WISCONSIN DEPARTMENT of HEALTH SERVICES

Recommended Public Health Groundwater Quality Standards

Scientific Support Documents for Cycle 10 Substances

January 2022

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WISCONSIN DEPARTMENT of HEALTH SERVICES

Table of Contents

Substances without Existing Groundwater Standards

Chromium, Hexavalent* 1
Strontium 19
Thiamethoxam* 29
Imidacloprid* 39
Clothianidin 61
Isoxaflutole* 70
Isoxaflutole DKN degradate 80
Isoxaflutole BA degradate 89
Thiencarbazone-methyl 101
Dacthal MTP degradate 108
Dacthal TPA degradate 118
Glyphosate 129
Glyphosate AMPA degradate 143
Sulfentrazone 154
Bacteria, *Escherichia coli* (*E. coli*) 161
Perfluorooctanoic acid (PFOA)* 166
Perfluorooctane Sulfonate (PFOS)* 190

Substances with Existing Groundwater Standards

Trichloroethylene (TCE) 217
Tetrachloroethylene (PCE) 227
1,2,3-Trichloropropane (1,2,3-TCP) 236
1,1-Dichloroethane (1,1-DCA) 247
Boron 254
Molybdenum* 265
Aluminum* 274
Cobalt 293
Barium 305
1,4-Dioxane* 314
Bacteria, Total coliform 327

*Support document updated based on feedback received during the public comment period.

Hexavalent Chromium | 2022

Substance Overview

Chromium is a metal that occurs naturally in the earth's crust.[1] People use chromium for many industrial purposes including the production of stainless steel and certain alloys, manufacturing of certain pigments, and in metal finishing, leather tanning, and wood preservation. It can exist in many forms in the environment. Chromium can change forms in the environment depending on pH and concentration. The most stable forms of chromium in the environment are trivalent chromium and hexavalent chromium. This review focuses on hexavalent chromium.

Recommendations

Wisconsin does not currently have a NR140 Groundwater Quality Public Health Enforcement Standard for hexavalent chromium.

DHS recommends an enforcement standard of 70 nanograms per liter (ng/L) for hexavalent chromium. The recommended standard is based on the EPA's cancer slope factor for hexavalent chromium.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

Recommended Standards	
Enforcement Standard:	70 ng/L
Preventive Action Limit:	7 ng/L

DHS recommends that the preventive action limit for hexavalent chromium be set at 10% of the enforcement standard because hexavalent chromium has been shown to have carcinogenic, mutagenic, teratogenic, and interactive effects.

Health Effects

While trivalent chromium is an essential nutrient and generally has little to no toxicity, hexavalent chromium has no known biological role and can cause toxicity. We know a lot about how hexavalent chromium affects the body if it is inhaled from studies among workers.[1] However, information on how chromium affects the body if it is swallowed (oral exposure) is more limited. Most of what we know about oral exposure comes from studies in animals. Animals that were exposed to large amounts of chromium had problems with their stomach and small intestines. Chromium also caused damage to sperm in male animals.

Recent studies have shown that exposure to large amounts of hexavalent chromium for a long time can cause cancer in research animals.[2] Previous studies have also shown that hexavalent chromium can

cause teratogenic effects and may cause mutagenic effects.[1] New studies have shown that hexavalent chromium may cause interactive effects with other substances such as benzo(a)pyrene and arsenic.[3-5]

Chemical Profile

	Hexavalent Chromium
Chemical Symbol:	Cr^{6+}
CAS Number:	18540-29
Molar Mass:	51.996 g/mol
Synonyms:	Chromium (VI) Chromium 6+

Exposure Routes

The general public may be exposed to chromium from water, soil, or air.[1] Hexavalent chromium can be found in water or soil from industrial uses. Hexavalent chromium can be in air from its production and from combustion of natural gas, oil, or coal.

Workers involved in chrome plating, chromate production, and stainless steel welding usually have the highest exposure to hexavalent chromium. Workers in these fields are typically exposed to hexavalent chromium through air or skin contact.

Current Standard

Wisconsin currently has groundwater standards for total chromium.[6] The current enforcement standard of 100 micrograms per liter (µg/L) for total chromium was adopted in 1992 and is based on EPA's maximum contaminant level for total chromium.

The current preventive action limit for total chromium is set at 10% of the enforcement standard because chromium has been shown to have mutagenic and reproductive effects.

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:	2.5 mg/kg-d	(1998)
Oncogenic Potential		
EPA OPP Cancer Slope Factor:	0.791 $(mg/kg\text{-}d)^{-1}$	(2008)
EPA IRIS Draft Cancer Slope Factor:	0.5 $(mg/kg\text{-}d)^{-1}$	(2010)
Guidance Values		
EPA Draft Oral Reference Dose:	0.0009 mg/kg-d	(2010)
ATSDR Chronic Oral Minimum Risk Level	0.0009 mg/kg-d	(2012)
Literature Search		
Search Dates:	2012 – 2019	
Total studies evaluated:	Approximately 930	
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 for total chromium, but does not have a separate level for hexavalent chromium.[7]

Health Advisory

The EPA does not have a health advisory for hexavalent chromium.[8]

Drinking Water Concentrations as Specified Risk Levels

The EPA has not established drinking water concentrations at specified cancer risk levels for hexavalent chromium.[9,10]

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 for total chromium, but does not have a separate level for hexavalent chromium.[11]

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.

The EPA's IRIS program has a final and draft oral reference dose for hexavalent chromium.

EPA Oral Reference Dose (1998)

The EPA's final oral reference dose of 2.5 mg/kg-d for hexavalent chromium was published in 1998.[10] The EPA based this dose on a study in rats exposed to potassium chromate in drinking water for one year. The EPA selected a No Observable Adverse Effect Level (NOAEL) of 2.5 mg/kg-d hexavalent chromium - the highest dose tested - because no significant adverse effects were seen in appearance, weight gain, or food consumption, and there were no pathologic changes in the blood or other tissues in any treatment group. They selected a total uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (10), and the use of a study with a less-than-lifetime duration (3) to derive a comparison value that is protective over a lifetime.

EPA Draft Oral Reference Dose (2010)

In 2010, the EPA proposed a chronic oral reference dose of 0.0009 mg/kg-d hexavalent chromium as part of their draft Toxicological Review of Hexavalent Chromium.[9] This dose is based on the incidence of diffuse epithelial hyperplasia of the duodenum in female mice from a 2 year study conducted by the National Toxicology Program. They selected a 10% benchmark dose (lower confidence limit) or $BMDL_{10}$ of 0.09 mg/kg-d hexavalent chromium and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (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 hexavalent chromium, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of hexavalent chromium. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

The EPA's Office of Pesticide Programs and Integrated Risk Information System (IRIS) have classified hexavalent chromium as likely to be carcinogenic to humans.[9,12]

EPA Cancer Slope Factors

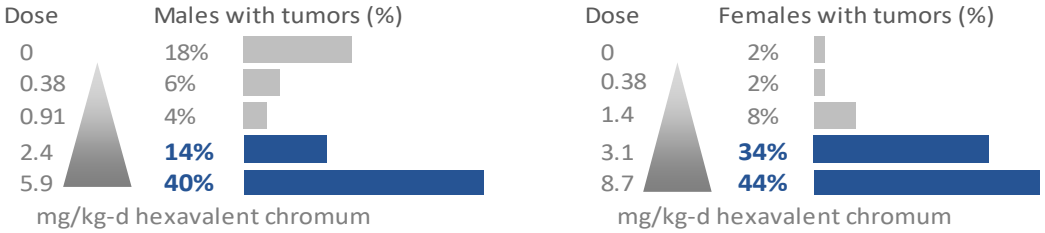
The EPA Office of Pesticide Programs (OPP) and Integrated Risk Information System (IRIS) have established or proposed cancer slope factors for hexavalent chromium.[9,12,13]

Both of these programs based their cancer slope factors on chronic/carcinogenicity studies carried out by the National Toxicology Program.[2] In these studies, rats or mice were exposed to four doses of hexavalent chromium as sodium dichromate dihydrate in drinking water for two years. In mice, they found that the two highest doses caused adenoma and carcinoma in the small intestines (duodenum, jejunum, or ileum) of males and females. In rats, they found that the highest dose caused squamous cell carcinoma in the oral mucosa of males and females.

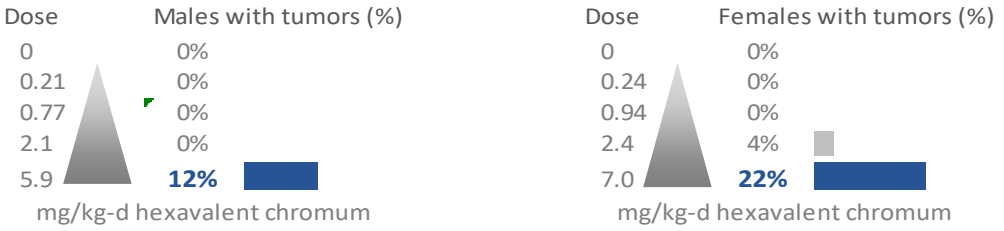
National Toxicology Program

Selected results from the *Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate*

High levels of hexavalent chromium caused a **siginficant increase in the incidence of adenomas and carcinomas** in the small intestines of mice.



High levels of hexavalent chromium caused a **significant increase in the incidence of carcinoma in the oral mucosa** of rats.



In 2008, EPA's Office of Pesticide Programs identified a cancer slope factor of 0.791 per milligrams hexavalent chromium per kilogram body weight per day $(mg/kg\text{-}d)^{-1}$ based on combined adenoma and carcinoma tumor rates in female mouse small intestines.[13]

In 2010, EPA's IRIS program identified a draft cancer slope factor of 0.5 $(mg/kg\text{-}d)^{-1}$ based on combined adenoma and carcinoma tumor rates in male mouse small intestines. They proposed using the male mouse data because the multistage model fit was better versus the female mouse data. Therefore, they determined that the male mouse data was associated with less uncertainty. This cancer slope factor is also used by the California EPA, in EPA's regional screening levels, and proposed to be used by the Agency for Toxic Substances and Disease Registry (ATSDR).[14-16]

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 hexavalent chromium, we searched for values that been published since 2012 when the EPA published their draft 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 2012, the ATSDR published their recommended chronic oral minimum risk level of 0.009 mg/kg-d for hexavalent chromium, which was the same value as EPA's draft oral reference dose from 2010.[1] The ATSDR based this level on the same critical effect, dose, and uncertainty factor selected by EPA.

Literature Search

Our literature review focused on the scientific literature published after the review by ATSDR in 2012. We conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from 2012 to January 2019. We searched for studies related to hexavalent chromium 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 a human lifetime.

Approximately 930 studies were returned by the search engine. Studies on trivalent chromium, total chromium, nanoparticles, effects on aquatic life, non-oral exposure routes (e.g. inhalation), acute exposures (i.e., poisoning), and studies not evaluating health risks were excluded. After applying these exclusion criteria, we identified 25 key studies (see table A-1 for 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.[b]

Since the National Toxicology Program study in 2008, there have been a number of studies evaluating the mode of action for the observed carcinogenicity. The majority of these studies were published by a single research organization.[18-29] The researchers hypothesize that the mode of action involves saturation of the reductive capacity of the gut lumen, uptake of hexavalent chromium into the intestinal epithelium, oxidative stress and inflammation within the epithelium leading to cell proliferation, and

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

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%).[14]

then DNA modification and mutagenesis. The authors concluded that the mode of action for hexavalent chromium has a threshold and, thus, recommended using a non-linear approach for evaluating risk.

There have also been other studies that have evaluated non-cancer effects of hexavalent chromium (see Table A-1 for a summary of these studies). While three of these studies meet the criteria to be considered a critical study, the effects observed did not occur at doses as low as those associated with carcinogenic effects (see Table A-2 details of the evaluation).

Standard Selection

DHS recommends an enforcement standard of 70 ng/L for hexavalent chromium.

Basis for Recommended Standard

- ☐ Federal Number
- ☑ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☐ Significant technical information

This recommendation applies specifically to hexavalent chromium and does not change recommendations for total chromium. There are no federal numbers for hexavalent chromium. The EPA has classified hexavalent chromium as a likely human carcinogen and both the Office of Pesticide Programs and IRIS have recommended cancer slope factors.[9,12,13] While EPA did not calculate drinking water concentrations for specified cancer risk levels, the slope factor for hexavalent chromium can be used to determine a drinking water concentration.[c]

Chapter 160, Wisc. Stats., requires that DHS evaluate the oncogenic (cancer) potential when establishing recommended groundwater standards. If a substance has oncogenic potential and there is no federal number, DHS must identify the level at which the estimated cancer risk is 1 in 1,000,000. Therefore, DHS recommends using EPA's cancer slope factor of 0.5 $(mg/kg\text{-}d)^{-1}$ to establish the recommended enforcement standard (ES) for hexavalent chromium. To do this, we used a cancer risk of 1 in 1,000,000, and, per EPA's latest recommendations, a body weight of 80 kg and water consumption rate of 2.4 L/d.[30]

c In March 2019, the EPA announced that they were proceeding with the IRIS Assessment of hexavalent chromium and released a draft of their Systematic Review Protocol for the Hexavalent Chromium IRIS Assessment.[26] This is the second step in the review process. The overall objective is to identify adverse health effects and characterize exposure-response relationships for the effects of hexavalent chromium to support the development of toxicity values.

DHS recommends a preventive action limit of 7 ng/L for hexavalent chromium.

DHS recommends that the preventive action limit for compound be set at 10% of the enforcement standard because some studies have shown that hexavalent chromium can cause carcinogenic, mutagenic, teratogenic, and interactive effects.[1,3-5]

Revised by Amarilys Gonzalez Vazquez, Ph.D. and Sarah Yang, Ph.D. – January 2022

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. Hexavalent Chromium Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses* (mg/kg-d)	Route	Form	Endpoints	Toxicity Value (mg/kg-d)	Reference
Short to Longer-term	Rat	15, 30, 60 d	20	Water	Hexavalent Chromium	Decrease in enzymatic and non-enzymatic antioxidants. Increased lipid peroxidation levels. Cytological lesions in hepatic tissue. Protective effect of melatonin.	LOAEL: 20	Banerjee, 2017 ([31])
Development	Rat	Gestation day 9.5 -14.5	4.3	Water	Potassium Chromate	Increased apoptosis in placenta cells. Downregulated cell survival proteins.	LOAEL:4.3	Banu, 2017 ([32])
Longer-term	Mouse	30 d	42	Water	Potassium Chromate	Increased oxidative stress in the liver. Protective effect of propylthiouracil.	LOAEL: 42	Ben Hamida, 2016 ([33])
Longer-term	Mouse	60 d	Chromium: 0.027, 0.37, 5.5 Benzo(a) pyrene: 50 mg/kg	Water plus injection of Benzo(a)pyrene	Hexavalent Chromium	Mixtures of chromium and benzo(a)pyrene inhibited expression of tumor suppressor genes.	N/A (preliminary results)	Fan, 2012 ([3])
Longer-term	Mouse	36 d	1, 4	Gavage	Hexavalent Chromium	Decreased body and liver weights; increased oxidative stress in the liver; altered gene expression in the liver. *Also exposed to cadmium	NOAEL: 1 LOAEL: 4	Jin, 2016 ([34])
Co-exposure	Mouse	60 d Cr (VI) + 90 d B[a]P	Hexavalent chromium: 15, 146, 1458 Benzo(a) pyrene:	Water plus Benzo(a)pyrene in diet	Sodium Dichromate Dihydrate	Cr(VI) alone: Enterocyte hypertrophy and increases in cell proliferation and DNA damage in the GI tract.	N/A	Sanchez-Martin, 2015 ([4])

			0, 1.25, 12.5, 125 mg/kg-d			*Mixture caused more histopathology than expected from the sum of effects of individual components in the liver. Effects were evaluated after 90 days exposure with or without benzo(a)pyrene.		
Longer-term	Mouse	30 d	5.7	Gavage	Potassium Chromate	Suppressed rate-limiting enzymes of TCA cycle and oxidative phosphorylation. Decreased protease activity.	LOAEL: 5.7	Shil, 2018 ([35])
Longer-term	Rat (Sprague-Dawley)	28 d	0.76, 3.0, 9.1, 27	Water	Sodium Dichromate Dihydrate	Decreased mean body weight and body weight gain at high doses. Decreased water consumption at high doses. No significant effect on immune parameters.	NOAEL: 3.0 LOAEL: 9.1	Shipkowski, 2017 ([36])
Longer-term	Rat (Fisher 33/N)	28 d	0.84, 3.4, 10, 30	Water	Sodium Dichromate Dihydrate	Decreased water consumption at high doses. No significant effect on immune parameters.	NOAEL: 3.4 LOAEL: 10	Shipkowski, 2017 ([36])
Longer-term	Mouse (B6C3F1)	28 d	1.4, 2.9, 5.8, 12, 23	Water	Sodium Dichromate Dihydrate	Decreased mean body weight and body weight gain at high doses. Decreased red blood cell parameters at highest dose. No significant effect on immune parameters	NOAEL: 2.9 LOAEL: 5.8	Shipkowski, 2017 ([36])
Development	Rat	GD 9-14	8, 16, 32	Water	Hexavalent Chromium	Attenuated expression of insulin receptor level, its downstream signaling	LOAEL: 8	Shobana, 2017 ([37])

						molecules, and organism-specific glucose transporters. Increase in serum insulin level in male progenies.		
Development	Rat	GD 9.5 – 14.5	2.2	Water	Potassium Chromate	Early reproductive senescence and decreased litter size in F1 female progeny.	LOAEL: 2.2	Sivakumar, 2014 ([38])
Development	Rat	GD 14 - PND 14	38	Water	Potassium Chromate	Oxidative stress in the liver of dams and pups. Liver damage and impaired function.	LOAEL: 38	Soudani, 2013 ([39])
Longer-term	Rat	90 d	0.02, 0.21, 2.9, 7.2, 21	Water	Sodium Dichromate Dihydrate	Dose-dependent decrease in iron levels in the duodenum, liver, serum, and bone marrow. Toxicogenomic responses in the duodenum consistent with iron deficiency.	NOAEL: 0.21 LOAEL: 2.9	Suh, 2014 ([26])
Longer-term	Mouse	90 d	0.02, 0.3, 1.1, 4.6, 12, 31	Water	Sodium Dichromate Dihydrate	Dose-dependent decrease in iron levels in the duodenum, liver, serum, and bone marrow. Toxicogenomic responses in the duodenum consistent with iron deficiency.	NOAEL: 1.1 LOAEL: 4.6	Suh, 2014 ([26])
Chronic	Mouse	140 d	Hexavalent chromium: 5.4, 15.4 Trivalent arsenic: 5.4, 15.4	Water plus trivalent arsenic in water and Azoxymethane injection	Sodium Dichromate Dehydrate	Used azoxymethane/dextran sodium sulfate-induced mouse colitis associated colorectal cancer model. Cr(VI) and As (III) together and alone increased tumor	LOAEL: 1.3	Wang, 2012 ([5])

			Azoxymethane (AOM): 12.5 mg/kg			incidence, multiplicity, size, and grade and cell inflammatory response.		
Development	Rat	GD 12 – 21	1.7, 3.4, 6.8	Gavage	Potassium Chromate	Biphasic effects on fetal Leydig cell development.	LOAEL: 1.7	Zheng, 2018 ([40])
* If dose was not reported as mg/kg-d hexavalent chromium in the study, it was calculated using the appropriate water consumption factor.[41]								

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?
Banerjee, 2017	✓	✓	✓	1	✓	No
Banu, 2017	✓	✓	✓	1	✓	No
Ben Hamida, 2016	⊘	✓	✓	1	✓	No
Fan, 2012	✓	✓	✓	3	⊘	No
Jin, 2016	⊘	✓	✓	2	✓	No
Sanchez-Martin, [illegible]	✓	✓	✓	3	⊘	No
Shil, 2018	⊘	✓	✓	1	✓	No
Shipkowski, 2017	⊘	✓	✓	4	✓	No
Shobana, 2017	✓	✓	✓	3	✓	**Yes**
Sivakumar, 2014	✓	✓	✓	1	✓	No
Soudani, 2013	✓	✓	✓	1	✓	No
Suh, 2014	✓	✓	✓	5 - 6	✓	**Yes**
Wang, 2012	✓	✓	✓	1	✓	No
Zheng, 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.

Strontium | 2019

Substance Overview

Strontium is a naturally occurring element and is a member of the alkaline earth metals.[1] Strontium exists as four stable isotopes and is present in the environment as mineral compounds.

Strontium also exists as radioactive elements that are formed during nuclear fission. Radioactive strontium is not naturally found in the environment. Wisconsin's groundwater standards apply to non-radioactive strontium.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for strontium.

DHS recommends an enforcement standard of 1,500 micrograms per liter (µg/L) for strontium. The recommended standard is based on the United States Environmental Protection Agency's (EPA's) Health Reference Level that was established in 2014 as part of their Unregulated Contaminant Monitoring Rulemaking Cycle Three (UCMR3) process.[2]

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for strontium be set at 10% of the enforcement standard because strontium has been shown to cause teratogenic effects.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

Recommended Standards	
Enforcement Standard:	1,500 µg/L
Preventive Action Limit:	150 µg/L

Health Effects

Because strontium is chemically similar to calcium, it can be deposited in the skeleton after exposure to high levels.[1,2] Studies in people and animals have shown that strontium can interfere with bone mineralization in the developing skeleton. Strontium can also compete with calcium in bones and suppress vitamin D metabolism and intestinal calcium absorption.

Some studies have shown that strontium can cause teratogenic effects.[1-3] Strontium has not been shown to cause carcinogenic, mutagenic, or interactive effects.[1,2]

Chemical Profile

	Strontium
CAS Number:	7440-24-6
Chemical Symbol:	Sr
Molar Mass:	87.6
Synonyms:	NA

Exposure Routes

People can be exposed to strontium from food, water, air, and soil (dirt). Strontium is naturally occurring, so people can be exposed to strontium in minerals from natural weathering by wind and water. Human activities that contribute strontium to the environment include mining, milling, refining and phosphate fertilizer use along with coal burning and pyrotechnic device use. Historically, the most important commercial use of strontium has been in the faceplate of cathode-ray tube televisions to block x-ray emissions.

Naturally-occurring strontium exists in the environment mainly in the +2 oxidation state and it can be found in drinking water, groundwater, and surface water.

Current Standard

Wisconsin does not currently have a groundwater enforcement standard for strontium.[4]

Standard Development

Federal Numbers		
Maximum Contaminant Level:	N/A	
Health Advisories (Draft)		
1-Day Child:	25,000 µg/L	(1993)
10-Day Child:	25,000 µg/L	(1993)
Lifetime:	4,000 µg/L	(1993)
Health Reference Level:	1,500 µg/L	(2014)
Drinking Water Concentration (Cancer Risk):	N/A	
State Drinking Water Standard		
NR 809 Maximum Contaminant Level:	N/A	
Acceptable Daily Intake		
EPA Oral Reference Dose (IRIS):	0.6 mg/kg-d	(1993)
EPA Oral Reference Dose (Office of Water):	0.3 mg/kg-d	(2014)
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
None available		
Literature Search		
Search Dates:	2014 – 2019	
Total studies evaluated:	Approximately 400	
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 not established a maximum contaminant level for strontium.[5]

Health Advisories

In 1993, the EPA established several draft health advisories for strontium.[6]

1-Day and 10-Day Child

The EPA based the 1-Day and 10-Day Child Health Advisories on a 1959 study that evaluated the effects of strontium supplementation in human patients. In this study, McCaslin and Janes gave people with ostoperosis strontium lactate (24 milligrams strontium per kilogram per day) every day for periods ranging from 3 months to 3 years.[7] Of the 32 patients who were available for follow-up, 84% experienced marked improvement. The EPA selected a No Observable Adverse Effect Level (NOAEL) of 25 mg/kg-d strontium from this study. They applied a total uncertainty factor of 10 to account for

differences among people. They used a body weight of 10 kg, water consumption rate of 1 liter per day (L/d), and a relative source contribution of 100% to obtain a health advisory level of 25 mg/L. The 1-day and 10-day health advisories are 25 mg/L (25,000 µg/L).

Lifetime

The EPA based the Lifetime Health Advisory on their 1993 oral reference dose of 0.6 mg/kg-d for strontium (see below for more details on the oral reference dose). They used a body weight of 70 kg, water consumption rate of 2 L/d, and relative source contribution of 20%. The lifetime health advisory is 4 mg/L (4,000 µg/L).

Health Reference Level

In 2014, the EPA established a Health Reference Level of 1.5 mg/L (1,500 µg/L) for strontium as part of their Unregulated Contaminant Monitoring Rulemaking Cycle Three (UCMR3) process.[2] The EPA defines a Health Reference Level as a risk-derived concentration against which to compare the occurrence data from public water systems to determine if a chemical occurs with a frequency and at levels of public health concern.[2] Because a Health Reference Level is a concentration of a substance in drinking water established to protect people from health effects and is similar in design and intent to a health advisory level, DHS considers these Health Reference Levels as federal numbers.

Table 1. Derivation of the Health Reference Level (HRL) for Strontium using Age-Specific Exposure Factors for the First 18 years (Adapted from the EPA's Health Effects Support Document[2])

Age Range	DWI/BWR[1] (L/kg-d)	Age-Specific Fractions[2]	Time-Weighted DWI/BWR[3] (L/kg-d)
Birth to < 1 month	0.235	0.004	0.001
1 to <3 months	0.228	0.009	0.002
3 to <6 months	0.148	0.013	0.002
6 to <12 months	0.112	0.026	0.003
1 to <2 years	0.056	0.053	0.003
2 to <3 years	0.052	0.053	0.003
3 to <6 years	0.043	0.158	0.007
6 to <11 years	0.035	0.263	0.009
11 to <16 years	0.026	0.263	0.007
16 to <18 years	0.023	0.105	0.002
18 to <21 years[#]	0.026	0.053	0.001
	Sum of the Time-Weighted DWI/BWRs:		0.040 L/kg-d
	Oral Reference Dose:		0.3 mg/kg-d
	Relative Source Contribution:		20%
	Health Reference Level[4]:		**1.5 mg/L**

DWI/BWR = drinking water intake to body weight ratio

1. DWI values are from 2011 version of the EPA's Exposures Factors Handbook.
2. The exposure duration adjustment was calculated by dividing the age-specific fraction of a 19 year exposure by the total exposure in months or years as appropriate.
3. The time-weighted DWI/BWR values are the product of the age-specific DWI/BWR multiplied by the age–specific fraction of a 19 year exposure.
4. $$\text{Health Reference Level} = \frac{\text{Oral Reference Dose x Relative Source Contribution}}{\text{Sum of}\left[\frac{\text{Drinking Water Intake}}{\text{Body Weight Ratio}} \text{x Age-Specific Fraction}\right]}$$

To set this level, the EPA first established an oral reference dose (see below for more details). They then used age-specific exposure factors to adjust for the risk associated with exposures from infancy through adolescence and to account for the periods of active bone growth and calcification during growth.

Drinking Water Concentration (Cancer Risk)

The EPA has not established drinking water concentrations based on cancer risk for strontium.[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 strontium.[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 (IRIS)

In 1993, the EPA's IRIS program established an oral reference dose of 0.6 mg/kg-d for strontium.[10] The EPA based this value on a 1961 study that evaluated the effects of strontium on bone calcification.[11] In this study, Storey et al. exposed young and adult female rats to different concentrations of strontium (0, 190, 380, 750, 1000, 1500, and 3000 mg/kg-d for juveniles and 95, 190, 375, 750, and 1500 mg/kg-d for adults) for 20 days. The EPA selected a No Observable Adverse Effect Level (NOAEL) of 190 mg/kg-d strontium from this study. They applied a total uncertainty factor of 300 to account for differences between people and research animals (10), differences between people (3) [a], and the limited availability of information (10).

EPA Oral Reference Dose (Office of Water)

In 2014, the EPA's Office of Water established an oral reference dose of 0.3 mg/kg-d for strontium.[2] They based this value on a 1985 study that evaluated the effects of strontium on bone calcification.[12] In this study, Marie et al. exposed young male rats to different concentrations of strontium (0, 316, 425, 525 and 633 mg/kg-d strontium) in water for 9 weeks. They observed a dose-related decrease in the

a The EPA applied an uncertainty factor of 3 to account for sensitive subpopulations instead of the default of 10 because the critical study was performed in young animals, a recognized sensitive subpopulation.

bone calcification rate at the two highest doses. The EPA used benchmark dose (BMD) modeling to obtain a BMD 95% confidence lower bound level of 328 mg/kg-d. They applied a total uncertainty factor of 1000 to account for differences between people and research animals (10), differences between people (10), and the limited availability of information (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 strontium, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of strontium. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

The EPA has determined that there is inadequate information to assess the carcinogenic potential of the non-radioactive forms of strontium.[2,10]

The International Agency for Research on Cancer (IARC) has not evaluated the cancer potential of the non-radioactive forms of strontium.[13]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for strontium.

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 strontium, we searched for values that have been published since EPA's review in 2014. 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 search focused on the scientific literature published after the review by EPA in 2014. We carried out a search on the National Institutes of Health's PubMed database for relevant articles published from January 2014 to January 2019 related to strontium toxicity or strontium effects on a disease state in which information on exposure or dose was included as part of the study.[b] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over exposure duration proportional to the lifetime of humans.

Approximately 400 studies were returned by the search engine. We excluded studies on non-mammalian species and studies on strontium nanoparticles. After applying these exclusion criteria, we located one key study (see Table A-1 contains a summary of this study). 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.[c] The key study met the requirements to be considered a critical study (see Table A-2 for details on evaluation).

Critical Study

Chiu, 2017

Chiu et al. evaluated the potential toxicological effect of strontium citrate on embryo-fetal development in rats. The scientists exposed pregnant rats to different concentrations of strontium citrate (0, 680, 1,360, and 2,267 mg/kg-d) by gavage from gestation days 6 to 15. They evaluated various organ and skeletal developmental endpoints and found that the highest dose caused anomalies in the bones and eyes of fetuses.

While this study provides important dose-response data for prenatal developmental toxicity in a rat model, the NOAEL of 1,360 mg/kg-day reported in this study was much higher than the BMD used to derive the EPA's Health Reference Level.

b The following search terms were used in the literature review:
Title/Abstract: strontium
Subject area: toxic* OR cancer AND (develop* OR repro* OR immuno*)
Language: English

c 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%).[16]

Standard Selection

DHS recommends an enforcement standard of 1,500 µg/L for strontium.

DHS recommends using the EPA's Health Reference Level as the groundwater enforcement standard for strontium. This is the most recent federal number available. We did not find any significant technical information that was not considered by EPA as part of our literature search.

Basis for Enforcement Standard

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

DHS recommends a preventive action limit of 150 µg/L for strontium.

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

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Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. Strontium Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Effect Type	Toxicity Value (mg/kg-d)	Reference
Development	Rat	Gestation Days 6 – 15	680, 1360, 2267	Gavage	Fetal bone and eye development affected at the highest dose.	NOAEL	NOAEL: 1360 LOAEL: 2267	Chiu et al., 2019

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?
Chiu et al., 2019	✓	✓	✓	**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.

Thiamethoxam | 2022

Substance Overview

Thiamethoxam is a neonicotinoid pesticide used to control a variety of indoor and outdoor insects.[1] Neonicotinoids are broad spectrum insecticides used on agricultural fields, gardens, pets, and in homes.

Neonicotinoid pesticides are similar to nicotine in their structure. They are specifically designed to act on insect nicotine receptors resulting in paralysis and death.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for thiamethoxam.

DHS recommends an enforcement standard of 120 micrograms per liter (µg/L) for thiamethoxam. The recommended standard is based on the United States Environmental Protection Agency's (EPA's) chronic oral reference dose for thiamethoxam.[1]

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for thiamethoxam be set at 10% of the enforcement standard because thiamethoxam has been shown to have teratogenic effects.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

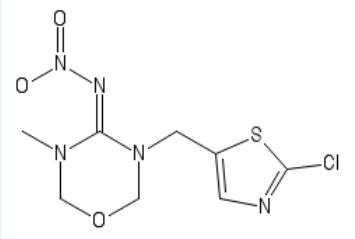
Recommended Standards	
Enforcement Standard:	120 µg/L
Preventive Action Limit:	12 µg/L

Health Effects

What we know about the health effects of thiamethoxam comes from studies with laboratory animals.[1] Animals that ate large amounts of thiamethoxam for long periods of time had problems with their liver, adrenal glands, and blood. Male animals had problems with their reproductive system.

Thiamethoxam has been shown to cause teratogenic effects (skeletal abnormalities) in several animal studies.[1] Thiamethoxam has not been shown to have carcinogenic, mutagenic, or interactive effects.[1]

Chemical Profile

	Thiamethoxam
Structure:	
CAS Number:	153719-23-4
Formula:	$C_8H_{10}ClN_5O_3S$
Molar Mass:	291.71 g/mol
Synonyms:	3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine CGA 293343

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of a number of commercial products containing thiamethoxam for controlling a variety of indoor and outdoor insects.[2]

People can be exposed to thiamethoxam from food, air, soil, and water.[1] Certain foods may have some thiamethoxam in or on them from its use as a pesticide. The EPA regulates how much pesticide residue can be in foods. Adults can be exposed to thiamethoxam in air or soil from using products that contain thiamethoxam in their gardens or homes. Young children can be exposed to thiamethoxam while playing in areas that have been recently treated with products containing thiamethoxam.

According to the EPA's HHRA, thiamethoxam has low water solubility and a high affinity to bind to soil. Thiamethoxam breaks down quickly in the soil. One of the chemicals that it can break down into is clothianidin, which is another neonicotinoid pesticide.

Current Standard

Wisconsin does not currently have any groundwater standards for thiamethoxam.[3]

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A	
Health Advisory Level:	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:	0.012 mg/kg-d	(2017)

Oncogenic Potential

EPA Cancer Slope Factor:	N/A	

Guidance Values

None available

Literature Search

Literature Search Dates:	2010 – 2019
Total studies evaluated:	Approximately 540
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 thiamethoxam.[4]

Health Advisory

The EPA has not established health advisories for thiamethoxam.[5]

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations based on cancer risk for thiamethoxam.[6]

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 thiamethoxam.[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 2017, the EPA Office of Pesticide Programs released a draft Human Health Risk Assessment as part of the registration of thiamethoxam. They selected 2 multi-generational reproduction studies in rats as their critical studies (MRIDS: 46402904 and 46402902). In these studies, groups of rats were exposed to different concentrations of thiamethoxam in their diet from before mating to lactation.

In the 1998 study (MRID: 46402904), thiamethoxam caused kidney damage in male offspring and reduced body weight for all offspring during the lactation period.[a] From the 1998 study, the EPA identified No Observable Adverse Effect Levels (NOAELs) and Lowest Observable Adverse Effect Levels (LOAELs) for systemic effects in parents and offspring and reproduction effects in parents only.

1998	Parent	Reproduction	Offspring
NOAEL:	0.61 mg/kg-d	0.61 mg/kg-d	61.25 mg/kg-d
LOAEL:	1.84 mg/kg-d	1.84 mg/kg-d	158.32 mg/kg-d
Basis:	Kidney damage in males	Tubular atrophy in testes of offspring.	Reduced body weight during lactation.
(expressed as milligrams thiamethoxam per kilogram per day (mg/kg-d))			

In the 2004 study (MRID: 46402902), thiamethoxam caused altered organ weight, kidney damage in male parents, lower total litter weight, and altered sperm parameters.[b] From this study, the EPA identified NOAELs and LOAELs for parent, reproduction, and offspring effects.

a Doses for 1998 study:

	Males	Females
F0 Generation	0, 1.2, 3.0, 61.7, 155.6 mg/kg-d	0, 1.7, 4.3, 84.4, 208.8 mg/kg-d
F1 Generation	0, 1.5, 3.7, 74.8, 191.5 mg/kg-d	0, 2.1, 5.6, 110.1, 276.6 mg/kg-d

b Doses for 2004 study:

	Males	Females
F0 Generation	0, 1.5, 3.7, 74.8, 191.5 mg/kg-d	0, 1.2, 3.0, 61.7,155.6 mg/kg-d
F1 Generation	0, 2.1, 5.6, 110.1, 276.6 mg/kg-d	0, 1.7, 4.3, 84.4, 208.8 mg/kg-d

2004	Parent	Reproduction	Offspring
NOAEL:	156 mg/kg-d	62 mg/kg-d	62 mg/kg-d
LOAEL:	N/A	156 mg/kg-d	156 mg/kg-d
Basis:	No observed adverse, treatment related effects in parents.	Germ cell loss in the testes of offspring.	Decreased total litter weights.

To set the oral reference dose for thiamethoxam, the EPA used combined data from both studies to give a NOAEL of 1.2 mg/kg-d. The EPA selected this value because the two studies used different terminology, criteria, and scoring for the histopathological evaluation leading to uncertainty in comparing the results across studies. The EPA selected a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). The EPA's chronic oral reference dose for thiamethoxam is of 0.012 mg/kg-d.

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

Cancer Classification

The EPA has classified thiamethoxam as is not likely to be a human carcinogen.[1]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for thiamethoxam.[1]

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 thiamethoxam, we searched for values that been published since 2017 when the EPA published their draft human health risk assessment. We did not find any relevant guidance values from the EPA, Agency

for Toxic Substances and Disease Registry (ATSDR), World Health Organization (WHO), or the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).

Literature Search

The most recent federal review on thiamethoxam was published in 2017 when the EPA's oral reference dose was established. Our literature review focused on the scientific literature published after the review by the EPA in 2017. A search on the National Institutes of Health's PubMed resource for articles published from January 2017 to February 2019 was carried out for studies related to thiamethoxam toxicity or its effects on a disease state in which information on thiamethoxam exposure or dose was included as part of the study.[c] 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 540 studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life, studies evaluating risk from non-mammalian species, studies using a product containing thiamethoxam, and monitoring studies from further review. After applying these exclusion criteria, we located one key study (Table A-1 contains a summary of this study). 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.[d] The key study did not meet the requirements to be considered a critical study (see Table A-2 for details on this evaluation).

Standard Selection

DHS recommends an enforcement standard of 120 µg/L for thiamethoxam.

There are no federal numbers for thiamethoxam. The EPA did not establish a cancer slope factor for thiamethoxam because they concluded that it is not likely to be carcinogenic to humans. Additionally, there is no drinking water standard for thiamethoxam in Ch. NR 809, Wisc. Admin Code.

Basis for Enforcement Standard

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

The EPA has an ADI (oral reference dose) for thiamethoxam. In our review, we did not find any significant technical information that was not considered when EPA established their oral reference

c The following search terms were used in the literature review:
Title/abstract: Thiamethoxam
Subject area: toxicology OR cancer
Language: English

d 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%).[8]

dose, nor has there been any published since then. Therefore, DHS calculated the recommended enforcement standard using EPA's oral reference dose for thiamethoxam and exposure parameters specified in s. 160.13, Wisc. Stats.: a body weight of 10 kg, a water consumption rate of 1 liter per day (L/d), and a relative source contribution of 100%.

DHS recommends a preventive action limit of 12 µg/L for thiamethoxam.

DHS recommends the preventive action limit for thiamethoxam be set at 10% of the enforcement standard because thiamethoxam has been shown to cause teratogenic effects (skeletal abnormalities) in some animal studies.[1]

Updated by Amarilys Gonzalez Vazquez, Ph.D. and Sarah Yang, Ph.D. – January 2022

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. Thiamethoxam Toxicity Studies – Additional Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Longer-term	Rabbit	90 d	250	Gavage	Increased oxidative stress response. Upregulated levels of proinflammatory cytokines. Elevated level of carcinoembryonic antigen.	LOAEL: 250	El Okle et al., 2018

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?
El Okle, 2018	✓	✓	✓	1	✓	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.

Imidacloprid | 2022

Substance Overview

Imidacloprid is a neonicotinoid pesticide used to control a variety of indoor and outdoor insects.[1] Neonicotinoids are broad spectrum insecticides used on agricultural fields, gardens, pets, and in homes.

Neonicotinoid pesticides are similar to nicotine in their structure. They are specifically designed to act on the nicotine receptors in insects, resulting in paralysis and death.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for imidacloprid.

