water concentrations based on a cancer risk level determination as the enforcement standard.

Basis for Enforcement Standard

- Federal Number
- Cancer Potential
- EPA Acceptable Daily Intake
- Technical information

When calculating an acceptable daily intake from cancer risk, Chapter 160 requires that DHS used a cancer risk of 1 in 1,000,000. To be consistent with this requirement, we recommend using EPA's drinking water concentration at a cancer risk level of 1 in 1,000,000 as the enforcement standard for PCE. In our review of recent information, we did not find any significant technical information that a different enforcement standard is appropriate.

DHS recommends a preventive action limit of 2 µg/L for PCE.

DHS recommends setting the preventive action limit for PCE at 10% of the enforcement standard because PCE has been shown to cause carcinogenic and mutagenic effects.^{1,2} PCE has not been shown to cause teratogenic or interactive effects.^{1,2}

^b Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect, and the BMD is an estimation of the dose that would cause a specific level of response (typically 5 or 10%).¹²

Prepared by Curtis Hedman, Ph.D.

Wisconsin Department of Health Services

References

1. ATSDR. Draft Toxicological Profile for Tetrachloroethylene In:2014.
2. USEPA. Toxicological review of tetrachloroethylene. In: System IRI, ed. Vol EPA/635/R-08/011F2012.
3. WIDNR. Groundwater Quality. In: Resources WDoN, ed. *Chapter NR 140*2017.
4. USEPA. National Primary Drinking Water Regulations. 2018; <https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations>.
5. USEPA. Six-Year Review 2 of Drinking Water Standards. 2010; <https://www.epa.gov/dwsixyearreview/six-year-review-2-drinking-water-standards>. Accessed June 5th, 2019.
6. USEPA. Six-Year Review 3 of Drinking Water Standards. 2016; <https://www.epa.gov/dwsixyearreview/six-year-review-3-drinking-water-standards>. Accessed June 5th, 2019.
7. USEPA. Drinking Water Contaminant Human Health Effects Information. 2019; <https://www.epa.gov/dwstandardsregulations/drinking-water-contaminant-human-health-effects-information#hh1>.
8. WIDNR. Safe Drinking Water In: Resources WDoN, ed. *Chapter NR 809*2018.
9. Cavalleri A, Gobba F, Paltrinieri M, Fantuzzi G, Righi E, Aggazzotti G. Perchloroethylene exposure can induce colour vision loss. *Neurosci Lett*. 1994;179(1-2):162-166.
10. Echeverria D, White RF, Sampaio C. A behavioral evaluation of PCE exposure in patients and dry cleaners: A possible relationship between clinical and preclinical effects. *J Occup Environ Med*. 1995;37(6):667-680.
11. IARC. List of Classification, Volumes 1-123. 2018; <https://monographs.iarc.fr/list-of-classifications-volumes/>. Accessed May 17, 2019.
12. USEPA. A Review of the Reference Dose and Reference Concentration Processes. 2002(EPA/630/P-02/002F).

Appendix A. Toxicity Data

Table A-I. Tetrachloroethylene Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Short term	B6C3F1 Mouse and 129S1/Sv1mj Mouse	24 hr	30, 100, 300, 1000	Gavage	Increased oxidative stress metabolite, trichloroacetic acid. Strong transcriptomic effect on peroxisomal Beta-oxidation pathway in liver and kidney	Human Equivalent Dose; 75 (kidney) and 900 (liver)	Zhou et al., 2017

Table A-2. Critical Study Selection

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity value identifiable?	Critical study?
Zhou, 2017	⊖	⊖	✓	4	✓	No

To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.

1,2,3-Trichloropropane | 2019

Substance Overview

1,2,3-Trichloropropane is a clear liquid that somewhat mixes with water.¹ It is currently used as a solvent in the manufacture of other chemicals. In the past, it was used as a fumigant (chemical used to treat soil), cleaning solvent, paint and varnish remover, and degreasing agent.

Recommendations

The current the NR140 Groundwater Quality Public Health Enforcement Standard for 1,2,3-trichloropropane of 60 µg/L is based on United States Environmental Protection Agency's (EPA's) oral reference dose from the 1990s.

DHS recommends lowering the enforcement standard to 3 µg/L. The recommended standard is based on EPA's cancer slope factor for 1,2,3-trichloropropane from 2009.²

DHS recommends that the preventive action limit for 1,2,3-trichloropropane be set at 10% of the enforcement standard because new studies have shown that 1,2,3-trichloropropane has carcinogenic and mutagenic effects.

Current Standards

Enforcement Standard:	60 µg/L
Preventive Action Limit:	12 µg/L
Year:	1997

Recommended Standards

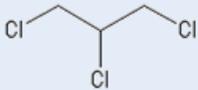
Enforcement Standard:	0.3 ng/L
Preventive Action Limit:	0.03 ng/L

Health Effects

The known health information on 1,2,3-trichloropropane comes from studies with laboratory animals. Rats and mice exposed to large amounts of 1,2,3-trichloropropane for a long time developed tumors in the liver, digestive system, Harderian gland, and uterus.²

The EPA determined that 1,2,3-trichloropropane is likely to be carcinogenic to humans.² Recent studies have shown that 1,2,3-trichloropropane can cause gene mutations and, therefore, is likely mutagenic.^{2,3} 1,2,3-Trichloropropane has not been shown to have teratogenic or interactive effects.²

Chemical Profile

1,2,3-Trichloropropane	
Structure:	
CAS Number:	96-18-4
Formula:	C ₃ H ₅ Cl ₃
Molar Mass:	147.423 g/mol
Synonyms:	Allyl trichloride Glycerol trichlorohydrin Trichlorohydrin

Exposure Routes

People can be exposed to 1,2,3-trichloropropane from air, soil, and water.¹ 1,2,3-Trichloropropane can get in the air or water from its current or former use at industrial sites. 1,2,3-Trichloropropane may be in soil or water from its past use as a fumigant in fruit orchards.

If released to soil, 1,2,3-trichloropropane generally volatilizes into the air or leaches into groundwater.¹ 1,2,3-Trichloropropane does not last long in surface water with half-lives ranging from hours to days.