DHS recommends an enforcement standard of 0.2 micrograms per liter (µg/L) for imidacloprid. The recommended enforcement standard is based on a study in 2017 that found that imidacloprid affected weight gain and glucose regulation in male mice.[2]

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for imidacloprid be set at 10% of the enforcement standard because recent studies have shown that imidacloprid can cause mutagenic, teratogenic, and interactive effects at high levels.[1, 3-6]

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	

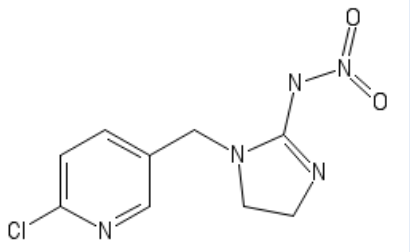
Recommended Standards	
Enforcement Standard:	0.2 µg/L
Preventive Action Limit:	0.02 µg/L

Health Effects

What we know about the health effects of imidacloprid comes from studies with laboratory animals. Animals that swallowed large amounts of imidacloprid for long periods of time had thyroid, neurological, reproductive, and glucose regulation problems.[1, 2, 7-11]

The EPA has classified imidacloprid as having evidence of non-carcinogenicity, meaning that it does not cause cancer in animal studies.[1] Some studies have shown that imidacloprid can cause teratogenic effects in animals.[1] Recent studies have shown that high levels of imidacloprid can cause mutagenic effects in mice and can have interactive effects with arsenic in rats.[4-6]

Chemical Profile

	Imidacloprid
Chemical Symbol:	
CAS Number:	138261-41-3
Formula:	$C_9H_{10}ClN_5O_2$
Molar Mass:	255.66 g/mol
Synonyms:	N-[1-[(6-Chloropyridin-3-yl)methyl]imidazolidin-2-ylidene]nitramide

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of a large number of products containing imidacloprid for controlling a variety of indoor and outdoor insects.[12]

People can be exposed to imidacloprid from food, air, soil, and water.[1] Certain foods may have some imidacloprid in or on them from its use as a pesticide. The EPA regulates how much pesticide residues can be in foods. Adults can be exposed to imidacloprid in air or soil from using products that contain imidacloprid in their gardens or homes. Young children can be exposed to imidacloprid while playing in areas that have been treated with products containing imidacloprid. People can also be exposed to imidacloprid from its use as flea treatment on pets.

Imidacloprid is persistent and mobile in the environment allowing it to reach groundwater.[1]

Current Standards

Wisconsin does not currently have any groundwater standards for imidacloprid.[13]

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:	0.057 mg/kg-d	(2010)
EPA Oral Reference Dose (Draft):	0.08 mg/kg-d	(2017)

Oncogenic Potential

EPA Cancer Slope Factor:	N/A	

Guidance Values

None available

Literature Search

Literature Search Dates:	Until January 2022
Total studies evaluated:	Approximately 900
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 imidacloprid.[14]

Health Advisory

The EPA does not have a health advisory for imidacloprid.[15]

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established any drinking water concentrations based on a cancer risk level for imidacloprid.[1]

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 imidacloprid.[16]

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 (2010)

As part of their Human Health Risk Assessment for imidacloprid in 2010, the EPA reviewed a number of toxicity studies.[1] To establish the oral reference dose, the EPA selected a chronic carcinogenicity study in rats as the critical study (MRID: 42256331). In this study, rats were exposed to different concentrations of imidacloprid in diet for 2 years (0, 5.7, 16.9, 51.3, 102.6 milligrams per kilogram body weight per day (mg/kg-d) for males and 0, 57.6, 24.9, 73.0, 143.7 mg/kg-d for males). Imidacloprid affected the thyroid of male rats by increased incidence of mineralized particles in thyroid colloid. The No Observable Adverse Effect Level (NOAEL) from this study was 5.7 mg/kg-d. EPA used a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). The chronic oral reference dose for imidacloprid is 0.057 mg/kg-d.

EPA Oral Reference Dose (2017 - Draft)

In 2017, the EPA released a draft Human Health Risk Assessment for imidacloprid.[17] To establish the oral reference dose, the EPA selected a subchronic toxicity study in dogs as the critical study (MRID: 42256328). In this study, dogs were exposed to different concentrations of imidacloprid in diet (males: 0, 7.7, 22.1, 45.0 mg/kg-d; females: 0, 8.0, 24.8, 45.7 mg/kg-d) for 90 days. Imidacloprid caused tremors within one week of exposure. The No Observable Adverse Effect Level (NOAEL) from this study was 7.7 mg/kg-d. EPA used a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). The chronic oral reference dose for imidacloprid is 0.08 mg/kg-d.

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

Cancer Classification

The EPA and Joint FAO/WHO Meeting on Pesticide Residues (JMPR) have evaluated carcinogenic potential of imidacloprid and found that it did not show evidence of carcinogenicity in animal studies.[1, 18] The international Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of imidacloprid.[19]

Cancer Slope Factor

The EPA has not established a cancer slope factor for imidacloprid.[20]

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 imidacloprid, we searched for values that been published since 2010 when the EPA published their risk assessment. We did not find any relevant guidance values from the EPA, Agency for Toxic Substances and Disease Registry (ATSDR), World Health Organization (WHO), or Joint FAO/WHO Meeting on Pesticide Residues (JMPR).

Literature Search

Our literature review focused on the scientific literature published until January 2022. We searched for studies related to imidacloprid toxicity or its effects on a disease state in which information on imidacloprid 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 900 studies were returned by the search engine. We excluded studies of short duration (< 60 days in rodents), studies on the effects on plant and aquatic life, studies evaluating risk from non-mammalians species, and monitoring studies from further review. After applying these exclusion criteria, we located 35 key studies (see table A-1 for more details on 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

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

evaluated more than one dose, and have an identifiable toxicity value.[b] Fifteen studies met the criteria to be considered a critical study (see Table A-2 for details on the evaluation).

Critical Studies

To compare between results between studies, we calculated acceptable daily intake (ADI) for each study/effect. The ADI is the estimated amount of imidacloprid that a person can be exposed to every day and not experience health impacts. The ADI equals the toxicity value divided by the total uncertainty factor. Uncertainty factors were included as appropriate to account for differences between people and research animals, differences in sensitivity to health effects within human populations, using data from short term experiments to protect against effects from long-term exposure, and using data where a health effect was observed to estimate the level that does not cause an effect.

Bal et al, 2012a

In their first study, Bal et al evaluated the effects of exposure to imidacloprid on reproduction in developing male rats.[22] Rats were exposed to 0, 0.5, 2, or 8 mg/kg-d of imidacloprid by gavage for 90 days. They found that imidacloprid decreased sperm concentration, reduced weight gain, and lowered testosterone and glutathione levels at all doses.

We calculated a candidate ADI of0.0002 mg/kg-d based on a Lowest Observed Adverse Effect Level (LOAEL) of 0.5 mg/kg-d and uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10). This and the following study were the first peer-reviewed publications to evaluate the effects of imidacloprid on the male reproductive system.

Bal et al, 2012b

In their second study, Bal et al repeated the study in adult male rats.[8] They found that imidacloprid affected several reproductive parameters, reduced antioxidant levels, and disturbed fatty acid composition at all doses. Rats were exposed to 0, 0.5, 2, or 8 mg/kg-d of imidacloprid by gavage for 90 days. They found that imidacloprid decreased sperm concentration, reduced weight gain, and lowered testosterone and glutathione levels at all doses.

For this study, we calculated a candidate ADI of0.0002 mg/kg-d based on a LOAEL of 0.5 mg/kg-d and an uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10). This and the previous study were the first peer-reviewed publications to evaluate the effects of imidacloprid on the male reproductive system.

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%).[17]

Bhardwaj et al, 2010

Bhardwaj et al evaluated the effects of exposure to imidacloprid on overall health in female rats.[23] Female rats were exposed to 0, 5, 10, or 20 mg/kg-d of imidacloprid by gavage for 90 days. They found that the highest dose of imidacloprid decreased body weight, increased liver, kidney, and adrenal weights, altered clinical parameters, and decreased spontaneous locomotor activity.

We calculated a candidate ADI of0.03 mg/kg-d based on a NOAEL of 10 mg/kg-d and uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3).

Gawade et al, 2013

Gawade et al evaluated the effects of exposure to imidacloprid on reproduction and development.[24] Pregnant rats were exposed to 0, 10, 30, or 90 mg/kg-d of imidacloprid by gavage during pregnancy (gestation days 6 to 20) to evaluate effects on maternal toxicity, fetal development, and the immune system. Additionally, a subset of the pups was exposed to imidacloprid by gavage until post-natal day 42 to evaluate effects on the immune system. They found that imidacloprid increased post-implantation loss, caused soft tissue abnormalities and skeletal alterations, and had adverse effects on immunity.

We calculated a candidate ADI of0.01 mg/kg-d based on a LOAEL of 10 mg/kg-d and uncertainty factor of 1000 to account for differences between people and research animals (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

Kapoor et al, 2010

In 2010, Kapoor et al evaluated the effects of exposure to imidacloprid on overall health in female rats.[25] Female rats were exposed to 0, 5, 10, or 20 mg/kg-d of imidacloprid by gavage for 90 days. They found that the highest dose of imidacloprid caused significant changes in biochemical changes in the liver, brain, and kidneys.

We calculated a candidate ADI of0.03 mg/kg-d based on a NOAEL of 10 mg/kg-d and uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3).

Kapoor et al, 2011

In 2011, Kapoor et al continued to evaluate the effects of exposure to imidacloprid on overall health in female rats.[26] Female rats were exposed to 0, 5, 10, or 20 mg/kg-d of imidacloprid by gavage for 90 days. They found that the highest dose of imidacloprid decreased ovarian weight and caused histological changes in follicles, antral follicles and atretic follicles.

We calculated a candidate ADI of0.03 mg/kg-d based on a NOAEL of 10 mg/kg-d and uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3).

Kahlil et al, 2017

Kahlil et al evaluated the effects of exposure to imidacloprid by gavage on rats.[10] Rats were exposed to 0, 0.5 and 1 mg/kg-d of imidacloprid for 60 days. They found that imidacloprid altered cortisone and catecholamine levels, caused behavioral deficits, and induced hyperglycemic effects at both doses in adults. They also found that imidacloprid (1 mg/kg-d) affected glucose, insulin, and glycogen levels in adults and developing rats.

We calculated a candidate ADI of0.0002 mg/kg-d based on a LOAEL of 0.5 mg/kg-d and uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10).

Kara et al, 2015

Kara et al evaluated the effects of exposure to imidacloprid by gavage on rats.[9] Infant and adult rats were exposed to 0, 0.5, 2, and 8 mg/kg-d of imidacloprid for 90 days. They found that the two high doses increased escape latency time of infants on the 4th and 5th days of the Morris water maze test. This corresponds to a decrease in learning and cognitive function. Infants were more sensitive to these effects. They also found that the highest dose decreased the time that animals spent in the target quadrant in the probe test. This corresponds to a decrease in memory function. Both infants and adults were affected.

We calculated a candidate ADI of0.00002 mg/kg-d based on a NOAEL of 0.5 mg/kg-d and an uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3).

Sun et al, 2016

In 2016, Sun et al evaluated the effects of exposure to imidacloprid on male mice.[2] Mice were exposed to 0, 0.06, 0.6, or 6 mg/kg-d of imidacloprid by gavage for 84 days. The study authors found that imidacloprid enhanced high fat diet-induced weight gain and adiposity and increased serum insulin levels at the two highest doses. Imidacloprid also affected several genes involved in lipid and glucose metabolism.

We calculated a candidate ADI of0.0002 mg/kg-d based a LOAEL of 0.06 mg/kg-d and an uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10).

Sun et al, 2017

In 2017, Sun et al repeated their experiment in female mice.[11] Mice were exposed to 0, 0.06, 0.6, or 6 mg/kg-d of imidacloprid by gavage for 84 days. Females were less sensitive to the effects of imidacloprid. They found that only the middle dose (0.6 mg/kg-d) enhanced high fat diet-induced weight gain and adiposity. They also found that only the highest dose of imidacloprid (6 mg/kg-d) increased insulin levels and did so without an effect on glucose levels. The authors hypothesized that estrogens may be responsible for the increased resistance to high fat-diet induced glucose intolerance and insulin

resistance observed in the female mice compared to male mice. They theorized that it might take longer for female mice to develop the same effects as the male mice.

We calculated a candidate ADI of0.0002 mg/kg-d based on a NOAEL of 0.06 and uncertainty factor of 300 to account for account for differences between people and research animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3).

Vohra et al, 2014

In their first study, Vohra et al evaluated the effects of exposure to imidacloprid on overall health in female rats.[27] Rats were exposed to 0, 10 or 20 mg/kg-d of imidacloprid by gavage for 60 days. They found that imidacloprid reduced feed intake, heart and spleen weight, decreased acetylcholinesterase activity in plasma and brain.

We calculated a candidate ADI of0.003 mg/kg-d based on a Lowest Observed Adverse Effect Level (LOAEL) of 10 mg/kg-d and uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10).

Vohra et al, 2015

In their second study, Vohra et al evaluated the effects of exposure to imidacloprid on multiple generations of animals.[28] Female rats were exposed to 0, 10 or 20 mg/kg-d of imidacloprid by gavage for 60 days and then mated with untreated males to obtain F1 and F2 generations and effects were evaluated in F2 animals. They found that the highest dose of imidacloprid reduced the average feed intake of females and increased the activity of alanine aminotransferase, alkaline phosphatase, and glucose 6-phosphate dehydrogenase in both sexes. Both doses of imidacloprid decreased acetylcholine esterase activity in plasma and brain in all treated animals and caused histopathological changes in the liver, kidney, and brain of females.

We calculated a candidate ADI of0.01 mg/kg-d based on a Lowest Observed Adverse Effect Level (LOAEL) of 10 mg/kg-d and uncertainty factor of 1000 to account for differences between people and research animals (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

Yang et al, 2020

Yang et al evaluated the effects of exposure to imidacloprid on male mice.[29] Rats were exposed to 0, 0.5, 1.57, or 5 mg/kg-d of imidacloprid through drinking water for 70 days. They found that imidacloprid reduced relative liver weights, altered hepatic tissue morphology, caused hepatic oxidative stress, and impaired gut barrier function.

We calculated a candidate ADI of0.0002 mg/kg-d based on a LOAEL of 0.5 mg/kg-d and uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10).

Yuan et al, 2020

Yuang et al evaluate the effects of exposure to imidacloprid on male mice.[29] Rats were exposed to 0, 0.5, 1.57, or 5 mg/kg-d of imidacloprid through drinking water for 70 days. They found that imidacloprid impaired testicular morphology; and decreased levels of serum testosterone and androgen receptor activity.

We calculated a candidate ADI of0.0002 mg/kg-d based on a LOAEL of 0.5 mg/kg-d and uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10).

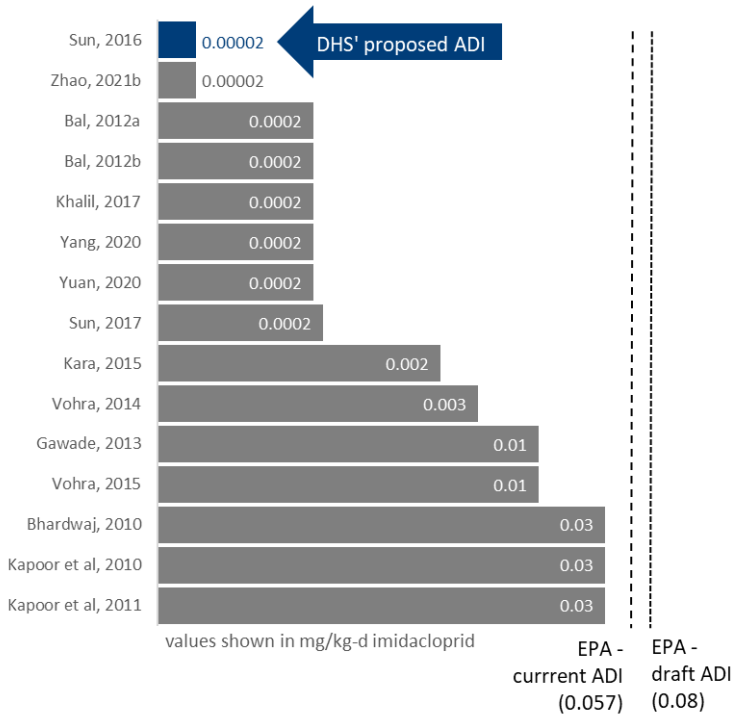
Zhao et al, 2021a

Zhao et al evaluated the effects of exposure to imidacloprid on male mice.[30] Rats were exposed to 0, 0.06, and 0.6 mg/kg-d of imidacloprid through gavage for 90 days. They found that imidacloprid caused abnormalities in sperm concentrations and morphologies and an imbalance of the gonadal hormone testosterone.

We calculated a candidate ADI of 0.00002 mg/kg-d based on a LOAEL of 0.06 mg/kg-d and uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10).

Summary

Review of data published since 2010 indicates that imidacloprid can cause health effects at values lower than EPA's chronic oral reference dose. Health effects observed in animal studies at these low levels include effects on overall health, male reproduction, insulin and glucose regulation, and learning and memory abilities. Together, these studies suggest that the groundwater standard should be based on a lower ADI to protect from serious health effects. Additionally, recent studies show that imidacloprid may cause mutagenic and interactive effects.[3-6] Data from recent studies suggest that the ADI used to set the groundwater standard should be lower than EPA's oral reference dose.



Standard Selection

DHS recommends an enforcement standard of 0.2 µg/L for imidacloprid.

Basis for Enforcement Standard

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

There are no federal numbers for imidacloprid and the EPA has not established a cancer slope factor for imidacloprid because they did not find evidence of carcinogenicity. Additionally, there is no drinking water standard for imidacloprid in Ch. NR 809, Wisc. Admin Code. The EPA does have an ADI (oral reference dose) for imidacloprid. However, we found several studies that have been published since EPA established their oral reference dose that indicate a different acceptable daily intake should be used to set the standard.

To calculate the ADI as specified in s. 160.13, Wisc. Statute, DHS selected the 2016 study by Sun et al as the critical study. We selected a LOAEL of 0.06 mg/kg-d because effects on weight gain, adipose cell size, kidney weight, and glucose level were observed at this dose. We selected a total uncertainty factor of 3000 to account for differences among people and research animals, differences among people, using data from a short-term study to protect against effects from long-term exposures, and having to use a LOAEL rather than a NOAEL in these calculations. To determine the recommended enforcement standard, DHS used the ADI, and, as required by Ch. 160, Wis. Stats., a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%.

DHS recommends a preventive action limit of 0.02 µg/L for imidacloprid.

DHS recommends that the preventive action limit for imidacloprid be set at 10% of the enforcement standard because recent studies have shown that imidacloprid can cause mutagenic and interactive effects at high levels.

Revised by Sarah Yang, Ph.D. – January 2022

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. Imidacloprid Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Reproduction	Rat (male)	65 d	0, 1	Gavage	Serious abnormalities in sperm morphology and concentration, imbalance of sexual hormones	NOAEL: N/A LOAEL: 1	Abdel-Rahman et al, 2017 ([31])
Co-Exposure	Rat (male)	30 d	Imidacloprid: 9 Cypermethrin: 5 Chloropyrifos: 1.9	Gavage	Significant reduction in serum testosterone, luteinizing hormone, follicle-stimulating hormone, testis superoxide dismutase, and glutathione levels. Increased levels of catalase, lipid peroxidation, and protein carbonyl content..	N/A	Abdel-Razik et al, 2021 ([32])
Short-term	Mice (male)	15 d	0, 5, 10, 15	Gavage	Decreased body weight, elevated serum chemistry, liver and kidney toxicity	NOAEL: 10 LOAEL: 15	Arfat et al, 2014 ([33])
Short-term	Mice (female)	28 d	0, 2.5, 5, 10	Gavage	Suppressed cell-mediated immune response, alterations to the spleen and liver, delayed type hypersensitivity response	NOAEL: 2.5 LOAEL: 5	Badgujar et al, 2013 ([34])
Short-term	Mice (both)	7, 14 and 28 d	0, 5.5, 11, 22	Gavage	Sperm head abnormality, mutagenic effects at spermatogonial stage	NOAEL: N/A LOAEL: 5.5	Bagri et al, 2015 ([3])
Short-term	Mice (female)	7, 14 and 28 d	0, 5.5, 11, 22	Gavage	Dose and time-dependent increase in frequencies of micronuclei per cell and chromosomal aberrations in bone marrow cells	NOAEL: 11 LOAEL: 22	Bagri et al, 2016 ([4])
Longer-term	Rat (female)	90 d	0, 0.5, 2, 8	Gavage	Decreased sperm concentration, weight gain, testosterone, and glutathione levels	NOAEL: N/A LOAEL: 0.5	Bal et al, 2012a ([7])

Longer-term	Rat (male)	90 d	0, 0.5, 2, 8	Gavage	Deterioration of sperm parameters, testosterone levels, increased apoptosis of germ cells, seminal DNA fragmentation, depletion of antioxidants, and disturbance of fatty acid composition	NOAEL: N/A LOAEL: 0.5	Bal et al, 2012b ([8])
Longer-term	Rat (female)	90 d	0, 5, 10, 20	Gavage	Decreased body weight, increased liver, kidney, and adrenal weight; altered clinical parameters; decreased spontaneous locomotor activity	NOAEL: 10 LOAEL: 20	Bhardwaj et al, 2010 ([23])
Co-exposure	Mouse (both)	PND 1 -28	Imidacloprid: 0.65 Mancozeb: 40 (endocrine disruptor)	Diet of lactating mother	In mixture exposed group, brain weight, dendritic spine density, and corticosterone level were impacted. Mixture also impacted learning as measured by T-maze task performance.	NOAEL: N/A LOAEL: 0.65	Bhaskar et al, 2017 ([35])
Reproduction	Mouse (female)	GD 4 – PND 21	0, 0.5	Implanted pump	Reduced fecundity. Decreased body weight in male pups. Offspring from IMI-treated mothers displayed lower triglycerides, elevated motor activity, enhanced social dominance, reduced depressive-like behavior, and a diminution in social aggression compared to vehicle treated controls.	NOAEL: N/A LOAEL: 0.5	Burke et al, 2018 ([36])
Developmental imunotoxicity	Rat (female)	Gestation Lactation Growth	0, 10, 30, 90	Gavage	Increased post-implantation loss, soft tissue abnormalities, skeletal alterations, adverse effects on immunity	NOAEL: N/A LOAEL: 10	Gawade et al, 2013 ([24])
Short-term	Rat (male)	21 d	0, 45, 90	Gavage	IMD increased ALT, AST, serum urea, creatinine, cholesterol and Glucose levels but decreased the levels of	NOAEL: N/A LOAEL: 45	Hassan et al, 2019 ([37])

					serum total protein, albumin and body weight with induction in triacylglycerol and cholesterol levels		
Short-term	Rat (Male)	21 d	0, 64.3	Gavage	Altered walking, body tension, alertness, and head movement; reduction in rats' body weight; biochemical and histological alterations with a significant increase in in live and kidneys,	NOAEL: N/A LOAEL: 64.3	Hassanen et al, 2022 ([38])
Longer-term	Rat (female)	90 d	0, 5, 10, 20	Gavage	Significant changes in biochemical changes in the liver, brain, and kidneys.	NOAEL: 10 LOAEL: 20	Kapoor et al, 2010 ([25])
Longer-term	Rat (female)	90 d	0, 5, 10, 20	Gavage	Decreased ovarian weight; histological changes in follicles, antral follicles and atretic follicles	NOAEL: 10 LOAEL: 20	Kapoor et al, 2011 ([26])
Longer-term	Rat (male)	90 d	0, 0.5, 2, 8	Gavage	Diminished learning activities	NOAEL: 0.5 LOAEL: 2	Kara et al, 2015 ([9])
Short-term	Rat (male)	28 d	0, 0.06, 0.8, 2.25	Gavage	Increased plasma levels of reactive oxygen species and lipid peroxidation; decreased activities of glutathione-peroxidase in plasma and brain and superoxide dismutase in erythrocytes; peripheral blood leukocyte damage; dose-dependent brain cell DNA damage	NOAEL: N/A LOAEL: 0.06	Katic et al, 2021 ([39])
Longer-term	Rat (male)	60 d	0, 0.5, 1.0	Gavage	Altered cortisone and catecholamine levels; behavioral deficits; hyperglycemic effect; altered mRNA level of glucose transporters; structural perturbations in the pancreas; decreased expression of	NOAEL: N/A LOAEL: 0.5	Khalil et al, 2017 ([10])

					insulin and GLUT4		
Short-term	Rat (male)	28 d	0, 45, 90	Gavage	Biochemistry altered in testis and plasma; histological alterations in testis and epididymis.	NOAEL: N/A LOAEL: 45	Lonare et al, 2016 ([40])
Co-exposure	Rat (both)	28 d	Imidacloprid: 16.9 Arsenic: 50, 100, 150 µg/L	Imid: gavage As: water	Imidacloprid alone increased markers of oxidative stress and reduced antioxidant levels in the liver. Co-administration with arsenic increased the severity of these effects.	NOAEL: N/A LOAEL: 16.9	Mahajan et al, 2018a ([6])
Co-exposure	Rat (male)	28 d	Imid: 16.9 As: 50, 100, 150 µg/L	Imid: gavage As: water	Imidacloprid alone increased markers of oxidative stress and reduced antioxidant levels in the testes. Co-administration with arsenic increased the severity of these effects.	NOAEL: N/A LOAEL: 16.9	Mahajan et al, 2018b ([5])
Co-exposure	Rat (male)	28 d	Imid: 16.9 As: 50, 100, 150 µg/L	Imid: gavage As: water	Imidacloprid alone increased markers of oxidative stress and reduced antioxidant levels in the kidneys. Co-administration with arsenic increased the severity of these effects.	NOAEL: N/A LOAEL: 16.9	Mahajan et al, 2018c ([41])
Short-term	Rat (male)	28 d	0, 0.21	Gavage	Increased total leukocyte counts; altered several biochemical parameters, and caused severe histological lesions in the liver, spleen and thymus	NOAEL: N/A LOAEL: 0.21	Mohany et al, 2012 ([42])
Reproduction	Rats (female)	Gestation	0, 44	Gavage	Alterations in antioxidant enzymes, MDA and liver function enzymes in mothers and offspring.	NOAEL: N/A LOAEL: 44	Ndonwi et al, 2019 ([43])

Longer-term	Rat (male)	90 d	0, 4	Gavage	Biochemical changes in kidneys	NOAEL: N/A LOAEL: 4	Ozsahin et al, 2014 ([44])
Immune challenge	Mice (male)	30 d	0, 6.55	Gavage	Animals challenged with E. *coli* lipopolysaccharides had increased total cell and neutrophil counts	NOAEL: N/A LOAEL: 6.55	Pandit et al, 2016 ([45])
Longer-term	Mice (male)	84 d	0, 0.06, 0.6, 6	Diet	Enhanced high fat diet-induced weight gain and adiposity, increased serum insulin levels	NOAEL: N/A LOAEL: 0.06	Sun et al, 2016 ([2]) Used by DHS for ADI
Longer-term	Mice (female)	84 d	0, 0.06, 0.6, 6	Diet	Enhanced high fat diet-induced weight gain and adiposity; increased serum insulin levels	NOAEL: 0.06 LOAEL: 0.6	Sun et al, 2017 ([11])
Longer-term	Rat (female)	60 d	0, 10, 20	Gavage	Reduced feed intake, heart and spleen weight, decreased acetylcholinesterase activity in plasma and brain	NOAEL: N/A LOAEL: 10	Vohra et al, 2014 ([27])
Generational	Rat (female)	3 generations	0, 10, 20	Gavage	Significantly reduced food intake in F2 females; altered biochemistry parameters	NOAEL: N/A LOAEL: 10	Vohra et al, 2015 ([28])
Longer-term	Mouse (male)	70 d	0, 0.5, 1.67, 5	Water	Reduced relative liver weights, altered liver tissue morphology; oxidative stress; impaired gut barrier function	NOAEL: N/A LOAEL: 0.5	Yang et al, 2020 ([29])
Longer-term	Mouse (male)	70 d	0, 0.5, 1.67, 5	Water	Impaired testicular morphology; decreased levels of serum testosterone and androgen receptor (AR)	NOAEL: N/A LOAEL: 0.5	Yuan et al, 2020 ([46])
Longer-term	Rat (male)	90 d	0, 0.06, 0.6	Gavage	Abnormalities in sperm concentrations and morphologies and an imbalance of the gonadal hormone testosterone.	NOAEL: N/A LOAEL: 0.06	Zhao et al, 2021a ([30])
Longer-term	Rat (male)	90 d	0, 0.06	Gavage	Increased intestinal permeability; elevated serum levels of endotoxin and inflammatory biomarkers	NOAEL: N/A LOAEL: 0.06	Zhao et al, 2021b ([47])

Table A-2. Critical Study Selection

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Multiple doses?	Toxicity value identifiable?	Critical study?
Abdel-Rahman et al, 2017	✓	✓	✓	⊘	✓	No
Abdel-Razik et al, 2021	⊘	✓	✓	⊘	⊘	No
Arfat et al, 2014	⊘	✓	✓	✓	✓	No
Badgujar et al, 2013	⊘	✓	✓	✓	✓	No
Bagri et al, 2015	⊘	✓	✓	✓	✓	No
Bagri et al, 2016	⊘	✓	✓	✓	✓	No
Bal et al, 2012a	✓	✓	✓	✓	✓	**Yes**
Bal et al, 2012b	✓	✓	✓	✓	✓	**Yes**
Bhardwaj et al, 2010	✓	✓	✓	✓	✓	**Yes**
Bhaskar et al, 2017	✓	✓	✓	⊘	✓	No
Burke et al, 2018	✓	✓	✓	⊘	✓	No
Gawade et al, 2013	✓	✓	✓	✓	✓	**Yes**
Hasan et al, 2019	⊘	✓	✓	✓	✓	No
Hassanen et al, 2022	⊘	✓	✓	⊘	✓	No
Kapoor et al, 2010	✓	✓	✓	✓	✓	**Yes**
Kapoor et al, 2011	✓	✓	✓	✓	✓	**Yes**
Kara et al, 2015	✓	✓	✓	✓	✓	**Yes**
Katic et al, 2021	⊘	✓	✓	✓	✓	No
Khalil et al, 2017	✓	✓	✓	✓	✓	**Yes**
Lonare et al, 2010	⊘	✓	✓	✓	✓	No
Mahajan et al, 2018a	⊘	✓	✓	⊘	✓	No
Mahajan et al, 2018b	⊘	✓	✓	⊘	✓	No
Mahajan et al, 2018b	⊘	✓	✓	⊘	✓	No
Mohany et al, 2012	⊘	✓	✓	⊘	✓	No
Ndonwi et al, 2019	✓	✓	✓	⊘	✓	No

Ozsahin et al, 2014	✓			⃠	✓	No
Pandit et al, 2016	✓	✓	✓	⃠	✓	No
Sun et al, 2016*	✓	✓	✓	✓	✓	**Yes**
Vohra, 2014	✓	✓	✓	✓	✓	**Yes**
Vohra, 2015	✓	✓	✓	✓	✓	**Yes**
Yang et al, 2020	✓	✓	✓	✓	✓	**Yes**
Yuan et al, 2020	✓	✓	✓	✓	✓	**Yes**
Zhao et al, 2021a	✓	✓	✓	⃠	✓	No
Zhao et al, 2021b	✓	✓	✓	✓	✓	**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.

*DHS selected the Sun et al, 2016 study as the critical study for calculating the recommend enforcement standard for imidacloprid.

Clothianidin | 2019

Substance Overview

Clothianidin is a neonicotinoid pesticide used to control a variety of indoor and outdoor insects.[1] Neonicotinoids are broad spectrum insecticides used on agricultural fields, gardens, pets, and in homes.

Neonicotinoid pesticides are similar to nicotine in their structure. They are specifically designed to act on insect nicotine receptors resulting in paralysis and death.

Recommendations

Wisconsin does not currently have a NR140 Groundwater Quality Public Health Enforcement Standard for clothianidin.

DHS recommends an enforcement standard of 1,000 micrograms per liter (µg/L) for clothianidin. The recommended standard is based on the United States Environmental Protection Agency's (EPA's) chronic oral reference dose for clothianidin.[2]

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for clothianidin be set at 20% of the enforcement standard because clothianidin has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

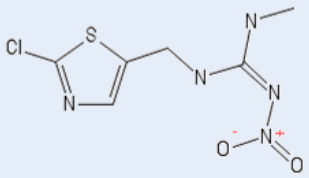
Recommended Standards	
Enforcement Standard:	1,000 µg/L
Preventive Action Limit:	200 µg/L

Health Effects

What we know about the health effects of clothianidin comes from studies with laboratory animals.[1] Animals that ate large amounts of clothianidin for long periods of time experienced liver, blood, and kidney problems.

The EPA has classified clothianidin as not likely to be carcinogenic to humans.[2] Clothianidin has not been shown to have mutagenic, teratogenic, or interactive effects.[1,2]

Chemical Profile

	Clothianidin
Structure	
Chemical Symbol:	$C_6H_8ClN_5O_2S$
CAS Number:	210880-92-5 (formerly 205510-53-8)
Molar Mass:	249.68 g/mol
Synonyms:	*(E)*-1-[(2-Chloro-1,3-thiazol-5-ylmethyl)]-3-methyl-2-nitroguanidine TI-435 V-10066

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of a number of commercial products containing clothianidin for controlling a variety of indoor and outdoor insects.[3]

People can be exposed to clothianidin from food, air, soil, and water.[2] Certain foods may have some clothianidin in or on them from its use as a pesticide. The EPA regulates how much pesticide residues can be in foods. Adults can be exposed to clothianidin in air or soil from using products that contain clothianidin in their gardens or homes. Young children can exposed to clothianidin while playing in areas that have been treated with products containing the substance.

According to the EPA's Human Health Risk Assessment, clothianidin is persistent in the environment and mobile allowing it to reach groundwater.

Current Standards

Wisconsin does not currently have a groundwater enforcement standard for clothianidin.[4]

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:	0.098 mg/kg-d	(2012)

Oncogenic Potential

EPA Cancer Slope Factor:	N/A	

Guidance Values

None available

Literature Search

Literature Search Dates:	2012 – 2018
Total studies evaluated:	Approximately 260
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 clothianidin.[5]

Health Advisory

The EPA has not established a health advisory for clothianidin.[6]

Drinking Water Concentration (Cancer Risk)

The EPA has not established drinking water concentrations based on cancer risk for clothianidin.[7]

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 clothianidin.[8]

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, the EPA Office of Pesticide Programs conducted a Human Health Risk Assessment as part of the registration of clothianidin.[2] In their assessment, the EPA reviewed a number of studies on the toxicity of clothianidin. They selected a 2-generation reproduction study in rats as the critical study (MRID: 45422715). In this study, 2 generations of rats were exposed to different concentrations of clothianidin in their diet before mating, during mating, and during gestation and lactation: 0, 9.8, 31.2, or 163.4 milligrams per kilogram body weight per day (mg/kg-d) in males and 0, 10.7, 34.3, or 188.8 mg/kg-d in females. Clothianidin affected parental body and thymus weights at the highest dose. Clothianidin also decreased body and thymus weights, delayed sexual maturation, and increased stillbirths in offspring at the two highest doses. The No Observable Adverse Effect Level (NOAEL) from this study was 9.8 mg/kg-d based on effects to the offspring. The EPA selected a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). The EPA's chronic oral reference dose for clothianidin is 0.098 mg/kg-d.

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

Cancer Classification

The EPA and Joint FAO/WHO Meeting on Pesticide Residues (JMPR) have classified clothianidin as not likely to be carcinogenic to humans.[1,2] The international Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of clothianidin.[9]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for clothianidin.[2]

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 clothianidin, we searched for values that been published since 2012 when the EPA published their human health risk assessment. We did not find any relevant guidance values from the EPA, Agency for Toxic Substances and Disease Registry (ATSDR), World Health Organization (WHO), or the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2012. We conducted a search on the National Institutes of Health's PubMed resource for articles published from January 2012 to August 2018 out for studies related to clothianidin toxicity or its effects on a disease state in which information on clothianidin 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 260 studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life, studies evaluating risk from non-mammalian species, and monitoring studies 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.[b] None of the studies met the requirements to be considered a critical study (see Table A-2 for details on the evaluation).

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

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%).[8]

Standard Selection

DHS recommends an enforcement standard of 1,000 µg/L for clothianidin.

There are no federal numbers, no state drinking water standard and no acceptable daily intake from the EPA does for clothiandin. The EPA did not establish a cancer slope factor for clothianidin because they determined that it is not likely to be carcinogenic to humans.

Basis for Enforcement Standard

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

The EPA does have an acceptable daily intake (oral reference dose) for clothianidin. In our review, we did not find any significant technical information that was published since the EPA established their oral reference dose. Therefore, DHS calculated the recommended enforcement standard (ES) using the EPA's oral reference dose for clothianidin, an average body weight of 10 kg, and a water consumption rate of 1 L/d as specified Chapter 160 of Wisconsin Statute.

DHS recommends a preventive action limit of 200 µg/L for clothianidin.

DHS recommends that the preventive action limit for clothianidin be set at 20% of the enforcement standard because clothianidin has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. Clothianidin Toxicity Studies – Additional Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Stress	Mouse	28 d	10, 50, 250 (estimated dose: 0, 8.82, 46.0, 182)	Water gel	**Clothianidin alone** Decreased body weight Increased anxiety-like behavior	LOAEL: 10	Hirano, 2015 ([11])
2-generation	Mouse	2 generation	0.003%, 0.006%, 0.012% Dose changed with changes to diet	Diet	**Parental** Time of movement, number of rearing, rearing time increased. **Offspring** Increased body weight Altered behavioral developmental parameters	N/A	Tanaka, 2012a ([12])
2-generation	Mouse	Gestation and lactation	0.002%, 0.006%, 0.018% Dose changed with changes to diet	Diet	**Offspring** Increased body weight Altered behavioral developmental parameters	N/A	Tanaka, 2012b ([13])
Reproduction	Mouse	GD 1 – PND 14	10, 50	Water Gel	No effect on steroidogenesis in Leydig cells	NOAEL: 50	Yanai, 2017 ([14])

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?
Hirano, 2015	✓	✓	✓	**3**	✓	No
Tanaka, 2012a	✓	✓	✓	**3**	⊘	No
Tanaka, 2012b	✓	✓	✓	**3**	⊘	No
Yanai, 2017	✓	⊘	⊘	**2**	✓	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.

Isoxaflutole | 2022

Substance Overview

Isoxaflutole is a pro-herbicide used to control certain broadleaf and grass weeds in field corn and soybeans.[1] In the environment, isoxaflutole quickly breaks down into isoxaflutole diketonitrile, which is the active herbicide. Isoxaflutole diketonitrile further breaks down into inactive benzoic acid derivatives (Figure A-1. Isoxaflutole degrades into isoxaflutole diketonitrile and benzoic acid-based structural derivatives in the environment).

This document provides the recommended Public Health Enforcement Standard for isoxaflutole.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for isoxaflutole.

DHS recommends a combined enforcement standard of 3 micrograms per liter (µg/L) for isoxaflutole and isoxaflutole diketonitrile. This standard is based on the United States Environmental Protection Agency's (EPA's) cancer slope factor for isoxaflutole.[1] Because we cannot exclude the possibility that isoxaflutole diketonitrile is contributing to toxicity observed in animals dosed with isoxaflutole, DHS recommends a combined enforcement standard for isoxaflutole and isoxaflutole diketonitrile.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

Recommended Standards	
Enforcement Standard:	3 µg/L
Preventive Action Limit:	0.3 µg/L
(Applies to isoxaflutole and isoxaflutole diketonitrile)	

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for isoxaflutole and isoxaflutole diketonitrile be set at 10% of the enforcement standard because the EPA has classified isoxaflutole as a likely human carcinogen and the likelihood that isoxaflutole diketonitrile contributes to these effects.

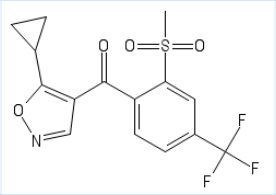
Health Effects

Rats that ate large amounts of isoxaflutole for two years experienced liver, thyroid, eye, nerve, and muscle problems.[1-3] Some rats also had tumors in their liver after eating isoxaflutole for several months to years. In these studies, scientists were not able to determine whether the effects were caused by isoxaflutole or isoxaflutole diketonitrile due to the fast conversion from isoxaflutole to isoxaflutole diketonitrile in the body (Figure A-2. Isoxaflutole is metabolized into isoxaflutole diketonitrile, benzoic acid, and other compounds in the body.).

The EPA has classified isoxaflutole as a likely human carcinogen.[1] Isoxaflutole has not been shown to

cause mutagenic, teratogenic, or interactive effects.[1-3]

Chemical Profile

	Isoxaflutole
Structure:	
IUPAC name:	5-cyclopropyl-4-(2-mesyl-4-trifluoromethylbenzoyl) isoxazole
CAS Number:	141112-29-0
Formula:	$C_{15}H_{12}F_3NO_4S$
Molar Mass:	359.32 g/mol
Synonyms:	RPA 201772

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of two products containing isoxaflutole on corn in Wisconsin.[4]

The main ways that people can be exposed to isoxaflutole and its degradates are from food, soil, and water.[1] Crops like corn or soybeans and certain foods made from corn or soybeans may have some isoxaflutole or its degradates in or on them from its use as an herbicide. The U.S. EPA regulates how much pesticide residue can be in foods.

In soil (dirt), isoxaflutole quickly breaks down (days to hours) into isoxaflutole diketonitrile, which slowly breaks down (months) into a benzoic acid derivative.[5] Isoxaflutole and its degradates can travel through soil into the groundwater.

Current Standards

Wisconsin does not currently have groundwater standards for isoxaflutole.[6]

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:	0.02 mg/kg-d	(2011)
Oncogenic Potential		
EPA Cancer Slope Factor:	0.0114 $(mg/kg\text{-}d)^{-1}$	(2011)
Guidance Values		
JMPR Average Daily Intake:	0.2 mg/kg-d	
Literature Search		
Search Dates:	2011 – 2018	
Total studies evaluated:	Approximately 10	
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 for isoxaflutole.[7]

Health Advisory

The EPA has not established a health advisory for isoxaflutole.[8]

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations based on cancer risk level determinations for isoxaflutole.[9]

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 isoxaflutole.[10]

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, EPA conducted a Human Health Risk Assessment (HHRA) as part of the Registration of Isoxaflutole for use on Soybeans.[1] In their assessment, EPA reviewed a number of studies on the toxicity of isoxaflutole. The EPA selected a chronic/carcinogenicity study in rats as the principal study (MRID: 43904806). In addition to cancer effects described above, liver, thyroid, ocular, and nervous system effects were observed at levels at and above 20 mg/kg-d. The EPA selected a NOAEL of 2 mg/kg-d and applied a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). The EPA's chronic oral reference dose for isoxaflutole is 0.02 mg/kg-d.

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

Cancer Classification

The EPA has classified isoxaflutole as likely to be carcinogenic to humans.[1]

The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of isoxaflutole.[11]

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that isoxaflutole is carcinogenic in mice and rats but is unlikely to pose a carcinogenic risk to humans from the diet due to a probable threshold mechanism and typical environmental exposures being below that threshold.[2,3a]

EPA Cancer Slope Factor

The EPA established a cancer slope factor of 0.0114 $(mg/kg\text{-}d)^{-1}$ for isoxaflutole.[1] They based the cancer slope factor on the results from two chronic/carcinogenicity studies: one in mice and one in rats. In the mouse study, animals were exposed to different concentrations of isoxaflutole (0, 3.2, 64.4, and 977.3 mg/kg-d for males and 0, 4.0, 77.9, and 1161.1 mg/kg-d for females) in their diet for 78 weeks (MRID: 43904807). A significant increase in liver tumors (adenomas and carcinomas) was observed in both sexes at the highest dose. In the rat study, animals were exposed to different concentrations of isoxaflutole (0.5, 2, 20, 500 milligrams per kilogram of body weight per day (mg/kg-d)) in their diet for 2 years (MRID: 43904806). The highest dose of isoxaflutole caused a significant increase in the percent of male and female rats with liver tumors (adenomas and carcinomas) and a significant increase in the percent of male rats with thyroid tumors.

The EPA also considered whether a non-threshold model could be used for the risk assessment.[12] Because disturbances in the thyroid hormone balance have been shown to cause tumor development and the development of these types of tumors involves a threshold, the EPA recommended using the threshold approach for the thyroid tumors and established a No Observable Adverse Effect Level (NOAEL) of 20 mg/kg-d for thyroid tumors. For the liver tumors, the EPA concluded that the information submitted by the product manufacturer as part of the review was suggestive of a threshold but not convincing and, therefore, established the cancer slope factor.

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.

a Isoxaflutole diketonitrile works as an herbicide by blocking the enzyme 4-hydroxylphenylpyruvate dioxygenase (HPPD). In humans, the enzyme HPPD is needed to regulate the level of tyrosine (an amino acid) in the blood. By inhibiting HPPD activity in the body, scientists believe that isoxaflutole and related compounds can increase the level of tyrosine in the blood resulting in secondary toxic effects like eye, development, liver, and kidney toxicity. The JMPR concluded that the mode of action for the liver and thyroid tumors observed in rodents were related to effects on tyrosine levels and, therefore, involve a threshold.

Guidance Values

For isoxaflutole, we searched for values that been published since 2011 when the EPA published their human health risk assessment. We found a relevant guidance value from the JMPR.

JMPR Average Daily Intake

The JMPR recommended a chronic oral reference dose of 0.02 mg/kg-d in 2013 as part of their review of the human health toxicity information for isoxaflutole.[2,3] They based this value on the same study and effects used by the EPA to establish their oral reference dose.

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2012. We conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2011 to August 2018 related to isoxaflutole toxicity or its effects on a disease state in which information on exposure or dose was included as part of the study.[b] 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 10 studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life and studies not evaluating health risks from further review. After applying these exclusion criteria, we did not locate any key studies.

Standard Selection

DHS recommends a combined enforcement standard of 3 µg/L for isoxaflutole and isoxaflutole diketonitrile.

The EPA does not have a maximum contaminant level or health advisory for isoxaflutole.

The EPA has classified isoxaflutole as likely to be carcinogenic to humans. While the EPA did not calculate any drinking water concentration at specified cancer risk levels, the slope factor for isoxaflutole can be used to determine a drinking water concentration.

Therefore, DHS recommends using EPA's cancer slope

Basis for Enforcement Standard

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

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

factor to establish the enforcement standard (ES) for isoxaflutole. To do this, we used a cancer risk of 1 in 1,000,000, as required by Ch. 160, Wis. Stats., and, per EPA's latest recommendations, a body weight of 80 kg and water consumption rate of 2.4 L/d.[13]

Because isoxaflutole quickly degrades into isoxaflutole diketonitrile in the environment (hours to days) and it is quickly metabolized into isoxaflutole diketonitrile in the body (hours to days), we cannot exclude the possibility that isoxaflutole diketonitrile is contributing to toxicity observed in animals dosed with isoxaflutole. Therefore, DHS recommends a combined enforcement standard for isoxaflutole and isoxaflutole diketonitrile.

DHS recommends a preventive action limit of 0.3 µg/L for isoxaflutole and isoxaflutole diketonitrile.

DHS recommends that the preventive action limit for these compounds be set at 10% of the enforcement standard because EPA has classified isoxaflutole as likely to be carcinogenic to humans. Isoxaflutole has not been shown to have mutagenic, teratogenic, or interactive effects.[1,2]

Updated by Amarilys Gonzalez Vazquez, Ph.D and Sarah Yang, Ph.D. – January 2022

Wisconsin Department of Health Services

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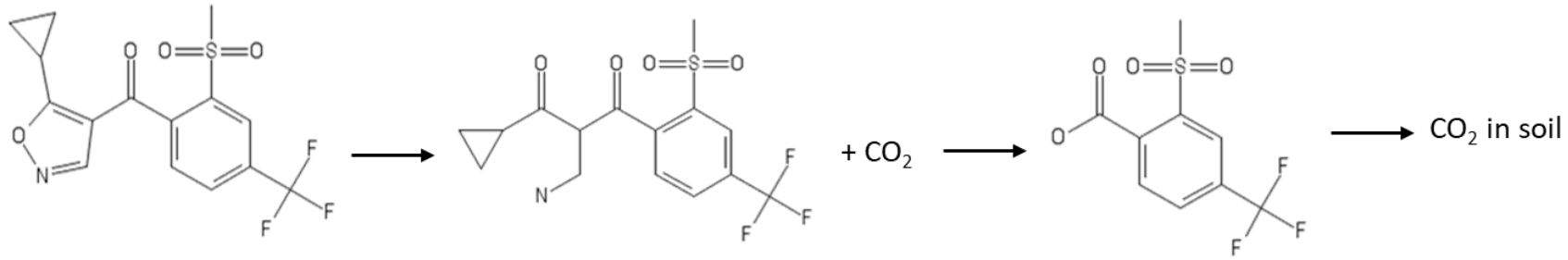
Appendix A: Isoxaflutole Degradation

Figure A-1. Isoxaflutole degrades into isoxaflutole diketonitrile and benzoic acid-based structural derivatives in the environment



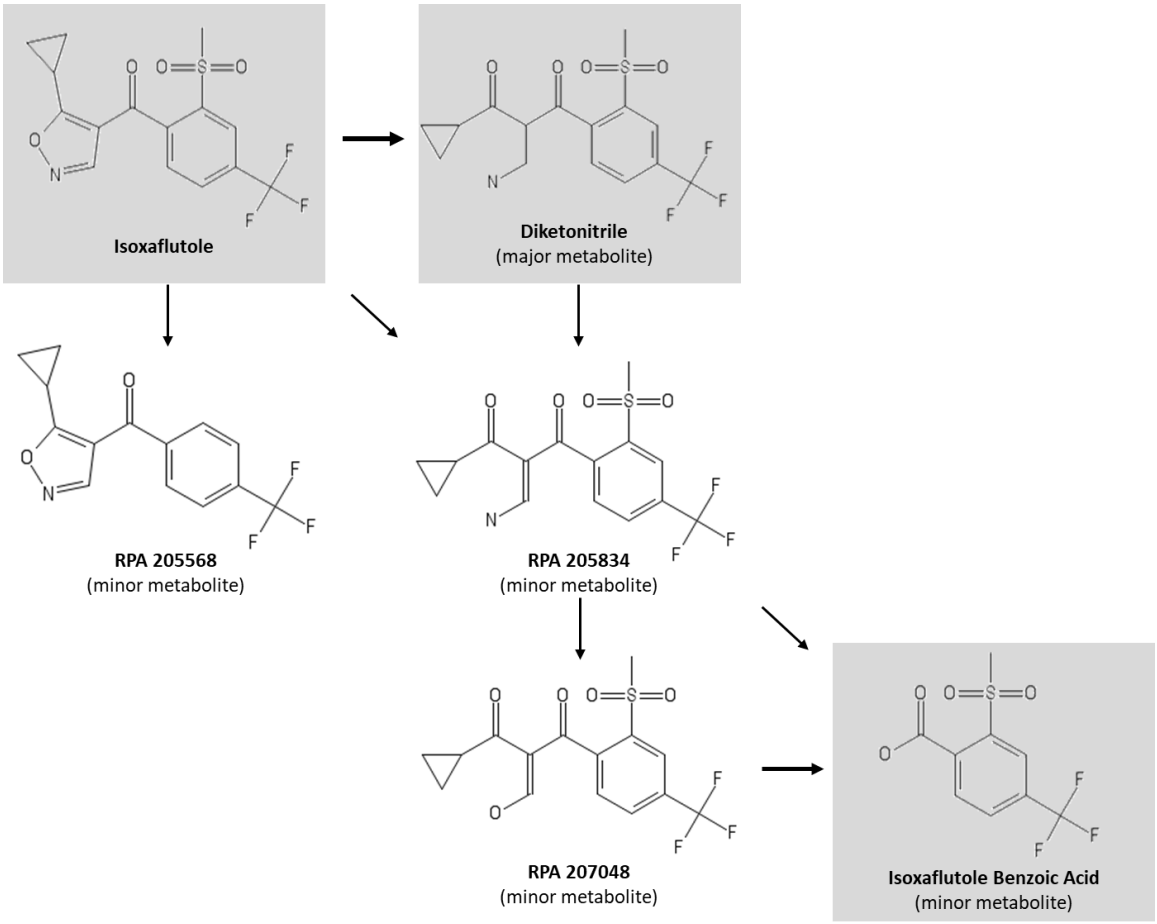
Isoxaflutole
(Pro-Herbicide)

Diketonitrile
(Herbicide)

Isoxaflutole
Benzoic Acid

Isoxaflutole is a pro-herbicide which is designed to degrade into the active herbicide, diketonitrile, in the environment. Transformation from isoxaflutole to diketonitrile occurs quickly (hours to days) while transformation from diketonitrile to the benzoic acid derivative takes longer (weeks to months).[2]

Figure A-2. Isoxaflutole is metabolized into isoxaflutole diketonitrile, benzoic acid, and other compounds in the body.



In the body, isoxaflutole is metabolized (broken down) into several different compounds. The half-life of isoxaflutole and/or its metabolites in rats is about 60 hours. After administration of isoxaflutole in animals, the major component identified in urine, feces and liver is diketonitrile and isoxaflutole benzoic acid.[2]

Isoxaflutole Diketonitrile | 2019

Substance Overview

Isoxaflutole diketonitrile (DKN) is a breakdown product of the pro-herbicide isoxaflutole. Isoxaflutole diketonitrile is the active herbicide of the formulation and is used to control certain broadleaf and grass weeds in field corn and soybeans.[1] In the environment, isoxaflutole quickly breaks down into isoxaflutole diketonitrile, which then further degrades into benzoic acid derivatives (Figure A-1. Isoxaflutole degrades into diketonitrile-and benzoic acid-based structural derivatives in the environment).

This document provides the recommended Public Health Enforcement Standard for isoxaflutole diketonitrile.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for isoxaflutole diketonitrile.

DHS recommends a combined enforcement standard of 3 micrograms per liter (µg/L) for isoxaflutole and isoxaflutole diketonitrile. This standard is based on the United States Environmental Protection Agency's (EPA's) cancer slope factor for isoxaflutole.[1] Because we cannot exclude the possibility that isoxaflutole diketonitrile is contributing to toxicity observed in animals dosed with isoxaflutole, DHS recommends a combined enforcement standard for isoxaflutole and isoxaflutole diketonitrile.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

Recommended Standards	
Enforcement Standard:	3 µg/L
Preventive Action Limit:	0.3 µg/L
(Applies to isoxaflutole and isoxaflutole diketonitrile)	

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for isoxaflutole and isoxaflutole diketonitrile be set at 10% of the enforcement standard because the EPA has classified isoxaflutole as a likely human carcinogen and the likelihood that isoxaflutole diketonitrile contributes to these effects.

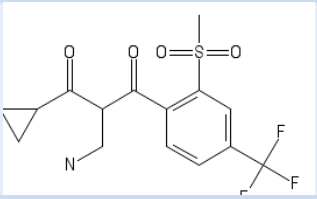
Health Effects

Rats that ate large amounts of isoxaflutole for two years experienced liver, thyroid, eye, nerve, and muscle problems.[1-3] Some rats also had tumors in their liver after eating isoxaflutole for several months to years. In these studies, scientists were not able to determine whether the effects were caused by isoxaflutole or isoxaflutole diketonitrile due to the fast conversion from isoxaflutole to isoxaflutole diketonitrile in the body (Figure A-2. Isoxaflutole is metabolized into diketonitrile, benzoic acid, and

other compounds in the body.).

The EPA has classified isoxaflutole as a likely human carcinogen.[1] Isoxaflutole has not been shown to cause mutagenic, teratogenic, or interactive effects.[1-3]

Chemical Profile

	Isoxaflutole Diketonitrile
Structure:	
IUPAC name:	1-(2-mesylsulfonyl-4-trifluoromethylphenyl)-2-cyano-3-cyclopropyl-propane-1,3-dione
CAS Number:	143701-75-1
Formula:	$C_{15}H_{12}F_3NO_4S$
Molar Mass:	359.32 g/mol
Synonyms:	RPA 202248

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of two products containing isoxaflutole on corn in Wisconsin.[4]

The main ways that people can be exposed to isoxaflutole diketonitrile are from food, soil, and water.[1] Crops like corn or soybeans and certain foods made from corn or soybeans may have some isoxaflutole diketonitrile in or on them from the use of isoxaflutole as a pro-herbicide.

In soil (dirt), isoxaflutole diketonitrile is formed quickly (days to hours) when isoxaflutole breaks down breaks down.[5] Isoxaflutole diketonitrile can travel through soil into the groundwater.

Current Standards

Wisconsin does not currently have groundwater standards for isoxaflutole diketonitrile.[6]

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
Guidance Values	
JMPR Average Daily Intake:	N/A
Literature Search	
Search Dates:	2011 – 2018
Total studies evaluated:	5
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 for isoxaflutole diketonitrile.[7]

Health Advisory

The EPA has not established a health advisory for isoxaflutole diketonitrile.[8]

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations based on cancer risk level determinations for isoxaflutole diketonitrile.[9]

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 isoxaflutole diketonitrile.[10]

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

While the EPA does not have a chronic oral reference dose for isoxaflutole diketonitrile, they proposed pesticide tolerances for the sum of isoxaflutole and isoxaflutole diketonitrile based on the toxicity information for isoxaflutole in 2011.[1a]

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

Cancer Classification

The EPA has not evaluated the carcinogenicity of isoxaflutole diketonitrile.[1] However, they have classified isoxaflutole as likely to be carcinogenic to humans.[1]

The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of isoxaflutole diketonitrile.[11]

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) has not evaluated the carcinogenicity of isoxaflutole diketonitrile.[2] However, they concluded that isoxaflutole is carcinogenic in mice and rats.[2,3]

EPA Cancer Slope Factor

a A pesticide tolerance is the maximum amount of a pesticide that is allowed by EPA to remain in or on a food.[1] To set the tolerance, EPA conducts dietary risk assessments to estimate the exposure of different populations (adults, infants, children, pregnant women) to the pesticide from food and selects a tolerance level to protect from potential health effects caused by pesticide residues.

The EPA has not established a cancer slope factor for isoxaflutole diketonitrile.[1] However, they did establish a cancer slope factor for isoxaflutole as part of their Human Health Risk Assessment in 2011.[1]

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 isoxaflutole diketonitrile, we searched for values that been published since 2011 when the EPA published their human health risk assessment. We found relevant information from the JMPR.

JMPR Average Daily Intake

While the JMPR did not establish an average daily intake for isoxaflutole diketonitrile as part of their review of isoxaflutole in 2013, they concluded the residue definition for isoxaflutole should include isoxaflutole diketonitrile because it is structurally similar to isoxaflutole and the possibility of a similar, and therefore additive, toxic mechanism could not be excluded.[2,3]

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2011. We conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2011 to August 2018 related to isoxaflutole diketonitrile toxicity or its effects on a disease state in which information on exposure or dose was included as part of the study.[b] 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.

Five studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life and studies not evaluating health risks from further review. After applying these exclusion criteria, we did not locate any key studies.

b he following search terms were used in the literature review:
Title/abstract: Isoxaflutole diketonitrile OR "RPA 202248" OR "RPA202248"
Subject area: toxicology OR cancer
Language: English

Standard Selection

DHS recommends a combined enforcement standard of 3 µg/L for isoxaflutole and isoxaflutole diketonitrile.

The EPA does not have a maximum contaminant level, health advisory, or drinking water concentration at specified cancer risk levels for isoxaflutole diketonitrile.

Basis for Enforcement Standard

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

Because isoxaflutole is quickly metabolized into isoxaflutole diketonitrile in the body (hours to days), we cannot exclude the possibility that isoxaflutole diketonitrile is contributing to toxicity observed in animals dosed with isoxaflutole. Chapter 160 of Wisconsin Statute requires that we considered the known chronic or subchronic effects of exposure to similar or related compounds when setting a groundwater standard. Therefore, DHS recommends a combined enforcement standard for isoxaflutole and isoxaflutole diketonitrile.

Since the EPA has classified isoxaflutole as likely to be carcinogenic to humans and has established a cancer slope factor for isoxaflutole, DHS recommends using EPA's cancer slope factor to establish the enforcement standard (ES) for isoxaflutole. To do this, we used a cancer risk of 1 in 1,000,000, as required by Ch. 160, Wis. Stats., and, per EPA's latest recommendations, a body weight of 80 kg and water consumption rate of 2.4 L/d.[12]

DHS recommends a preventive action limit of 0.3 µg/L for isoxaflutole and isoxaflutole diketonitrile.

DHS recommends that the preventive action limit for these compounds be set at 10% of the enforcement standard because EPA has classified isoxaflutole as likely to be carcinogenic to humans. Isoxaflutole has not been shown to have mutagenic, teratogenic, or interactive effects.[1,2]

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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3. JMPR. Isoxaflutole. In: (JMPR) JFWMoPR, ed2013.
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7. USEPA. National Primary Drinking Water Regulations. 2018; https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations.
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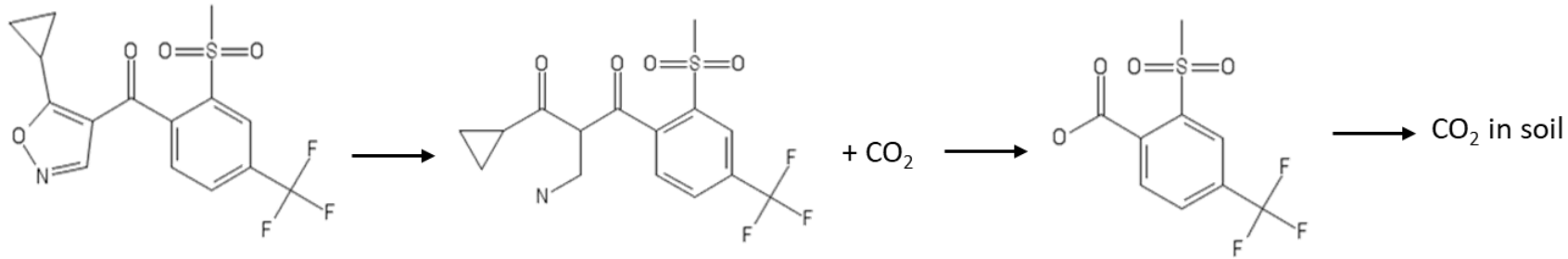
10. WIDNR. Safe Drinking Water In: Resources WDoN, ed. *Chapter NR 809*2018.
11. IARC. List of Classification, Volumes 1-123. 2018; https://monographs.iarc.fr/list-of-classifications-volumes/. Accessed May 17, 2019.
12. USEPA. EPA's Exposure Factors handbook. 2019; https://www.epa.gov/expobox/about-exposure-factors-handbook?_sm_au_=iHV5B5HjsMP7lBnr.

Appendix A: Isoxaflutole Degradation

Figure A-1. Isoxaflutole degrades into diketonitrile-and benzoic acid-based structural derivatives in the environment



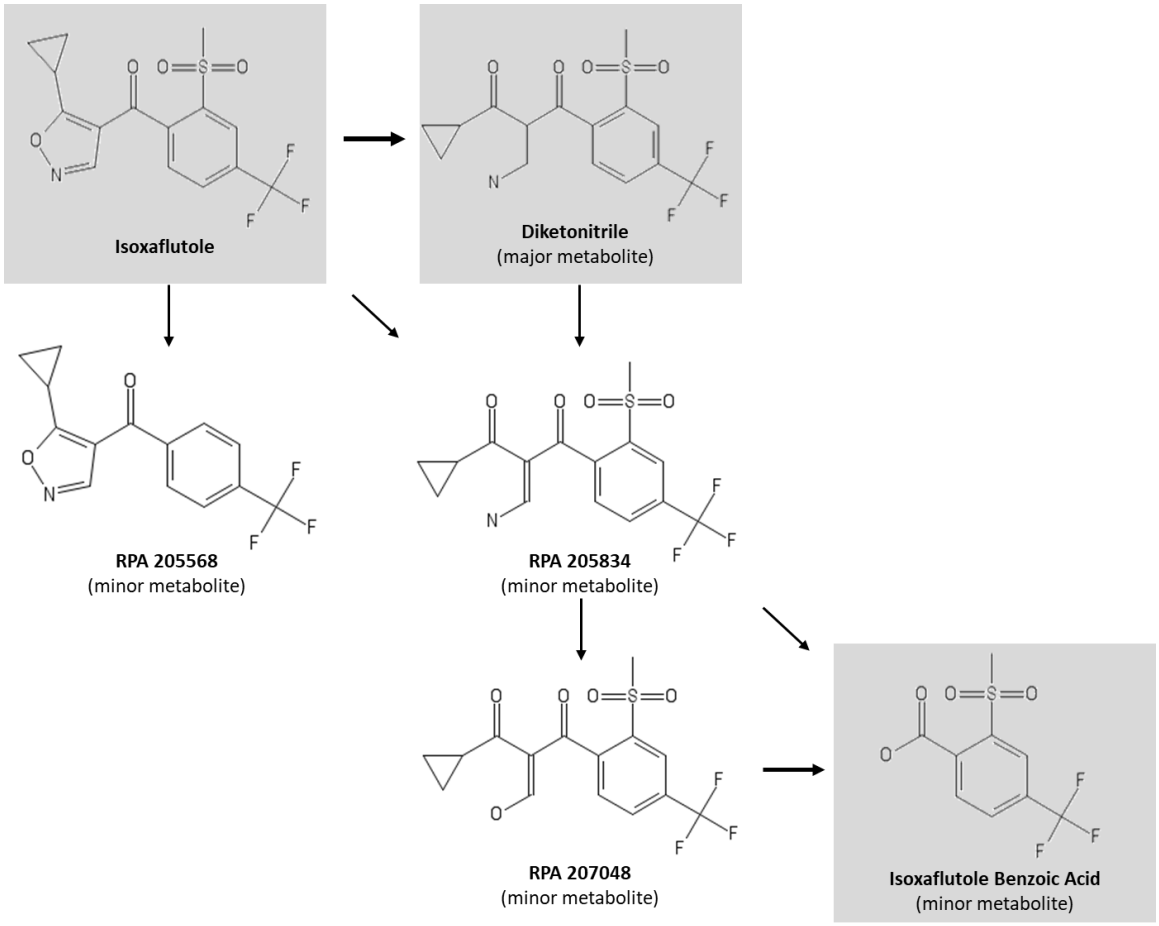
Isoxaflutole
(Pro-Herbicide)

Diketonitrile
(Herbicide)

Isoxaflutole
Benzoic Acid

Isoxaflutole is a pro-herbicide which is designed to degrade into the active herbicide, diketonitrile, in the environment. Transformation from isoxaflutole to diketonitrile occurs quickly (hours to days) while transformation from diketonitrile to the benzoic acid derivative takes longer (weeks to months).[2]

Figure A-2. Isoxaflutole is metabolized into diketonitrile, benzoic acid, and other compounds in the body.



In the body, isoxaflutole is metabolized (broken down) into several different compounds. The half-life of isoxaflutole and/or its metabolites in rats is about 60 hours. After administration of isoxaflutole in animals, the major component identified in urine, feces and liver is diketonitrile and isoxaflutole benzoic acid.[2]

Isoxaflutole Benzoic Acid | 2019

Substance Overview

Isoxaflutole benzoic acid is a breakdown product of the pro-herbicide, isoxaflutole. Isoxaflutole is used to control certain broadleaf and grass weeds in field corn and soybeans.[1] In the environment, isoxaflutole quickly breaks down into isoxaflutole diketonitrile, which then further degrades into benzoic acid derivatives (Figure A-1. Isoxaflutole degrades into diketonitrile-and benzoic acid-based structural derivatives in the environment).

This document provides the recommended Public Health Enforcement Standard for isoxaflutole benzoic acid.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for isoxaflutole benzoic acid.

DHS recommends an enforcement standard of 800 micrograms per liter (µg/L) for isoxaflutole benzoic acid. The recommended standard is based on a study that found that isoxaflutole benzoic acid decreased weight gain and feed consumption in pregnant animals.

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for isoxaflutole benzoic acid be set at 20% of the enforcement standard because it has not been shown to cause mutagenic, teratogenic, or interactive effects

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

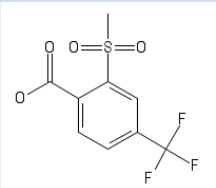
Recommended Standards	
Enforcement Standard:	800 µg/L
Preventive Action Limit:	160 µg/L
(Applies to isoxaflutole benzoic acid)	

Health Effects

Compared to experiments with isoxaflutole, isoxaflutole benzoic acid has been shown to be much less toxic.[1-3] High levels of isoxaflutole benzoic acid caused decreased weight gain and food consumption, increased salivation, and changes in clinical chemistry markers in rats. [1-3]

Isoxaflutole benzoic acid has not been shown to cause mutagenic, teratogenic, or interactive effects.[1-3]

Chemical Profile

	Isoxaflutole Benzoic Acid
Structure:	
IUPAC name:	2-Methylsulfonyl-4-trifluoromethylbenzoic acid
CAS Number:	142994-06-7
Formula:	$C_9H_7F_3O_4S$
Molar Mass:	268.21 g/mol
Synonyms:	RPA 203328

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of two products containing isoxaflutole on corn in Wisconsin.[4]

The main ways that people can be exposed to isoxaflutole benzoic acid are from food, soil, and water.[1] Crops like corn or soybeans and certain foods made from corn or soybeans may have some isoxaflutole benzoic acid in or on them from the use of isoxaflutole as a pro-herbicide.

In soil (dirt), isoxaflutole quickly breaks down (days to hours) into isoxaflutole diketonitrile which slowly breaks down (months) into a benzoic acid derivative.[5] Isoxaflutole benzoic acid can travel through soil into the groundwater.

Current Standards

Wisconsin does not currently have groundwater standards for isoxaflutole benzoic acid.[6]

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
Guidance Values	
JMPR Average Daily Intake:	N/A
Literature Search	
Search Dates:	2011 – 2018
Total studies evaluated:	2
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 for isoxaflutole benzoic acid.[7]

Health Advisory

The EPA has not established a health advisory for isoxaflutole benzoic acid.[8]

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations based on cancer risk level determinations for isoxaflutole benzoic acid.[9]

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 isoxaflutole benzoic acid.[10]

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 isoxaflutole benzoic acid.[1]

As part of their Human Health Risk Assessment for Isoxaflutole, the EPA reviewed a handful of studies on the toxicity of isoxaflutole benzoic acid (Table B-2). While these studies were not used by EPA to set an oral reference dose for isoxaflutole benzoic acid, one meets our criteria to be considered a critical study for use in establishing an acceptable daily intake (see the *Literature Search* section below for a summary of this study).

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

Cancer Classification

The EPA has not evaluated the carcinogenicity of isoxaflutole benzoic acid.[1]

The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of isoxaflutole benzoic acid.[11]

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) has not evaluated the carcinogenicity of isoxaflutole benzoic acid.[2,3]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for isoxaflutole benzoic acid.[1]

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 isoxaflutole diketonitrile, we searched for values that been published since 2011 when the EPA published their human health risk assessment. We found relevant information from the JMPR.

JMPR Average Daily Intake

While the JMPR has not established an average daily intake for isoxaflutole benzoic acid, they also reviewed a handful of studies on the toxicity of isoxaflutole benzoic acid (Table B-2).[2,3] While these studies were not used by JMPR to set an average daily intake for isoxaflutole benzoic acid, one meets our criteria to be considered a critical study for use in establishing an acceptable daily intake (see the *Literature Search* section below for a summary of this study).

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2011. We conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2011 to August 2018 related to isoxaflutole diketonitrile 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. Two studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life and studies not evaluating health risks from further review. After applying these exclusion criteria, we did not locate any key studies.

We also evaluated the four studies that EPA and JMPR considered in their human risk assessment using these same criteria (as described in the *EPA Oral Reference Dose* and *JMPR Average Daily Intake* sections above). 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]

a The following search terms were used in the literature review:
Title/abstract: Isoxaflutole benzoic acid OR "RPA 203328" OR "RPA203328"
Subject area: toxicology OR cancer
Language: English
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

Critical Study

Repetto-Larsay, 1999

Repetto-Larsay evaluated the effects of exposure to isoxaflutole benzoic acid on development and overall health in female rats.[13] Pregnant rats were exposed to 75, 250, or 750 mg/kg-d of isoxaflutole benzoic acid by gavage from gestation days 6 to 20. They found that the two highest doses of isoxaflutole benzoic acid decreased weight gain and feed consumption in the pregnant animals. They did not observe any effects on development at any of the doses tested.

Standard Selection

DHS recommends an enforcement standard of 800 µg/L for isoxaflutole benzoic acid.

There are no federal numbers for isoxaflutole benzoic acid. Additionally, there is no drinking water standard for isoxaflutole benzoic acid in Ch. NR 809, Wisc Admin Code, and the EPA does not have an oral reference dose for this degradate.

Basis for Enforcement Standard

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

Although the EPA did not include isoxaflutole benzoic acid in the pesticide tolerances for isoxaflutole, several studies have been conducted with the substance. One of these studies meets DHS's definition of a critical study. Because these studies indicate that isoxaflutole benzoic acid is less toxic than isoxaflutole, DHS recommends setting a separate standard for isoxaflutole benzoic acid using the identified critical study and the procedures in s. 160.13(2).

To calculate the acceptable daily intake, DHS used information from a developmental toxicity study.[13] From this study, we selected a NOAEL of 75 mg/kg-d and a total uncertainty factor of 100 to account for differences between research animals and people (10) and differences among people (10). To determine the recommended ES, DHS used the acceptable daily intake and exposure parameters specified in Ch. 160, Wis. Stats.: a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%.

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%).[17]

DHS recommends a preventive action limit of 160 µg/L for isoxaflutole benzoic acid.

DHS recommends that the preventive action limit for isoxaflutole benzoic acid be set at 20% of the enforcement standard because it has not been shown to have carcinogenic, mutagenic, teratogenic or interactive effects.[1-3]

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

References

1. USEPA. Isoxaflutole. Section 3 Registration for Use on Soybeans. Human-Health Risk Assessment. In: Preventation OoCSaP, ed. Vol EPA-HQ-OPP-2010-08452011.
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3. JMPR. Isoxaflutole. In: (JMPR) JFWMoPR, ed2013.
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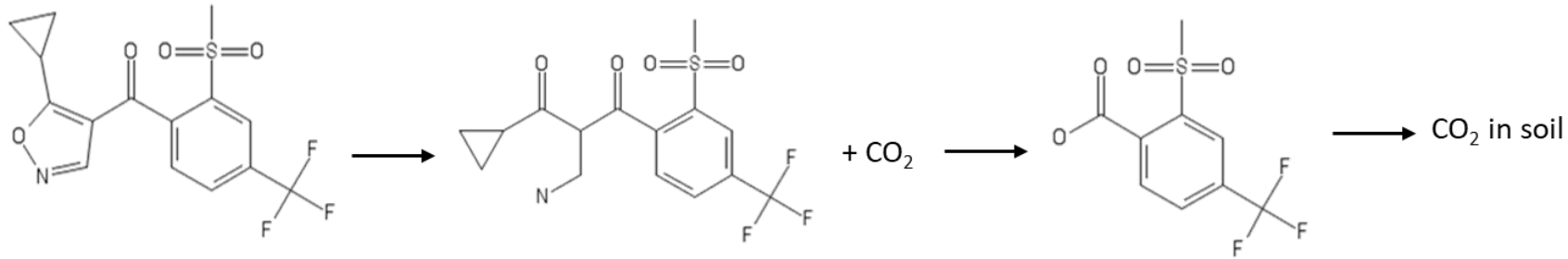
15. Bigot D. SRPA 203328: 90-day toxicity study in the rat by dietary administration. In. *Rhone-Poulenc Agrochimie*. Sophia Antipolis Cedex, France1998:MRID: 45655903.
16. Dange M. RPA 203328 – exploratory 14-day toxicity study in the rat by gavage. In: Recherche R-PSACd, ed. Sophia Antipolis, France1994.

Appendix A: Isoxaflutole Degradation

Figure A-1. Isoxaflutole degrades into diketonitrile-and benzoic acid-based structural derivatives in the environment



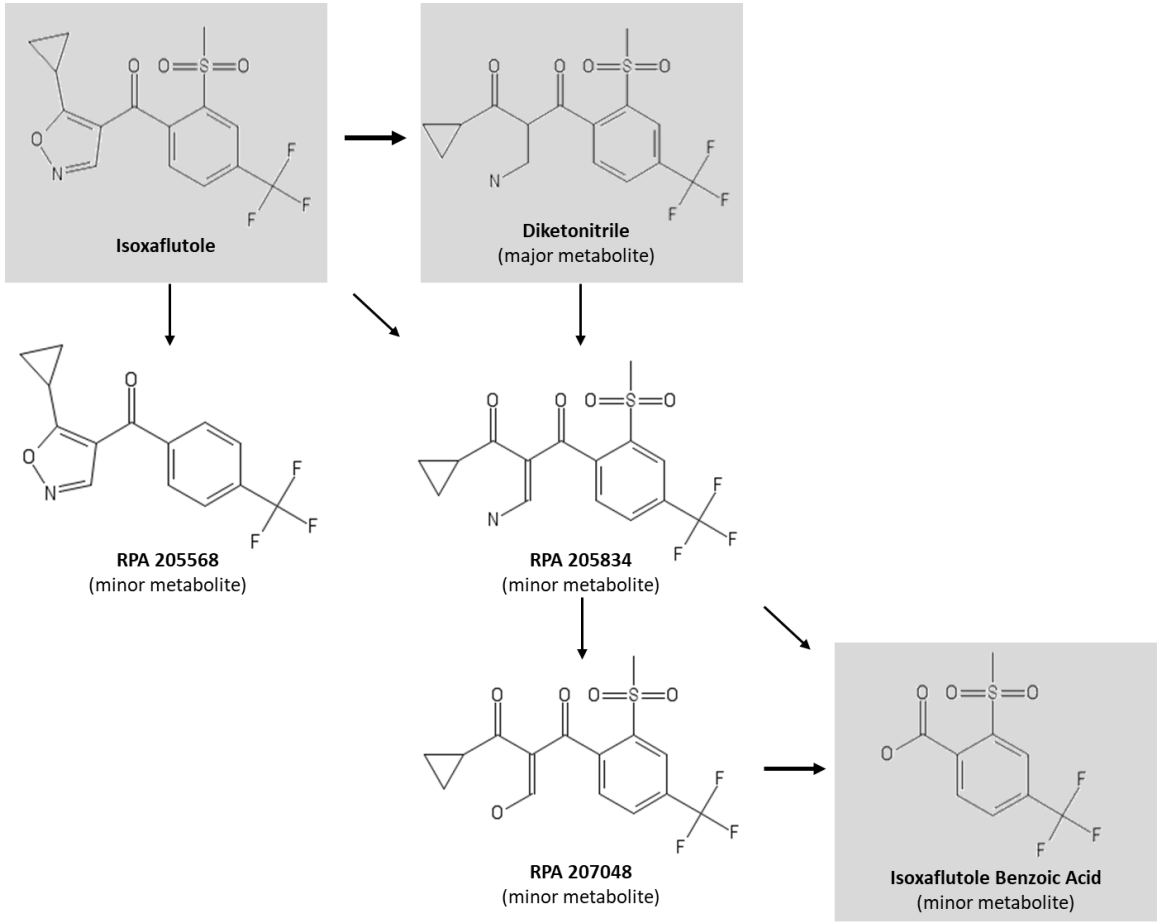
Isoxaflutole
(Pro-Herbicide)

Diketonitrile
(Herbicide)

Isoxaflutole
Benzoic Acid

Isoxaflutole is a pro-herbicide which is designed to degrade into the active herbicide, diketonitrile, in the environment. Transformation from isoxaflutole to diketonitrile occurs quickly (hours to days) while transformation from diketonitrile to the benzoic acid derivative takes longer (weeks to months).[2]

Figure A-2. Isoxaflutole is metabolized into diketonitrile, benzoic acid, and other compounds in the body.



In the body, isoxaflutole is metabolized (broken down) into several different compounds. The half-life of isoxaflutole and/or its metabolites in rats is about 60 hours. After administration of isoxaflutole in animals, the major component identified in urine, feces and liver is diketonitrile and isoxaflutole benzoic acid.[2]

Appendix B: Isoxaflutole Benzoic Acid Toxicity

Table B-1. Isoxaflutole benzoic acid studies evaluated by EPA and JMPR[1,2]

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
28-d oral range finding	Rat	28 d	Males: 11.14, 37.57, 377.0, 1118 Females: 12.68, 42.70, 421.5, 1268.7	Diet	No effect	NOAEL: 1118	Dange, 1995 (MRID: 43904813) ([14])
90-day oral	Rat	90 d	Males: 73.21, 306.1, 768.9 Females: 93.10, 371.4, 952.4	Diet	No effect	NOAEL: 768.9	Bigot, 1998 (MRID: 45655903) ([15])
Developmental	Rat	GD 6 -20	75, 250, 750	Gavage	**Maternal** Decreased weight gain and feed consumption **Developmental** No effects on fetal development at all doses	**Maternal** NOAEL: 75 LOAEL: 250 **Developmental** NOAEL: 750	Repetto-Larsay, 1999 (MRID: 45655906) ([13])
Short-term	Rat	14 d	30, 100, 300, 1000	Gavage	Increased salivation Slightly decreased weight gain Changes in hematology and clinical chemistry parameters	NOAEL: 30 LOAEL: 300	Dange, 1994 ([16])

Table B-2. Critical study selection for isoxaflutole benzoic acid

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity value identifiable?	Critical study?
Dange, 1995 (MRID: 43904813)	⦸	⦸	⦸	**4**	✓	No
Bigot, 1998 (MRID: 45655903)	✓	⦸	⦸	**3**	✓	No
Repetto-Larsay, 1999 (MRID: 45655906)	✓	✓	✓	**3**	✓	**Yes**
Dange, 1994	⦸	✓	✓	**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.