Current Standard

The current NR140 Groundwater Quality Public Health Enforcement Standard of 60 µg/L for 1,2,3-trichloropropane was established in 1997.⁴ This standard is based on the EPA's oral reference dose of 0.006 milligrams per kilogram body weight per day (mg/kg-d) from 1995, a body weight of 10 kilograms (kg), a water consumption rate of 1 liter per day (L/d), and a relative source contribution of 100%.

The current preventive action limit is set at 20% of the enforcement standard because the EPA was reviewing the carcinogenicity of 1,2,3-trichloropropane at the time the standards were set. Additionally, 1,2,3-trichloropropane had not been shown to have mutagenic, teratogenic or interactive effects at the time.

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A
Health Advisory:	N/A
Drinking Water Concentration (Cancer Risk):	N/A

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A
----------------------------------	-----

Acceptable Daily Intake

EPA Oral Reference Dose:	0.004 mg/kg-d	(2009)
--------------------------	---------------	--------

Oncogenic Potential

EPA Cancer Slope Factor:	30 (mg/kg-d) ⁻¹	(2009)
--------------------------	----------------------------	--------

Guidance Values

None available

Literature Search

Search Dates:	2009 – 2019
Total studies evaluated:	Approximately 30
Key studies found?	Yes

Federal Numbers

Chapter 160, Wis. Stats., requires that DHS use the most recent federal number as the recommended enforcement standard unless one does not exist or there is significant technical information that was not considered when the federal number was established and that indicates a different number should be used.

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for 1,2,3-trichloropropane.⁵

Health Advisory

The EPA has not established a health advisory for 1,2,3-trichloropropane.⁶

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations based on a cancer risk level determination for 1,2,3-trichloropropane.²

State Drinking Water Standard

Chapter 160, Wis. Stats., requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for 1,2,3-trichloropropane.⁷

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation. Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. The EPA provides ADIs, termed oral reference doses, as part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Assessment System (IRIS) program.

EPA Oral Reference Dose

In 2009, the EPA published an oral reference value for 1,2,3-trichloropropane as part of their IRIS assessment.² The EPA selected a 2 year chronic/carcinogenicity study in rats conducted by the National Toxicology Program as the critical study. In this study, rats were exposed to different concentrations of 1,2,3-trichloropropane by gavage (0, 3, 10, or 30 mg/kg-d) for 2 years. 1,2,3-Trichloropropane caused effects on the liver, kidney, forestomach, and pancreas.

The EPA used benchmark dose modeling to obtain the toxicity value for the oral reference dose. The EPA selected the value corresponding to the 95% lower bound benchmark dose that was adjusted to approximate continuous daily exposures ($BMDL_{adj} = 3.8 \text{ mg/kg-d}$). The EPA applied a total uncertainty factor of 300 to account for differences between people and research animal (10), differences among people (10), and the limited availability of data (3) resulting in a chronic oral reference dose of 0.004 mg/kg-d for 1,2,3-trichloropropane.

Oncogenic Potential

Chapter 160, Wis. Stats., requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard. If we determine that something is carcinogenic and there is no federal number or ADI from the EPA, DHS must set the standard at a level that would result in a cancer risk equivalent to 1 case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than 1 in 1,000,000.

To evaluate the oncogenic potential of 1,2,3-trichloropropane, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of 1,2,3-trichloropropane. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

The EPA has classified 1,2,3-trichloropropane as likely to be carcinogenic to humans.²

The International Agency for Research on Cancer (IARC) has classified 1,2,3-trichloropropane as probably carcinogenic to humans.⁸

EPA Cancer Slope Factor

In 2009, the EPA established a cancer slope factor of $30 \text{ (mg/kg-d)}^{-1}$ for 1,2,3-trichloropropane as part of their IRIS assessment. They used a 2 year chronic/carcinogenicity study in rats conducted by the National Toxicology Program as the critical study. In this study, rats were exposed to 0, 3, 10, or 30 mg/kg-d of 1,2,3-trichloropropane by gavage for 2 years. 1,2,3-Trichloropropane caused tumors in the liver, digestive system, Harderian gland, and uterus. 1,2,3-trichloropropane has been shown to cause cancer by causing DNA damage.

Additional Technical Information

Chapter 160, Wis. Stats., allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For 1,2,3-trichloropropane, we searched for values that been published since 2009 when the EPA published their latest IRIS review. We did not find any relevant guidance values from the EPA, Agency for Toxic Substances and Disease Registry (ATSDR), or World Health Organization (WHO).

Literature Search

Our literature review focused on the scientific literature published since the review by EPA in 2009. We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2009 to February 2019 for studies related to 1,2,3-trichloropropane toxicity or its effects on a disease state in which information on exposure or dose was included as part of the study.^a Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

Approximately 30 studies were returned by the search engine. Studies on the effects on plant and aquatic life and studies not evaluating health risks were excluded from further review. After applying these exclusion criteria, we located three key studies (see Tables A-1 and A-2 for more details on the studies). To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant

^a The following search terms were used in the literature review:
Title/Abstract: 1,2,3-trichloropropane
Subject area: toxicology OR cancer
Language: English

for humans, have evaluated more than one dose, and have an identifiable toxicity value.^b None of the studies met the criteria to be considered a critical study (see Table A-3 for details on the evaluation).

Standard Selection

DHS recommends an enforcement standard of 0.3 ng/L for 1,2,3-trichloropropane.

The EPA has classified 1,2,3-trichloropropane as likely to be carcinogenic to humans. The EPA does not have a maximum contaminant level or health advisory for 1,2,3-trichloropropane. While the EPA did not calculate any drinking water concentration at specified cancer risk levels, the slope factor for 1,2,3-trichloropropane can be used to determine a drinking water concentration. EPA's practice is to use a non-threshold approach for evaluating carcinogenicity unless there is specific evidence to indicate that there is a threshold to the cancer effects. A number of studies have shown that 1,2,3-trichloropropane causes DNA damage. As such, the EPA assumed these mutagenic effects are responsible for the observed tumors and that the dose response for 1,2,3-trichloropropane is linear in the low dose range and recommends calculating concentrations based on the age of the individuals in the exposed group.

Basis for Enforcement Standard

- Federal Number
- EPA Acceptable Daily Intake
- Cancer Potential
- Technical information

DHS recommends using the EPA's cancer slope factor to establish the enforcement standard for 1,2,3-trichloropropane. To do this, we used a lifetime cancer risk of 1 in 1,000,000 and a lifetime of 70 years as specified by Chapter 160 and the EPA's age dependent adjustment factors approach to ensure adequate protection of sensitive populations.^{2,10} In this approach, adjustment factors were used to account for relevant risk at various ages (see Appendix B for details on the calculation).

DHS recommends a preventive action limit of 0.03 ng/L for 1,2,3-trichloropropane.

DHS recommends that the preventive action limit for 1,2,3-trichloropropane be set at 10% of the enforcement standard because studies have shown that 1,2,3-trichloropropane can cause carcinogenic and mutagenic effects in animals. 1,2,3-trichloropropane has not been shown to cause teratogenic or interactive effects.

^b Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect, and the BMD is an estimation of the dose that would cause a specific level of response (typically 5 or 10%).⁹

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

References

1. 1,2,3-Trichloropropane. *Report on carcinogens : carcinogen profiles*. 2011;12:426-428.
2. USEPA. Toxicological Review of 1,2,3-Trichloropropane (CAS No. 96-18-4) In Support of Summary Information on the Integrated Risk Information System (IRIS). In:2009.
3. Kimura M, Mizukami S, Watanabe Y, et al. Disruption of spindle checkpoint function in rats following 28 days of repeated administration of renal carcinogens. *The Journal of toxicological sciences*. 2016;41(1):91-104.
4. WIDNR. Groundwater Quality. In: Resources WDoN, ed. *Chapter NR 140*2017.
5. USEPA. National Primary Drinking Water Regulations. 2018; <https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations>.
6. USEPA. Drinking Water Contaminant Human Health Effects Information. 2019; <https://www.epa.gov/dwstandardsregulations/drinking-water-contaminant-human-health-effects-information#hh1>.
7. WIDNR. Safe Drinking Water In: Resources WDoN, ed. *Chapter NR 809*2018.
8. IARC. List of Classification, Volumes 1-123. 2018; <https://monographs.iarc.fr/list-of-classifications-volumes/>. Accessed May 17, 2019.
9. USEPA. A Review of the Reference Dose and Reference Concentration Processes. 2002(EPA/630/P-02/002F).
10. USEPA. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens In: Forum RA, ed. Vol EPA/630/R-03/003F2005.
11. Brender JD, Shinde MU, Zhan FB, Gong X, Langlois PH. Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: a case-control study. *Environmental health : a global access science source*. 2014;13:96.
12. Tardiff RG, Carson ML. Derivation of a reference dose and drinking water equivalent level for 1,2,3-trichloropropane. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association*. 2010;48(6):1488-1510.

Appendix A. Toxicity Studies

Table A-1. Epidemiology studies on 1,2,3-trichloropropane from the literature search

Study Type	Population	Time period	Data Source	Exposure	Outcomes	Results	Reference
Case-control	Infants born in Texas	1996 – 2008	Texas Birth Defects Registry	Estimated residential exposure to solvent emissions for 14 chlorinated solvents	Neural tube, oral cleft, limb deficiency, and congenial heart defects	Adjusted OR:1.49 (95%CI: 1.08-2.06) in $\geq 90^{\text{th}}$ percentile exposure group (≥ 9.8 ppb)	Brender et al, 2014 ⁽¹¹⁾

OR = odds ratio; CI = confidence

Table A-2. Toxicity studies on 1,2,3-trichloropropane from the literature search

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Mechanistic	Rat	3, 7, 28 d	125	Gavage	Induction of spindle checkpoint dysfunction	LOAEL: 125	Kimura, 2016 (3)
Re-evaluation	Rat Mouse	Up to 2 years	Various	Gavage and Water	Re-evaluation of the mode of action using data from the studies conducted by the National Toxicology Program in 1993	Oral Reference Dose: 0.039 Cancer Value: 0.010 – 0.014	Tardiff, 2010 (12)

Table A-3. Critical Study Evaluation

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity Value identifiable?	Effect more sensitive than that used by the EPA?	Critical study?
Brender et al, 2014	⊖	✓	✓	N/A	⊖	N/A	No
Kimura et al, 2016	⊖	✓	⊖	1	✓	✓	No
Tardiff et al, 2010	Because the data presented in this study were already considered by EPA in setting the cancer slope factor, it cannot be considered a critical study.						No

To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.

DRAFT

Appendix B. Recommended Enforcement Standard Determination

$$\text{Recommended Enforcement Standard} = \frac{\text{Cancer Risk}}{(\text{SF} \times \text{ADAF}_{\text{Infant}} \times \text{WC}_{\text{Infant}} \times 2) + (\text{SF} \times \text{ADAF}_{\text{Child}} \times \text{WC}_{\text{Child}} \times 14) + (\text{SF} \times \text{ADAF}_{\text{Adult}} \times \text{WC}_{\text{Adult}} \times 54) / 70}$$

Where:

Cancer Risk:	1 in 1,000,000
Body Weight:	80 kg
Cancer Slope Factor (SF):	30 (mg/kg-d) ⁻¹
Age Dependent Adjustment Factor (ADAF):	ADAF _{Infant} : 10 (used for ages under 2) ADAF _{Child} : 3 (used for ages 2 to 15) ADAF _{Adult} : 1 (used for ages 16 and over)
Water consumption (WC):	WC _{Infant} : 0.137 L/kg-d (used for ages under 2) WC _{Child} : 0.047 L/kg-d (used for ages 2 to 15) WC _{Adult} : 0.039 L/kg-d (used for ages 16 and over)

Recommended Enforcement Standard = 0.3 ng/L

1,1-Dichloroethane | 2019

Substance Overview

1,1-Dichloroethane is a colorless, oily liquid with a sweet odor.¹ 1,1-Dichloroethane is used mostly as an intermediate in the manufacture of other organic solvents. It evaporates easily at room temperature and burns easily. It does not occur naturally in the environment.