Thiencarbazone-methyl | 2019

Substance Overview

Thiencarbazone-methyl is a triazolone herbicide used to control weeds on corn, wheat, turf, and garden plants.[1] Triazolone pesticides work by blocking an enzyme needed for the development of chlorophyll in the plant.

Recommendations

Wisconsin does not currently have a NR140 Groundwater Quality Public Health Enforcement Standard for thiencarbazone-methyl.

DHS recommends an enforcement standard of 10 mg/L for thiencarbazone-methyl. The recommended standard is based on the United States Environmental Protection Agency's (EPA's) chronic oral reference dose for thiencarbazone-methyl.[1]

DHS recommends that the preventive action limit for thiencarbazone-methyl be set at 20% of the enforcement standard because thiencarbazone-methyl has not been shown to be carcinogenic, mutagenic, teratogenic, or interactive effects.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

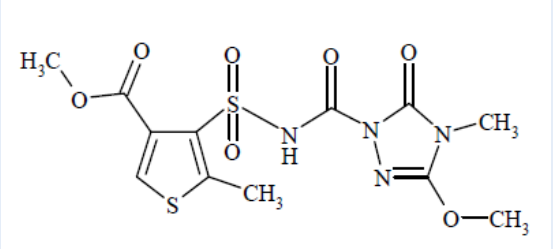
Recommended Standards	
Enforcement Standard:	10 mg/L
Preventive Action Limit:	2 mg/L

Health Effects

What we know about the health effects of thiencarbazone-methyl comes from studies with laboratory animals.[1] Animals that ate large amounts of thiencarbazone-methyl for long periods of time experienced problems with their kidney, bladder, and urinary tract.

The EPA determined that thiencarbazone-methyl is not likely to be carcinogenic to humans at levels needed to cause the kidney, bladder, and urinary tract problems.[1] Thiencarbazone-methyl has not been shown to have mutagenic, teratogenic, or interactive effects.

Chemical Profile

	Thiencarbazone-methyl
Structure:	
CAS Number:	317815-83-1
Formula:	$C_{12}H_{14}N_4O_7S_2$
Molar Mass:	390.385 g/mol
Synonyms:	Methyl 4-[(4,5-dihydro-3-methoxy-4-methyl-5-oxo-1H-1,2,4-triazol-1-yl)--carbonylsulfamoyl]-5- methylthiophene-3-carboxylate

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved seven products containing thiencarbazone-methyl for controlling a variety of weeds.

People can be exposed to thiencarbazone-methyl from food, air, soil, and water.[1] Certain foods may have some thiencarbazone-methyl in or on them from its use as a pesticide. The EPA regulates how much pesticide residues can be in foods. Adults can be exposed to thiencarbazone-methyl in air or soil from using products that contain thiencarbazone-methyl in their gardens. Young children can be exposed to thiencarbazone-methyl while playing in areas that have been treated with products containing thiencarbazone-methyl.

Thiencarbazone-methyl has low water solubility and a high affinity to bind to soil. [1] Thiencarbazone-methyl can break down quickly (days to months) in the soil. However, thiencarbazone-methyl still has the potential to move through the soil and enter groundwater.

Current Standard

Wisconsin does not currently have groundwater enforcement standards for thiencarbazone-methyl.[2]

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	1.17 mg/kg-d	(2008)

Oncogenic Potential

EPA Cancer Slope Factor:	N/A	

Guidance Values

None available

Literature Search

Search Dates:	2008 – 2019
Total studies evaluated:	5
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 for thiencarbazone-methyl.[3]

Health Advisory:

The EPA has not established a health advisory for thiencarbazone-methyl.[4]

Drinking Water Concentration (Cancer Risk)

The EPA has not established concentrations based on cancer risk for thiencarbazone-methyl.[1]

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 thiencarbazone-methyl.[5]

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 2008, the EPA Office of Pesticide Programs released a Human Health Risk Assessment (HHRA) as part of the registration of thiencarbazone-methyl.[1] The EPA selected the chronic study in dogs as the critical study (MRID: 47040133). In this study, dogs were exposed to increasing concentrations of thiencarbazone-methyl (0, 29, 117, or 179 milligrams thiencarbazone-methyl per kilogram body weight per day or mg/kg-d in males and 0, 27, 127, or 200 mg/kg-d in females) in their diet for 2 years. Thiencarbazone-methyl caused urothelial effects (transitional cell hyperplasia, slight congestion, hemorrhage, inflammation, calculus, and ulceration in the bladder at high doses). The EPA selected a NOAEL of 117 mg/kg-d based on these effects. The EPA selected a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10) to give a chronic oral reference dose of 1.17 mg/kg-d for thiencarbazone-methyl.

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

Cancer Classification

The EPA has determined that thiencarbazone-methyl is not likely to be carcinogenic to humans at levels needed to cause the kidney, bladder, and urinary tract problems.[1]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for thiencarbazone-methyl.[1]

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 thiencarbazone-methyl, we searched for values that been published since 2008 when the EPA published their human health risk assessment. We found a relevant guidance value from the European Food Safety Authority (EFSA).

EFSA Acceptable Daily Intake

In 2013, the EFSA reviewed the human health toxicity information for thiencarbazone-methyl and recommended an acceptable daily intake of 0.23 mg/kg-d. The EFSA selected a 2 year study in rats as the critical study (MRID: 47070134).[6] In this study, rats were exposed to different concentrations of thiencarbazone-methyl (0, 22.8, 115.2, and 234 mg/kg-d for males and 0, 29.9, 152.9, 313.4 mg/kg-d for females). They selected a NOAEL of 22.8 mg-kg-d based on kidney and urinary bladder irritation, inflammation and hyperplasia associated with urolithiasis at levels greater than this. They applied a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

Literature Search

The most recent federal number for thiencarbazone-methyl is the EPA's oral reference dose which was published in 2008. Therefore, our literature review focused on the scientific literature published after the review by the EPA in 2008. A search on the National Institutes of Health's PubMed resource for articles published from January 2008 to February 2019 was carried out looking for studies related to thiencarbazone-methyl toxicity or its effects on a disease state in which information on thiencarbazone-methyl 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.

Five studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life, studies evaluating risk from non-mammalian species, and monitoring studies from further review. After applying these exclusion criteria, we did not locate any key studies.

1 The following search terms were used in the literature review:
Title/abstract: Thiencarbazone-methyl
Subject area: toxicology AND cancer
Language: English

Standard Selection

DHS recommends an enforcement standard of 10 mg/L for thiencarbazone-methyl.

There are no federal numbers for thiencarbazone-methyl. The EPA did not establish a cancer slope factor for thiencarbazone-methyl because they determined that is not likely to be carcinogenic to humans. Additionally, there is no drinking water standard for thiencarbazone-methyl in NR 809, Wisc. Admin Code.

Basis for Enforcement Standard

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

The EPA has an acceptable daily intake (oral reference dose) of 1.17 mg/kg-d for thiencarbazone-methyl. While the ESFA established an acceptable daily intake of 0.23 mg/kg-d for thiencarbazone-methyl in 2013, the critical study that they selected was also reviewed by EPA and cannot be considered significant new technical information. Therefore, DHS calculated the recommended enforcement standard (ES) using the EPA's oral reference dose for thiencarbazone-methyl, an average body weight of 10 kg, and a water consumption rate of 1 L/d as specified in specified Chapter 160 of Wisconsin Statute.

DHS recommends a preventive action limit of 2 mg/L for thiencarbazone-methyl.

DHS recommends that the preventive action limit for thiencarbazone-methyl be set at 20% of the enforcement standard because thiencarbazone-methyl has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

References

1. USEPA. Thiencarbazone-methyl: Human Health Risk Assessment for Proposed Uses on Corn (Field, Sweet, and Pop), Wheat, Residential Turfs and Ornamental. In:2008.
2. WIDNR. Groundwater Quality. In: Resources WDoN, ed. *Chapter NR 140*2017.
3. USEPA. National Primary Drinking Water Regulations. 2018; https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations.
4. USEPA. Drinking Water Contaminant Human Health Effects Information. 2019; https://www.epa.gov/dwstandardsregulations/drinking-water-contaminant-human-health-effects-information#hh1.
5. WIDNR. Safe Drinking Water In: Resources WDoN, ed. *Chapter NR 809*2018.
6. EFSA. Conclusion on the peer review of the pesticide risk assessment of the active substance thiencarbazone-methyl. *EFSA Journal.* 2013;11(7):3270.

Monomethyl Tetrachloroterephthalic Acid | 2019

Substance Overview

Monomethyl tetrachloroterephthalic acid (MTP) is a breakdown product (degradate) of the herbicide dacthal.[1] Dacthal is a pre-emergence herbicide used to control annual grasses and some broadleaf weeds in a variety of crops (turf, ornamentals, herbs, strawberries, garden vegetables, beans, alfalfa). In the environment, dacthal breaks down into MTP which then breaks down into tetrachloroterephthalic acid (TPA) (Figure A-1. Dacthal Degradation in the Environment).

This document provides the recommended Public Health Enforcement Standard for MTP.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for MTP.

DHS recommends a combined enforcement standard of 70 micrograms per liter (µg/L) for dacthal, MTP, and TPA. The recommended standard is based on the EPA's lifetime health advisory for dacthal, MTP, and TPA.[1]

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for dacthal, MTP, and TPA be set at 10% of the enforcement standard because dacthal has been shown to have carcinogenic effects.

Current Standards

Enforcement Standard:	70 µg/L
Preventive Action Limit:	14 µg/L
Year:	2005

(Applies to dacthal only)

Recommended Standards

Enforcement Standard:	70 µg/L
Preventive Action Limit:	7 µg/L

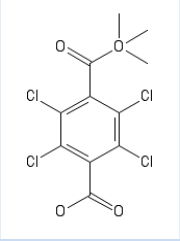
(Applies to dacthal, MTP, and TPA)

Health Effects

In the body, dacthal can turn into MTP and then TPA (Figure A-2. Metabolism of Dacthal in the Body).[1] While the studies on MTP are limited, dacthal has been studied more extensively. Animals that ate large amounts of dacthal for long periods of time experienced liver, lung, kidney, and thyroid problems. Some studies have shown that dacthal can cause carcinogenic effects in animals and the EPA considers dacthal a possible human carcinogen.

The EPA classified MTP as having inadequate information to assess carcinogenic potential.[2] While the mutagenic, teratogenic, and interactive effects of MTP have not been evaluated, dacthal has not been shown to cause mutagenic, teratogenic, or interactive effects.[1,3]

Chemical Profile

	MTP
Chemical Symbol:	
CAS Number:	887-54-7
Formula:	$C_9H_4Cl_4O_4$
Molar Mass:	317.94 g/mol
Synonyms:	Monomethyl Tetrachloroterephthalic Acid Chlorthal-monomethyl

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of two products containing dacthal for use on a variety of plants in Wisconsin.[4]

People can be exposed MTP through the use of dacthal.[1] Because dacthal is used as an herbicide, it can get into the air, soil, and water and then break down into MTP. MTP can also be in or on certain foods like produce and fish.

Degradation of dacthal into MTP in soil depends on temperature and water content.[5] While dacthal is considered immobile in soil, MTP is extremely mobile and will leach to groundwater wherever dacthal is used.

Current Standard

The current groundwater standard of 70 µg/L applies to dacthal alone and was adopted in 2005.[6] The current standard is based on the EPA's lifetime health advisory level for dacthal from 1994.

To calculate the health advisory level, the EPA used the oral reference dose of 0.1 mg/kg-d (see below for more details), a body weight of 70 kg, a water intake rate of 2 L/d, and a relative source contribution factor of 20%.

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A	
Lifetime Health Advisory:	70 µg/L	(2008)
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

Guidance Values

None available

Literature Search

Literature Search Dates:	2008 – 2018
Total studies evaluated:	None
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 for MTP or dacthal.[7]

Health Advisories

In 2008, the EPA established several Health Advisories for dacthal(See Table B-1. EPA's Health Advisories for Dacthal for a summary of the advisories).[1] However, they determined that there was not enough toxicity information to establish health advisories for MTP. The EPA concluded that the lifetime health advisory level for dacthal is protective of the sum of dacthal and its degradates (MTP and TPA) due the relative toxicity for dacthal and TPA in subchronic studies.

The lifetime health advisory is based on EPA's oral reference dose of 0.01 mg/kg-d for dacthal (see below for more details), an average body weight of 70 kg, drinking water intake of 2 L/d, and relative source contribution of 20%.

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations at specified cancer risk levels for MTP or dacthal.[1,3]

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 MTP or dacthal.[8]

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.

Oral Reference Dose

The EPA does not have an oral reference dose for MTP.[9]

The EPA does have an oral reference dose for dacthal which was established in 1994.[10] The EPA selected a study by ISK Biotech Corporation that evaluated effects of dacthal in rats (Sprague-Dawley CD) exposed for 2 years in diet as the critical study. In this study, dacthal caused effects on lung, liver, kidney, thyroid and thyroid hormones in males and females and on the eyes in females. The EPA used a No Observable Adverse Effect Level (NOAEL) of 1 milligram per kilogram per day (mg/kg-d) as the toxicity value and a total uncertainty factor of 100 to account for differences among people and research animals (10) and differences among people (10). This resulted in a reference dose of 0.1 mg/kg-d.[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 MTP, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of MTP. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

The EPA has not evaluated the carcinogenicity of MTP, but has classified dacthal as a possible human carcinogen based on evidence of increased incidence of thyroid tumors in both sexes of the rat and liver tumors in female rats and mice.[11]

The International Agency for Research on Cancer (IARC) and the Joint FAO/WHO Meeting on Pesticide Residues have not evaluated the carcinogenicity of MTP or dacthal.[12,13]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for MTP. However, the EPA established a cancer slope factor of 1.49×10^{-3} $(mg/kg\text{-}d)^{-1}$ for dacthal in 1995. As part of this review, the EPA evaluated the potential for impurities in the dacthal formulation used in the studies to cause cancer. They concluded that these impurities may have contributed to the tumor response with dacthal but cautioned that their presence cannot fully account for the cancer responses observed.

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 MTP, we searched for values that been published since 2008 when the EPA published their health advisory. We did not find any relevant guidance values from the EPA, Agency for Toxic Substances and Disease Registry (ATSDR), World Health Organization (WHO), Joint FAO/WHO Meeting on Pesticide Residues (JMPR), or Health Canada.

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2008. We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2008 to April 2018 related to MTP toxicity or effects on a disease state in which information on MTP 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. No studies were returned by the search engine.

a The following search terms were used in the literature review:
Title/Abstract: MTP OR "Monomethyl tetrachloroterephthalic acid" OR "Chlorthal-monomethyl"
Subject area: toxicology OR cancer
Language: English

Standard Selection

DHS recommends a combined enforcement standard of 70 µg/L for dacthal, MTP, and TPA.

Basis for Enforcement Standard

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

DHS considers health advisories established by the EPA to be federal numbers. The EPA recommends that the health advisory for dacthal apply to the sum of dacthal and its degradates after molar conversion of the degradate concentration to dacthal equivalents. We did not find any significant technical information suggesting that a different value is more appropriate for MTP. Therefore, we recommend a combined enforcement standard of 70 µg/L for dacthal, MTP, and TPA.

DHS recommends a preventive action limit of 7 µg/L for dacthal, MTP, and TPA.

DHS recommends that the preventive action limit for dacthal, MTP, and TPA be set at 10% of the enforcement standard because dacthal has been shown to have carcinogenic effects. The EPA classified MTP as having inadequate information to assess carcinogenic potential and the mutagenic, teratogenic, and interactive effects of MTP have not been evaluated.[2] Dacthal has not been shown to cause mutagenic, teratogenic, or interactive effects.[1,3]

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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2. USEPA. Reregistration Eligibility Decision (RED) DCPA. In:1998.
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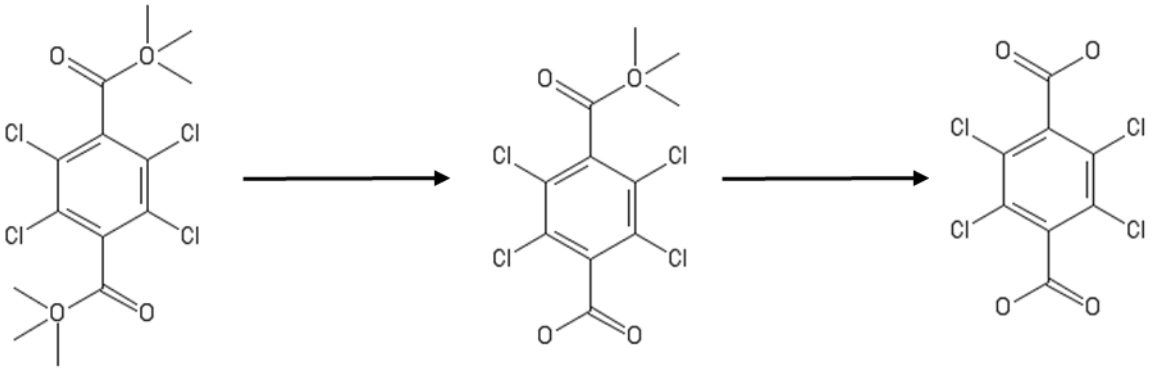
16. ISK. In: Corporation IB, ed1993:HED Doc. No. 010513.

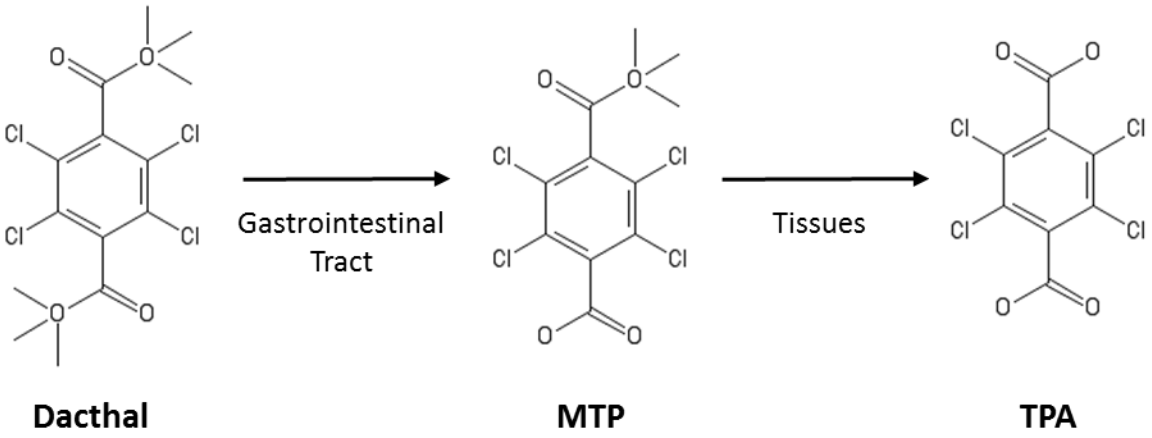
Appendix A

Figure A-1. Dacthal Degradation in the Environment



Degradation of dacthal in soil depends on temperature and water content with most rapid degradation occurring at 68 – 86 °F. Dacthal first degrades into MTP which then rapidly degrades into TPA. Dacthal first degrades into MTP, which can take days to weeks. MTP then rapidly degrades into TPA, which can take hours to days. TPA is considered persistent in the environment. See Figure 1 in appendix A for environmental fate details.

Figure A-2. Metabolism of Dacthal in the Body



It is expected that metabolism of dacthal in the body occurs in a two-step process based on what is known about the metabolism of other phthalate esters. In the first step, dacthal is hydrolyzed to MTP in the gastrointestinal tract. In the second step, MTP is hydrolyzed to TPA in tissues.

Appendix B. Health Advisories

Table B-1. EPA's Health Advisories for Dacthal

	10-Day Child	Longer-term child	Longer-term Adult	Lifetime*
Critical Study:	ISK Biotech Corp, 1990 ([14])	ISK Biotech Corp, 1991 ([15])	ISK Biotech Corp, 1991 ([15])	ISK Biotech Corp, 1993 ([16])
Test compound:	Dacthal	Dacthal	Dacthal	Dacthal
Test species:	Rat	Rat	Rat	Rat
Endpoint:	Increased liver weight Centrilobular hepatocyte hypertrophy	Centrilobular hepatocyte hypertrophy	Centrilobular hepatocyte hypertrophy	Thyroid and liver toxicity
Toxicity Value (mg/kg-d):	215	10	10	0.01
Value type:	LOAEL	LOAEL	LOAEL	NOAEL
Study duration:	28 d	90 d	90 d	2 year
Total uncertainty factor:	1000	100	100	100
Body weight (kg):	10	10	70	70
Daily water intake (L/d):	1	1	2	2
Relative source contribution:	100%	100%	100%	20%
Health Advisory Level (µg/L):	**2,000**	**1,000**	**4,000**	**70**

* EPA's lifetime health advisory applies to the sum of dacthal, MTP, and TPA.

Tetrachloroterephthalic Acid | 2019

Substance Overview

Tetrachloroterephthalic acid (TPA) is a breakdown product (degradate) of the herbicide dacthal.[1] Dacthal is a pre-emergence herbicide used to control annual grasses and some broadleaf weeds in a variety of crops (turf, ornamentals, herbs, strawberries, garden vegetables, beans, alfalfa). In the environment, dacthal breaks down into monomethyl tetrachloroterephthalic acid (MTP), which then breaks down into TPA (Figure A-1).

This document provides the recommended Public Health Enforcement Standard for TPA.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for TPA.

DHS recommends a combined enforcement standard of 70 micrograms per liter (µg/L) for dacthal, MTP, and TPA. The recommended standard is based on the United States Environmental Protection Agency's (EPA's) lifetime health advisory for dacthal, MTP, and TPA.[1]

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for dacthal, MTP, and TPA be set at 10% of the enforcement standard because dacthal has been shown to have carcinogenic effects.

Current Standards

Enforcement Standard:	70 µg/L
Preventive Action Limit:	14 µg/L
Year:	2005

(Applies to dacthal only)

Recommended Standards

Enforcement Standard:	70 µg/L
Preventive Action Limit:	7 µg/L

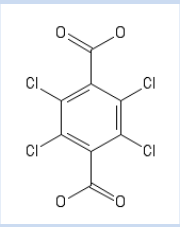
(Applies to dacthal, MTP, and TPA)

Health Effects

In the body, dacthal can turn into MTP and then TPA (Figure A-2).[1] While the studies on TPA are limited, dacthal has been studied more extensively. Animals that ate large amounts of dacthal for long periods of time experienced liver, lung, kidney, and thyroid problems. Some studies have shown that dacthal can cause carcinogenic effects in animals and the EPA considers dacthal a possible human carcinogen.

The EPA classified TPA as having inadequate information to assess carcinogenic potential.[2] While the mutagenic, teratogenic, and interactive effects of TPA have not been evaluated, dacthal has not been shown to cause mutagenic, teratogenic, or interactive effects.[1,3]

Chemical Profile

	TPA
Chemical Symbol:	
CAS Number:	2136-79-0
Formula:	$C_8H_2Cl_4O_4$
Molar Mass:	303.91 g/mol
Synonyms:	Tetrachloroterephthalic Acid Chlorthal

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of two products containing dacthal for use on a variety of plants in Wisconsin.[4]

People can be exposed TPA through the use ofdacthal.[1] Because dacthal is used as an herbicide, it can get into the air, soil, and water and then break down into TPA. TPA can also be in or on certain foods like produce and fish.

Degradation of dacthal into TPA in soil depends on temperature and water content.[5] While dacthal is considered immobile in soil, TPA is extremely mobile and will leach to groundwater wherever dacthal is used.

Current Standard

The current groundwater standard of 70 µg/L applies to dacthal alone and was adopted in 2005.[6] The current standard is based on the EPA's lifetime health advisory (LHA) for dacthal from 1994.

To calculate the LHA, the EPA used the oral reference dose of 0.1 mg/kg-d (see below for more details), a body weight of 70 kg, a water intake rate of 2 L/d, and a relative source contribution factor of 20%.

Standard Development

Federal Numbers		
Maximum Contaminant Level:	N/A	
Health Advisory Levels		
10-day Child:	100,000 µg/L	(2008)
Longer-term Child:	50,000 µg/L	(2008)
Longer-term Adult:	200,000 µg/L	(2008)
Lifetime:	70 µg/L	(2008)
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	
Guidance Values		
None available		
Literature Search		
Literature Search Dates:	2008 – 2019	
Total studies evaluated:	5	
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 for TPA or dacthal.[7]

Health Advisories

In 2008, the EPA established several Health Advisories for TPA (See Table B-1 for a summary of the advisories).[1]

10-day Child

The EPA based the 10-Day Child Health Advisory on two studies using rats that were exposed to varying amounts of TPA for 10 and 30 days.[8,9] The EPA established a No Observable Adverse Effect Level (NOAEL) value of 1250 milligrams of TPA per kilogram body weight per day (mg TPA/kg-day) and a Lowest Observable Adverse Effect Level (LOAEL) value of 2500 milligrams mg TPA/kg-day based on soft stools, red mucus in the feces, and effects on food consumption and weight gain. The EPA applied a total uncertainty factor of 100 to account for differences between people and research animals (10) and

differences among people (10). To obtain the health advisory, they used a body weight of 10 kg, water consumption rate of 1 L/d, and relative source contribution of 100%.

Longer-term Child

The EPA based the Longer-term Child Health Advisory on a 90 day study in rats that found no effects at all doses examined (0, 2.5, 25, 50, and 500 mg TPA/kg-d).[10] They established a NOAEL of 500 mg/kg-d. The EPA applied a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). To obtain the health advisory, they used a body weight of 10 kg, water consumption rate of 1 L/d, and relative source contribution of 100%.

Longer-term Adult

The EPA based the Longer-term Adult Health Advisory on the 90 day study in rats that found no effects at all doses examined that was also used for the longer-term child advisory.[10] They used the NOAEL of 500 mg/kg-d and total uncertainty factor of 100. To obtain the health advisory, they used a body weight of 70 kg, water consumption rate of 2 L/d, and relative source contribution of 100%.

Lifetime

The EPA determined that the data were inadequate to establish a standalone lifetime health advisory level for TPA. Instead, they concluded that the lifetime health advisory level for dacthal is protective of the sum of dacthal and its degradates (MTP and TPA) due the relative toxicity for dacthal and TPA in subchronic studies.

The lifetime health advisory is based on EPA's oral reference dose of 0.01 mg/kg-d for dacthal (see below for more details), an average body weight of 70 kg, drinking water intake of 2 L/d, and relative source contribution of 20%.

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations at specified cancer risk levels for TPA or dacthal.[1,3]

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 TPA or dacthal.[11]

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.

Oral Reference Dose

The EPA does not have an oral reference dose for TPA.[12]

The EPA does have an oral reference dose for dacthal which was established in 1994.[13] The EPA selected a study by ISK Biotech Corporation that evaluated effects of dacthal in rats (Sprague-Dawley CD) exposed for 2 years in diet as the critical study. In this study, dacthal caused effects on lung, liver, kidney, thyroid and thyroid hormones in males and females and on the eyes in females. The EPA used a No Observable Adverse Effect Level (NOAEL) of 1 milligram per kilogram per day (mg/kg-d) as the toxicity value and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). This resulted in a reference dose of 0.1 mg/kg-d.[13]

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

Cancer Classification

The EPA has not evaluated the carcinogenicity of TPA, but has classified dacthal as a possible human carcinogen based on evidence of increased incidence of thyroid tumors in both sexes of the rat and liver tumors in female rats and mice.[14]

The International Agency for Research on Cancer (IARC) and the Joint FAO/WHO Meeting on Pesticide Residues have not evaluated the carcinogenicity of TPA or dacthal.[15,16]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for MTP. However, the EPA established a cancer slope factor of 1.49×10^{-3} $(mg/kg\text{-}d)^{-1}$ for dacthal in 1995. As part of this review, the EPA evaluated the potential for impurities in the dacthal formulation used in the studies to cause cancer. They concluded that these impurities may have contributed to the tumor response with dacthal but cautioned that their presence cannot fully account for the cancer responses observed.

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 TPA, we searched for values that been published since 2008 when the EPA published their health advisory. We did not find any relevant guidance values from the EPA, Agency for Toxic Substances and Disease Registry (ATSDR), World Health Organization (WHO), or the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2008. We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2008 to May 2019 related to TPA toxicity or effects on a disease state in which information on TPA 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.

Five studies were returned by the search engine. We excluded studies on non-oral exposure routes (e.g. inhalation) and studies not evaluating health risks from further review. After applying these exclusion criteria, we did not identify any key studies.

Standard Selection

DHS recommends a combined enforcement standard of 70 µg/L for dacthal, MTP, and TPA.

DHS considers health advisories established by the EPA as federal numbers. The EPA recommends that the health advisory for dacthal apply to the sum of dacthal and its degradates after molar conversion of the degradate concentration to dacthal equivalents. We did

Basis for Enforcement Standard

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

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

not find any significant technical information suggesting that a different value is more appropriate for TPA. Therefore, we recommend a combined enforcement standard of 70 µg/L for dacthal, MTP, and TPA.

DHS recommends a preventive action limit of 7 µg/L for dacthal, MTP, and TPA.

DHS recommends that the preventive action limit for dacthal, MTP, and TPA be set at 10% of the enforcement standard because dacthal has been shown to have carcinogenic effects. The EPA classified TPA as having inadequate information to assess carcinogenic potential and the mutagenic, teratogenic, and interactive effects of TPA have not been evaluated.[2] Dacthal has not been shown to cause mutagenic, teratogenic, or interactive effects.[1,3]

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

References

1. USEPA. Drinking Water Health Advisory For Dacthal and Dacthal Degradates: Tetrachloroterephthalic acid (TPA) and Monomethyl Tetrachloroterephthalic acid (MTP). In:2008.
2. USEPA. Reregistration Eligibility Decision (RED) DCPA. In:1998.
3. USEPA. Health Effects Support Document for Dacthal Degradates: Tetrachloroterephthalic Acid (TPA) and Monomethyl Tetrachloroterephthalic Acid (MTP). 2008(822-R-08-005).
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12. USEPA. IRIS Assessments. 2019; https://cfpub.epa.gov/ncea/iris_drafts/AtoZ.cfm.
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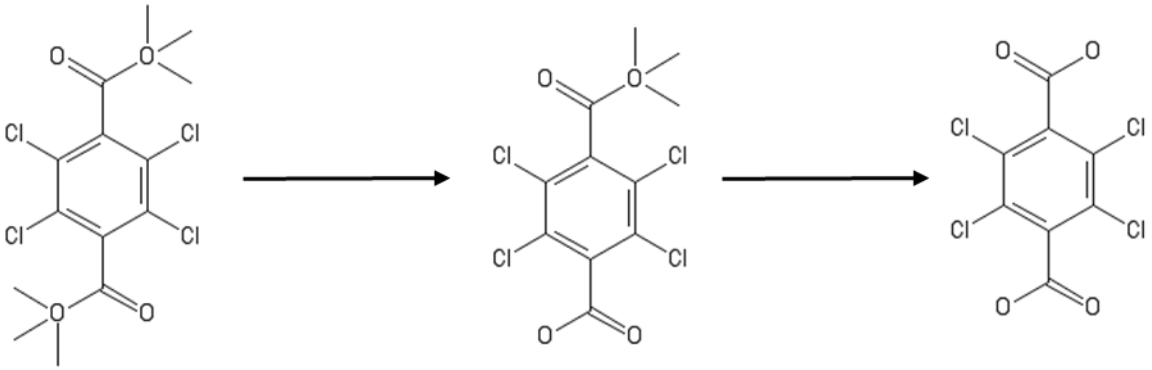
17. ISK. In: Corporation IB, ed1993:HED Doc. No. 010513.

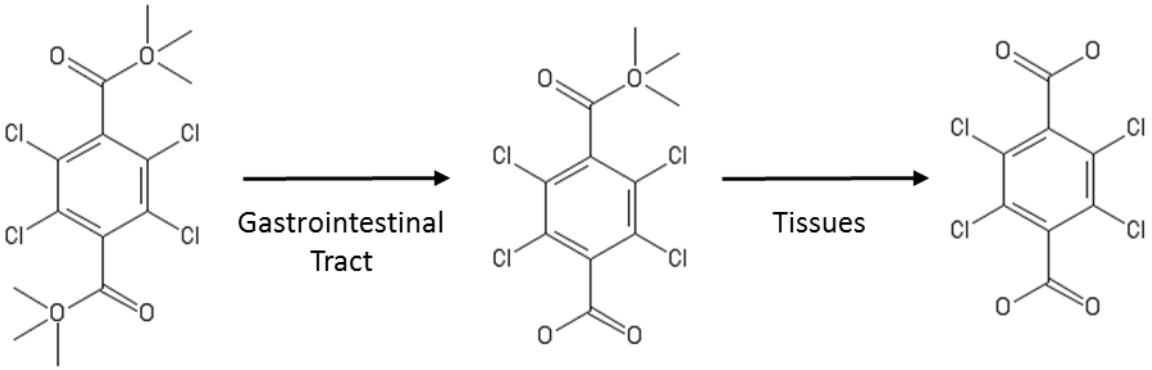
Appendix A

Figure A-1. Dacthal Degradation in the Environment



Degradation of dacthal in soil depends on temperature and water content with most rapid degradation occurring at 68 – 86 °F. Dacthal first degrades into MTP which then rapidly degrades into TPA. Dacthal first degrades into MTP, which can take days to weeks. MTP then rapidly degrades into TPA, which can take hours to days. TPA is considered persistent in the environment. See Figure 1 in appendix A for environmental fate details.

Figure A-2. Metabolism of Dacthal in the Body



It is expected that metabolism of dacthal in the body occurs in a two-step process based on what is known about the metabolism of other phthalate esters. In the first step, dacthal is hydrolyzed to MTP in the gastrointestinal tract. In the second step, MTP is hydrolyzed to TPA in tissues.

Appendix B. Health Advisories

Table B-1. EPA's Health Advisories for TPA

	10-Day Child	Longer-term child	Longer-term Adult	Lifetime*
Critical Study:	Mizen, 1985 ([8]) Major, 1985 ([9])	Goldenthal, 1977 ([10])	Goldenthal, 1977 ([10])	ISK Biotech Corp, 1993 ([17])
Test compound:	TPA	TPA	TPA	Dacthal
Test species:	Rat	Rat	Rat	Rat
Endpoint:	Soft stools in rats	No effect at highest dose	No effect at highest dose	Thyroid and liver toxicity
Toxicity Value (mg/kg-d):	1250	500	500	0.01
Value type:	NOAEL	NOAEL	NOAEL	NOAEL
Study duration:	30 d	90 d	90 d	2 year
Total uncertainty factor:	100	100	100	100
Body weight (kg):	10	10	70	70
Daily water intake (L/d):	1	1	2	2
Relative source contribution:	100%	100%	100%	20%
Health Advisory Level (µg/L):	**100,000**	**50,000**	**200,000**	**70**

* EPA's lifetime health advisory applies to the sum of dacthal, MTP, and TPA.

Glyphosate | 2019

Substance Overview

Glyphosate is a post-emergence herbicide that is used worldwide in agriculture, forestry, gardening, lawn-care, and for weed control in industrial areas. Glyphosate is also used for aquatic weed control. In the environment, glyphosate can degrade (turn) into aminomethylphosphonic acid (AMPA).

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for glyphosate.

DHS recommends an enforcement standard of 10 milligrams per liter (mg/L) for glyphosate. This standard is based on the United States Environmental Protection Agency (EPA) Office of Pesticide Program's draft oral reference dose for glyphosate.[1]

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for glyphosate be set at 10% of the enforcement standard because glyphosate has been shown to cause mutagenic and teratogenic effects.[1-4]

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

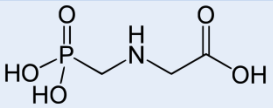
Recommended Standards	
Enforcement Standard:	10 mg/L
Preventive Action Limit:	1 mg/L

Health Effects

Studies in animals have shown that glyphosate can cause gastrointestinal effects and developmental effects. Ingestion of a large amount of glyphosate also caused inflammation in the gastrointestinal system in animal studies. High levels of glyphosate has also been shown to cause unossified breastbone (teratogenic effects) in offspring of pregnant animals given large amounts of glyphosate orally (MRID 00046362).[1]

The carcinogenic potential of glyphosate has been intensively discussed by multiple federal and international agencies. While the International Agency for Research on Cancer (IARC) classified glyphosate as "probably carcinogenic to humans" in 2015, the EPA has recently affirmed their position that glyphosate is not likely to be carcinogenic to humans.[1-3,5] Appendix A contains more details on these evaluations. Some studies have shown that glyphosate can have mutagenic effects.[1,4] Glyphosate has not been shown to cause interactive effects.[1,4]

Chemical Profile

	Glyphosate
Structure:	
CAS Number:	1071-83-6
Formula:	$C_3H_8NO_5P$
Molar Mass:	169.07 g/mol
Synonyms:	N-(phosphonomethyl)glycine

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of a number of commercial herbicides containing glyphosate for controlling weeds and grasses.[6]

People can be exposed to glyphosate from air, soil, water and food.[1,4] People can get exposed to glyphosate by breathing when products containing glyphosate are sprayed on plants. Glyphosate may get on unprotected skin and eyes when it is sprayed. People can also get exposed to glyphosate by walking through recently sprayed areas and touching sprayed soil. Young children can be exposed to glyphosate while playing in areas that have been recently treated with products containing the substance. Very small amounts of glyphosate enter the body through food.

In general, glyphosate does not enter water unless it is directly sprayed onto water surfaces. [1,4] Glyphosate sticks tightly to soil and is quickly broken down by bacteria. Microbial biodegradation of glyphosate occurs in soil, aquatic sediment, and water. The major metabolite is AMPA. In soil, AMPA breaks down in several weeks. In general, glyphosate that is bound to soil particles is not taken up by the roots of plants.

Current Standard

Wisconsin does not currently have a groundwater enforcement standard for glyphosate.[7]

Standard Development

Federal Numbers		
Maximum Contaminant Level (MCL):	700 µg/L	(1994)
Health Advisories		
10-Day child:	20 mg/L	(1989)
Lifetime Health Advisory:	800 µg/L	(1989)
Drinking water concentration (cancer risk):	N/A	
State Drinking Water Standard		
NR809 Maximum Contaminant Level:	700 µg/L	(2016)
Acceptable Daily Intake		
EPA Oral Reference Dose (IRIS):	0.1 mg/kg-d	(1987)
EPA Draft Oral Reference Dose (OPP):	1 mg/kg-d	(2017)
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
ATSDR Draft Chronic Oral Minimum Risk Level:	1 mg/kg-d	(2019)
Literature Search		
Literature Search Dates:	2019	
Total studies evaluated:	Approximately 40	
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 established a Maximum Contaminant Level (MCL) for glyphosate of 700 micrograms per liter (µg/L) in 1994.[8] The EPA reviewed the MCL in 2002 as part of the first six-year review.[9] They determined that the MCL was not appropriate for revision because it was currently undergoing an EPA health risk assessment.

Health Advisories

The EPA Office of Water established several Health Advisories for glyphosate in 1989.[8,10]

10-Day Health Advisory

The EPA based the 10-Day Child Health Advisory on a study using rabbits that were exposed to different amounts of glyphosate (0, 75, 175, and 350 milligrams glyphosate per kilogram body weight per day (mg/kg-d)) during pregnancy (gestation days 6-27) (MRID 00046363). The EPA established a No Observable Adverse Effect Level (NOAEL) of 175 mg/kg-d and a Lowest Observable Adverse Effect Level (LOAEL) of 350 mg/kg-d based on increased diarrhea, soft stools, and nasal discharge. The EPA selected

a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). To obtain the 10-Day Child Health Advisory, they used a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%. Because suitable information was not available to develop a 1-Day Health Advisory, EPA recommended using the 10-Day Health Advisory for shorter exposures as well.

Lifetime Health Advisory

The EPA based the Lifetime Health Advisory on a three-generational reproductive study in rats. Rats were exposed to different amounts of glyphosate (0, 3, 10, and 30 mg/kg-d) from 60 days prior to breeding through lactation for 2 successive generations (MRID 00105995). The EPA selected a NOAEL of 10 mg/kg-d and LOAEL of 30 mg/kg-d based on impacts to the kidney in the third generation of male pups. They selected a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). They obtained an oral reference dose of 0.1 mg/kg-d. To obtain the health advisory value, the EPA used a body weight of 70 kg, a water consumption rate of 2 L/d, and a default relative source contribution of 20%.

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 700 µg/L for glyphosate.[11] This value is based on the EPA's MCL from 1994.

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 (IRIS)

In 1987, the EPA's IRIS program established an oral reference dose of 0.1 mg/kg-d for glyphosate.[12] In establishing this value, the EPA used the same rat study (MRID 00105995) that was used for the lifetime health advisory (see above) and applied the same total uncertainty factor of 100 (see above for more details).