Recommendations

The current NR140 Groundwater Quality Public Health Enforcement Standard for 1,1-dichloroethane is based on a study that found that breathing 1,1-dichloroethane can cause liver damage in animals. Because 1,1-dichloroethane in water can evaporate quickly into the air, DHS used this study to determine how much can be in water without there being an appreciable health risk.

DHS recommends no change in the Enforcement Standard and Preventive Action Limit for 1,1-dichloroethane. DHS did not find any new significant technical information to indicate that a change is warranted.

Current Standards

Enforcement Standard:	850 µg/L
Preventive Action Limit:	85 µg/L
Year:	1988

Recommended Standards

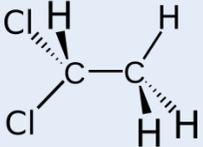
Enforcement Standard:	850 µg/L
Preventive Action Limit:	85 µg/L

Health Effects

What we know about the health effects of 1,1-dichloroethane comes from studies of humans and laboratory animals. In humans, breathing high levels of 1,1-dichloroethane for a short amount of time can cause central nervous system depression and an irregular heartbeat. In animals, 1,1-dichloroethane has been shown to cause kidney and liver damage, affect weight gain in pregnant animals, delay bone development of offspring, and death at very high levels.

A study by the National Toxicology Program found that high levels of 1,1-dichloroethane cause tumors in mice after oral exposure.² The United States Environmental Protection Agency (EPA) has classified 1,1-dichloroethane as a possible human carcinogen by oral exposure.

Chemical Profile

1,1-Dichloroethane	
Structure	
Chemical Symbol:	75-34-3
CAS Number:	C ₂ H ₄ Cl ₂
Molar Mass:	98.96 g/mol
Synonyms:	Ethylidene dichloride Ethylidene chloride 1,1-DCA

Exposure Routes

Exposure to 1,1-dichloroethane occurs mainly from eating contaminated food, but may also occur from skin contact, breathing contaminated air, or drinking water contaminated by industrial releases or hazardous waste sites.¹ 1,1-Dichloroethane does not dissolve easily or break down rapidly in water. It can evaporate from the water into the air. 1,1-Dichloroethane breaks down slowly in air and has the potential for long-range transport. Small amounts of 1,1-dichloroethane released to soil can evaporate into the air or move into groundwater.

Current Standard

The current NR140 Groundwater Quality Public Health Enforcement Standard of 850 µg/L for 1,1-dichloroethane was adopted in 1988.³ This standard is based on a study that found that breathing 1,1-dichloroethane can cause liver damage in animals.⁴ In this study, rats, guinea pigs, rabbits, and dogs were exposed to 1,1-dichloroethane in air (0, 500 or 1000 parts per million or ppm) for seven hours per day; five days a week for six months. Because 1,1-dichloroethane in water can evaporate quickly into the air, DHS used this study to determine how much can be in water without there being an appreciable health risk. DHS selected a No Observable Adverse Effect Level (NOAEL) of 500 ppm from this inhalation study and converted the value to a protective drinking water concentration by using the EPA's procedures. DHS applied a total uncertainty factor of 1000.

The current NR140 Groundwater Quality Public Health Preventive Action Limit for 1,1-dichloroethane is set at 10% of the enforcement standard because studies in animals have shown that 1,1-dichloroethane may be carcinogenic at high levels.⁵

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A
Health Advisory:	N/A
Drinking Water Concentration (Cancer Risk):	N/A

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A
----------------------------------	-----

Acceptable Daily Intake

EPA Oral Reference Dose:	N/A
--------------------------	-----

Oncogenic Potential

EPA Cancer Slope Factor:	N/A
CalEPA Cancer Slope Factor:	0.0057 (mg/kg-d) ⁻¹ (1992)

Guidance Values

EPA Provisional Peer-Reviewed Toxicity Value:	0.2 mg/kg-d (2006)
---	--------------------

Literature Search

Search Dates:	2006 – 2018
Total studies evaluated:	Approximately 25
Key studies found?	No

Federal Numbers

Chapter 160, Wis. Stats., requires that DHS use the most recent federal number as the recommended enforcement standard unless one does not exist or there is significant technical information that was not considered when the federal number was established and that indicates a different number should be used.

Maximum Contaminant Level

The EPA does not have a maximum contaminant level (MCL) for 1,1-dichloroethane.⁶

Health Advisory

The EPA has not established a health advisory for 1,1-dichloroethane.⁷

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established a drinking water concentration based on a cancer risk level determination for 1,1-dichloroethane.⁸

State Drinking Water Standard

Chapter 160, Wis. Stats., requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for 1,1-dichloroethane.⁹

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation. Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. The EPA provides ADIs, termed oral reference doses, as part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Assessment System (IRIS) program.

EPA Oral Reference Dose

The EPA does not have an oral reference dose for 1,1-dichloroethane.¹⁰

Oncogenic Potential

Chapter 160, Wis. Stats., requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard. If we determine that something is carcinogenic and there is no federal number or ADI from the EPA, DHS must set the standard at a level that would result in a cancer risk equivalent to 1 case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than 1 in 1,000,000.

To evaluate the oncogenic potential of 1,1-dichloroethane, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of 1,1-dichloroethane. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

The EPA has classified 1,1-dichloroethane as a possible human carcinogen.⁸

The International Agency for Research on Cancer (IARC) has not reviewed the carcinogenicity of 1,1-dichloroethane.¹¹

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for 1,1-dichloroethane.⁸

CalEPA Cancer Slope Factor

The California Environmental Protection Agency (CalEPA) published an oral cancer slope factor of 0.0057 (mg/kg/day)⁻¹ for 1,1-dichloroethane in 1992.¹² They based this value on a 1978 study that observed mammary gland adenocarcinomas in female rats by oral exposure.² In this study, high incidence of tumors was found only at the highest dose tested.