EPA Draft Oral Reference Dose (Office of Pesticide Programs)

In 2017, the EPA Office of Pesticide Programs proposed an oral reference dose of 1 mg/kg-d based on a rabbit study (MRID 4430616) where pregnant rabbits were exposed to different concentrations of

glyphosate during gestation for 21 days by gavage.[1] This study showed that the highest concentration of glyphosate caused early mortality, nasal discharge, and diarrhea in rabbits. The EPA selected a NOAEL of 100 mg/kg-d and applied a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). Similar toxicity endpoints were observed in a dose-dependent manner in the previous rabbit study (MRID 00046362) at a similar dose, which supports the decision of using the study as a critical study.

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

Cancer Classification

In March 2015, IARC determined that glyphosate was a probable carcinogen (group 2A).[3] This classification is based on IARC's conclusions that there is "limited evidence" in humans, "sufficient evidence" in animals, and evidence that glyphosate is genotoxic and can induce oxidative stress.

In 2017, the EPA assessed the carcinogenicity of glyphosate as part of their Office of Pesticide Program review and determined that glyphosate is unlikely to be carcinogenic to humans. Appendix A contains more information on these cancer evaluations.

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for glyphosate.[1]

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 glyphosate, we searched for guidance values that were published since 1988 when the EPA published their latest IRIS review. We found relevant guidance values from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Draft Chronic Oral Minimum Risk Level

In 2019, ATSDR reviewed the available documents and proposed a draft chronic minimum risk level for glyphosate of 1 mg/kg-d.[4] This is based on a chronic rat study (MRID: 41643801) where inflammation of gastric squamous mucosa was observed in female rats administered high doses of glyphosate in the diet for 2 years. ATSDR selected a NOAEL of 113 mg/kg-d and applied a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).[4]

Literature Search

Our literature review focused on the scientific literature published after the review by ATSDR in 2019. We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from April 2019 to May 2019 for studies related to glyphosate 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 40 studies were returned by the search engine. We excluded studies that did not evaluate health effects, studies from non-mammalian species, and studies for plants from further review. After applying these exclusion criteria, we did not locate any key studies.

Standard Selection

DHS recommends an enforcement standard of 10 mg/L for glyphosate.

The most recent federal number is EPA's Maximum Contaminant (MCL) Level of 700 µg/L , which was adopted in 1994 and reviewed in 2003. The current state drinking water standard is based on the current federal MCL. Since the MCL was established, the EPA Office of Pesticide Programs proposed an updated oral reference dose of 1 mg/kg-d in 2017. The ASTDR released a draft MRL in 2019 and this value is consistent with EPA's most recent reference dose.

Basis for Enforcement Standard

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

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

Because EPA's oral reference dose from 2017 is based on the latest scientific information on glyphosate, DHS recommends using this value as an ADI. As such, we calculated the recommended enforcement standard (ES) using the EPA's oral reference dose for glyphosate. DHS applied an average body weight of 10 kg, a water consumption rate of 1 L/d, and assumed that water is the only source of exposure to the substance, as required by Chapter 160 of Wisconsin Statute.

DHS recommends a preventive action limit of 1 mg/L for glyphosate.

DHS recommends that the preventive action limit for glyphosate be set at 10% of the enforcement standard because studies have shown that glyphosate can cause mutagenic and teratogenic effects in animals.[1,4] Based on our evaluation, DHS concludes that glyphosate is unlikely to cause carcinogenic effects after oral exposure (see Appendix A for more details). Glyphosate has not been shown to have interactive effects. [1,4]

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Wisconsin Department of Health Services

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Appendix A. Carcinogenic Potential of Glyphosate

In order to evaluate the carcinogenic potential of glyphosate, DHS reviewed available studies in humans and animals that focused on the association between glyphosate exposure and carcinogenic effects. Many federal and international agencies have evaluated the human carcinogenic potential of glyphosate since its registration as an herbicide. While the European Food Safety Authority (EFSA), the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), and the EPA have determined that glyphosate is unlikely to pose a carcinogenic risk, the IARC has classified glyphosate as a probable human carcinogen (group 2A).[1-3,13] It should be noted that agencies apply different evaluation criteria and consider different individual studies for their review which could result in different conclusions.

To date, approximately 60 epidemiological studies in workers focusing on the association of glyphosate exposure with carcinogenic potential have been published.[b] Many of the available studies have utilized a case-control design to evaluate the association between cancer risk and use of pesticides containing glyphosate. These studies found no evidence of an association between glyphosate use and solid tumors, leukemia, Hodgkin lymphoma, and multiple myeloma,[14-26] but some have shown a significant association between glyphosate exposure and increased non-Hodgkin's lymphoma (NHL) incidence.[27-30] Case-control studies provide an advantage when assessing rare diseases with long latency periods but are subject to recall bias and have limited ability to assess causation compared to cohort studies.

In contrast, several prospective cohort studies have found no associations with any type of cancer, including NHL.[31-38] Many of these studies have utilized data from the Agricultural Health Study (AHS). The AHS is a dataset on cancer and other health outcomes in a cohort of licensed pesticide applicators and their spouses from Iowa and North Carolina.[39] For this study, the AHS recruited approximately 52,000 licensed private pesticide applicators and nearly 32,000 of their spouses between 1993 and 1997 in North Carolina and about 5,000 commercial pesticide applicators in Iowa. An advantage of cohort studies is that they allow for better assessment of causation as subjects are followed from exposure to onset of disease.

Together, the epidemiology data has not found evidence of an association between glyphosate use and solid tumors, leukemia, Hodgkin lymphoma, and multiple myeloma. At this time, the available epidemiologic data are inconsistent regarding associations between glyphosate exposure and NHL.

Glyphosate has been extensively studied in rodents to evaluate its carcinogenic potential as well. In evaluating carcinogenicity, IARC considered 10 animal carcinogenicity studies and EPA evaluated a total of 14 rodent carcinogenicity studies for their 2017 evaluation (see Table A-1 for more details on these studies).[3,13] Three out of ten rodent studies reviewed by the IARC were conducted with glyphosate-based formulations, not with technical grade glyphosate. Thus, these three studies were not considered by the EPA.

b More details on these studies can be found in EPA's Revised Glyphosate Issue Paper[13] and ATSDR's toxicological profile[4].

Tumor incidences were observed in 8 of the 14 rodent studies reviewed by the EPA. Specific tumor types identified from these studies include hemangiosarcomas, malignant lymphoma, hemangiomas, kidney, lung, testicular, pancreatic, hepatocellular, thyroid C-cell, and mammary gland. However, none of the evaluated tumors are sufficient to determine the carcinogenic potential of glyphosate for several reasons. First, tumors observed in individual rodent studies were not reproduced in other studies conducted in the same animal species at similar or higher doses. For example, hemangiosarcomas that were observed in male mice treated with glyphosate for 104 weeks (MRID 49631702) were not observed in other 5 mice studies (MRIDs 49957404, 00061113, 00130406, 49957402, 50017108-9, and 40214006) that were administered similar amounts of glyphosate long-term.[13] Additionally, no statistically significant dose-related trends were observed in studies for pancreatic, hepatocellular, thyroid, kidney, and lung tumors. Thus, current animal carcinogenicity studies are insufficient to demonstrate a carcinogenic potential in humans after exposure to glyphosate.

Overall, based on our review of available epidemiological studies and rodent studies, DHS concludes that glyphosate exposure is unlikely to cause carcinogenic effects to humans. This is an area of active research and DHS will continue to monitor the scientific literature for new evidence of carcinogenicity linked to glyphosate exposure.

Table A-1. Glyphosate Carcinogenicity Studies from the EPA's Human Health Risk Assessment (2017)

Species	Duration	Dose (mg/kg-d)	Route	Endpoints	Reference	Reviewed by IARC?	Reviewed by EPA?
Rat	26 months	Males: 0, 3.05, 10.3, 31.49 Females: 0, 3, 11, 34	diet	Increased incidence of testicular interstitial tumors.	Lankas 1981 MRID: 00093879	Yes	Yes
Rat	24 months	Males: 0, 89, 362, 940 Females: 0, 113, 457, 1183	diet	Increased incidence of liver adenoma. Increased incidence of thyroid adenomas and combined adenomas/carcinomas in females. Thyroid C-cell hyperplasia observed. No evidence of progression from adenoma to carcinoma in pancreas, liver, and thyroid	Stout and Ruecker 1990 MRIDs: 41643801 41728701	Yes	Yes
Rat	104 weeks	Males: 0, 11, 112, 320, 1147 Females: 0, 12, 109, 347, 1134	diet	No histopathological changes.	Atkinson 1993a MRID: 49631701	No	Yes
Rat	24 months	Males: 0, 121, 361, 1214 Females: 0, 145, 437, 1498	diet	No treatment-related non-neoplastic lesions. Increased incidence of liver adenomas in males.	Brammer 2001 MRID: 49704601	No	Yes
Rat	2 years	Males: 0, 4.2, 21.2, 41.8 Females: 0, 5.4, 27, 55.7	diet (sulfosate, 56.2% pure)	No histopathological changes.	Pavkov and Wyand 1987 MRIDs: 40214007 41209905 41209907	Yes	Yes
Rat	24 months	Males: 0, 6.3, 59.4, 595.2 Females: 0, 8.6, 88.5, 886	diet	No histopathological changes.	Suresh 1996 MRID: 49987401	Yes	Yes

Rat	24 months	Males: 0, 104, 354, 1127 Females: 0, 115, 393, 1247	diet	No histopathological changes.	Enemoto 1997 MRIDs: 50017013 50017014 50017105	Yes	Yes
Rat	80 weeks	0, 95, 316.9, 1229.7	diet	Increased incidence of mammary gland adenocarcinoma in females.	Wood 2009a MRID: 49957404	No	Yes
Mouse	18 months	0,17, 50	diet	No histopathological changes.	Reyna and Gordon 1973 MRID: 00061113	No	Yes
Mouse	24 months	Males: 0, 161, 835, 4945 Females: 0, 195, 968, 6069	diet	Low incidence of renal tubule adenoma in males. Tubular epithelial changes in kidney (observed in all treatment groups including the controls).	Knezevich and Hogan 1983 MRID: 00130406	Yes	Yes
Mouse	104 weeks	Males: 0, 98, 297, 988 Females: 0, 102, 298, 1000	diet	Increased incidence of hemangiosarcomas in male.	Atkinson 1993b MRID: 49631702	Yes	Yes
Mouse	80 weeks	Males: 0, 71.4, 234.2, 810 Females: 0, 97.9, 299.5, 1081.2	diet	Increased incidence of malignant lymphoma.	Wood 2009b MRID: 49957402	No	Yes
Mouse	18 months	Males: 0, 165, 838.1, 4348 Females: 0, 153.2, 786.8, 4116	diet	Increased incidence of hemangiomas in female. * Highest dose was more than 4times the limit dose.	Sugimoto 1997 MRIDs: 50017108 50017109	No	Yes
Mouse	2 year	Males: 0, 11.7, 118, 991 Females: 0, 16, 159, 1341	diet (sulfosate, 56.2% pure)	No effects.	Pavkov and Turnier 1987 MRIDs: 40214006 41209907	No	Yes

Aminomethylphosphonic Acid (AMPA) | 2019

Substance Overview

Aminomethylphosphonic acid (AMPA) is the major breakdown product of glyphosate. Glyphosate is a post-emergence herbicide that is used worldwide in agriculture, forestry, gardening and lawn care, and for weed control in industrial areas. The chemical structure of AMPA is very similar to that of glyphosate.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for AMPA.

DHS recommends an enforcement standard of 10 milligrams per liter (mg/L) for AMPA. The recommended standard is based on a study that found that AMPA caused hyperplasia in urinary tracts in rats.[1,2]

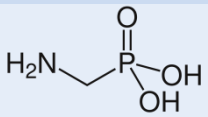
DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for AMPA be set at 20% of the enforcement standard because AMPA has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A
Recommended Standards	
Enforcement Standard:	10 mg/L
Preventive Action Limit:	2 mg/L

Health Effects

What we know about the health effects of AMPA comes from studies with laboratory animals. Studies have shown that AMPA can affect the gastrointestinal tract and the urinary tract, including bladder, and cause liver injury in animals given very large amounts of AMPA. Decreased fetal body weight was also observed in animals given larger amounts of AMPA during gestation. AMPA has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

Chemical Profile

	AMPA
Structure:	
CAS Number:	1066-51-9
Formula:	CH_6NO_3P
Molar Mass:	111.04 g/mol
Synonyms:	AMeP Aminomethylphosphonic acid

Exposure Routes

People can get exposed to small amounts of AMPA through consuming food treated with glyphosate. People may be exposed to low levels of AMPA by walking through glyphosate sprayed areas and touching sprayed soil. Young children can be exposed to AMPA while playing in areas that have been recently treated with products containing glyphosate. People may also be exposed to very low levels of AMPA in drinking water.

AMPA is the major microbial biodegradation product of glyphosate in plants, soil, and water. In soil, AMPA breaks down in several weeks. Only a small amount of glyphosate may be metabolized to AMPA in the body and most absorbed glyphosate is rapidly excreted in the urine as parent compound.

Current Standard

Wisconsin does not currently have a groundwater standard for AMPA.[3]

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	
Guidance Values		
JMPR (sum of AMPA and glyphosate)	1 mg/kg-d	(2016)
Literature Search		
Literature Search Dates:	2017 – 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 United States Environmental Protection Agency (EPA) does not have a maximum contaminant level for AMPA.[4]

Health Advisories

The EPA does not have a health advisory for AMPA.[4]

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 not established a state maximum contaminant level for AMPA.[5,6]

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 (Office of Pesticide Program)

The EPA does not have an oral reference dose for AMPA.[4] As part of their Human Health Risk Assessment for glyphosate, the EPA reviewed a handful of studies on the toxicity of AMPA (Table B-2). While these studies were not used by EPA to set an oral reference dose for AMPA, one of these studies met our criteria to be considered a critical study for use in establishing an acceptable daily intake (see the *Literature Search* section below for a summary of this study).

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

Cancer Classification

The EPA has not determined the cancer classification for AMPA.

The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of AMPA.

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) has not evaluated the carcinogenicity of AMPA.

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 AMPA, we searched for relevant guidance values that have been published from national or international agencies and found ADI values from the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).[2]

JMPR Acceptable Daily Intake

In 2016, the JMPR established a group acceptable daily intake (ADI) of 1 milligram per kilogram body weight per day (mg/kg-day) for the sum of glyphosate and AMPA.[1] The meeting concluded that with AMPA and glyphosate having similar chemical structure and similar toxicological profiles, it is not necessary to develop a full database for AMPA toxicity. The group ADI established in 2016 was based on a study where salivary gland effects were observed in a chronic study in rats given glyphosate orally. The no observable adverse effect level (NOAEL) was 100 mg/kg-d and JMPR selected a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10) to derive the group ADI.

Literature Search

Our literature review focused on the scientific literature published after the review by the EPA Office of Pesticide Programs in 2017.[2] We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from 2017 to May 2019 for studies related to AMPA 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 60 studies were returned by the search engine. We excluded studies on effects on plants and non-mammalian species, as well as non-toxicity related articles. After applying these exclusion criteria, no key studies were identified.

We also evaluated the three studies that EPA and JMPR considered in their human risk assessment using these same criteria. 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.

Critical Studies

To compare results between studies, we calculated an ADI for each study. The ADI is the estimated amount of AMPA that a person can be exposed to every day and not experience health impacts. The ADI equals the toxicity value divided by the total uncertainty factor. Uncertainty factors were included as appropriate to account for differences between people and research animals, differences in sensitivity to health effects within human populations, using data from short-term experiments to protect against

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

effects from long-term exposure, and using data where a health effect was observed to estimate the level that does not cause an effect.

Estes et al, 1979 (MRID: 00241351)

Estes et al evaluated the effects of exposure to AMPA on overall health in rats. Rats were exposed to 0, 400, 1200, or 4800 mg/kg-d of AMPA in the diet for 90 days. They found that the highest dose of AMPA in females and the two highest doses of AMPA in males caused decreases in body weight. They also observed an increase in lactate dehydrogenase activity and cholesterol level, a decrease in urinary pH, and hyperplasia of the urinary tract.

We estimated an ADI of 1 mg/kg-d based on a NOAEL of 400 mg/kg-d and an uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3).

Holson et al, 1979 (MRID: 43334705)

Holson et al evaluated the developmental effects of exposure to AMPA in rats. Pregnant female rats were exposed to 0, 150, 400, or 1000 mg/kg-d of AMPA by gavage during gestational days 6-19. They observed a dose-related increase in the incidence of soft stool, mucoid feces and hair loss in dams. They also found that the highest dose of AMPA caused a decrease in fetal body weight.

We estimated an ADI of 4 mg/kg-d based on a NOAEL of 400 mg/kg-d and an uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

Summary

Review of available data suggests that AMPA can affect the gastrointestinal system and the urinary tract. Between the two critical studies, DHS decided to use the study with a lower ADI as a basis of the groundwater standard to be protective for all possible health effects.

Standard Selection

DHS recommends an enforcement standard of 10 mg/L for AMPA.

There are no federal numbers for AMPA. Additionally, there is no drinking water standard for AMPA in Ch. NR 809, Wisc Admin Code, and the EPA does not have an oral reference dose for this degradate.

Basis for Enforcement Standard

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

Although the EPA did not include AMPA in the pesticide tolerances for glyphosate, several studies have been conducted on AMPA. One of these studies meets DHS's definition of a critical study. Because glyphosate does not metabolize into AMPA quickly in the body (most are excreted as a parent compound), it is unlikely that AMPA is contributing to toxicity observed in animals dosed with glyphosate. At this time, little is known about how AMPA causes toxicity and whether it causes toxicity in the same manner as glyphosate.[2,7] Additionally, AMPA can be found in the environment through the breakdown of phosphoric acids in detergents.[8] For these reasons, DHS recommends setting a separate standard for AMPA using the identified critical study and the procedures in s. 160.13(2) instead of establishing a combined standard for glyphosate and AMPA.

To calculate the ADI, DHS used information from a 90-day toxicity study in rats (MRID: 00241351).[9] From this study, we selected a NOAEL of 400 mg/kg-d and a total uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3). To determine the recommended ES, DHS used the ADI and exposure parameters specified in Ch. 160, Wis. Stats.: a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%.

DHS recommends a preventive action limit of 2 mg/L for AMPA.

DHS recommends that the preventive action limit for AMPA be set at 20% of the enforcement standard because AMPA has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.[1,2]

Prepared by Clara Jeong, Ph.D.

Wisconsin Department of Health Services

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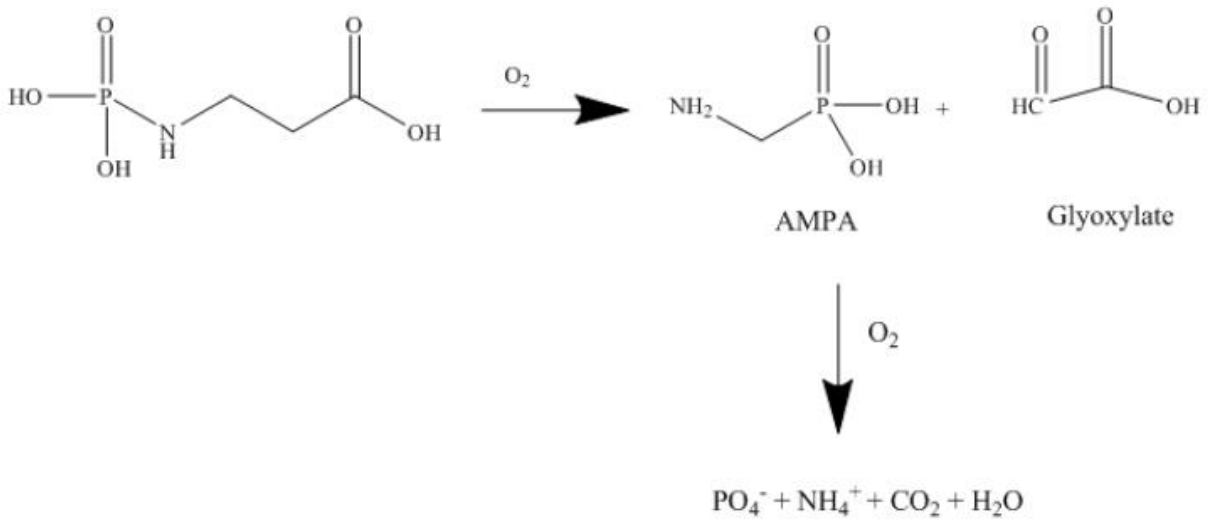
Appendix A: Glyphosate Degradation

Figure A-1. Glyphosate readily degrades into AMPA in the environment (figure from ATSDR Toxicological Profile)

Glyphosate is readily and completely degraded in the environment mainly by microbial processes. AMPA has been identified as the major metabolite in both soils and water.[7]



Source: Schuette 1998

Appendix B. Toxicity Data

Table B-1. AMPA Toxicity Studies from the JMPR Literature Review (2016) and the EPA Office of Pesticide Program Review (2017)

Study Type	Species	Duration	Dose (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference	MRID
Longer-term	Rat	90 days	0, 400, 1200, 4800	diet	Decreased body weight in males and females. Increased lactate dehydrogenase activity, aspartate aminotransferase activity, cholesterol level, and calcium oxalate crystals in urine. Decreased urinary pH. Increased histopathological lesions of the urinary bladder.	NOAEL: 400 LOAEL: 1200	Estes et al. (1979)[9] From EPA 2017[2]	00241351
Short term Developmental	Rat	GD 6-19	0, 150, 400, 1000	gavage	Increased incidences of soft stool and hair loss. Decreased body weight gain and food consumption. Decreased fetal body weight.	Maternal NOAEL: 400 LOAEL: 1000	Holson (1991)[10] From WHO 2005[11] and EPA 2017[2]	43334705
Longer-term	Dog	90 days	0, 8.8, 26.4, 88, 264	diet	No effects	NOAEL: 264	Tompkins et al. (1991)[12] From EPA 2017[2]	43334702

Table B-2. Critical study selection for Aminomethylphosphonic acid (AMPA)

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity value identifiable?	Critical study?
Estes et al. (1979) [9] MRID: 00241351	✓	✓	✓	**4**	✓	**Yes**
Holson et al. (1991) [10] MRID: 43334705	✓	✓	✓	**4**	✓	**Yes**
Tompkins et al. (1991) [12] MRID: 43334702	✓	⦸	⦸	**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.

Sulfentrazone | 2019

Substance Overview

Sulfentrazone is an herbicide used to control a broad variety of weeds by inhibiting photosynthesis in plants. There are a large number of products registered with sulfentrazone as the active ingredient. Sulfentrazone pesticides are used on agricultural crops, Christmas tree farms, golf courses, seedling nurseries, landscape ornamentals, and non-crop use sites such as railroad tracks, highways, and residential/commercial turf.

Recommendations

Wisconsin does not currently have a NR140 Groundwater Quality Public Health Enforcement Standard for sulfentrazone.

DHS recommends an enforcement standard of 1,000 micrograms per liter (µg/L) for sulfentrazone. The recommended standard is based on the United States Environmental Protection Agency's (EPA's) chronic oral reference dose for sulfentrazone.[1]

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for sulfentrazone be set at 10% of the enforcement standard because sulfentrazone has been shown to have teratogenic effects.[1,2]

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

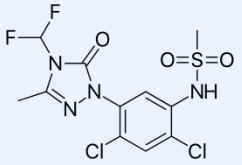
Recommended Standards	
Enforcement Standard:	1,000 µg/L
Preventive Action Limit:	100 µg/L

Health Effects

What we know about the health effects of sulfentrazone comes from studies with laboratory animals. Animals that ate large amounts of sulfentrazone for long periods of time experienced developmental and reproductive toxicity. When pregnant animals were fed sulfentrazone for a long period of time, decrease in body weight and disruption in male reproductive system happened to the fetuses (unborn babies) at levels that did not cause effects in the mother. In some studies, similar reproductive toxic effects were mainly observed in the second generation pups of the sulfentrazone-fed animals. In developmental studies in rats, increased number of stillborn fetuses and delayed bone formation was observed in pups (teratogenic effects).[1,2]

The EPA has classified sulfentrazone as not likely to be carcinogenic to humans. Sulfentrazone has not been shown to have mutagenic or interactive effects.[1]

Chemical Profile

	Sulfentrazone
Structure:	
CAS Number:	122836-35-5
Formula:	$C_{11}H_{10}Cl_2F_2N_4O_3S$
Molar Mass:	387.18 g/mol
Synonyms:	N-(2,4-Dichloro-5-[4-(difluoromethyl)-3-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]phenyl) methanesulfonamide

Exposure Routes

The Wisconsin Department of Agriculture, Trade, and Consumer Protection (DATCP) has approved the use of a number of commercial products (> 40 products) containing sulfentrazone for agricultural use.[3]

People can be exposed to sulfentrazone from food, air, soil, and water.[1] Certain foods may have some sulfentrazone in or on them from its use as a pesticide. The EPA regulates how much pesticide residues can be in foods. People can get exposed to sulfentrazone by walking through recently sprayed areas by breathing in air or touching sprayed soil. Adults can be exposed to sulfentrazone in air or soil from using products that contain sulfentrazone in their gardens or homes. Children can be exposed to sulfentrazone while playing in areas that have been treated with products containing sulfentrazone.

Sulfentrazone is highly mobile in groundwater and persistent in the environment.[1] Thus, once it is applied in an agricultural field, it has a strong potential to leach (travel through the soil) into groundwater or move offsite to surface water. Sulfentrazone can get into surface water from spray drift as well.

Current Standard

Wisconsin does not currently have a groundwater enforcement standard for sulfentrazone.[4]

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:	0.14 mg/kg-d	(2014)
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
None available		
Literature Search		
Literature Search Dates:	2014 – 2018	
Total studies evaluated:	15	
Key studies evaluated:	None	
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 for sulfentrazone.[5]

Health Advisory

The EPA has not established a health advisory for sulfentrazone.[6]

Drinking Water Concentration (Cancer Risk)

The EPA has not established drinking water concentrations based on cancer risk for sulfentrazone.[1]

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 sulfentrazone.[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 2014, the EPA Office of Pesticide Programs conducted a Human Health Risk Assessment as part of the registration of sulfentrazone. In their assessment, the EPA reviewed a number of studies on the toxicity of sulfentrazone.

The EPA selected a 2-generation reproductive toxicity study in rats as the critical study (MRID: 43345408).[2] In this study, groups of rats were exposed to different doses of sulfentrazone for two generations: 0, 14, 33, or 46 milligrams per kilogram body weight per day (mg/kg-d) in males and 0, 16, 40, or 56 mg/kg-d in females. The researchers observed decreased maternal body weight and decreased maternal body-weight gain during gestation in both first and second generation and reduced premating body-weight gain in first generation males. The No Observable Adverse Effect Level (NOAEL) from this study was 1.4 mg/kg-d. The EPA used a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). The EPA's chronic oral reference for sulfentrazone is 0.14 mg/kg-d.

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

Cancer Classification

The EPA has classified sulfentrazone as not likely to be carcinogenic to humans.[1,8]

The international Agency for Research on Cancer (IARC) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) have not evaluated the carcinogenicity of sulfentrazone. [9]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for sulfentrazone.[1]

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 sulfentrazone, we searched for values that been published since 2014 when the EPA published their human health risk assessment. 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 after the review by EPA in 2014. We conducted a search on the National Institutes of Health's PubMed resource for articles published from January 2014 to August 2018 out for studies related to sulfentrazone toxicity or its effects on a disease state in which information on sulfentrazone 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.

A total of 15 studies were returned by the search engine. We excluded monitoring studies, studies evaluating risk from non-mammalian species, and studies on the effects on plants from further review. After applying these exclusion criteria, we did not locate any key studies.

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

Standard Selection

DHS recommends an enforcement standard of 1,000 µg/L for sulfentrazone.

Basis for Enforcement Standard

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

There are no federal numbers for sulfentrazone and the EPA has not established a cancer slope factor for sulfentrazone because they did not find evidence of carcinogenicity. Additionally, there is no drinking water standard for sulfentrazone in Ch. NR 809, Wisc. Admin Code. The EPA does have an ADI (oral reference dose) for sulfentrazone. In our review, we did not find any significant technical information that was published since the EPA established their oral reference dose. Therefore, DHS calculated the recommended enforcement standard (ES) using the EPA's oral reference dose for sulfentrazone, an average body weight of 10 kg, a water consumption rate of 1 liter per day (L/d), and a relative source contribution of 100% as specified in Chapter 160 of Wisconsin Statute.

DHS recommends a preventive action limit of 100 µg/L for sulfentrazone.

DHS recommends that the preventive action limit for sulfentrazone be set at 10% of the enforcement standard because sulfentrazone has been shown to have teratogenic effects.[1,2] Sulfentrazone has not been shown to have carcinogenic, mutagenic, or interactive effects.[1,2]

Prepared by Clara Jeong, Ph.D.

Wisconsin Department of Health Services

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Bacteria (E. coli) | 2019

Substance Overview

The groundwater standard for bacteria protects people from illness caused by microbial pathogens. These pathogens are small organisms, such as bacteria, viruses, and parasites, that can cause disease.[1] Microbial indicators usually measure a group of bacteria or just one type of bacterium to indicate the possible presence of pathogens. These indicators are used to set the standard because they are more efficient to measure than every single pathogen. Two microbial indicators are used today to protect drinking water:

- **Coliform** are a group of bacteria that are naturally present in the environment.
- ***E. coli*** (*Escherichia coli*) are a type of coliform bacteria that are found in the environment, food, and gut of people and animals.

This document provides the recommended Public Health Enforcement Standard for E. coli.

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for *E. coli*.

DHS recommends an enforcement standard of zero for *E. coli*. The recommended standard is based on EPA's maximum contaminant level (MCL) for *E. coli*.

DHS recommends a NR140 Groundwater Quality Public Health Preventive Action Limit of 0 for *E. coli*.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Recommended Standards	
Enforcement Standard:	0
Preventive Action Limit:	0

Health Effects

Pathogens in water can cause a variety of illnesses.[1,2] Most common illnesses are acute (short-term) gastrointestinal illnesses causing diarrhea, abdominal discomfort, nausea, and vomiting. Less common illnesses are chronic (long-term) and include kidney failure, hepatitis, and bloody diarrhea.

Infants and young children, the elderly, and people with compromised immune systems are at the highest risk for illness from pathogens in water.[1]

Exposure Routes

Pathogens can get into drinking water from human and animal feces. People can be exposed to waterborne pathogens from drinking contaminated water, coming into contact with a contaminated surface, or being in contact with a person who is carrying the pathogen.

Current Standard

Wisconsin does not currently have groundwater standards for *E. coli*.[3]

Standard Development

Federal Numbers		
Maximum Contaminant Level:	0	(2016)
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	
Guidance Values		
None available		
Literature Search		
Search Dates:	2016 – 2019	
Total studies evaluated:	None	
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

In April 2016, EPA made changes to how bacteria are regulated in public water systems as part of the Revised Total Coliform Rule (RTCR).[1] The RTCR replaced the non-acute MCL for total coliform with an acute MCL for *E. coli* (*Escherichia coli*). This change was because more recent studies have shown that *E. coli* is a more specific indicator of contamination from feces and many coliform bacteria detected by total coliform tests are not pathogenic and occur naturally in the environment.

Health Advisory

The EPA has not established a health advisory for *E. coli*.[4]

Drinking Water Concentrations at Specified Cancer Risk Levels

Because *E. coli* are microbial indicators, this evaluation is not appropriate.

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. available.

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for *E. coli*.[5]

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 *E. coli*.

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.

Because *E. coli* are microbial indicators, this evaluation is not appropriate.

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 E. coli, we searched for values that been published since 2016 when RTCR was published. We did not find any relevant guidance values from the EPA, Agency for Toxic Substances and Disease Registry (ATSDR), World Health Organization (WHO), or Health Canada.

Literature Search

The latest research indicates that *E. coli* is a very strong indicator of fecal contamination in drinking water because it thrives in the gastrointestinal tract of warm-blooded animals.[1,6-8]

Standard Selection

DHS recommends an enforcement standard of 0 for *E. coli*.

The EPA has an MCL of 0 for *E. coli*. State statute requires that DHS recommend a federal number (including MCL) if one is available and there is no significant technical information that was not considered when the federal number was set that demonstrates another number is more appropriate. Available scientific information indicates that *E. coli* is an appropriate pathogen indicator for the protection of groundwater.

Basis for Enforcement Standard

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

DHS recommends a preventive action limit of 0 for *E. coli*.

Because DHS recommends an enforcement standard of zero for *E. coli*, the recommended preventive action limit is also zero.

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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Perfluorooctanoic acid (PFOA) | 2022

Substance Overview

Perfluorooctanoic acid (PFOA) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS). Because of its chemical properties, PFOA has been used as stain repellants in commercial products like carpet and fabric, as a coating for packaging, and in some fire-fighting foams.[1] PFOA can persist in the environment and in the body for long periods of time.[1]

Recommendations

Wisconsin does not currently have an NR140 Groundwater Quality Public Health Enforcement Standard for PFOA.

DHS recommends a combined enforcement standard of 20 nanograms per liter (ng/L) for PFOA. The recommended standard is based on a study that used modeling to estimate how much PFOA a mother has to be exposed to in order to protect the infant from developmental effects. **This standard applies to the sum of PFOA and PFOS concentrations in groundwater.**

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for PFOA be set at 10% of the enforcement standard because PFOA has been shown to have carcinogenic, teratogenic, and interactive effects.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

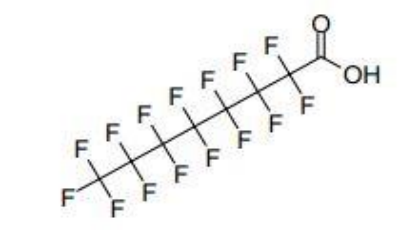
Recommended Standards	
Enforcement Standard:	20 ng/L
Preventive Action Limit:	2 ng/L
(Sum of PFOA and PFOS)	

Health Effects

Studies in workers and people living in areas with high levels of PFOA show that PFOA may increase cholesterol, damage the liver, cause pregnancy-induced hypertension, increase the risk for thyroid disease, decrease antibody response to vaccines, decrease fertility, and cause small decreases in birth weight.[1] Studies in research animals have found that PFOA can cause damage to the liver and the immune system, birth defects, delayed development, and newborn deaths in lab animals.[1]

The International Agency for Research on Cancer (IARC) classifies PFOA as possibly carcinogenic to humans and the EPA states there is suggestive evidence of carcinogenic potential for PFOA. PFOA has been shown to be genotoxic in some tests, but has not been shown to be mutagenic.[2,3] Both PFOA and PFOS have been shown to cause the same or similar effects on the immune system, development, and reproduction in people and research animals indicating that PFOA can cause interactive effects.[1,4,5]

Chemical Profile

	PFOA
Structure:	
CAS Number:	335-67-1
Formula:	C8HF15O2
Molar Mass:	414.069 g/mol
Synonyms:	Perfluorooctanoic acid Pentadecafluoro-1-octanoic acid pentadecafluoro-n-octanoic acid pentadecafluoroctanoic acid perfluorocaprylic acid perfluoroheptanecarboxylic acid 2,2,3,3,4,4,5,5,6,6,7,7,8,8, 8-pentadecafluoro octanoic acid

Exposure Routes

People can be exposed to PFOA by drinking contaminated water, eating fish caught from contaminated waterbodies, swallowing contaminated soil or dust, eating food that was packaged in material that contains PFOA, and using consumer products such as non-stick cookware, stain resistant carpeting, and water repellant clothing.[1]

Research has shown that the majority of exposure to PFOA comes from food. Drinking water can be a major source of PFOA if levels are high.[1] Babies born to mothers exposed to PFOA can be exposed during pregnancy and during breastfeeding.[1]

Current Standard

There are no current groundwater standards for PFOA in Wisconsin.[6]

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A	
Lifetime Health Advisory Level:	70 ng/L	(2016)
Drinking Water Concentration (Cancer Risk):	500 ng/L	(2016)

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A	

Acceptable Daily Intake

EPA Oral Reference Dose:	0.00002 mg/kg-d (20 ng/kg-d)	(2016)

Oncogenic Potential

EPA Cancer Slope Factor:	0.07 $(mg/kg\text{-}d)^{-1}$	(2016)

Guidance Values

ATSDR Minimum Risk Level:	0.000003 mg/kg-d (3 ng/kg-d)	(2018)

Literature Search

Search Dates:	2016 – 2019
Total studies evaluated:	Approximately 280
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 PFOA.[7]

Health Advisory Level

In 2016, the EPA published a lifetime Health Advisory of 70 ng/L for PFOA.[2,3] The EPA evaluated several studies including those that observed effects on immune response, development, and liver and kidney toxicity. They selected a 2006 study by Lau et al. as the critical study.[8] In this study, the researchers gave pregnant mice different concentrations of PFOA (0, 1, 3, 5, 10, 20, or 40 mg/kg-d) by gavage during pregnancy (GD 1 to 17). In these mice, PFOA caused early pregnancy loss, compromised postnatal survival, delayed general growth and development, and sex-specific alterations in pubertal maturation. The EPA identified a Lowest Observable Adverse Effect Level (LOAEL) of 1 milligram PFOA per kilogram body weight per day

Summary of EPA's Health Advisory for PFOA	
LOAEL:	1 mg/kg-d (1,000,000 ng/kg-d)
Half-life used:	2.3 years
Human equivalent dose:	0.0053 mg/kg-d (530 ng/kg-d)
Total uncertainty factor:	300
Oral reference dose:	0.00002 mg/kg-d (20 ng/kg-d)
Water Concentration:	**70 ng/L**

(mg/kg-d) based on decreased bone development and accelerated male puberty in offspring after maternal exposure from this study.

Pharmacokinetic models are mathematical modeling techniques that can be used to predict the movement of chemicals in the body. The EPA used pharmacokinetic modeling for PFOA to estimate a human equivalent dose, which is the amount that a person would have to ingest every day to cause this effect. The model used by EPA converted the level of PFOA in animal serum at which adverse effects were observed to a corresponding level in human serum. The human equivalent dose was then estimated by taking into consideration the amount of time that PFOA stays in the body (half-life) and how much blood is in the human body.

The EPA estimated a human equivalent dose of 530 ng/kg-d for PFOA by using the LOAEL and a half-life of 2.3 years. The EPA selected the half-life a 2010 study by Bartell et al.[9] This study estimated half-life after treatment was installed to remove PFOA from the water supply in Lubeck, WV and Little Hocking, OH. The EPA's rationale for selecting this study is that it applies to the general population and reflects exposure that is primarily from drinking water.

The EPA applied a total uncertainty factor of 300 to account for differences between people and research animals (3), differences among people (10), and the use of a LOAEL instead of a NOAEL (10). This resulted in an oral reference dose of 20 ng/kg-d. To set the advisory, the EPA used a water consumption rate for pregnant women (0.054 liters per kilogram body weight per day or L/kg-d) because the effect occurred in offspring after the maternal exposure during pregnancy. They applied the default relative source contribution of 20% to account for exposure from other sources (such as food and air).

The EPA recommended that the lifetime health advisory of 70 ng/L apply to the sum of PFOA and PFOS. They recommended this combined approach because the adverse effects in humans and animals are the same or similar and the critical effect used to set the oral reference dose for both PFOA and PFOS are developmental endpoints.

Drinking Water Concentration as Specified Risk Levels

In 2016, EPA also determined a drinking water concentration that corresponds to a lifetime cancer risk of 1 in 1,000,000 for PFOA.[2] They used a cancer slope factor of 0.07 $(mg/kg\text{-}d)^{-1}$ (see *EPA Cancer Slope Factor* section below for more details), an average body weight of 80 kg, and a daily water consumption rate of 2.5 L/d to calculate a water concentration of 500 ng/L. Because this concentration is higher than the level that was calculated to protect against developmental effects, the EPA concluded that the lifetime health advisory of 70 ng/L is protective of potential cancer effects.

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 drinking water standard for PFOA.[6]

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 setting the lifetime health advisory for PFOA, the EPA Office of Water established an oral reference dose of 20 ng/kg-d (see above for more details).[2,3]

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

Cancer Classification

In 2016, the EPA also evaluated the cancer potential of PFOA when developing the health advisory and determined that there is suggestive evidence that PFOA has carcinogenic potential in humans.[2,3]

The International Agency for Research on Cancer (IARC) have not evaluated the cancer potential of PFOA.[10]

EPA Cancer Slope Factor

In 2016, the EPA established a cancer slope factor of 0.07 $(mg/kg\text{-}d)^{-1}$ from a 2012 study by Butenhoff that that evaluated effects in rats exposed to PFOA by gavage for 2 years.[2,3,11] The slope factor is based off an increased incidence of testicular cancer in male rats.

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 PFOA, we searched for values that have been published since 2016 when the EPA published their health advisory level. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Intermediate Oral Minimum Risk Level

In 2020, the Agency for Toxic Substances and Disease Registry (ATSDR) finalized their Toxicological Profile for Perfluoroalkyls.[1] In this Profile, they established an intermediate oral minimum risk level of 3 ng/kg-d for PFOA.[a]

Summary of ATSDR's Minimum Risk Level for PFOA	
LOAEL:	0.3 mg/kg-d (300,000 ng/kg-d)
Half-life used:	3.8 years
Human equivalent dose:	0.000821 mg/kg-d (821 ng/kg-d)
Total uncertainty factor:	300
Minimum risk level:	0.000003 mg/kg-d (3 ng/kg-d)

The ATSDR evaluated several studies including those that observed effects on immune response, development, and liver toxicity. They selected two studies as their critical studies: a 2011 study by Onishchenko et al.[12] and a 2016 study by Koskela et al.[13] In these studies, female mice were exposed to PFOA during pregnancy and offspring had impaired neurological development and skeletal alterations. The ATSDR identified a LOAEL of 0.3 mg/kg-d from these studies.

The ATSDR also used pharmacokinetic modeling to estimate a human equivalent dose by converting the level of PFOA in animal serum to a level in serum that would cause the same effect in humans. They estimated a human equivalent dose of 821 ng/kg-d for PFOA by using the LOAEL and a half-life of 3.8 years. The ATSDR selected this half-life from a 2007 study by Olsen et al that estimated the half-life in occupationally-exposed workers.[14] The ATSDR selected this study because the follow-up time was longer than the Bartell et al., 2010 study (more than 5 years in the Olsen et al. study compared to 6-12 months in the Bartell et al. study) and that a study found that estimates of the terminal half-life for PFOA can increase with longer follow-up.[15]

To obtain the intermediate oral minimum risk level, the ATSDR applied a total uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (3), and using a LOAEL instead of a NOAEL (10).

a The ATSDR's intermediate minimum risk levels are protective of exposures between 15 and 364 days. The ATSDR did not recommend a chronic oral reference dose for PFOA because they felt that that the available data for chronic exposure (more than 1 year) are limited and were uncertain whether the most sensitive endpoint for chronic exposure has been identified in the current research.

Literature Search

To identify recent publications, we conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from 2016 (when EPA's lifetime health advisory was published) to April 2019. We searched for studies related to PFOA toxicity or PFOA effects on a disease state in which information on exposure or dose was included as part of the study or studies related to modeling PFOA exposure or dose using pharmacokinetics in animals or humans.[b] Previous research has shown that effects on the immune system, development, and reproduction are the most sensitive, so we searched for new toxicity studies in these areas.[1,2] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an appropriate exposure duration.

Approximately 280 studies were returned by the search engine. We excluded studies on non-mammalian or cell systems, non-oral exposure routes, those that did not evaluate health risks, and those only examining a single point of exposure from further review. After applying these exclusion criteria, we located five key toxicity studies and three key pharmacokinetic studies on PFOA.

To be considered a critical toxicity 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.[c] Four of the key studies met the criteria to be considered a critical toxicity study (see Tables A-1 and A-2 for more details). To be considered a critical pharmacokinetics study, the study must model oral exposure in humans or rodents. Three of the key studies met the criteria to be considered a critical pharmacokinetic study (the section below has more details on these studies).

Critical Toxicity Studies

To compare between results between studies, we calculated acceptable daily intake (ADI) for each study/effect. The ADI is the estimated amount of PFOA that a person can be exposed to every day and not experience health impacts. The ADI equals the toxicity value divided by the total uncertainty factor. Uncertainty factors were included as appropriate to account for differences between humans and research animals, differences in sensitivity to health effects within human populations, using data from short-term experiments to protect against effects from long-term exposure, and using data where a health effect was observed to estimate the level that does not cause an effect.

Chen et al., 2017

b The following search terms were used in the literature review:
Title/abstract: PFOA or "Perfluorooctane sulfonate"
Keywords: Development OR immune OR reproduction OR pharmacokinetics OR modeling
Subject area: toxicology OR cancer
Language: English

c 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%).[8]

In 2017, Chen et al. evaluated the effects of PFOA exposure by gavage on development.[16] Pregnant mice were exposed to 2.5, 5, or 10 mg/kg-d of PFOA from gestational days (GD) 1 to 7 or 1 to 13. The highest concentration of PFOA significantly increased the number of resorbed embryos at GD13. All doses of PFOA affected serum progesterone levels and decreased transcription levels of key steroidogenic enzymes.

From this study, we identified a LOAEL of 2.5 mg/kg-d based on altered serum progesterone levels. We estimated an ADI of 0.0025 mg/kg-d based on the LOAEL and a total uncertainty factor of 1000 to account for differences between people and research animals (10), differences among people (10), and using a LOAEL instead of a NOAEL (10).

Goulding et al., 2017

In 2017, Goulding et al. evaluated the effects of PFOA exposure by gavage on development.[17] Pregnant mice were exposed to 0.1, 0.3, or 1 mg/kg-d of PFOA from gestational days 1 to 17. In this study, PFOA caused minimal effects on neurological development in male offspring. The only statistically significant effect was higher ambulatory activity in offspring at postnatal day (PND) 18 in mice exposed to 1 mg/kg-d. This effect was not observed at PND 19 and 20. The NOAEL from this study is 0.3 mg/kg-d and the LOAEL is 1 mg/kg-d.

From this study, we identified a NOAEL of 0.3 mg/kg-d and LOAEL of 1 mg/kg-d based on higher ambulatory activity in offspring at PND 18. We estimated an ADI of 0.003 mg/kg-d based on the NOAEL and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

Song et al., 2018

In 2018, Song et al. evaluated the effects of PFOA exposure by gavage on development.[18] Pregnant mice were exposed to 1, 2.5, or 5 mg/kg-d of PFOA from gestational days 1 to 17. The highest concentration of PFOA caused a significant decrease in offspring survival. PFOA exposure also caused non-dose respondent serum testosterone level changes and testis structural changes. The NOAEL from this study is 2.5 mg/kg-d and the LOAEL is 5 mg/kg-d.

From this study, we identified a NOAEL of 2.5 mg/kg-d and a LOAEL of 5 mg/kg-d based on decreased offspring survival. We estimated an ADI of 0.025 mg/kg-d based on the NOAEL and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

Van Esterik et al., 2016

In 2016, van Esterik et al. evaluated the impact of PFOA exposure *in utero* and during lactation on metabolic effects.[19] Pregnant mice were exposed to 0.003, 0.01, 0.03, 0.1, 0.3, 1, or 3 mg/kg-d of PFOA from gestation through lactation. In this study, PFOA decreased body weight at week 21 and decreased cortical density in the tibia in male offspring. In female offspring, PFOA decreased body weight at week 21 and 27, decreased femur length and weight, decreased quadriceps femoris muscle and perirenal fat pad weight, and decreased tibia composition/function (including cortical density, ability to resist torsion,

bending strength, and trabecular area). PFOA also decreased serum cholesterol and triglycerides levels. The most sensitive effect measured was the effect on serum triglyceride levels in female mice.

From this study, we identified a benchmark dose (95% Lower Confidence Limit) of 0.0062 mg/kg-d PFOA. Based on altered serum triglyceride levels in female mice. We estimated an ADI of 0.000062 mg/kg-d based on the BMDL and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

Critical Pharmacokinetic Studies

Cheng and Ng, 2017

In 2017, Cheng and Ng published a study in which they adapted an existing pharmacokinetic model to estimate serum levels of PFOA in rats.[20] The advantage of this model is that it considers cell membrane permeability instead of blood flow rate as the rate limiting process. This is important because large molecules like PFOA are more likely to be limited by cell membrane permeability than blood flow kinetics. This model was used to estimated serum levels of PFOA after exposure to 0.1 and 1 mg/kg-orally and 0.041 and 1 mg/kg intravenously. The authors found that the model was able to predict plasma toxicokinetics and tissue distribution of PFOA within a factor of 5.

Some of the limitations of this model are that some parameter values used are based on a single study or extrapolated from *in vitro* studies, which adds uncertainty to the model predictions. Additionally, some protein-binding parameters were not included and the model did not consider females due to limited data.

Goeden et al., 2019

In 2019, Goeden et al**.** published a study in which they developed a pharmacokinetic model to estimate PFOA serum levels in infants at birth from placental transfer and predict serum levels after early life exposure from bottle- or breastfeeding.[21] In this model, they used a maternal serum concentration of 38 mg/L to estimate PFOA serum levels in infants after bottle and breastfeeding. This maternal serum level corresponds to the dose that caused developmental effects in the Lau et al. study, which was used by EPA to set the LHA. Goeden et al. then used this estimated infant serum level to determine a health-based guidance value for PFOA in drinking water (for more details on this value, see Table A-1).

The authors found that predicted serum concentration following 6 months of breastfeeding aligned closely with reported mean and 95th percentile infant serum concentrations at 6 months of age (R^2 = 0.7044). They also found that predicted infant serum concentrations were 40% higher than previously estimated adult levels when placental transfer was considered and, when both placental transfer and breastmilk transfer are taken into account, infant concentrations are 600% higher than adult steady-state levels.

One limitation of this model is that it assumes the mother's serum concentration at delivery is at steady-state. It also assumes that maternal exposure to PFOA during lactation is the same as prior to delivery and estimates maternal exposure from serum concentration at delivery.

Kieskamp et al., 2018

This study combined two existing models of developmental exposure (one in mice and one in humans) to estimate fetal and pup plasma levels resulting from maternal exposure to the LOAEL used by EPA. They then used these fetal and pup plasma levels to predict the human equivalent dose (HED) in women that would result in fetal and child plasma levels that match the levels in animals. Finally, they evaluated how the estimated HEDs were influenced by breastfeeding duration and half-life by using breastfeeding durations of 6, 12, and 24 months and half-lives of 2.3 and 3.8 years.

The authors obtained a distribution of HEDs for 24 combinations based on estimated dose, half-life, and breastfeeding duration and reported the 1st and 50th percentile estimated HEDs. They found that using the shorter half-life resulted in lower estimated HEDs. They also found that estimated HED generally decreased with increasing breastfeeding duration. All of the predicted HEDs based on pup/child dosimetry were below the adult HED used by EPA to set the health advisory level for PFOA (530 ng/kg-d).

Predicted Human Equivalent Doses (HEDs) for Given Half-Life and Breastfeeding Duration (ng/kg-d)

		1st Percentile		50th Percentile	
	Half-life:	2.3 year	3.8 year	2.3 year	3.8 year
Breastfeeding duration	6 months	99	62	700	430
	12 months	78	50	540	330
	24 months	73	47	500	310
Adapted from Table 1 in Kieskamp et al. 2018 ([22])					

One limitation of this model is that, for some parameters, values from rats were used due to limited available information for mice. The authors noted that additional data in animals and humans would provide better understanding of how PFOA partitions into milk over time and improve estimates of lactational transfer.

Summary

While a large number of epidemiology studies on the effects of PFOA have been published since 2016 (see Appendix B for a summary of these studies), the long half-life of PFOA in people, multiple potential exposure sources, and the ability for other PFAS compounds to cause similar health effects prohibit using these data to establish a health-based value for PFOA.[21,23-117] As such, animal and modeling studies are crucial for the development of a protective standard.

Animal studies published since 2016 indicate that development is a significant endpoint for PFOA and that effects may occur at levels lower than those previously studied.[17-19,101] New modeling studies have better characterized how PFOA levels in infants are affected due to exposure *in utero* and from breastfeeding.[20-22]

Standard Selection

DHS recommends a combined enforcement standard of 20 ng/L for PFOA and PFOS.

There is a federal number for PFOA – EPA's lifetime health advisory level.[2,3] However, recent modeling studies have indicated that the approach used by EPA to set their advisory may not be adequately protective of infants.[21,22]

Basis for Recommended Standard

- ☐ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☑ **Significant technical information**

Toxicity studies in animals continue to show that development is a critical effect for PFOA with effects occurring in offspring after exposure during pregnancy and lactation.[16-19] Recent modeling studies with PFOA have indicated that modeling approach taken by EPA may not be adequate to protect infants from exposure during pregnancy and while breastfeeding.[21,22] PFOA can cross the placenta during pregnancy and pass through breastmilk. [1,2] To set their lifetime health advisory level, the EPA estimated how much PFOA a woman has to be exposed to orally during pregnancy for her serum levels to be equivalent to the level where health effects were seen in mice pups (babies).[2,3] The modeling studies with PFOA modeling of maternal exposure levels may not be adequate to protect infants from exposure during pregnancy and while breastfeeding. These studies suggest that modeling of infant exposure may be a more appropriate approach to protecting this sensitive population.

From this information, DHS concludes that there is significant technical information that was not considered when EPA set the lifetime health advisory for PFOA. Therefore, DHS recommends setting the enforcement standard for PFOA using procedures in s. 160.13(2). DHS selected the 2018 study by Kieskamp et al. as the principal study.[22] In this study, the authors use a model to estimate how much a pregnant woman would have to be exposed to orally for the baby to plasma levels equivalent to the LOAEL used by EPA. They looked at how half-life and breastfeeding duration affected exposure levels.

From this study, we selected the HED of 0.00054 mg/kg-d as the toxicity value, which is the median HED for a half-life of 2.3 years and breastfeeding duration of 12 months. We used the median HED because it represents a more realistic exposure scenario than the 1st percentile HED. We selected the HED that corresponds with the half-life of 2.3 years from the Bartell et al. study.[9] The half-life of 2.3 years is consistent with the half-life reported in a recent study by Li et al.[118] In this 2018 study, researchers estimated half-life after clean water was provided to individuals exposed to municipal drinking water contaminated with a number of PFAS in Ronneby, Sweden. The researchers measured PFOA, PFOS, and PFHxS levels in 104 individuals from June 2014 through September 2016. They estimated a half-life of 2.7 years for PFOA. We selected the HED that corresponds with a breastfeeding duration of 12 months as the American Academy of Pediatrics (AAP) recommends that infants are breastfed for up to 12 months.[119] As such, using a breastfeeding duration of less than 12 months may not provide adequate protection while using a duration of more than 12 months may overestimate PFOA exposure.

We applied a total uncertainty factor of 300 to account for differences between people and research animals (3), differences among people (10), and using a LOAEL instead of a NOAEL (10). To determine the recommended enforcement standard, DHS used the ADI, and, as required by Ch. 160, Wis. Stats., a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%.

DHS recommends a combined enforcement standard of 20 ng/L for PFOA and PFOS. Studies have shown that PFOA and PFOS can cause similar effects in humans and in animals. The critical studies used by DHS to establish the ADI for PFOA and PFOS are developmental studies and recent studies have shown that PFOA and PFOS may cause toxicity through similar mechanisms of action. This approach is consistent with that taken by the EPA when developing the lifetime health advisory.[2,3] EPA recommended that the advisory apply to the sum of PFOA and PFOS because the adverse effects in humans and animals are same or similar and the critical effect used to set the oral reference dose for both PFOA and PFOS are developmental endpoints.

DHS recommends a combined preventive action level of 2 ng/L for PFOA and PFOS.

DHS recommends that the preventive action level be set at 10% of the enforcement standard because PFOS and PFOA have both been shown to have carcinogenic and teratogenic effects.[1-3] Both PFOA and PFOS have been shown to cause the same or similar effects on the immune system, development, and reproduction in people and research animals indicating that PFOS can cause interactive effects.[1-3]

Updated by Amarilys Gonzalez Vazquez, Ph.D and Sarah Yang, Ph.D. – January 2022

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Appendix A: Key Toxicity Studies for PFOA

Table A-1. Toxicity Studies Published since ATSDR's Toxicological Profile

Study Type	Species	Exposure Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Development	Mouse	GD 1-7 GD 1 -13	2.5, 5, 10	Gavage	At GD13, PFOA treatment significantly increased numbers of resorbed embryos at 10 mg/kg. Reduced serum progesterone levels and decreased transcription levels of key steroidogenic enzymes. Reduced number and size of corpora lutea in the ovaries.	LOAEL: 2.5	Chen et al, 2017 ([16])
Development	Mouse	GD 1-17	0.1, 0.3, 1.0	Gavage	Shift in the developmental pattern with an elevated activity level observed at 1.0 mg/kg-d at PND 18-20.	NOAEL: 0.3 LOAEL: 1.0	Goulding et al., 2017 ([17])
Reproduction	Mouse	28 d	1.25, 5, 20	Gavage	Decrease in mated and pregnant females per male mouse and litter size. Blood-testes barrier damage.	NOAEL: 1.25 LOAEL: 5	Lu et al, 2016 ([120])
Development	Mouse	GD 1 -17	1, 2.5, 5	Gavage	Significant decrease in offspring survival at 5 mg/kg Non-dose respondent serum testosterone level changes and testis structural changes	NOAEL: 2.5 LOAEL: 5	Song et al. 2018 ([18])
Development	Mouse	GD 1 – PND 21	0.003, 0.01, 0.03, 0.1, 0.3, 1, 3	Diet	Dose-dependent decrease in body weight from PND 4 to adulthood. Under high fat diet, growth was increased in male offspring and decreased in female offspring in the last 4-6 weeks. Increased liver weights and cellular alterations in offspring. Reduced fat pad weights, serum triglycerides, and cholesterol in female offspring.	BMDL: 0.0062 (triglycerides)	van Esterik et al, 2016 ([19])

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?
Chen, 2017	✓	✓	✓	**3**	✓	**Yes**
Goulding, 2017	✓	✓	✓	**3**	✓	**Yes**
Lu, 2016	⊘	✓	✓	**3**	✓	No
Song et al. 2018	✓	✓	✓	**3**	✓	**Yes**
Van Esterik, 2016	✓	✓	✓	**7**	✓	**Yes**

To be considered a critical toxicity 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.

Appendix B: Epidemiology Studies of PFAS Published since ATSDR's Toxicological Profile[d]

Category	Examples	Number of Studies
Metabolic	Diabetes (type 1, 2, and gestational), glucose tolerance, insulin resistance, BMI, obesity/overweight, adiposity, cholesterol, triglycerides	41
Birth outcomes	Birth size (weight, length, etc), gestation age, small for gestational age, fetal growth, anogenital distance at birth	25
Neurological	Attention, impulse control, visual and spatial ability, cognitive development, executive function, autism spectrum disorder, intellectual disability	18
Reproductive	Endometriosis, preeclampsia, reproductive hormones, time to pregnancy, fertility, semen characteristics, pregnancy loss, menopause, puberty onset	13
Immune	Asthma, vaccine antibodies, allergic conditions, infectious disease incidence, atopic dermatitis	12
Thyroid	Thyroid hormones, thyroid function	10
Cardiovascular	heart attack, stroke, heart failure, arterial wall stiffness, coronary heart disease, blood pressure, hypertension	7
kidney	Chronic kidney disease, kidney function, glomerular filtration	7
Other	Vitamin D, bone density, lung function, dental carries, gut bacteria and metabolites, mortality,	6
DNA	Telomere length, DNA methylation	5
Liver	ALT (alanine aminotransferase), other liver function biomarkers	4
Cancer	Breast cancer	2

d The following search terms were used in the literature review:
Subject: "(PFOS OR PFOA OR PFAS OR PFC) AND epidemiology
Language: English
We excluded studies that did not evaluate health effects from our analysis.

Perfluorooctane sulfonic acid (PFOS) | 2022

Substance Overview

Perfluorooctane sulfonate (PFOS) is a chemical in a group of contaminants called per- and polyfluoroalkyl substances (PFAS). Because of its chemical properties, PFOS has been used as stain repellants in commercial products like carpet and fabric, as a coating for packaging, and in some fire-fighting foams.[1] PFOS can persist in the environment and in the body for long periods of time.[1]

Recommendations

Wisconsin does not currently have a NR140 Groundwater Quality Public Health Enforcement Standard for PFOS.

DHS recommends an enforcement standard of 20 nanograms per liter (ng/L) for PFOS. This standard is based on the Agency for Toxic Substances and Disease Registry's (ATSDR's) intermediate oral minimum risk level for PFOS. **This standard applies to the sum of PFOS and PFOA concentrations in groundwater.**

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for PFOS be set at 10% of the enforcement standard because PFOS have been shown to have carcinogenic, teratogenic, and interactive effects.

Current Standards	
Enforcement Standard:	N/A
Preventive Action Limit:	N/A
Year:	N/A

Recommended Standards	
Enforcement Standard:	20 ng/L
Preventive Action Limit:	2 ng/L
(sum of PFOS and PFOA)	

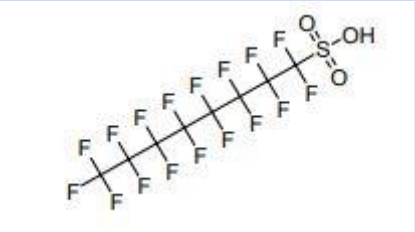
Health Effects

Studies in workers and people living in areas with high levels of PFOS in drinking water show that PFOS may increase cholesterol, damage the liver, cause pregnancy-induced hypertension, increase the risk for thyroid disease, decrease antibody response to vaccines, decrease fertility, and cause small decreases in birth weight.[1-3] Studies in research animals have found that PFOS can cause damage to the liver and the immune system. PFOS has also been shown to cause birth defects, delayed development, and newborn deaths in animals, indicating that PFOS can cause teratogenic effects.

The EPA has classified PFOS as having suggestive evidence of carcinogenic potential.[2, 3] PFOS has not been shown to have mutagenic effects.[1-3] Both PFOA and PFOS have been shown to cause the same or

similar effects on the immune system, development, and reproduction in people and research animals indicating that PFOS can cause interactive effects.[1-3]

Chemical Profile

	PFOS
Structure:	
CAS Number:	1763-23-1
Formula:	$C_8HF_{17}O_3S$
Molar Mass:	500.03 g/mol
Synonyms:	perfluorooctane sulfonate 1-perfluorooctanesulfonic acid heptadecafluoro-1-octanesulfonic acid heptadecafluorooctan-1-sulphonic acid perfluorooctylsulfonic acid 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro 1-octanesulfonic acid

Exposure Routes

People can be exposed to PFOS by drinking contaminated water, eating fish caught from contaminated waterbodies, swallowing contaminated soil or dust, eating food that was packaged in material that contains PFOS, and using consumer products such as non-stick cookware, stain resistant carpeting, and water-repellant clothing.[1]

Research indicates that the majority of exposure to PFOS comes from food. Drinking water can be a major source of PFOS if levels are high.[1] Babies born to mothers exposed to PFOS can be exposed during pregnancy and during breastfeeding.[1]

Current Standard

There are no current groundwater standards for PFOS in Wisconsin.[4]

Standard Development

Federal Numbers		
Maximum Contaminant Level:	N/A	
Lifetime Health Advisory Level:	70 ng/L	(2016)
Drinking Water Concentration (Cancer Risk):	N/A	
State Drinking Water Standard		
NR809 Maximum Contaminant Level:	N/A	
Acceptable Daily Intake		
EPA Oral Reference Dose:	0.00002 mg/kg-d	(2016)
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
ATSDR Minimum Risk Level:	0.0000027 mg/kg-d	(2018)
Literature Search		
Search Dates:	2016 – 2019	
Total studies evaluated:	Approximately 300	
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 PFOS.[5]

Health Advisory

In 2016, the EPA Office of Water established a Lifetime Health Advisory of 70 ng/L for PFOS.[2, 3] The EPA evaluated several studies including those that observed effects on development, reproduction, and liver and kidney toxicity. They selected a 2005 study by Luebker et al. that observed reduced body weight in offspring after maternal exposure during pregnancy as the critical

Summary of EPA's Health Advisory for PFOS	
NOAEL:	0.1 mg/kg-d (100,000 ng/kg-d)
Half-life used:	5.4 years
Human equivalent dose:	0.00051 mg/kg-d (510 ng/kg-d)
Total uncertainty factor:	30
Oral reference dose:	0.00002 mg/kg-d (20 ng/kg-d)
Water concentration:	**70 ng/L**

study.[6] In this study, pregnant rats were exposed to PFOS for two generations. PFOS caused delayed eye opening and reduced weight in offspring.[6] The EPA identified a No Observable Adverse Effect Level (NOAEL) of 0.1 milligrams PFOS per kilogram body weight per day (mg/kg-d) from this study.

The EPA used pharmacokinetic modeling to estimate a human equivalent dose, which is the amount that a person would have to ingest every day to cause this effect. The model used by EPA converted the level of PFOS in animal serum at which adverse effects were observed to a corresponding human serum level. The human equivalent dose was then estimated by taking into consideration the amount of time that PFOS stays in the body (half-life) and how much blood is in the human body.

The EPA estimated a human equivalent dose of 510 nanograms PFOS per kilogram body weight per day (ng/kg-d) for PFOS by using the NOAEL and a half-life of 5.4 years from a 2010 study by Olsen et al. that estimated the half-life in occupationally-exposed workers.[7] The EPA applied a total uncertainty factor of 30 to account for differences between people and research animals (10) and differences among people (3). This resulted in an oral reference dose of 20 ng/kg-d.

To set the advisory, the EPA used a water consumption rate for pregnant women (0.054 L/kg-d) because the effect occurred in offspring after maternal exposure to PFOS during pregnancy. The EPA applied the default relative source contribution of 20% to account for exposure from other sources (such as food and air).

The EPA recommended that the lifetime health advisory of 70 ng/L applies to the sum of PFOA and PFOS. They recommended this combined approach because the adverse effects observed in humans and animals are the same or similar for the two substances and the critical effect used to set the oral reference doses for both PFOA and PFOS are developmental endpoints.

Drinking Water Concentration as Specified Risk Levels

The EPA has not established drinking water concentrations at specified cancer risk levels for PFOS.[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 drinking water standard for PFOS.[5]

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 setting the lifetime health advisory for PFOS, the EPA Office of Water established an oral reference dose of 20 ng/kg-d (see the *Health Advisory* section above for details).[2, 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 PFOS, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of PFOS. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

In 2016, the EPA also evaluated the cancer potential of PFOS when developing their health advisory and determined that there is suggestive evidence that PFOS has carcinogenic potential in humans.[2, 3]

The International Agency for Research on Cancer (IARC) has not evaluated the cancer potential of PFOS.[8]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for PFOS.[2, 3] In setting the health advisory, they determined that the weight of evidence for relevance to humans was too limited to support a quantitative assessment and that modeling of the liver and thyroid adenomas observed in rats was not possible because a dose-response relationship was not observed.

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 PFOS, we searched for values that have been published since 2016 when the EPA published their health advisory level. We found a relevant guidance value from the Agency for Toxic Substances and Disease Registry (ATSDR).

ATSDR Intermediate Oral Minimum Risk Level

In 2020, the Agency for Toxic Substances and Disease Registry (ATSDR) released their final Toxicological Profile for Perfluoroalkyls.[1] In this Profile, they established an intermediate oral minimum risk level of 0.000002 mg/kg-d for PFOS.[a]

The ATSDR evaluated several studies including those that observed effects on immune response, development, and liver toxicity. The ATSDR also selected the 2005 Luebker et al. study as their critical study and identified a NOAEL of 0.1 mg/kg-d.

The ATSDR also used pharmacokinetic modeling to estimate a human equivalent dose by converting the level of PFOS in animal serum at which adverse effects were observed to a corresponding human serum level. They estimated a human equivalent dose of 0.000515 mg/kg-d for PFOS by using the NOAEL of 0.1 mg/kg-d and a half-life of 5.4 years. The ATSDR, like EPA, selected a half-life of 5.4 years from a 2007 study by Olsen et al.[7]

To obtain the intermediate oral minimum risk level, they applied a total uncertainty factor of 30 to account for differences between people and research animals (3) and differences among people (10). The ATSDR also applied a modifying factor of 10 due to concern that immunotoxicity effects may be a more sensitive

Summary of ATSDR's Minimum Risk Level for PFOS	
NOAEL:	0.1 mg/kg-d (100,000 ng/kg-d)
Half-life used:	5.4 years
Human equivalent dose:	0.00051 mg/kg-d (510 ng/kg-d)
Total uncertainty factor:	30
Modifying factor:	10
Minimum risk level:	0.000002 mg/kg-d (2 ng/kg-d)

a The ATSDR's intermediate minimum risk levels are protective of exposures between 15 and 364 days. The ATSDR did not recommend a chronic oral reference dose for PFOS because they felt that that the available data for chronic exposure (more than 1 year) are limited and were uncertain whether the most sensitive endpoint for chronic exposure has been identified in the current research.

endpoint than developmental toxicity.[b] In their review, ATSDR compared measured serum levels of PFOS from studies evaluating immune responses with those evaluating developmental toxicity. They found that the measured serum PFOS levels associated with altered immune responses were approximately 10–100% of that predicted to occur at the NOAEL dose.

Literature Search

To identify recent publications, we conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2016 (the year that EPA's health advisory was published) to April 2019. We searched for studies related to PFOS toxicity or PFOS effects on a disease state in which information on exposure or dose was included as part of the study or studies related to modeling PFOS exposure or dose using pharmacokinetics in animals or humans.[c] Previous research has shown that effects on the immune system, development, and reproduction are the most sensitive, so we searched for new toxicity studies in these areas.[1, 10] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an appropriate exposure duration.

Approximately 300 studies were returned by the search engine. We excluded studies on non-mammalian or cell systems, non-oral exposure routes, those that did not evaluate health risks, and those only examining a single point of exposure from further review. After applying these exclusion criteria, we located six key toxicity studies and no key pharmacokinetic studies on PFOS (Table A-1 contains a summary of these studies).

To be considered a critical toxicity 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.[d] One of the key

b Modifying factors are used in a similar manner as uncertainty factors. Modifying factors are typically used on a case-by-case basis and help address additional uncertainty in the available data. For more information on modifying factors, see Ritter et al, 2007.[6]

c The following search terms were used in the literature review:
Title/abstract: PFOS or "Perfluorooctane sulfonate"
Keywords: Development OR immune OR reproduction OR pharmacokinetics OR modeling
Subject area: toxicology OR cancer
Language: English

d 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%).[8]

studies met the criteria to be considered a critical toxicity study (see Tables A-1 and A-2 for more details).

Critical Toxicity Studies

Lai et al., 2017

Lai et al. exposed pregnant mice to different concentrations of PFOS (0, 0.3, and 3 mg/kg-d) through gavage during pregnancy. They found that both doses caused changes to the lipid mediators in testes and high dose reduced serum testosterone and epididymis sperm count in male offspring at postnatal day (PND) 63.

From this study, we identified a LOAEL of 0.3 mg/kg-d based on changes to the lipid mediators in testes. We estimated an ADI of 0.003 mg/kg-d based on the LOAEL and a total uncertainty factor of 1000 to account for differences between people and research animals (10), differences among people (10), and using a LOAEL instead of a NOAEL.[e]

Summary

A large number of epidemiology studies on the effects of PFOS have been published since 2016 (see Appendix B for a summary of these studies). However, using epidemiology studies for establishing a health-based value is challenging because exposed people are generally exposed to more than one PFAS compounds, and the various PFAS compounds likely have similar health effects.[11-107] As such, animal studies where subjects are exposed to a single compound in a controlled environment provide the most useful data for risk assessment. Animal studies published since 2016 confirm that development is a significant endpoint for PFOS.[108, 109]

e The ADI is the estimated amount of PFOS that a person can be exposed to every day and not experience health impacts. The ADI equals the toxicity value divided by the total uncertainty factor. Uncertainty factors were included as appropriate to account for differences between humans and research animals, differences in sensitivity to health effects within human populations, using data from short term experiments to protect against effects from long-term exposure, and using data where a health effect was observed to estimate the level that does not cause an effect.

Standard Selection

DHS recommends a combined enforcement standard of 20 ng/L for PFOS and PFOA.

Basis for Recommended Standard

- ☐ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☑ **Significant technical information**

There is a federal number for PFOS – EPA's lifetime health advisory level.[2, 3] However, recent studies in people and animals indicate that this level may not be adequately protective.

In establishing their health advisory level, the EPA reviewed a number of studies that evaluated the effect of PFOS on the immune system, but did not quantitatively assess immunotoxicity because of uncertainties related to the mode of action, level, duration, and timing of exposure.[2, 3] Since EPA established their advisory, a number of epidemiological studies have been published evaluating the potential immune effects of PFOS (see Table B-2 for more details on these studies).[110-113, 47, 114, 115-118] While the long half-life of PFOS in people, multiple potential exposure sources, and the ability for other PFAS compounds to cause similar health effects prohibit using these data to establish a health-based value for PFOS, these studies indicate the need to account for this effect. For this reason, the ATSDR included a modifying factor to account for the potential for immunotoxicity effects to be a more sensitive endpoint than developmental toxicity when establishing their minimum risk level for PFOS.[1]

Additionally, recent modeling studies with PFOA have indicated that modeling approach taken by EPA may not be adequate to protect infants from exposure during pregnancy and while breastfeeding.[38, 119] PFOS (like PFOA) can cross the placenta during pregnancy and pass through breastmilk. To set their lifetime health advisory level, the EPA estimated how much PFOS a woman has to be exposed to orally during pregnancy for her serum levels to be equivalent to the level where health effects were seen in mice pups (babies).[10, 120] The modeling studies with PFOA modeling of maternal exposure levels may not be adequate to protect infants from exposure during pregnancy and while breastfeeding. These studies suggest that modeling of infant exposure may be a more appropriate approach to protect this sensitive population.

From this information, DHS concludes that there is significant technical information that was not considered when EPA set the lifetime health advisory for PFOS. Therefore, we recommend setting the enforcement standard for PFOS using procedures in s. 160.13(2). DHS selected ATSDR's intermediate oral minimum risk level of 20 ng/kg-d as the ADI for PFOS. While the ATSDR used the same human equivalent dose and total uncertainty factor as EPA, the ATSDR also applied a modifying factor of 10 when setting their minimum risk level. The ATSDR applied this factor due to concern that immunotoxicity may be a more sensitive endpoint than developmental toxicity. DHS maintains that the

addition of the modifying factor provides protection from potential immune effects and helps address concerns about infant exposures to PFOS during pregnancy and breastfeeding. DHS maintains that using ATSDR's intermediate minimum risk level is appropriate for use in setting the public health enforcement standard, as the critical effect for PFOS is developmental effects with exposure happening during pregnancy (an exposure period of about 9 months). To determine the recommended enforcement standard (ES), DHS used the ADI, and, as required by Ch. 160, Wis. Stats., a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%.

DHS recommends a combined enforcement standard of 20 ng/L for PFOS and PFOA. Studies have shown that PFOS and PFOA can cause similar effects in humans and in animals. The critical studies used by DHS to establish the ADI for PFOS and PFOA are developmental studies and recent studies have shown that PFOS and PFOA may cause toxicity through similar mechanisms of action. This approach is consistent with that taken by the EPA in their LHA level.[10, 120] They recommended that the advisory apply to the sum of PFOA and PFOS because the adverse effects in humans and animals are same or similar and the critical effect used to set the oral reference dose for both PFOS and PFOA are developmental endpoints.

DHS recommends a combined preventive action level of 2 ng/L for PFOS and PFOA.

DHS recommends that the preventive action level be set at 10% of the enforcement standard because PFOS and PFOA have both been shown to have carcinogenic and teratogenic effects.[1-3] Both PFOA and PFOS have been shown to cause the same or similar effects on the immune system, development, and reproduction in people and research animals indicating that PFOS can cause interactive effects.[1-3]

Updated by Amarilys Gonzalez Vazquez, Ph.D and Sarah Yang, Ph.D. – January 2022

Wisconsin Department of Health Services

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Appendix A: Key Toxicity Studies for PFOS

Table A-1. Toxicity Studies Published since ATSDR's Toxicological Profile

Study Type	Species	Exposure Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Development	Mouse	Gestation	0.3, 3	Gavage	Perturbations of lipid mediators in testes. Reduced serum testosterone and epididymis sperm count at PND63.	LOAEL: 0.3	Lai et al, 2017 ([108])
Longer-term	Mouse	49 d	0.3, 3	Diet	Disturbances in lipid and glucose metabolism. Modulated the abundance of metabolism-associated bacteria, but did not affect diversity of gut bacterial species.	LOAEL: 0.3	Lai et al, 2018 ([109])
Development	Rat	21 d	5, 10	Gavage	Lowered sperm testosterone levels without altering luteinizing hormone and follicle-stimulating hormone levels on PND 56. Downregulated mRNA and protein levels of Leydig cells.	LOAEL: 5	Li et al, 2018 ([121])
Development	Rat	28 d	1, 3, 6	Gavage	Alterations to hormones involved in the hypothalamic-pituitary-testis axis	LOAEL: 1	Lopez-Doval et al, 2016 ([122])
Immune	Mouse	25 d	2	Gavage	Caused failure to clear Citrobacter rodentium infection	LOAEL: 2	Suo, 2017 ([123])
Development	Rat	Gestation – Adulthood	0.023, 0.67, 2.0 (1.7, 5, 15 mg/L)	Water	Alterations in biomarkers of cognitive function	LOAEL: 0.023	Zhang, 2019 ([124])

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?
Lai et al., 2017	✓	✓	✓	**2**	✓	**Yes**
Lai et al., 2018	⊘	✓	✓	**2**	✓	No
Li et al., 2018	⊘	✓	✓	**2**	✓	No
Lopez-Doval et al., 2106	⊘	✓	✓	**3**	✓	No
Suo et al., 2017	⊘	✓	✓	1	✓	No
Zhang et al., 2019	✓	✓	✓	**3**	See note	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.

Note: While a LOAEL can be identified from this study, expressing this dose in mg/kg-d is challenging given that the authors reported exposure as mg/L, animals were exposed over a lifetime, and water consumption rates were not reported.

Appendix B: Epidemiology Studies of PFOS Published since ATSDR's Toxicological Profile

Table B-1. Summary of Recent Epidemiology Studies of PFAS[f]

Category	Examples	Number of Studies
Metabolic	Diabetes (type 1, 2, and gestational), glucose tolerance, insulin resistance, BMI, obesity/overweight, adiposity, cholesterol, triglycerides	41
Birth outcomes	Birth size (weight, length, etc), gestation age, small for gestational age, fetal growth, anogenital distance at birth	25
Neurological	Attention, impulse control, visual and spatial ability, cognitive development, executive function, autism spectrum disorder, intellectual disability	18
Reproductive	Endometriosis, preeclampsia, reproductive hormones, time to pregnancy, fertility, semen characteristics, pregnancy loss, menopause, puberty onset	13
Immune	Asthma, vaccine antibodies, allergic conditions, infectious disease incidence, atopic dermatitis	12
Thyroid	Thyroid hormones, thyroid function	10
Cardiovascular	heart attack, stroke, heart failure, arterial wall stiffness, coronary heart disease, blood pressure, hypertension	7
kidney	Chronic kidney disease, kidney function, glomerular filtration	7
Other	Vitamin D, bone density, lung function, dental carries, gut bacteria and metabolites, mortality,	6
DNA	Telomere length, DNA methylation	5
Liver	ALT (alanine aminotransferase), other liver function biomarkers	4
Cancer	Breast cancer	2

f The following search terms were used in the literature review:

Table B-2. Recent Epidemiology Studies evaluating the effects of PFOS on the immune system

Study Type	Population	Time period	Data Source	Outcomes	Results	Reference
Case Control	Adolescents with and without asthma (Taiwan)	2009-2010	The Genetic and Biomarkers study for Childhood Asthma	Interaction between PFAS and reproductive hormones on asthma	After controlling for hormone levels, associations between PFAS exposure and asthma were consistently stronger among children with higher than lower estradiol (For PFOS, OR for asthma was 1.25 among boys (95% CI: 0.90, 1.72) and 1.25 (95% CI: 0.84, 1.86) among girls.	Zhou et al. 2017 ([112])
Cross Sectional	Adolescents (USA)	1999 – 2000 2003 – 2004 2005 -2006	NHANES	Association between PFAS serum concentrations and measles, mumps, and rubella antibody concentrations and to allergic conditions Association between PFAS serum concentrations and allergic sensitization	Doubling of perfluorooctane sulfonate (PFOS) concentration among seropositive children was associated with a 13.3% (95% CI: -19.9, -6.2) decrease in rubella antibody concentration and a 5.9% decrease in mumps antibody concentration (95% CI: -9.9, -1.6). No adverse association between exposure and current allergic conditions, including asthma. Children with higher PFOS concentration were less likely to be sensitized to any allergen (OR: 0.74; 95% CI: 0.58, 0.95).	Stein et al. 2016 ([110])
Case Control	Adolescents with and without asthma (Taiwan)	2009 – 2010	The Genetic and Biomarkers study for	Association between PFAS serum concentrations and the level of 16-kDa club cell secretory protein (CC16)[1]	After adjusting for confounding factors, urinary CC16 was significantly, negatively associated with PFASs. In males, For PFOS (β = -0.003, 95% CI: -0.004, -0.002),	Zhou et al. 2017 ([113])

Subject: "(PFOS OR PFOA OR PFAS OR PFC) AND epidemiology
Language: English
We excluded studies that did not evaluate health effects from our analysis.