Additional Technical Information

Chapter 160 of Wisconsin Statute allows DHS to recommend a value other than a federal number or acceptable daily intake for the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For 1,1-dichloroethane, we searched for values that been published since 1988 when the current groundwater standards were adopted. We found relevant guidance values from the EPA's Office of Superfund Remediation and Technology Innovation and the California Environmental Protection Agency (CalEPA). We also found reviews conducted by the World Health Organization (WHO) and Agency for Toxic Substances and Disease Registry (ATSDR) in 2003 and 2015, respectively.^{1,13} However, neither agency established guidelines for 1,1-dichloroethane due to limited information.

EPA Provisional Peer-Reviewed Toxicity Value

In 2006, the EPA's Office of Superfund Remediation and Technology Innovation conducted a peer-review of human health toxicity information on 1,1-dichloroethane and published a provisional chronic oral reference dose of 0.2 milligrams per kilogram body weight per day (mg/kg-d). This value is based on a longer-term study in male rats where they found clinical signs of adverse central nervous system effects and potential neurological effects by oral exposure.¹⁴ They applied a total uncertainty factor of 3000 to account for differences between people and research animals (10), difference among people (10), the exposure not lasting the lifetime of the animal (10), and limited data (3).

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2006. We carried out a search on the National Institutes of Health's PubMed resource for articles published from January 2006 to May 2019 related to 1,1-dichloroethane toxicity or its effects on a disease state in which information on 1,1-dichloroethane exposure or dose was included as part of the study.¹ Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

Approximately 25 studies were returned by the search engine. We excluded studies that did not evaluate health risk and studies in non-relevant species, like wildlife from further review. After applying these exclusion criteria, we did not find any key studies on 1,1-dichloroethane.

¹ The following search terms were used in the literature review:
Title/abstract: 1,1-dichloroethane
Subject area: toxicology OR cancer
Language: English

Standard Selection

DHS recommends no change to the current enforcement standard for 1,1-dichloroethane.

There are no federal numbers, no state drinking water standard, and no acceptable daily intake from the EPA for 1,1-dichloroethane.

The California EPA developed a cancer slope factor for 1,1-dichloroethane in 1992. However, DHS has determined that this value is not appropriate for use in setting the recommended enforcement standard. DHS reviewed this study when the current enforcement standard was established in 1988 and concluded that the carcinogenicity of 1,1-dichloroethane is inconclusive. In our current review, we evaluated the study used by the California EPA to develop the cancer slope factor and found that a dose-response relationship was not apparent for the observed tumors.^{2,12} In addition, the study showed deaths in all treatment groups including controls, a finding that reduces the sensitivity of the study.

The current enforcement standard for 1,1-dichloroethane is based on a short-term inhalation study in animals.⁴ In this study, rats, guinea pigs, rabbits, and dogs were exposed to 1,1-dichloroethane in air for 7 hours per day for 6 months. DHS did not find any new significant technical information to indicate that a change to the standard is warranted.

Basis for Enforcement Standard

- Federal Number
- EPA Acceptable Daily Intake
- Cancer Potential
- Technical information

DHS recommends no change to the preventive action limit for 1,1-dichloroethane.

The current preventive action limit for 1,1-dichloroethane (85 µg/L) is set at 10% of the enforcement standard because studies have shown that 1,1-dichloroethane causes carcinogenic and teratogenic effects at high levels in animals.^{2,15} We did not find any significant new technical information that would warrant changing this limit.

Prepared by Clara Jeong, Ph.D.

Wisconsin Department of Health Services

References

1. ATSDR. Toxicological Profile for 1,1-Dichloroethane. In: Registry AfTSA, ed. Atlanta, GA2015.
2. National Toxicology P. Bioassay of 1,1-dichloroethane for possible carcinogenicity. *National Cancer Institute carcinogenesis technical report series*. 1978;66:1-107.
3. WIDNR. Groundwater Quality. In: Resources WDoN, ed. *Chapter NR 140*2017.
4. AIHA. American Industrial Hygiene Association - Hygienic Guide Series: 1,1-Dichloroethane. *Am Ind Hyg Assn J* 1971;32(67).
5. USEPA. US EPA Exposure Factors Handbook: Chapter 6. Inhalation Rates. 2011.
6. USEPA. National Primary Drinking Water Regulations. 2018; <https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations>.
7. USEPA. Drinking Water Contaminant Human Health Effects Information. 2019; <https://www.epa.gov/dwstandardsregulations/drinking-water-contaminant-human-health-effects-information#hh1>.
8. USEPA. 1,1-Dichloroethane - Chemical Risk Assessment Summary. In: (IRIS) IRIS, ed1990.
9. WIDNR. Safe Drinking Water In: Resources WDoN, ed. *Chapter NR 809*2018.
10. USEPA. IRIS Assessments. 2019; https://cfpub.epa.gov/ncea/iris_drafts/AtoZ.cfm.
11. IARC. List of Classification, Volumes 1-123. 2018; <https://monographs.iarc.fr/list-of-classifications-volumes/>. Accessed May 17, 2019.
12. CalEPA. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. . In: Agency CEP, ed. Berkeley, CA1992.
13. WHO. 1,1-dichloroethane in drinking-water. 2004(WHO/SDE/WSH/03.04/19).
14. Muralidhara S, Ramanathan R, Mehta SM, Lash LH, Acosta D, Bruckner JV. Acute, subacute, and subchronic oral toxicity studies of 1,1-dichloroethane in rats: application to risk evaluation. *Toxicological sciences : an official journal of the Society of Toxicology*. 2001;64(1):135-145.
15. Schwetz BA, Leong BK, Gehring PJ. Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. *Toxicology and applied pharmacology*. 1974;28(3):452-464.

1,4-Dioxane | 2019

Substance Overview

1,4-Dioxane is a clear liquid that mixes easily with water.¹ It is used as a solvent in the manufacture of other chemicals and as a laboratory reagent. It can also be found as a contaminant in cosmetics, detergents, and shampoos and is a byproduct of the manufacture of some common plastics. Some pesticides used to treat crops also contain 1,4-dioxane.