			Childhood Asthma			
Cross Sectional	Adolescents (USA)	2005 -2006 2007 – 2010	NHANES	Association between PFAS serum concentrations and food sensitization and food allergies	Serum PFOS was statistically significantly associated with higher odds to have self-reported food allergies in NHANES 2007-2010.	Buser et al. 2016 ([114])
Birth Cohort	Infants (Norway)		The Environment and Childhood Asthma (ECA) prospective birth cohort study	Association between prenatal exposure to PFAS and asthma or other allergic diseases or respiratory tract infections in childhood	The number of reported airways infections were significantly associated with cord blood concentrations of PFAS For PFOS, lower respiratory tract infections (β = 0.50 (0.42-0.57)) from 0 to 10 years of age with PFOS	Impinen et al. 2018 ([47])
Birth Cohort	Mother-infant pairs (Japan)		Hokkaido Study on Environment and Children's Health	Association between prenatal exposure to PFAS and prevalence of infectious diseases in children up to 4 years of age	PFOS levels in the highest quartile were associated with increased ORs of total infectious diseases (Q4 vs. Q1 OR: 1.61; 95% CI: 1.18, 2.21; p for trend=0.008) in all children.	Goudarzi et al. 2017 ([115])
Cross sectional	Adults and Children (USA)	1999-2000 2003-2004	NHANES	Association between serum PFAS concentrations and rubella immunization	There was no significant effect of PFASs on rubella immunity in youths but a significant effect of PFOS in adults, as well as a borderline significant interaction of PFOS x sex.	Pilkerton et al. 2018 ([116])
Cross sectional	Healthy Adults (USA)	2010-2011	Adults vaccinated during the 2010-2011 influenza season	Association between PFAS serum concentrations and immune response to vaccination with FluMist[2]	No readily discernable or consistent pattern between PFAS concentration and baseline cytokine, chemokine, or mucosal IgA concentration, or between PFAS concentration and change in these immune markers between baseline and FluMist-response states was seen.	Stein et al. 2016 ([111])
Birth cohort	Mother-infant pairs (China)	July – October 2013	Guangzhou Birth Cohort Study	Association between prenatal exposure to PFAS	Cord blood PFAS exposure is associated with lower Hand, Foot and Mouth Disease antibody in infancy. For total	Zeng et al. 2019 ([117])

				and Hand, Foot and Mouth Disease virus antibodies	PFOS: cord blood OR: 1.66 (1.12, 2.45). Three-month infant: OR: 2.25 (1.44, 3.51).	
Case Control	Adolescents with and without asthma (Taiwan)	2009-2010	The Genetic and Biomarkers study for Childhood Asthma	Association between serum PFAS concentrations and T-lymphocyte-related immunological markers of asthma in children	Asthmatics had significantly higher serum PFAAs concentrations compared with the healthy controls. When stratified by gender, a greater number of significant associations between PFAAs and asthma outcomes were found in males than in females (OR for PFOS in males: 4.38 (95% CI: 2.02, 9.50)).	Zhu et al. 2016 ([118])

NHANES stands for the National Health and Nutrition Examination Survey; OR = odds ratio; CI = confidence interval

1. CC16 is a prominent biomarker of asthma, among adolescents.
2. FluMist is an intranasal live attenuated influenza vaccine

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

Current Standards	
Enforcement Standard:	5 µg/L
Preventive Action Limit:	0.5 µg/L
Year:	2011

Recommended Standards	
Enforcement Standard:	0.5 µg/L
Preventive Action Limit:	0.05 µg/L

The current NR140 Groundwater Quality Public Health Enforcement Standard of 5 micrograms per liter (µg/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 µg/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 µg/L corresponds with a lifetime cancer risk level of 1 in 1,000,000.

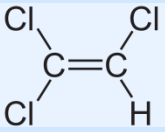
DHS recommends setting the NR140 Groundwater Quality Public Health Preventive Action Limit for TCE at 10% of the enforcement standard because it has been shown to have carcinogenic, mutagenic, and teratogenic effects.

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]

Chemical Profile

	Trichloroethylene
Structure:	
CAS Number:	79-01-6
Formula:	C_2HCl_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 volatiles 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 5 µg/L 0.5 µg/L	(2011)
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 $(mg/kg\text{-}d)^{-1}$	(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 $(mg/kg\text{-}d)^{-1}$ 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.

Basis for Enforcement Standard

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

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.

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%).[8]

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

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. 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 >=90th 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 (µg/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 µg/L. The recommended t 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 µg/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.

Current Standards	
Enforcement Standard:	5 µg/L
Preventive Action Limit:	0.5 µg/L
Year:	2011

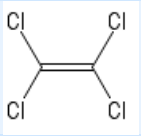
Recommended Standards	
Enforcement Standard:	20 µg/L
Preventive Action Limit:	2 µg/L

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]

Chemical Profile

	Tetrachloroethylene
Structure:	
CAS Number:	127-18-4
Formula:	C_2Cl_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 $(mg/kg\text{-}d)^{-1}$	(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 $(mg/kg\text{-}d)^{-1}$ 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 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 20 µg/L for PCE.

Basis for Enforcement Standard

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

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.

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%).[8]

Prepared by Curtis Hedman, Ph.D.

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. 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.

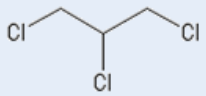
Current Standards	
Enforcement Standard:	60 µg/L
Preventive Action Limit:	12 µg/L
Year:	1997
Recommended Standards	
Enforcement Standard:	0.3 ng/L
Preventive Action Limit:	0.03 ng/L

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:	$C_3H_5Cl_3$
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 $(mg/kg\text{-}d)^{-1}$	(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 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 $(mg/kg\text{-}d)^{-1}$ 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%).[8]

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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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 >=90th 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-trichloroproprane 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.

Appendix B. Recommended Enforcement Standard Determination

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

Where:

Cancer Risk:	1 in 1,000,000	
Body Weight:	80 kg	
Cancer Slope Factor (SF):	30 $(mg/kg\text{-}d)^{-1}$	
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

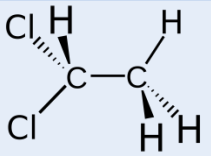
Recommended Standards	
Enforcement Standard:	850 µg/L
Preventive Action Limit:	85 µg/L

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:	$C_2H_4Cl_2$
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 $(mg/kg\text{-}d)^{-1}$	(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.

Basis for Enforcement Standard

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

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.

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

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Boron | 2019

Substance Overview

Boron is an element that is commonly found in soil and rocks.[1] In nature, boron is rarely found as a pure element, but rather in combination with other substances forming borates, boric oxides, or boric acid. Borates are used mostly in the production of glass. They are also used in the manufacture of leather tanners, fire-retardant materials, cosmetics, photographic materials, and in some high-energy fuels. Some pesticides used for cockroach control and wood preservatives also contain borates.

Recommendations

The current NR140 Groundwater Quality Public Health Enforcement Standard of 1,000 micrograms per liter (µg/L) for boron is based on EPA's lifetime health advisory from the 1990s.

DHS recommends raising the enforcement standard to 2,000 µg/L. The recommended standard is based on the EPA's Longer-term Child Health Advisory from 2008, which is protective of the most sensitive population (children) to the adverse effects of boron.[2]

DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for boron be set at 20% of the enforcement standard because boron has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

Current Standards	
Enforcement Standard:	1,000 µg/L
Preventive Action Limit:	200 µg/L
Year:	2010

Recommended Standards	
Enforcement Standard:	2,000 µg/L
Preventive Action Limit:	400 µg/L

Health Effects

Recent studies in people suggest that small amounts of boron in the diet have beneficial effects. In fact, the World Health Organization (WHO) has added boron to the possible essential elements category for nutritional purposes.[3] On the other hand, eating or drinking large amounts of boron can impact human health.[1] Some people who ate large amounts of boron have experienced effects on the stomach, intestines, liver, kidney, and brain and some have died. Male animals that ate large amounts of boron had damage to their reproductive organs. Boron has also been shown to decrease the weight of newborn animals if given to the mothers when pregnant. Boron has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

Chemical Profile

	Boron
Chemical Symbol:	B
CAS Number:	7440-42-8
Molar Mass:	10.81 g/mol
Synonyms:	N/A

Exposure Routes

Boron is widely distributed in nature.[1] People can be exposed to borate from food, water, or contact with insecticides used to control roaches. Inhalation of boron-containing dusts or absorption of boron from cosmetics or medical preparations through mucous membranes or damaged skin can also occur. Occupational exposures to boron may be higher than the general public. Workers may be exposed by inhalation of dusts or gaseous boron compounds. Dermal absorption may also occur but this is considered to be a minor exposure pathway.

Since boron is an element, it is not subject to decomposition and can remain in the environment indefinitely. Its mobility is dependent on its chemical form. Boron salts and acids are water soluble and have a tendency to leach from soils into ground and surface water. Boron dusts and gases discharged into the atmosphere may be carried great distances before removal by wet or dry deposition.

Current Standard

The current NR140 Groundwater Quality Public Health Enforcement Standard for boron is 1,000 µg/L and was established in 2010.[4]

The current preventive action limit for boron was set at 20% of the enforcement standard because boron has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

Standard Development

Federal Numbers		
Maximum Contaminant Level:	N/A	
Health Advisories		
10-day child:	3,000 µg/L	(2008)
Longer-term child:	2,000 µg/L	(2008)
Longer-term adult:	5,000 µg/L	(2008)
Lifetime:	6,000 µg/L	(2008)
Drinking Water Concentration (Cancer Risk):	N/A	
State Drinking Water Standard		
NR 809 Maximum Contaminant Level:	N/A	
Acceptable Daily Intake		
EPA Oral Reference Dose:	0.2 mg/kg-d	(2004)
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
ATSDR Chronic Oral Minimum Risk Level:	0.2 mg/kg-d	(2010)
WHO Drinking Water Guideline:	2,400 µg/L	(2009)
Literature Search		
Literature Search Dates:	2010 – 2018	
Total studies evaluated:	Approximately 1,200	
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 boron.[5]

Health Advisories

The EPA Office of Water established several Health Advisories for boron in 2008.[2,6] See Table A-1 for a comparison of the different advisories.

10-day Child

The EPA based the 10-Day Child Health Advisory on a study using rats that were exposed to varying amounts of boron for either 30 or 60 days.[7,8] The EPA established a No Observable Adverse Effect Level (NOAEL) value of 25 milligrams of boron per kilogram body weight per day (mg boron/kg-day) and a Lowest Observable Adverse Effect Level (LOAEL) value of 50 mg boron/kg-day based on decreased epididymis weight, germinal aplasia, and changes in marker enzymes associated with spermatogenic

cells. The EPA applied a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). To obtain the health advisory, they used a body weight of 10 kg, water consumption rate of 1 L/d, and relative source contribution of 100%.

Longer-term Child

The EPA based the longer-term Child Health Advisory on a chronic toxicity study in rats that found testicular toxicity. They established a NOAEL of 17.5 mg boron/kg-day and a LOAEL of 58 mg boron/kg-day.[9,10] The EPA applied a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). To obtain the health advisory, they used a body weight of 10 kg, water consumption rate of 1 L/d, and relative source contribution of 100%.

Longer-term Adult

The EPA based the longer-term Adult Health Advisory on two chronic studies in rats that found exposure during pregnancy caused decreased fetal body weight.[11,12] They established a 5% Benchmark Dose Lower Confidence Limit ($BMDL_{05}$) of 10.3 mg boron/kg-day (converted to boron equivalent) from these studies. The EPA used a data-derived adjustment factor of 66 instead of using default uncertainty factors to account for differences between people and research animals and differences among people.[a] To obtain the health advisory, they used a body weight of 67 kg (the assumed weight of a pregnant woman), water consumption rate of 2 L/d, and relative source contribution of 100%.

Lifetime

For the lifetime health advisory, the EPA used $BMDL_{05}$ of 10.3 mg boron/kg-day as the toxicity value obtained for the longer-term adult health advisory. They applied the data-derived adjustment factor of 66 to account for differences among people and animals.[b] To obtain the health advisory, they used a body weight of 67 kg (the assumed weight of a pregnant woman), water consumption rate of 2 L/d, and relative source contribution of 80%.[b]

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations at specified cancer risk levels for boron. [2,14] 2,14 2,14 2,14 2,14 2,14 2,14

a The uncertainty factors that account for differences between people and research animals (interspecies variation) and differences among people (intraspecies variation) consists of two components: one for differences in toxicokinetics and one for differences in toxicodynamics. The default values for these two components are 3.16, but can be adjusted up or down if species specific toxicokinetic or toxicodynamic data are available.[7] For boron, the EPA adjusted the factors that account for toxicokinetics in animals (3.3) and humans (2.0) due to specific toxicokinetic data on boron.[2]

b The EPA used a subtraction calculation method to determine the relative source contribution for boron. They determined that this method is appropriate used this method because dietary sources represent the main background intake for boron. For more information on this, see the EPA's Drinking Water Health Advisory document.[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 boron.[15]

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.

Oral Reference Dose

In 2004, the EPA's IRIS program updated the oral reference dose for boron.[14] The current oral reference dose is 0.2 mg/L.

The EPA selected decreased fetal body weight in rats as the critical effect for the development of a reference dose. The EPA calculated a $BMDL_{05}$ value of 10.3 mg/kg-d from studies performed by Heindel et al. and Price et al. The EPA applied a total uncertainty factor of 66 to the $BMDL_{05}$ to derive the oral reference dose.[a]

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

Cancer Classification

The EPA has classified boron as not likely to be carcinogenic to humans by oral exposure.[2,14]

The International Agency for Research on Cancer (IARC) has not evaluated the cancer potential of boron.[16]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for boron.[2,14]

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 boron, we searched for values that have been published since 2009 when the EPA published their health advisories. We found relevant guidance values from the Agency for Toxic Substances and Disease Registry (ATSDR) and World Health Organization (WHO).

ATSDR Chronic Oral Minimum Reference Level

In 2010, the Agency for Toxic Substances and Disease Registry (ATSDR) published their Toxicological Profile for boron.[1] The ATSDR recommends a chronic oral minimum reference level of 0.2 mg/kg-d. This value is based on the same study that the EPA used to establish their oral reference dose.

WHO Drinking Water Guideline Value

In 2009, the World Health Organization (WHO) issued a drinking water guideline value of 2.4 mg/L (2,400 µg/L).[3] This value was based on studies that showed decreased fetal body weight in rats. The $BMDL_{05}$ of 10.3 mg/kg was used along with a total uncertainty factor of 60 to account for differences between people and research animals (6) and differences among people (10), a body weight of 60 kg, a daily water consumption rate of 2 L/d, and a water source allocation factor of 40%.

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 April 2018 related to boron toxicity or effects on a disease state in which information on boron exposure or dose was included as part of the study.[c] 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.

c The following search terms were used in the literature review:
Title/Abstract: Boron
Subject area: toxicology OR cancer
Keywords: Reproduction, hypertension or blood pressure, nephropathy or kidney, genotoxicity or oxidative stress
Language: English

Approximately 1,200 studies were returned by the search engine. Studies on boron nanoparticles, effects on aquatic life, non-oral exposure routes (e.g. inhalation), acute exposures (i.e., poisoning), and studies not evaluating health risks were excluded from further review. After applying these exclusion criteria, we identified two key studies (see Table A-1 for more details on 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.[d] One of the studies met the requirements to be considered a critical study (see Table A-2 for details on evaluation).

Critical Studies

Jin et al, 2017

Jin et al. investigated the effects of boron supplementation via drinking water and immune function in a rat model.[18] Rats were exposed to different concentrations of boron in drinking water (equivalent to 1.5, 3, 6, 12, 24, 48, and 96 mg/kg/day). Their findings suggested that supplementation with 3 mg/kg/day or 6 mg/kg-d boron could improve humoral and cellular immune functions, while boron supplementation above 48 mg/kg-d can exert an inhibitory or toxic effect on immune functions.

This study provides added evidence for improved metabolic function with low levels of boron exposure and toxicity at higher boron exposure levels. However, the reduced fetal body weight and testicular toxicity effects that the EPA used to establish their health advisories continue to be the most sensitive toxicological endpoints studied to date (see Table A-1 for more details).

Standard Selection

DHS recommends an enforcement standard of 2,000 µg/L for boron.

DHS recommends using the EPA's long-term child health advisory level as the groundwater enforcement standard for boron. This enforcement standard is protective of the most sensitive population (children).

Basis for Enforcement Standard

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

DHS recommends a preventive action limit of 400 µg/L for boron.

DHS recommends that the preventive action limit for boron be set at 20% of the enforcement standard because boron has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

d 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%).[16]

Prepared by Curtis Hedman, Ph.D.

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Appendix A. EPA's Health Advisories for Boron

	10-Day Child	Longer-term* child	Longer-term* Adult	Lifetime
Critical Study:	Dixon et al, 1979 ([8]) Lee et al, 1978 ([7])	Weir and Fisher, 1972 ([9]) Weir and Crews, 1967 ([10])	Heindel et al, 1992 ([11]) Price et al, 1996 ([12])	Heindel et al, 1992 ([11]) Price et al, 1996 ([12])
Test species:	Rat	Rat	Rat	Rat
Endpoint:	Testicular toxicity	Testicular toxicity	Decreased fetal body weight	Decreased fetal body weight
Toxicity Value (mg/kg-d):	25	17.5	10.3	10.3
Value type:	NOAEL	NOAEL	BMDL	BMDL
Study duration:	30 d	2-year	Pregnancy	Pregnancy
Total uncertainty factor:	100	100	66	66
Body weight (kg):	10	10	67	67
Daily water intake (L/d):	1	1	2	2
Relative source contribution:	100%	100%	100%	80%
Health Advisory Level (µg/L):	3,000	2,000	5,000	5,000

* Longer-term covers an exposure period of approximately 7 years (10% of an individual's lifetime)

Appendix B: Toxicity Studies for Boron

Table B-1. Boron Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Longer-term	Rat	60 d	1.1, 2.1, 4.3, 8.5, 17	Water	Levels above 2.2 mg/kg-d boron caused spleen damage and toxicity.	NOAEL: 1.1 LOAEL: 2.1	Hu et al, 2014
Longer-term	Rat	60 d	1.5, 3, 6, 12, 24, 48, 96	Water	Reduced serum IgG, splenic IL-2 and IL-10 expression, number of CD3+, CD4+ and PCNA+ cells; increased number of splenic CD8+ and caspase-3+ cells and promoted caspase-3 expression in CD3+ cells.	LOAEL: 48	Jin et al, 2017

Table B-2. Critical Study Selection

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of Doses	Toxicity value identifiable?	Critical study?
Hu et al, 2014	✓	See Note	See Note	**5**	✓	No
Jin et al, 2017	✓	✓	✓	**7**	✓	**Yes**

Note: Studies in people suggest that small amounts of boron in the diet have beneficial effects. The American Institute of Medicine recommends an upper tolerable upper intake level of 3 to 20 mg boron per day depending on age. Because the toxicity values reported in this study are lower than these values, the consistency of this study with others and its relevance to humans are unclear.

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.

Molybdenum | 2022

The recommended enforcement standard was erroneously calculated to be 10-fold lower than it should have been. As such, these recommendations were withdrawn in April 2024.

Substance Overview

Molybdenum is a mineral that occurs naturally in all plants and animals. It does not occur naturally as a pure metallic form on Earth. Instead, it is principally found in various oxidation states in minerals. Low levels of molybdenum are required for good health in humans and animals. Because molybdenum has a very high melting point, it is widely used in industry to make steel alloys.

Recommendations

The current NR140 Groundwater Quality Public Health Enforcement Standard of 40 micrograms per liter (µg/L) for molybdenum is based the United States Environmental Protection Agency's (EPA's) Lifetime Health Advisory for molybdenum established in 1993.[1]

DHS recommends raising the enforcement standard to 60 micrograms per liter (µg/L) for molybdenum. The recommended standard is based on the Agency for Toxic Substances and Disease Registry's (ATSDR's) intermediate oral minimum risk level for molybdenum.[2]

Current Standards	
Enforcement Standard:	40 µg/L
Preventive Action Limit:	8 µg/L
Year:	2006

Recommended Standards	
Enforcement Standard:	60 µg/L
Preventive Action Limit:	6 µg/L

DHS recommends that the NR140 Groundwater Quality Public Health preventive Action Limit for molybdenum be set at 10% of the enforcement standard because molybdenum has been shown to cause teratogenic and interactive effects.[2-4]

Health Effects

Low levels of molybdenum are essential for good health. The Institute of Medicine's Food and Nutrition Board has recommended dietary molybdenum levels of 45 micrograms per day for adults. However, high levels of molybdenum can be harmful.[2, 5] Studies in animals suggested that ingesting very large amounts of molybdenum might damage the male and female reproductive system and might cause kidney and liver damage. Studies indicate that the copper content in the body can affect the toxicity of molybdenum.[2, 3]

The U. S. Environmental Protection Agency (EPA) did not evaluate the carcinogenic potential of molybdenum.[5] Molybdenum has shown to have interactive effects with copper in the body and cause teratogenic effects.[2-4] Molybdenum has not been shown to cause carcinogenic or mutagenic effects.

Chemical Profile

	Molybdenum
Chemical Symbol:	Mo
CAS Number:	7439-98-7
Molar Mass:	95.94 g/mol
Synonyms:	N/A

Exposure Routes

Molybdenum is common in the environment. The primary way that people can be exposed to molybdenum is by eating food containing molybdenum.[2, 5] Legumes such as peas, beans, and lentils, have the highest levels of molybdenum. Grains, nuts, and dairy products are also rich sources of molybdenum. People may also be exposed to molybdenum in some nutritional supplements.

People can also be exposed to small amounts of molybdenum by breathing air, drinking water, and touching soil.[2, 5] The primary source of molybdenum in air is from coal combustion. Molybdenum can be released from mining, milling, and coal-fired power plants and enter the environment. Molybdenum released to the air will settle to the ground by gravity or in rain and snow. Molybdenum can also be directly released into surface water or soil from the production and use of molybdenum compounds through various waste streams.

When molybdenum is released into water or soil, it can attach to the organic material and other components such as clay and sand in the top layers of the soil.[2, 5] Once attached to organic materials, molybdenum usually does not move far from the location where it was released. The soil conditions, especially the acidity of the soil, will influence the binding of molybdenum to soil and sediment. Molybdenum does not break down in the environment.

Current Standard

The current NR140 Groundwater Quality Public Health Enforcement Standard of 40 µg/L for molybdenum was adopted in 2006. This standard is based on EPA's lifetime health advisory level from 1993.

The current NR140 Groundwater Quality Public Health Preventive Action Limit for molybdenum is set at 20% of the enforcement standard because molybdenum has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects at the time when the standard was established.

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A	
Health Advisories		
10-Day child:	80 µg/L	(1993)
Lifetime Health Advisory:	40 µg/L	(1993)
Drinking Water Concentration (Cancer Risk):	N/A	

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A	

Acceptable Daily Intake

EPA Oral Reference Dose:	0.005 mg/kg-d	(1992)

Oncogenic Potential

EPA Cancer Slope Factor:	N/A	

Guidance Values

DHS Interim Health Advisory Level:	90 µg/L	(2013)
ATSDR Intermediate Oral Minimum Risk Level:	0.06 mg/kg-d	(2020)

Literature Search

Literature Search Dates:	2019 – 2020
Total studies evaluated:	Approximately 30
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 molybdenum.[6]

Health Advisories

The EPA Office of Water established several draft Health Advisories for molybdenum in 1993.[7]

10-Day Health Advisory

The EPA based the 10-Day Child Health Advisory on a 6-week oral toxicity study using rats that were exposed to different amounts of molybdenum (0, 7.5, and 30 milligrams molybdenum per kilogram body weight per day (mg/kg-d)).[4] The EPA established a Lowest Observable Adverse Effect Level (LOAEL) of 7.5 mg/kg-d based on body weight loss, development of bone deformities, and increase in copper and

molybdenum levels in liver. The EPA selected a total uncertainty factor of 1000 to account for the use of a LOAEL rather than a NOAEL (10), differences among people and research animals (10) and differences among people (10). To obtain the 10-Day Child Health Advisory, the EPA used a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%. Because suitable information was not available to develop a 1-Day Health Advisory, EPA recommended using the 10-Day Health Advisory for shorter exposures as well.

Lifetime Health Advisory

In 1993, the EPA established a Lifetime Health Advisory for molybdenum of 40 µg/L based on the EPA oral reference dose of 0.005 mg/kg-d for molybdenum.[5] (see section "Acceptable Daily Intake: EPA Oral Reference Dose (IRIS)" for details on the basis of the critical study). To establish the advisory, the EPA used 70 kg to represent the average weight of an adult, a default relative source contribution of 20%, and 2 L/day for average water intake of an adult.

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations at specified cancer risk levels for molybdenum.[5]

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 molydenum.[8]

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 (IRIS)

In 1992, the EPA established the oral reference dose of 0.005 mg/kg-d for molybdenum.[5] The EPA selected a cross-sectional epidemiology study in a molybdenum-rich part of Armenia as the principal

study.[9] This study correlated the dietary intake of molybdenum with serum uric acid levels, several biochemical endpoints, and gout-like sickness affecting the adult population in two settlements: Ankava village (well established) and the adjoining village as a control (newly established). The Ankava village was selected because of its high molybdenum content in the soil and plants (up to 190 times higher than that of the control area) and low copper content.

The authors found that the group of villagers from Ankava had a higher rate of gout-like symptoms compared to the control group. Adults in the Ankave area also had higher uric acid content in blood compared to the adults in the control area. EPA selected a LOAEL of 0.14 mg/kg-d from this study. A NOAEL was not identified. To establish the oral reference dose for molybdenum, EPA used a total uncertainty factor of 30 to account for differences among people (3) and using a LOAEL instead of a NOAEL (10). In 2003, an EPA contractor conducted a screening-level review to search for more recent toxicology literature pertinent to the oral reference dose and did not identify any critical new studies.

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

Cancer Classification

The EPA has not evaluated the carcinogenicity of molybdenum.[5]

The international Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of molybdenum.[10] The IARC classified molybdenum trioxide as a possible carcinogen to humans.[11]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for molybdenum.[5]

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

DHS Interim Health Advisory Level

In 2013, DHS reviewed toxicity information on molybdenum and recommended an interim health advisory level of 90 µg/L based on a reproductive toxicity study in rats conducted by Fungwe et al.[12] In this study, female rats were allowed to freely access drinking water that was supplemented with sodium molybdate (0, 5, 10, 50, or 100 mg/L molybdenum). The amount of molybdenum that animals were exposed to was determined by the amount of consumed drinking water on a weekly basis. The authors reported the corresponding weekly molybdenum intakes of 0.9, 1.6, 8.1, and 16.3, respectively.[13] This study found that molybdenum concentrations of 10 mg/L and higher prolonged the estrous cycle and delayed fetal esophageal development. They also observed increased plasma ceruloplasmin and sulfite oxidase activity. To establish the interim health advisory level, DHS used the NOAEL of 0.9 mg/kg-d and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). To be in alignment with the requirements of Chapter 160, Wis. Stats., DHS used a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%.

ATSDR Intermediate Oral Minimum Reference Level

In 2020, the Agency for Toxic Substances and Disease Registry (ATSDR) recommended an intermediate-duration oral minimal risk level (MRL) of 0.06 mg/kg-d for molybdenum based on a subchronic toxicity study in rats conducted by Murray et al.[2] In this study, male and female rats were exposed to varirous levels of sodium molybdate by diet for 90 days.[141] This study found that molybdenum affected body weight, weight gain, and food conversion efficiency, and caused kidney damage in females. ATSDR based their MRL on a NOAEL of 17 mg/kg-d molybdenum, a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10), and a modifying factor of 3 to address concern that reproductive/developmental alterations may be sensitive

1 Males: 0, 4.5, 15.1, and 54.8 $mg_{molybdenum}$/kg-d
Females: 0, 5.4, 19.0, and 65.2 $mg_{molybdenum}$/kg-d

outcomes in populations with marginal copper intakes). The MRL is calculated based on the assumption of healthy dietary levels of molybdenum and copper and represents the level of exposure above and beyond the normal diet.

Literature Search

The DHS reviewed the literature on molybdenum toxicity published since 2020 (the year that ATSDR published their revised toxicological profile). We carried out a search on the Web of Science resource for relevant articles published from 2020 to Janurary 2022 for studies related to molybdenum toxicity or its effects on a disease state in which information on exposure or dose was included as part of the study.[2] 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.

The search enginge returned 30 studies. Approximately 20 studies were returned by the search engines. We excluded monitoring studies, studies evaluating risk from non-mammalian species, and studies on the effects on plants from further review. After applying these exclusion criteria, we did not identify any key studies.

Standard Selection

DHS recommends an enforcement standard of 60 µg/L for molybdenum.

Basis for Enforcement Standard

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

The current enforcement standard for molybdenum is based on a lifetime health advisory set by the EPA in 1993. Since this time, a number of studies have been published evaluating the health risk of molybdenum. In 2020, the Agency for Toxic Substances and Disease Registry (ATSDR) updated their intermediate-duration oral miniumum risk level to be based on a 2014 subchronic toxicity study in rats by Murray et al.[2, 14, 15]

DHS calculated the recommended enforcement standard (ES) using ATSDR's intermediate-duration oral minimum risk level for molybdenum (0.06 mg/kg-d), an average body weight of 10 kg, a water consumption rate of 1 liter per day (L/d), and a relative source contribution of 100% as specified in Chapter 160 of Wisconsin Statute.

2 The following search terms were used in the literature review:
Title/Abstract: Molybdenum
Subject area: Toxicology OR cancer
Language: English

DHS recommends a preventive action limit of 6 µg/L for molybdenum.

DHS recommends that the preventive action limit for molybdenum be set at 10% of the enforcement standard because recent studies have shown that molybdenum can cause teratogenic and interactive effects.[2-4] Molybdenum has not been shown to have carcinogenic or mutagenic effects.[2]

Updated by Sarah Yang, Ph.D. – April

Wisconsin Department of Health Services

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Aluminum | 2022

Substance Overview

Aluminum is a naturally occurring metal and an abundant earth element.[1] It occurs in nature primarily in combination with silica or an oxide. Aluminum also forms a wide range of organic and inorganic salts. Aluminum and aluminum alloys are used in a variety of industrial and commercial applications including cookware, food containers, and water treatment.

Recommendations

The current NR140 Groundwater Quality Public Health Enforcement Standard of 200 micrograms per liter (µg/L) for aluminum is based on a 2005 study that found that aluminum affected sperm in male rabbits.[2] DHS recommends no change in the enforcement standard for aluminum.

The current NR140 Groundwater Quality Public Health Preventive Action Limit (PAL) for aluminum is 40 µg/L- 20% of the enforcement standard. DHS recommends the PAL to be set at 10% of the enforcement standards due to potential carcinogenic effects.

Current Standards	
Enforcement Standard:	200 µg/L
Preventive Action Limit:	40 µg/L
Year:	2010

Recommended Standards	
Enforcement Standard:	200 µg/L
Preventive Action Limit:	20 µg/L

Health Effects

While most people do not experience health effects from exposure to aluminum, some groups are at higher risk for aluminum toxicity.[1] Most cases of human aluminum toxicity have involved patients with impaired kidney function or patients who were exposed to high levels of aluminum from contaminated water used in medical fluids. Premature babies are at risk for aluminum toxicity because of their immature kidney function. Full-term infants with normal kidney function may also be at risk because they have lower kidney excretion rates than adults which affect their ability to excrete aluminum. Studies with laboratory animals have shown that exposure to high levels of aluminum over a long period of time can affect testosterone levels, body weight, memory, and sperm.

The United States Environmental Protection Agency (EPA) has not evaluated the carcinogenicity of aluminum, but at least two studies suggest a possible effect in animals.[3,4] Aluminum has not been shown to have mutagenic, teratogenic, or interactive effects.[1]

Chemical Profile

	Aluminum
Chemical Symbol:	Al
CAS Number:	7429-90-5
Molar Mass:	26.98 g/mol
Synonyms:	Bauxite

Exposure Routes

People are exposed to aluminum from air, food, water, and cookware.[1] Due to the abundance of aluminum in bedrock, soil, and groundwater, and its use in cookware, food containers, and water treatment, baseline human exposure to aluminum is typical.

Naturally-occurring aluminum in groundwater in Wisconsin generally ranges up to 100 micrograms per liter (µg/L). Municipal water supplies may contain a greater concentration of aluminum because alum is often used as a flocculent.

Current Standard

The current NR140 Groundwater Quality Public Health Enforcement Standard of 200 µg/L for aluminum was adopted in 2010.[5] This standard is based on the results from a study conducted in rabbits in 2005.[2] In this study, rabbits were exposed to 34 milligrams aluminum per kilogram body weight (mg aluminum per kg) every other day for 16 weeks. At this level of aluminum, effects on male spermatogenesis (sperm generation and production) were observed. DHS applied a modifying factor of 2 to convert the every-other-day dosing regimen into a daily dose, resulting in a Lowest Observable Adverse Effect Level (LOAEL) of 17 milligrams per kilogram body weight per day (mg/kg-d). DHS applied three uncertainty factors of 10 to convert the LOAEL to a No Observable Adverse Effect Level (NOAEL) and to account for differences between people and animals and differences between people. DHS calculated an enforcement standard of 170 µg/L and rounded to 200 µg/L to be consistent with a federal standard set by the Food and Drug Administration (FDA) for aluminum in bottled drinking water, as well as with the international standard developed by the World Health Organization (2010). The current NR140 Groundwater Quality Public Health Preventive Action Limit for aluminum was set at 20% of the enforcement standard because aluminum has been shown to have carcinogenic properties in animals.

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A	
Health Advisory:	N/A	
Drinking Water Concentration (Cancer Risk):	N/A	
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	
Guidance Values		
WHO Drinking Water Guideline:	100 – 200 µg/L	(2010)
Literature Search		
Search Dates:	2010 – 2018	
Total studies evaluated:	Approximately 370	
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 aluminum.[6]

The EPA does have a secondary maximum contaminant level (SMCL) for aluminum of 50 to 200 µg/L.[7] SMCLs are non-mandatory water quality standards established by the EPA to help public water systems address aesthetic issues, such as taste, color, and odor.

Health Advisory

The EPA has not established health advisories for aluminum.[8]

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations at specified cancer risk levels for aluminum.[9]

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 drinking water standard for aluminum.[10]

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 aluminum.[9]

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

Cancer Classification

The EPA has not evaluated the cancer potential of aluminum.[9]

The International Agency for Research on Cancer (IARC) has not evaluated the cancer potential of aluminum.[11]

EPA Cancer Slope Factor

The EPA have not established a cancer slope factor for aluminum.[9]

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

WHO Drinking Water Guideline Value

In 2010, the World Health Organization (WHO) recommended a drinking water guideline value of 100 to 200 µg/L.[12] The WHO noted that aluminum is widely used as a flocculant for drinking water treatment and concluded that the "population attributable risk cannot be calculated with precision." The WHO recommendation was instead based on "practicable levels based on optimization of the coagulation process in drinking-water plants using aluminum-based coagulants are 100 µg/L or less in large water treatment facilities and 200 µg/L or less in small facilities."

Literature Search

Our literature review focused on the scientific literature published after the current groundwater standard for aluminum was adopted in 2010. Thus, we conducted a search on the National Institutes of Health's PubMed resource for relevant aluminum articles published from January 2010 to December 2018. We looked for studies related to aluminum toxicity or aluminum effects on a disease state in which information on aluminum exposure or dose was included as part of the study.[1] We focused our review on studies evaluating effect on reproduction as our previous review found it to be the critical effect for aluminum. 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 370 were returned by the search engine. Studies on nanoparticles or aluminum-containing materials, studies not evaluating health risks, studies in aquatic species, and studies

1 The following search terms were used in the literature review:
Title/abstract: Aluminum
Subject area: toxicology OR cancer
Keyword: reproduction
Language: English

evaluating non-oral exposure routes (e.g. inhalation) were excluded from further review. After applying these exclusion criteria, we identified 19 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. [2] Eight of the key studies met the requirements to be considered a critical study (see Table A-2 for details on evaluation).

Critical Studies

To compare between results from recently found studies and the study used to set the current enforcement standard, we calculated an acceptable daily intake (ADI) for each study/effect. The ADI is the estimated amount of aluminum that a person can be exposed to every day and not experience health impacts. The ADI is derived by dividing a toxicity value identified in a study by a factor accounting for various sources of scientific uncertainty. Uncertainty factors were included, as appropriate, to account for differences between humans and animals, differences between healthy and sensitive human populations, using data from short-term experiments to protect against effects from long-term exposure, and using data where a health effect was observed to estimate the level that does not cause an effect.

Fu et al, 2014

Fu et al conducted a 120 day study in rats provided water at 64, 128, or 256 mg/kg-d aluminum through drinking water.[14] They reported disruption in the structure of ovaries, altered activity of various enzymes, and increased copper content at the lowest dose examined.

We estimated an ADI of 0.064 mg/kg-d aluminum from this study based on a LOAEL of 64 mg/kg-d and a total uncertainty factor of 1000 to account for differences between research animals and humans (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

Martinez et al, 2017

Martinez et al conducted a 60 day study in rats provided 1.5 or 8.3 mg/kg-d aluminum through drinking water.[15] At the lower dose, they observed decreases in sperm count, daily sperm production, and normal morphological sperm; increased oxidative stress and inflammation in testes; and impaired testis histology.

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%).[12]

We estimated an ADI of 0.001 mg/kg-d aluminum from this study based on a LOAEL of 1.5 mg/kg-d and a total uncertainty factor of 3000 to account for differences between research animals and humans (10), differences among people (10), use of a LOAEL rather than a NOAEL (10), and use of a shorter duration study to protect against effects from long-term exposures (3).

Miska-Schramm et al, 2017

Miska-Schramm et al exposed groups of bank voles (*Myodes glareolus*) to one of two doses of aluminum chloride in drinking water (equivalent to 1.5 or 100 mg/kg-d aluminum) for 84 days.[16] They observed decreased sperm count at both doses. At the high dose, they also observed increased sperm abnormalities and altered number of ovarian follicles.

We estimated an ADI of 0.001 mg/kg-d aluminum from this study is based on a LOAEL of 1.5 mg/kg-d and a total uncertainty factor of 3000 to account for differences between research animals and humans (10), differences among people (10), use of a LOAEL rather than a NOAEL (10), and use of a shorter duration study to protect against effects from long-term exposures (3).

Poirier et al, 2011

Poirier et al conducted a neurodevelopmental study in rat pups from gestation through weaning, where the rat dams were provided 30, 100, or 300 mg/kg-d aluminum through drinking water.[17] At levels at and above 100 mg/kg-d, the researchers observed body weight changes, renal toxicity in male pups, and dose-dependent effects on hind limb and fore-limb grip strength.

We estimated an ADI of 0.1 mg/kg-d aluminum from this study based on a LOAEL of 1.5 mg/kg-d and a total uncertainty factor of 3000 to account for differences between research animals and humans (10), differences among people (10), use of a LOAEL rather than a NOAEL (10), and use of a shorter duration study to protect against effects from long-term exposures (3).

Sun et al, 2011

In their 2011 study, Sun et al conducted a 120 day reproductive study in rats provided aluminum chloride equivalent to 13, 26, or 52 mg/kg-d aluminum in water.[18] Levels of testosterone and luteinizing hormone, as well as androgen receptor protein expression, were lower at the two highest doses. Androgen receptor mRNA levels were affected in a dose-dependent manner.

We estimated an ADI of 0.013 mg/kg-d aluminum from this study based on a LOAEL of 13 mg/kg-d and a total uncertainty factor of 1000 to account for differences between research animals and humans (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

Sun et al, 2018

In their 2018 study, Sun et al conducted another 120 day reproductive study in rats provided aluminum chloride in water equivalent to 13, 26, or 52 mg/kg-d aluminum.[19] At the lowest dose tested (13 mg/kg-d), the histological structure of testes was damaged, and mRNA expression of ATPases in testes was altered.

We estimated an ADI of 0.013 mg/kg-d aluminum from this study based on a LOAEL of 13 mg/kg-d and a total uncertainty factor of 1000 to account for differences between research animals and humans (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

Wang et al, 2012

Wang et al conducted a 120 day reproductive study in rats provided aluminum chloride in water equivalent to 13, 26, or 52 mg/kg-d aluminum.[20] Estrogen, progesterone, and follicle-stimulating hormone levels were lowered at all doses. The level of testosterone was higher at the two lowest doses.