Recommendations

The current NR140 Groundwater Quality Public Health Enforcement Standard for 1,4-dioxane of 3 micrograms per liter (µg/L) is based on EPA's cancer slope factor from the 1990s.

DHS recommends lowering the enforcement standard to 0.35 µg/L. The recommended standard is based on the United States Environmental Protection Agency's cancer slope factor for 1,4-dioxane.²

DHS recommends that the preventive action limit for 1,4-dioxane be set at 10% of the enforcement standard because the 1,4-dioxane has been shown to have carcinogenic, mutagenic, and teratogenic effects in animals.

Health Effects

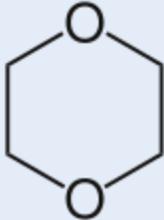
At high levels or long-term exposure, 1,4-dioxane can cause severe kidney and liver effects.¹ Animals that drank water with high levels of 1,4-dioxane for a long time developed cancer in the liver and nasal passages.

Because of these effects, EPA has classified 1,4-dioxane as a likely human carcinogen.² Recent studies have shown that 1,4-dioxane may be mutagenic.^{3,4} Limited data in animals suggest that 1,4-dioxane may be teratogenic.⁵ 1,4-dioxane has not been shown to have interactive effects.¹

Current Standards	
Enforcement Standard:	3 µg/L
Preventive Action Limit:	0.3 µg/L
Year:	2010

Recommended Standards	
Enforcement Standard:	0.35 µg/L
Preventive Action Limit:	0.035 µg/L

Chemical Profile

1,4-Dioxane	
Structure:	
CAS Number:	123-91-1
Formula:	C ₄ H ₈ O ₂
Molar Mass:	88.10 g/mol
Synonyms:	Diethylene ether 1,4-diethylene dioxide Diethylene oxide Dioxyethylene ether Dioxane

Exposure Routes

People can be exposed to 1,4-dioxane from air, food, and water.¹ People can also be exposed to 1,4-dioxane by using products that contain this substance as a byproduct, like paint strippers, dyes, greases, antifreeze, aircraft deicing fluid, deodorants, shampoos, and cosmetics. Traces of 1,4-dioxane may be present in some food supplements, in food containing residues from packaging adhesives, or food crops treated with pesticides containing 1,4-dioxane.

1,4-Dioxane can be present in the soil or groundwater around manufacturing facilities where it is used or produced during the manufacturing process or waste disposal sites (landfills). 1,4-Dioxane has been found as a contaminant in at least 34 sites on the National Priorities List (Superfund sites). 1,4-Dioxane moves rapidly from soil to groundwater and is relatively resistant to biodegradation in water and soil, though some bacteria may aid in degradation. It does not build up (bioaccumulate, biomagnify or bioconcentrate) in the food chain.

Current Standard

The current enforcement standard of 3 µg/L for 1,4-dioxane was adopted in 2010. This standard is based on EPA's cancer slope factor of 0.011 (mg/kg-d)⁻¹ from 1990.⁶ In establishing this recommendation, we used a lifetime cancer risk of 1 in 1,000,000, a body weight of 70 kg, a water consumption rate of 2 L/d, and a relative source contribution of 100%.

The current preventive action limit for 1,4-dioxane was set at 10% of the enforcement standard because of the observed carcinogenic effects in animals.

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A	
Health Advisory:	N/A	
Drinking Water Concentration (Cancer Risk):	35 µg/L 3.5 µg/L 0.35 µg/L	(2010)

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A
----------------------------------	-----

Acceptable Daily Intake

EPA Oral Reference Dose:	0.03 mg/kg-d	(2010)
--------------------------	--------------	--------

Oncogenic Potential

EPA Cancer Slope Factor:	0.01 (mg/kg-d) ⁻¹	(2010)
--------------------------	------------------------------	--------

Guidance Values

ATSDR Chronic Oral Minimum Risk Level:	0.1 mg/kg-d	(2012)
--	-------------	--------

Literature Search

Search Dates:	2010 – 2018
Total studies evaluated:	Approximately 250
Key studies found?	Yes

Federal Numbers

Chapter 160, Wis. Stats., requires that DHS use the most recent federal number as the recommended enforcement standard unless one does not exist or there is significant technical information that was not considered when the federal number was established and that indicates a different number should be used.

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for 1,4-dioxane.⁷

Health Advisory

The EPA has not established health advisories for 1,4-dioxane.⁸

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has established the following drinking water concentrations at specific cancer risk levels based on a cancer slope factor of 0.01 (mg/kg-d)⁻¹, an average body weight of 70 kg and water consumption rate of 2 L/d (see below for more details on the cancer slope factor).

Cancer Risk Level	Water Concentration
1 in 10,000	35 µg/L
1 in 100,000	3.5 µg/L
1 in 1,000,000	0.35 µg/L

State Drinking Water Standard

Chapter 160, Wis. Stats., requires that DHS use a state drinking water standard as the recommended enforcement standard if there are no federal numbers and a state drinking water standard is available.

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for 1,4-dioxane.⁹

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, ch. 160, Wis. Stats., requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation. Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. The EPA provides ADIs, termed oral reference doses, as part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Assessment System (IRIS) program.

EPA Oral Reference Dose

In 2010, EPA's IRIS program updated the oral reference dose for 1,4-dioxane.² The current oral reference dose for 1,4-dioxane is 0.03 milligrams per kilogram of body weight per day (mg/kg-d).

EPA selected a study by Kociba et al that evaluated effects in rats exposed to 1,4-dioxane in drinking water for 2 years as the critical study.¹⁰ EPA selected liver and kidney toxicity as the critical effects as these were the primary and most sensitive effects observed in animals and human occupational studies. EPA selected a No Observable Adverse Effect Level (NOAEL) of 9.6 mg/kg-d for liver and kidney degeneration. To obtain the oral reference dose, the EPA applied a total uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (10), and the limited availability of information (3).

Oncogenic Potential

Chapter 160, Wis. Stats., requires that DHS evaluate the oncogenic (cancer-causing; carcinogenic) potential of a substance when establishing the groundwater standard. If we determine that something is carcinogenic and there is no federal number or ADI from the EPA, DHS must set the standard at a level that would result in a cancer risk equivalent to 1 case of cancer in 1,000,000 people. DHS must also set the standard at this level if the EPA has an ADI but using it to set the groundwater standard would result in a cancer risk that is greater than 1 in 1,000,000.

To evaluate the oncogenic potential of 1,4-dioxane, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of 1,4-dioxane. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

The EPA has classified 1,4-dioxane as likely carcinogenic to humans.²

The International Agency for Research on Cancer (IARC) has classified 1,4-dioxane as possibly carcinogenic to humans.^{2,11}

EPA Cancer Slope Factor

In 2010, the EPA established a cancer slope factor of 0.01 (mg/kg-d)⁻¹ from a study by Kano et al that evaluated effects in female mice exposed to 1,4-dioxane in drinking water for 2 years.¹² The critical effect was hepatocellular adenomas and carcinomas, which occurred with greater frequency than mammary gland, peritoneal, or nasal cavity tumors.

Additional Technical Information

Chapter 160, Wis. Stats., allows DHS to recommend a value other than a federal number or ADI from the EPA if there is significant technical information that was not considered when the value was established and indicates a different value is more appropriate.

To ensure the recommended groundwater standards are based on the most appropriate scientific information, we search for relevant health-based guidance values from national and international agencies and for relevant data from the scientific literature.

Guidance Values

For 1,4-dioxane, we searched for values that been published since 2010 when EPA published their latest IRIS review. We found relevant a guidance values from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Chronic Oral Minimum Risk Level

In 2012, ATSDR published their Toxicological Profile on 1,4-dioxane in which they recommend a chronic oral minimum risk level of 0.1 mg/kg-d.¹ This value is based on the same study used by EPA to set the oral reference dose. ATSDR selected a NOAEL of 9.6 mg/kg-d for liver and kidney degeneration and used a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2010. We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2010 to October 2018 for studies related to 1,4-dioxane toxicity or 1,4-dioxane effects on a disease state in which information on exposure or dose was included as part of the study.^a Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

a The following search terms were used in the literature review:
Title/Abstract: Dioxane
Subject area: toxicology OR cancer
Language: English

Approximately 250 were returned by the search engine. Studies on dioxane-containing compounds, studies not evaluating health risks, and studies evaluating non-oral exposure routes (e.g. inhalation) were excluded from further review. After applying these exclusion criteria, we located four key studies (see Table A-1 for more details on the studies). To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.^b Two studies met the criteria to be considered a critical study (see Table A-2 for details on the evaluation).

Critical Studies

Dourson et al., 2014

In 2014, Dourson et al reanalyzed liver pathology slides from the 1978 National Cancer Institute study.¹⁴ In the original study, Osborne-Mendel rats and B6C3F1 mice were administered 1,4-dioxane at concentrations of either 0.5% or 1.0% in drinking water. Rats were dosed for 110 weeks and mice for 90 weeks. In the original study, only the most severe pathology on each slide was reported. The reanalysis reported on the complete pathology of each slide to better elucidate the mechanism of action for the carcinogenicity of 1,4-dioxane. Re-evaluation of slides showed proliferative changes that increased with dose. This result was consistent with biochemical markers of liver damage and the presence of proliferative changes at lower doses. They also reported that 1,4-dioxane exposure did not cause point mutations, DNA repair, or initiation. The authors concluded that the mode of action for the liver tumors is regenerative hyperplasia and that this type of effect has a threshold.

Giet et al., 2018

In 2018, Gi et al evaluated the effects of short term exposure of 1,4-dioxane in drinking water on mutagenicity in rats.³ In two experiments, male gpt delta transgenic F344 rats were exposed to doses of 0, 200, 1000, or 5000 ppm of 1,4-dioxane in their drinking water (experiment 1) or doses of 0, 0.2, 2 or 20 ppm of 1,4-dioxane in their drinking water (experiment 2) for 16 weeks. In a third experiment, wild-type F344 rats were exposed to doses of 0, 2, 20, 200, 2000, or 5000 ppm of 1,4-dioxane in their drinking water for 16 weeks and injected with bromodeoxyuridine (100 mg/kg) prior to euthanasia to evaluate cell proliferative activity in the liver .

Endpoints were evaluated for animal and liver weight, liver histopathology, and mutagenicity. Rats exposed to 5000 ppm (the highest dose) had lower body weights compared to the controls. There were no histopathological changes. Mutagenicity analyses showed genotoxic effects, but no evidence of oxidative stress, cytotoxicity, or nuclear receptor activation.

^b Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect, and the BMD is an estimation of the dose that would cause a specific level of response (typically 5 or 10%).¹³

Standard Selection

DHS recommends an enforcement standard of 0.35 µg/L for 1,4-dioxane.

The EPA does not have a maximum contaminant level or health advisory for 1,4-dioxane, but they have identified drinking water concentrations based on a cancer risk level determination. Per Ch. 160, Wis. Stats., these are considered federal numbers. EPA's practice is to use a non-threshold approach for evaluating carcinogenicity

unless there is specific evidence to indicate that there is a threshold to the cancer effects. Studies to date are still unclear as to the exact mode of action for 1,4-dioxane with some suggesting a non-genotoxic mode of action and others indicating a genotoxic mode of action.^{3,4,14,15} Therefore, DHS recommends using a non-threshold approach to set the recommended enforcement standard for 1,4-dioxane.

When calculating an acceptable daily intake from cancer risk, Chapter 160 requires that DHS used a cancer risk of 1 in 1,000,000. To be consistent with this requirement, we recommend using EPA's drinking water concentration at a cancer risk level of 1 in 1,000,000 as the enforcement standard for 1,4-dioxane. With rounding, this gives a recommended enforcement standard of 0.4 µg/L for 1,4-dioxane.

DHS recommends a preventive action limit of 0.035 µg/L for 1,4-dioxane.

DHS recommends that the preventive action limit for 1,4-dioxane be set at 10% of the enforcement standard because 1,4-dioxane has been shown to have carcinogenic, mutagenic, and teratogenic effects.^{1,3-5,16} 1,4-Dioxane has not been shown to have interactive effects.¹

Basis for Enforcement Standard

- Federal Number
- EPA Acceptable Daily Intake
- Cancer Potential
- Technical information

References

1. ATSDR. Toxicological profile for 1,4 dioxane. In: Registry AftSaD, ed. Atlanta, GA2012.
2. USEPA. *Toxicological review of 1,4-Dioxane (with inhalation update)* Washington, DC2013. EPA-635/R-11/003-F.
3. Gi M, Fujioka M, Kakehashi A, et al. In vivo positive mutagenicity of 1,4-dioxane and quantitative analysis of its mutagenicity and carcinogenicity in rats. *Archives of toxicology*. 2018;92(10):3207-3221.
4. Furihata C, Toyoda T, Ogawa K, Suzuki T. Using RNA-Seq with 11 marker genes to evaluate 1,4-dioxane compared with typical genotoxic and non-genotoxic rat hepatocarcinogens. *Mutation research*. 2018;834:51-55.
5. Giavini E, Vismara C, Broccia ML. Teratogenesis study of dioxane in rats. *Toxicology letters*. 1985;26(1):85-88.
6. Stickney JA, Sager SL, Clarkson JR, et al. An updated evaluation of the carcinogenic potential of 1,4-dioxane. *Regulatory Toxicology and Pharmacology*. 2003;38(2):183-195.
7. USEPA. National Primary Drinking Water Regulations. 2018; <https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations>.
8. USEPA. Drinking Water Contaminant Human Health Effects Information. 2019; <https://www.epa.gov/dwstandardsregulations/drinking-water-contaminant-human-health-effects-information#hh1>.
9. WIDNR. Safe Drinking Water In: Resources WDoN, ed. *Chapter NR 8092018*.
10. Kociba RJ, McCollister SB, Park C, Torkelson TR, Gehring PJ. 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. *Toxicology and applied pharmacology*. 1974;30(2):275-286.
11. IARC. List of Classification, Volumes 1-123. 2018; <https://monographs.iarc.fr/list-of-classifications-volumes/>. Accessed May 17, 2019.
12. Kano H, Umeda Y, Kasai T, et al. Carcinogenicity studies of 1,4-dioxane administered in drinking-water to rats and mice for 2 years. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association*. 2009;47(11):2776-2784.
13. USEPA. A Review of the Reference Dose and Reference Concentration Processes. 2002(EPA/630/P-02/002F).
14. Dourson M, Reichard J, Nance P, et al. Mode of action analysis for liver tumors from oral 1,4-dioxane exposures and evidence-based dose response assessment. *Regulatory Toxicology and Pharmacology*. 2014;68(3):387-401.
15. Dourson ML, Higginbotham J, Crum J, et al. Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1,4-dioxane. *Regulatory Toxicology and Pharmacology*. 2017;88:45-55.

16. USEPA. Integrated Risk Information System (IRIS) Chemical Assessment Summary for 1,4-Dioxane; CASRN 123-91-1. In: Assessment NCfE, ed2013.

Appendix A. Toxicity Data

Table A-I. 1,4-Dioxane Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Effect Type	Toxicity Value (mg/kg-d)	Reference
Re-evaluation	Rat	2 years	Males: 240, 530 Females: 350, 640	Water	Re-evaluation of liver pathology slides and mode of action using data from the study conducted by the National Cancer Institute in 1978	Proposed MCL	0.35 mg/L	Doursonet al., 2014 ⁽¹⁴⁾
Re-evaluation	Mouse	1.5 years	Males: 720, 830 Females: 380, 860	Water	Re-evaluation of liver pathology slides and mode of action using data from the study conducted by the National Cancer Institute in 1978	Proposed MCL	0.35 mg/L	Doursonet al., 2014 ⁽¹⁴⁾
Re-evaluation	Rat Mouse	2 years	Males; 11, 55, 274 Female: 18, 83, 429	N/A	Re-evaluation of the mode of action using data from the study conducted by the Japan Bioassay Research Center in 1990	NA	NA	Doursonet al., 2017 ⁽¹⁵⁾
Re-evaluation	Rat Mouse	91 d	Males: 52, 126, 274, 657, 1554 Females: 83, 185, 427, 756, 1614	N/A	Re-evaluation of the mode of action using data from the study conducted by the Japan Bioassay Research Center in 1990	NA	NA	Doursonet al., 2017 ⁽¹⁵⁾
Shorter-term	Rat	28 d	0.5%	Water	Compared gene expression profile to that of known genotoxic and non-genotoxic hepatocarcinogens	NA	NA	Furihataet al., 2018 ⁽⁴⁾

Longer-term	Rat	112 d	Experiment 1 18.7, 2.3, 440 Experiment 2 0.02, 0.2, 1.9 Experiment 3 0.2, 2.2, 21.9, 222, 562	Water	Animal body and liver weight Liver histopathology Mutation frequency DNA repair enzyme induction	NOEL BMDL ₁₀ BMDL _{1SD}	GST-P positive foci NOEL: 200 ppm* BMDL ₁₀ : 1.66 ppm* BMDL _{1SD} : 1018 ppm* Mutagenicity NOEL: 200 ppm* BMDL ₁₀ : 0.98 ppm BMDL _{1SD} : 576 ppm	Giet al., 2018 (³)
-------------	-----	-------	---	-------	---	---	--	------------------------------------

*Corresponds to the lower values in experiments 1 and 3

Table A-2. Critical Study Evaluation

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity Value identifiable?	Critical study?
Doursonet al., 2014 (rat – 2 year)	✓	✓	✓	2	✓	Yes
Doursonet al., 2014 (mouse – 1.5 year)	✓	✓	✓	2	✓	Yes
Doursonet al., 2017 (2 year)	✓	✓	✓	3	⊘	No
Doursonet al., 2017 (90 d)	✓	✓	✓	5	⊘	No
Furihataet al., 2018	⊘	✓	✓	1	⊘	No
Giet al., 2018	✓	✓	✓	3	✓	Yes

To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.