We estimated an ADI of 0.013 mg/kg-d aluminum from this study based on a LOAEL of 13 and uncertainty factor of 1000 to account for differences between research animals and humans (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

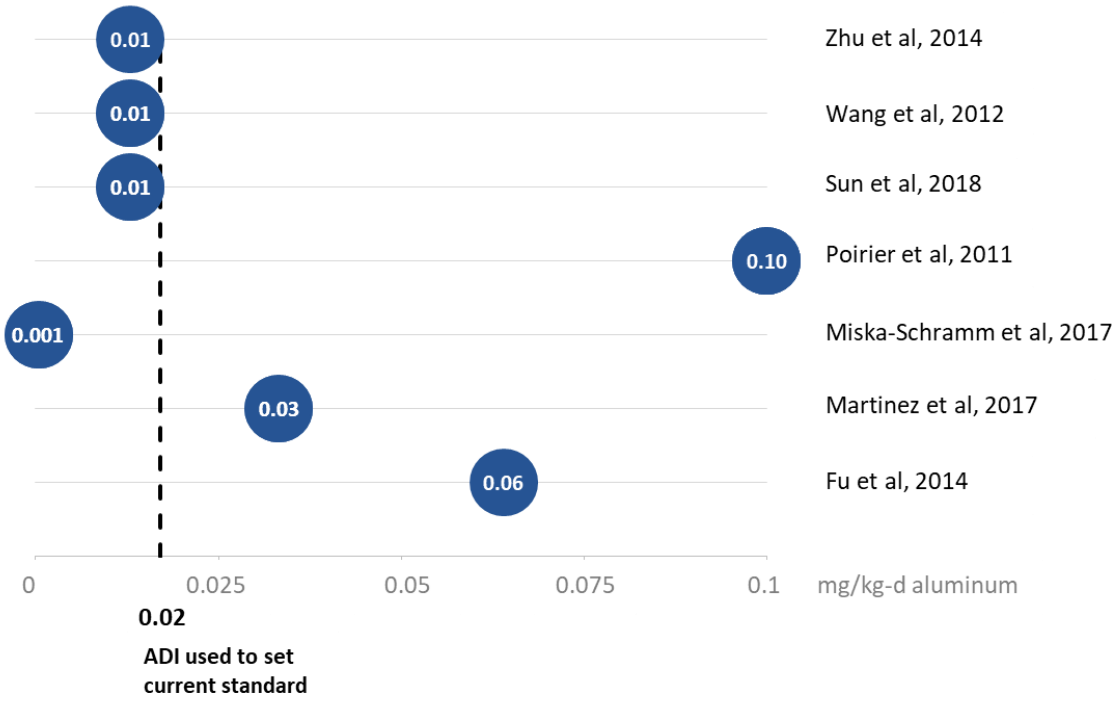
Zhu et al, 2014

Zhu et al conducted a 120 day reproductive study in rats provided aluminum chloride in water equivalent to 13, 26, or 52 mg/kg-d aluminum.[21] At the lowest dose tested (13 mg/kg-d), copper levels, sperm count, and enzyme activities in testes were decreased. At the same concentration, zinc and iron levels and sperm malformations were increased.

We estimated an ADI of 0.013 mg/kg-d aluminum from this study based on a LOAEL of 13 and uncertainty factor of 1000 to account for differences between research animals and humans (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

Summary

Review of the data published since 2010 confirms that aluminum can cause reproductive effects in laboratory animals. The ADI used to set the current groundwater standard is consistent with results of studies published since 2010 that have evaluated the risk of aluminum exposure on development and reproduction.



Data from recent studies suggest that the acceptable daily intake used to set the **existing groundwater standard for aluminum is protective**.

Standard Selection

DHS recommends no change to the enforcement standard for aluminum.

Basis for Enforcement Standard

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

The current groundwater standard is based on a research study that found that aluminum exposure caused reproductive toxicity in rabbits. There are no federal numbers, no state drinking water standard and no acceptable daily intake from the EPA for aluminum. While several key studies were obtained, the results of these studies are consistent with the acceptable daily intake used to establish the current groundwater standard. Therefore, DHS recommends no change to the enforcement standard for aluminum.

DHS recommends a preventive action limit of 20 µg/L for aluminum.

DHS recommends lowering the Preventive Action Limit (PAL) for aluminum to be set at 10% of the enforcement standards due to potential carcinogenic effects.[3,4] Aluminum has not been shown to have mutagenic, teratogenic, or interactive effects.[1]

Revised by Sarah Yang, Ph.D. – January 2022

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. Aluminum Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses (mg_{Al}/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Reproduction	Rabbit	112 d	34 mg/kg every other day (equivalent to 17 mg/kg-d)	Gavage	Increased reaction time, decreased ejaculate volume, sperm concentration, total sperm output, sperm motility, total motile sperm per ejaculate, packed sperm volume, total function sperm fraction, normal and live sperm and semen initial fructose. Increased sperm pH and dead and abnormal sperm. Decreased body weight, feed intake, relative weight of testes and epididymis.	LOAEL: 17	Yousef et al, 2005 (2) **Basis for current standard**
Neurodevelopmental	Mouse	Perinatal	300, 600	Gavage	Dose-dependent reduction in body weight gain, delay in eye opening and appearance of body hair fuzz, deficits in sensory motor refluxes in pups. Dose-dependent deficiencies in locomotor activity, learning capability, and cognitive behavior in adolescent males. Dose-dependent disturbance of neurotransmitter levels in the forebrain.	LOAEL: 300	Abu-Taweel et al, 2012 ([22])
Reproduction	Rat	30 d	37	Water	Streptozotocin-induced diabetic rats exposed to aluminum had more severe reproductive toxicity (erosion of testicular parenchyma and stroma, reduced sperm motility and serum follicle stimulating hormone, elevated serum testosterone and oestradiol) than in diabetic rats not exposed to aluminum.	LOAEL:7.5	Akinola et al, 2016 ([23])

Short-term	Rat	28 d	10	Gavage	Altered oxidative stress response in liver, kidney, testes, and temporal cortex.	LOAEL: 10	Chaitanya et al, 2012 ([24])
Longer-term	Guinea pig	91 d	300	Gavage	Reduced number and elevated abnormal ratio of sperm Decreased serum testosterone. Reduced P450scc protein expression	LOAEL: 300	Dong et al, 2016 ([25])
Longer-term	Rat	59 d	75, 150, 300	Gavage	Significant reduction in sperm count, motility, morphology, and testosterone. Testicular damage – abnormal seminiferous tubules with incomplete maturation of germinal cell layers and absence of spermatozoa in lumen.	NOAEL: 150 LOAEL: 300	Falana et al, 2017 ([26])
Reproduction	Rat	120 d	64, 128, 256	Water	Structure of ovaries was disrupted, activity of various enzymes altered, and copper content of ovaries was increased.	LOAEL: 64	Fu et al, 2014 ([14])
Development	Rat	GD 14 to PND 14	50	Water	Altered oxidative stress response in cerebellum in mothers and pups. Co-exposure to acrylamide resulted in synergistic effect.	LOAEL: 50	Ghorbel et al, 2016 ([27])
Development	Rat	Up to 150 d	100	Water	Reduced body weight, serum pH, disordered metabolism of calcium and potassium.	LOAEL: 100	Li et al, 2011 ([28])
Reproduction	Rat	60 d	1.5, 8.3	Water	Decreases in sperm count, daily sperm production, and normal morphological sperm; impaired testis histology; and increased oxidative stress and inflammation in testes	LOAEL: 1.5	Martinez et al, 2017 ([15])
Reproduction	Rat	42 d	100	Water	Decreases in sperm count, daily sperm production, and normal morphological sperm; impaired testis histology; and increased oxidative stress and inflammation in testes	LOAEL: 100	Martinez et al, 2017 ([15])

Reproduction	Vole	84 d	1.5, 100	Water	Decreased sperm count, quality, increased sperm abnormalities. Altered number of ovarian follicles	LOAEL: 1.5	Miska-Schramm et al, 2017 ([16])
Neurodevelopmental	Rat	Gestation through weaning	30, 100, 300	Water	Body weight changes, renal toxicity in male pups, dose-dependent effects on hind limb and fore-limb grip strength	NOAEL: 30 LOAEL: 100	Poirier et al, 2011 ([17])
Reproduction	Rat	120 d	13, 26, 52	Water	Levels of testosterone and luteinizing hormone were lower in 2 highest doses. Androgen receptor protein expression was lower in 2 highest doses. Androgen receptor mRNA level affected in dose-dependent manner	LOAEL: 13	Sun et al, 2011 ([18])
Development	Rat	Up to 120 d	64	Water	Decreased bone mineral density of the distal and proximal femoral metaphysis, disrupted histological structure of femur bones, and altered mRNA levels of factors in the Wnt/beta-catenin signaling pathway	LOAEL: 64	Sun et al, 2015 ([29])
Development	Rat	Up to 120 d	64	Water	Altered expression of factors involved in Wnt/beta-catenin signaling pathway	LOAEL: 64	Sun et al, 2017 ([30])
Reproduction	Rat	120 d	13, 26, 52	Water	Histological structure of testes damaged, altered mRNA expression of ATPases in testes	LOAEL: 13	Sun et al, 2018 ([19])
Reproduction	Rat	120 d	13, 26, 52	Water	Estrogen, progesterone, and follicle-stimulating hormone levels lowered in all doses. Level of testosterone was higher in the two lowest doses.	LOAEL: 13	Wang et al, 2012 ([20])
Development	Rat	GD 1 to GD 18	193	Gavage	Dam weight significantly lower. Fetal weight, malformation and crown rump length reduced. Severe limited area of preossification in fetuses vertebrae.	LOAEL: 193	Yassa et al, 2017 ([31])

Reproduction	Rat	120 d	13, 26, 52	Water	Aluminum and copper levels, sperm count, enzyme activities in testes decreased; zinc and iron levels and sperm malformations increased	LOAEL: 13	Zhu et al, 2014 ([21])

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?
Abu-Taweel et al, 2012	⦸	✓	✓	1	✓	No
Akinola et al, 2016	⦸	✓	✓	**2**	✓	No
Chaitanya et al, 2012	⦸	✓	✓	1	✓	No
Dong et al, 2016	✓	✓	✓	1	✓	No
Falana et al, 2017	⦸	✓	✓	**3**	✓	No
Fu et al, 2014	✓	✓	✓	**3**	✓	**Yes**
Ghorbel et al, 2016	✓	✓	✓	1	✓	No
Li et al, 2011	✓	✓	✓	1	✓	No
Martinez et al, 2017 (60 days)	✓	✓	✓	**2**	✓	**Yes**
Martinez et al, 2017 (42 days)	✓	✓	✓	1	✓	No
Miska-Schramm, et al 2017	✓	✓	✓	**2**	✓	**Yes**
Poirier et al, 2011	✓	✓	✓	**3**	✓	**Yes**
Sun et al, 2011	✓	✓	✓	**3**	✓	**Yes**
Sun et al, 2015	✓	✓	✓	**3**	✓	No
Sun et al, 2017	✓	✓	✓	1	✓	No
Sun et al, 2018	✓	✓	✓	**3**	✓	**Yes**
Wang et al, 2012	✓	✓	✓	**3**	✓	**Yes**
Yassa et al, 2017	✓	✓	✓	1	✓	No
Zhu et al, 2014	✓	✓	✓	**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.

Cobalt | 2019

Substance Overview

Cobalt is a naturally occurring element found in rocks, soil, water, plants, and animals.[1] Cobalt is used to produce alloys that are used in aircraft engines, magnets, tools, and artificial hip and knee joints. Cobalt compounds are also used to color glass, ceramics and paints. Small amounts of cobalt are found in the vitamin B_{12}, which is required for good health in humans. Cobalt also exists as radioactive elements that are used for commercial and medical purposes. Radioactive cobalt is not naturally found in the environment. Wisconsin's groundwater standards apply to non-radioactive cobalt.

Recommendations

The NR140 Groundwater Quality Public Health Enforcement Standard of 40 µg/L for cobalt is based on the lowest observable adverse effect level (LOAEL) for cardiomyopathy in chronic beer drinkers identified by the Agency for Toxic Substances and Disease Registry in 1992.

DHS recommends no change in the NR140 Groundwater Quality Public Health Enforcement Standard for cobalt. DHS found new technical information that is consistent with the data used to set the current standard.

DHS recommends changing the NR140 Groundwater Quality Public Health Preventive Action Limit for cobalt to be set at 10% of the enforcement standard because cobalt has recently been shown to cause teratogenic effects in animals.

Current Standards	
Enforcement Standard:	40 µg/L
Preventive Action Limit:	8 µg/L
Year:	1997

Recommended Standards	
Enforcement Standard:	40 µg/L
Preventive Action Limit:	4 µg/L

Health Effects

Exposure to high levels of cobalt can result in lung and heart effects and dermatitis.[1] Liver and kidney effects have also been observed in animals exposed to high levels of cobalt. Birth defects have been observed in animals exposed to high levels of nonradioactive cobalt.

Cobalt has not been shown to have mutagenic, carcinogenic or interactive effects following exposure in food or water.[1,2] However, a recent study has shown that cobalt can cause teratogenic effects in mice and rats.[3]

Chemical Profile

	Cobalt
Chemical Symbol:	Co
CAS Number:	7440-84-4
Molar Mass:	58.93 g/mol
Synonyms:	N/A

Exposure Routes

People can be exposed to cobalt from the air, food, and water.[1] Cobalt enters the environment from natural sources, the burning of coal or oil, and the production of cobalt alloys. In the air, cobalt is associated with particles that settle to the ground within a few days. The level of cobalt in most foods is low. However, food is usually the largest source of exposure to cobalt for people.

Cobalt released into water may stick to particles and stay in the water column or settle to the bottom of the waterbody. What happens to cobalt in water depends on many factors such as the chemistry of the water and sediment at a site as well as the cobalt concentration and water flow.

Current Standard

The current NR140 Groundwater Quality Public Health Enforcement Standard of 40 µg/L for cobalt was established in 1997.[4] This standard is based on a Lowest Observable Adverse Effect Level (LOAEL) identified by the Agency for Toxic Substances and Disease Registry (ATSDR) as part of their 1992 toxicological review of cobalt.[5] The ATSDR's value was based on cardiomyopathy in heavy beer drinkers during the 1950s and 60s because several breweries in North America and Europe added cobalt to beer as a foam stabilizer at this time. Because of their heavy beer consumption, these individuals were exposed to fairly high amounts of cobalt on a daily basis for months to years. More recent analysis has concluded that the individuals affected by this disease had a number of health issues (liver disease and anorexia) that made them a sensitive population. This likely resulted in these individuals having greater amounts of free cobalt ions in their blood resulting in toxicity. To identify the recommended enforcement standard, DHS applied an uncertainty factor of 10 to account for using a LOAEL rather than a No Observable Adverse Effect Level (NOAEL) in the calculation, and exposure parameters specified in Ch. 160, Wis. Stats.: a body weight of 10 kilograms (kg), a drinking water consumption rate of 1 liter per day (L/d), and a relative source contribution of 100%.

The current NR140 Groundwater Quality Public Health Preventive Action Limit for cobalt is set at 20% of the enforcement standards because cobalt had not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects after oral exposure.

Standard Development

Federal Numbers

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

State Drinking Water Standard

NR 809 Maximum Contaminant Level:	N/A	

Acceptable Daily Intake

EPA Oral Reference Dose:	N/A	

Oncogenic Potential

EPA Cancer Slope Factor:	N/A	

Guidance Values

ATSDR Intermediate Oral Maximum Risk Level:	0.01 mg/kg-d	(2004)
EPA Chronic Oral Peer-Reviewed Toxicity Value:	0.0003 mg/kg-d	(2008)

Literature Search

Literature Search Dates:	2008 – 2018
Total studies evaluated:	Approximately 1,200
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 cobalt.[6]

Health Advisory

The EPA has not established a health advisory for cobalt.[7]

Drinking Water Concentrations at Specified Cancer Risk Levels

The EPA has not established drinking water concentrations at specified cancer risk levels for cobalt.[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 cobalt.[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 cobalt.[8]

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

Cancer Classification

The EPA has not evaluated the carcinogenicity of cobalt.[8]

The International Agency for Research on Cancer (IARC) has classified cobalt as possibly carcinogenic to humans, but this classification is based only on non-oral exposure routes.[10]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for cobalt.[8]

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 cobalt, we searched for values that been published since 1997 when the current enforcement standard was adopted. We found relevant guidance values from the Agency for Toxic Substances and Disease Registry (ATSDR) and EPA's superfund program.

ATSDR Oral Maximum Contaminant Level

In 2004, the ATSDR recommends an intermediate-duration oral minimum risk level of 0.01 milligrams per kilogram body weight per day (mg/kg-d) for cobalt.[1] They selected a 1958 study by Davis et al that evaluated effects of cobalt treatment on red blood cell production in healthy adult males as the critical study.[11] This study found that cobalt exposure increased red blood cell numbers (critical effect) in all six patients after exposure for 22 days. To establish the minimum risk level, ATSDR used a LOAEL of 1 mg/kg-d and a composite uncertainty factor of 100 to account for differences among people (10) and using a LOAEL instead of a NOAEL (10).

The ATSDR did not recommend a chronic oral minimum reference level for cobalt. They stated that they were unable to find chronic oral studies in animals and did not use the studies that observed cardiomyopathy in people drinking large amounts of beer that contained cobalt. Their rationale for not using these studies is that the effects were serious (death) and the study did not control for the effects of concurrent alcoholism.

EPA Chronic Provisional Peer Reviewed Toxicity Value

In 2008, the EPA's Superfund program recommended a chronic provisional peer reviewed toxicity value (PPRTV) of 0.0003 mg/kg-d for cobalt.[2]

The EPA selected two studies that evaluated the effect of cobalt treatment on thyroid toxicity in humans as the critical studies.[11,12] These studies found that cobalt decreased iodine uptake by the thyroid after short-term exposure (up to 25 days) in humans. To establish this value, the EPA used a LOAEL of 1 mg/kg-d and a total uncertainty factor of 3000 to account for differences between people (10), using results from a short-term study to protect against effects from long-term exposures (10), using a LOAEL instead of a NOAEL (10), and limited availability of information (3).

Literature Search

Our literature review focused on the scientific literature published after the reviews by ATSDR in 2004. We conducted a search on the National Institutes of Health's PubMed resource to look for studies published from January 2008 to April 2018 related to cobalt toxicity or cobalt effects on a disease state in which information on cobalt exposure or dose was included as part of the study. 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 1,700 studies were returned by the search engine. We excluded studies of short duration, studies on the effects on plant and aquatic life, studies evaluating risk from non-mammalians species, and monitoring studies from further review. After applying these exclusion criteria, seven studies remained (see Table A-1 for 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.[a] Two studies met the requirements to be considered a critical study (see Table A-2 for details on the evaluation).

Critical Studies

To compare results among recently found studies and the study used to set the current enforcement standard, we calculated an acceptable daily intake (ADI) for each study/effect. The ADI is the estimated amount of cobalt that a person can be exposed to every day and not experience health impacts. The ADI is derived by dividing a toxicity value identified in a study by a factor accounting for various sources of scientific uncertainty. Uncertainty factors were included, as appropriate, to account for differences between people and research animals, differences among people, using data from short term experiments to protect against effects from long-term exposures, and using data where a health effect was observed to estimate the level that does not cause an effect.

Szakmary et al, 2001

Szakmary et al conducted several experiments to examine the effect of cobalt sulfate on prenatal development in mice, rats, and rabbits.[3] From this study, we evaluated two experiments (one in rats and one in rabbits) in further detail because they were of sufficient duration, examined more than one dose, and investigated health effects. Because the experiments in rats and rabbits exposed animals during prenatal development, used multiple doses, and found significant health effects, DHS considers them critical studies.

In the rat experiment, Szakmary et al exposed pregnant animals from gestation days 1 through 20 to cobalt sulfate through gavage at an equivalent of 10, 19, or 38 mg/kg-d cobalt. They found that the two highest doses decreased perinatal growth and survival; retarded skeletal development; and caused skeletal and urogenital malformations. We estimated an ADI of 0.1 mg/kg-d from this experiment based on a NOAEL of 10 mg/kg-d and a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10).

In the rabbit experiment, Szakmary et al exposed pregnant animals from gestation days 6 through 20 to cobalt sulfate through gavage at an equivalent of 10, 19, or 38 mg/kg-d cobalt. They found that the all doses caused fetal resorption and maternal death. We estimated an ADI 0.01 mg/kg-d from this experiment based on a LOAEL of 10 mg/kg-d and a total uncertainty factor of 1000 to account for differences between research animals and humans (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

Elbetieha, et al, 2008

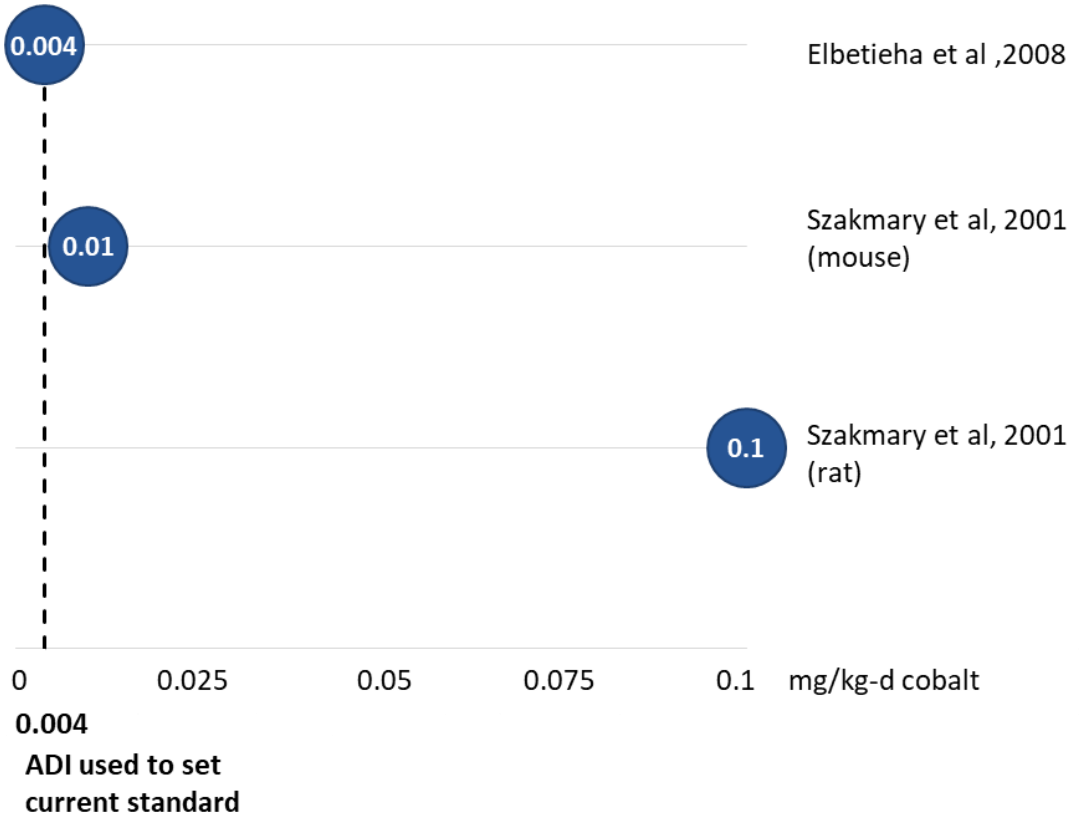
a Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect,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

Elbetieha et al evaluated the effect of cobalt on male reproduction.[14] They exposed groups of male mice to cobalt chloride in drinking water at an equivalent of 12, 21, or 42 mg/kg-d cobalt for 84 days and were then mated with untreated females. The researchers found that cobalt reduced body weight and fluid intake, altered testes and preputial gland weights, decreased sperm counts, decreased number of implantation sites, decreased number of viable fetuses and increased resorptions.

Wehe estimated an ADI of 0.004 mg/kg-d from this study based on a LOAEL of 12 mg/kg-d and a total uncertainty factor of 3000 to account for differences between research animals and humans (10), differences among people (10), use of a LOAEL rather than a NOAEL (10), and use of a shorter duration study to protect against effects from long-term exposures (3).

Summary

Review of the data published since 1997 shows that cobalt can affect reproduction and development in laboratory animals. However, the acceptable daily intake used to set the current groundwater standard is protective of these effects.



Data from recent studies suggest that the acceptable daily intake used to set the **existing groundwater standard for cobalt is protective**.

Standard Selection

DHS recommends no change to the enforcement standard for cobalt.

The current standard for cobalt is based on studies reporting cardiomyopathy in people who drank large amounts of beer containing cobalt. There are no federal numbers, no state drinking water standard and no acceptable daily intake from the EPA for cobalt.

Basis for Enforcement Standard

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

In our review, we did not find significant technical information to warrant change to the enforcement standard for cobalt. While several key studies were obtained, the results of these studies are consistent with the acceptable daily intake used to establish the current groundwater standard. Therefore, DHS recommends no change to the enforcement standard for cobalt.

DHS recommends a preventive action limit of 4 µg/L for cobalt.

DHS recommends changing the preventive action limit for cobalt to be set at 10% of the enforcement standard because cobalt has recently been shown to cause teratogenic effects in in mice and rats.[3] Cobalt has not been shown to have mutagenic, carcinogenic or interactive effects following exposure in food or water.[1,2]

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. Cobalt Toxicity Studies – Humans

Age	Population	Duration	Doses (mg/kg-d)	Form	Endpoints	Toxicity Value (mg/kg-d)	Reference
Adult	Healthy	31 d	0.014	Capsule	No effect on blood count, thyroid, cardiac, liver, or kidney functions No significant overt adverse events No effect on metal sensitization	NOAEL: 0.014	Finley, 2013

Table A-2. Cobalt Toxicity Studies – Animals

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Chronic	Rat	168 d	8.4	Diet	Reduced enzymes in cardiac tissue	LOAEL: 8.4	Clyne, 2001
Development	Mouse	GD 6 – 15	19	Gavage	Slowed skeletal development; eye, kidney, and skeleton malformations	LOAEL: 19	Szakmary, 2001
Development	Rat	GD 1 – 20	10, 19, 38	Gavage	Decreased perinatal growth and survival, slowed skeletal development, skeletal and urogenital malformations	NOAEL: 10 LOAEL: 19	Szakmary, 2001
Development	Rabbit	GD 6 – 20	10, 19, 38	Gavage	Fetal resorption Maternal death	LOAEL: 10	Szakmary, 2001
Longer-term	Mouse	84 d	12, 21, 42	Water	Reduced body weight and fluid intake. Altered testes and preputial gland weights. Decreased sperm counts Decreased number of implantation sites, number of viable fetuses, increased resorptions	LOAEL: 12	Elbetieha,2008
Short-term	Rat	7 d	12.5	Gavage	No effect on levels of monocytes, granulocytes and white blood cells	NOAEL: 12.5	Shrivastava, 2010
Short-term	Rat	21 d	3.75	Water	Oxidative stress in the liver of dams and pups	LOAEL: 3.75	Garoui, 2011
Short-term	Rat	7 d	14, 27, 55	Water	Oxidative stress in the liver	LOAEL: 14	Awoyemi, 2017

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?
Finley, 2013	⊘	⊘	✓	1	✓	No
Clyne, 2001	✓	✓	✓	1	✓	No
Szakmary, 2001 (Mouse)	✓	✓	✓	1	✓	No
Szakmary, 2001 (Rat)	✓	✓	✓	**3**	✓	**Yes**
Szakmary, 2001 (Rabbit)	✓	✓	✓	**3**	✓	**Yes**
Elbetieha,2008	✓	✓	✓	**3**	✓	**Yes**
Shrivastava, 2010	⊘	⊘	⊘	1	✓	No
Garoui, 2011	⊘	✓	✓	1	✓	No
Awoyemi, 2017	⊘	✓	✓	**3**	✓	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.

Barium | 2019

Substance Overview

Barium is a naturally occurring metal found in many types of rock.[1] High levels of barium have been found in drinking water in certain parts of the country including Iowa, Illinois, Kentucky and Georgia. Barium can also get into the environment from oil and gas drilling muds, coal fired power plants, fillers for automotive paints and specialty compounds used in bricks, tiles, and jet fuels.

Recommendations

The current NR140 Groundwater Quality Public Health Enforcement Standard of 2 mg/L for barium is based on the United States Environmental Protection Agency's (EPA's) maximum contaminant level for barium.[2]

DHS recommends no change to the enforcement standard and preventive action limit for barium. DHS did not find any new significant technical information to indicate that a change is warranted.

Current Standards	
Enforcement Standard:	2 mg/L
Preventive Action Limit:	0.4 mg/L
Year:	2005

Recommended Standards	
Enforcement Standard:	2 mg/L
Preventive Action Limit:	0.4 mg/L

Health Effects

Some people who eat or drink amounts of barium above background levels found in food and water for a short period may experience vomiting, abdominal cramps, diarrhea, difficulties in breathing, increased or decreased blood pressure, numbness around the face, and muscle weakness.[1] Eating or drinking very large amounts of barium compounds that easily dissolve can cause changes in heart rhythm or paralysis and possibly death. Animals that drank barium over long periods had damage to the kidneys, decreases in body weight, and some died.

Barium has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.[1] The EPA has classified barium as not likely to be carcinogenic to humans.[2]

Chemical Profile

	Barium
Chemical Symbol:	Ba
CAS Number:	7440-39-3
Molar Mass:	137.33 g/mol
Synonyms:	N/A

Exposure Routes

People can be exposed barium from air, food, or water.[1] Barium gets into the air during the mining, refining, and production of barium compounds, and from the burning of coal and oil. The length of time that barium will last in air, land, water, or sediments depends on the form of barium released.

Certain foods can contain high levels of barium. Certain nuts like pecans and Brazil nuts naturally contain high levels of barium. Fish and other aquatic life can accumulate barium from natural or manmade sources.

Barium compounds that do not dissolve in water (like barium sulfate and barium carbonate) can last a long time in the environment. On the other hand, barium compounds that easily dissolve in water (like barium chloride, barium nitrate, or barium hydroxide) do not usually last a long time in the environment.

Current Standard

The current NR140 Groundwater Quality Public Health Enforcement Standard of 2 mg/L for barium was adopted in 1992.[3] This standard is based on the EPA's maximum contaminant level for barium.

The current NR140 Groundwater Quality Public Health Preventive Action Limit for barium is set at 20% of the enforcement standard because barium has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

Standard Development

Federal Numbers		
Maximum Contaminant Level:	2 mg/L	(2003)
Health Advisory:	N/A	
Drinking Water Concentration (Cancer Risk):	N/A	
State Drinking Water Standard		
NR 809 Maximum Contaminant Level:	2 mg/L	(2016)
Acceptable Daily Intake		
EPA Oral Reference Dose:	0.2 mg/kg-d	(2005)
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
ATSDR Chronic Oral Minimum Risk Level:	0.2 mg/kg-d	(2007)
Literature Search		
Literature Search Dates:	2007 – 2018	
Total studies evaluated:	Approximately 380	
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 established a maximum contaminant level (MCL) for 2 milligrams per liter (mg/L) for barium in 1993.[4] The EPA set the MCL equal to the maximum contaminant level goal (MCLG) because treatment technology is available to achieve the MCLG. The EPA's MCLG for barium is based on an oral reference dose of 0.007 milligrams per kilogram body weight per day (mg/kg-d) that was established by EPA in 1990. This dose was based on a clinical study evaluating cardiovascular effects in women after exposure to barium in drinking water. The EPA used a daily water intake of 2 liters per day (L/d) and an average body weight of 70 kilograms (kg) to calculate the MCLG. In 2003, the EPA reviewed the MCL for barium and determined that MCL was still protective of human health.

Health Advisory

The EPA has not established health advisories for barium.[5]

Drinking Water Concentration (Cancer Risk)

The EPA has not established drinking water concentration based cancer risk for barium.[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

As of March 2016, Wisconsin has a maximum contaminant level of 2 mg/L for barium.[6] 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 2005, the EPA's IRIS program updated the oral reference dose for barium.[2] The current oral reference dose for barium is 0.2 mg/kg-d.

The EPA selected a study by the National Toxicology Program that evaluated effects of barium in mice exposed for 2 years in drinking water as the critical study. The EPA selected kidney damage (nephropathy) as the critical effect because it provided the best evidence of a dose-response relationship. To select the dose, the EPA modeled the incidence of kidney damage in mice using their Benchmark Dose Modeling Software (v 1.3.2). They selected the 5% lower bound benchmark dose ($BMDL_{05}$ = 63 mg/kg-d) as the toxicity value.

The EPA applied a total uncertainty factor of 300 to determine the oral reference dose. They applied uncertainty factors 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 barium, we looked to see if the EPA, the International Agency for Research on Cancer (IARC), or another agency has classified the cancer potential of barium. If so, we look to see if EPA or another agency has established a cancer slope factor.

Cancer Classification

The EPA has classified barium as not likely to be carcinogenic to humans by oral exposure.[2]

The International Agency for Research on Cancer (IARC) have not evaluated the cancer potential of barium.[7]

EPA Cancer Slope Factor

The EPA has not established a cancer slope factor for barium.[2]

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 barium, we searched for values that been published since 2005 when the EPA published their latest IRIS review. We found relevant guidance values from the Agency for Toxic Substances and Disease Registry (ATSDR) and World Health Organization (WHO).

ATSDR Chronic Oral Minimum Reference Level

In 2007, the Agency for Toxic Substances and Disease Registry (ATSDR) recommended a chronic oral minimum risk level of 0.2 mg/kg-d for barium.[1] This value is based on the same study and endpoint that the EPA used to establish their oral reference dose.

Literature Search

Our literature review focused on the scientific literature published after the review by ATSDR in 2007. We conducted a search on the National Institutes of Health's PubMed resource for relevant barium articles published from January 2007 to April 2018 looking for studies related to barium toxicity or barium effects on a disease state in which information on barium 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: Barium
Subject area: toxicology OR cancer
Language: English

Approximately 380 studies were returned by the search engine. Studies on barium nanoparticles, effects on aquatic life, non-oral exposure routes (e.g. inhalation), acute exposures (i.e., poisoning), and studies not evaluating health risks were excluded from further review. After applying these exclusion criteria, we identified two key studies (see table A-1 for 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.[b] Neither 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 no change to the enforcement standard for barium.

The current enforcement standard for barium is based on the EPA's maximum contaminant level of 2 mg/L. DHS recommends no change to this standard because we did not find any significant technical information to suggest a different value is more appropriate.

Basis for Enforcement Standard

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

DHS recommends no change to the preventive action limit for barium.

The current preventive action limit for barium is set at 20% of the enforcement standard. DHS recommends no change to this limit because barium has not been shown to have carcinogenic, mutagenic, 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%).[8]

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Appendix A. Toxicity Data

Table A-1. Barium Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Shorter-Term	Rat	21 d	10, 22, 44	Water	Dose-dependent increase in several oxidative stress biomarkers in the liver. Lipid peroxidation, protein oxidative damage, inhibition of ATPase function and increased metallothionein levels in the liver.	LOAEL: 10	Elwej, 2017 ([9])
Longer-Term	Mouse	60 days	0.14, 1.4	Water	Significant decrease in hearing at 20 kHz. Significant decreases in hearing at 4, 12, and 20 kHz.	LOAEL: 0.14	Ohgami, 2012 ([10])

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?
Elwej, 2017	⃠	⃠	✓	**2**	✓	No
Ohgami, 2012	⃠	⃠	✓	**2**	✓	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.

1,4-Dioxane | 2022

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.

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

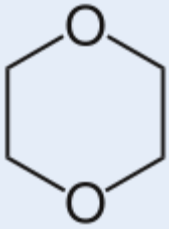
Recommended Standards	
Enforcement Standard:	0.35 µg/L
Preventive Action Limit:	0.035 µg/L

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]

Chemical Profile

	1,4-Dioxane
Structure:	
CAS Number:	123-91-1
Formula:	$C_4H_8O_2$
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 $(mg/kg\text{-}d)^{-1}$ 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:	0.1 $(mg/kg\text{-}d)^{-1}$	(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 0.1 $(mg/kg\text{-}d)^{-1}$, 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 0.1 $(mg/kg\text{-}d)^{-1}$ 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.

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

Doursonet 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

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

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 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.

Standard Selection

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

Basis for Enforcement Standard

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

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-dixoane.

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]

Updated by Amarilys Gonzalez Vazquez, Ph.D and Sarah Yang, Ph.D. – January 2022

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. 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 conduction 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 conduction 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.

Bacteria (Total Coliform) | 2019

Substance Overview

The groundwater standard for bacteria protects people from illness caused by microbial pathogens. These pathogens are small organisms, such as bacteria, viruses, and parasites, that can cause disease.[1] Microbial indicators usually measure a group of bacteria or just one type of bacterium to indicate the possible presence of pathogens. These indicators are used to set the standard because they are more efficient to measure than every single pathogen. Two microbial indicators are used today to protect drinking water:

- **Coliform** are a group of bacteria that are naturally present in the environment.
- ***E. coli*** (*Escherichia coli*) are a type of coliform bacteria that are found in the environment, food, and gut of people and animals.

This document provides the recommended Public Health Enforcement Standard for Total Coliform.

Recommendations

The current NR140 Groundwater Quality Public Health Enforcement Standard of zero for total coliform is based on EPA's MCL from the 1980s.

DHS recommends no change to the enforcement standard. The recommended standard for total coliform is based on EPA's treatment technique requirements for total coliform.

DHS recommends an NR140 Groundwater Quality Public Health Preventive Action Limit of zero for total coliform.

Current Standards	
Enforcement Standard:	0
Preventive Action Limit:	0
Year:	1985
Recommended Standards	
Enforcement Standard:	0
Preventive Action Limit:	0

Health Effects

Pathogens in water can cause a variety of illnesses.[1,2] Most common illnesses are acute (short-term) gastrointestinal illnesses causing diarrhea, abdominal discomfort, nausea, and vomiting. Less common illnesses are chronic (long-term) and include kidney failure, hepatitis, and bloody diarrhea.

Infants and young children, the elderly, and people with compromised immune systems are at the highest risk for illness from pathogens in water.[1]

Exposure Routes

Pathogens can get into drinking water from human and animal feces. People can be exposed to waterborne pathogens from drinking contaminated water, coming into contact with a contaminated surface, or being in contact with a person who is carrying the pathogen.

Current Standard

The current NR140 Groundwater Quality Public Health Enforcement Standard of zero for total coliform was established in 1985.[3] This standard is based on the EPA's 1989 maximum contaminant level for total coliform.[4] The current NR140 Groundwater Quality Public Health Preventive Action Limit for total coliform is also zero.

Standard Development

Federal Numbers	
Maximum Contaminant Level:	See below
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
Guidance Values	
None available	
Literature Search	
Search Dates:	2000 – 2019
Total studies evaluated:	Approximately 5,600
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

In April 2016, EPA made changes to how bacteria are regulated in public water systems as part of the Revised Total Coliform Rule (RTCR).[1] The RTCR replaced the non-acute MCL for total coliform with an acute MCL for *E. coli* (*Escherichia coli*).[1] Instead of having an MCL for total coliform in the RTCR, the EPA

uses a treatment technique for total coliform in public water systems. For total coliform, the treatment technique is set at zero meaning that if total coliform are detected in a public water system, the system must conduct follow-up assessments and correct sanitary defects. More specifically, public water systems that collect 40 or more bacteria samples per month are required to take additional actions if more than 5.0% of those samples have total coliform. For systems that collect fewer than 40 samples per month, follow-up action is required if more than one sample has total coliform.

Health Advisory

The EPA has not established a health advisory for total coliform.[5]

Drinking Water Concentrations at Specified Cancer Risk Levels

Because total coliform bacteria are microbial indicators, this evaluation is not appropriate.

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 total coliform.[6]

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 total coliform.

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.

Because total coliform bacteria are microbial indicators, this evaluation is not appropriate.

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 total coliform, we searched for values that have been published since 2016 when the RTCR was published. We did not find any relevant guidance values from the EPA, Agency for Toxic Substances and Disease Registry (ATSDR), World Health Organization (WHO), or Health Canada.

Literature Search

We conducted a search for studies that evaluated the applicability of total coliform as an indicator for microbial pathogens in drinking water and groundwater.

To conduct our literature review, we searched the National Institutes of Health's PubMed database for articles published from January 2000 to January 2019 related to groundwater or drinking water contamination that evaluated the applicability of total coliform as an indicator for microbial pathogens.[a] Approximately 5,600 studies were returned by the search engine. We excluded studies that focused on pathogens that do not present a potential human health risk, studies of laboratory methods, and studies that evaluated water treatment technologies. We focused on studies that assessed correlations between coliform bacteria and the occurrence of microbial pathogens in water, such as enteric viruses, protozoa, and certain pathogenic bacteria.

While not a direct indicator of health risk, there are coliform bacteria that can cause disease in humans, particularly in infants, people with weakened immune systems, and people undergoing treatment in healthcare settings. These include species in the *Klebsiella, Citrobacter,* and *Enterobacter* genera.

- *Klebsiella* species can be found in feces or the environment.[7] *Klebsiella pneumoniae* is an opportunistic pathogen (one that only affects people under rare circumstances – usually when someone has a weakened immune system) and a frequent cause of hospital-borne infections. It predominately causes urinary tract infections and respiratory infections.
- *Citrobacter* species can be found primarily in feces.[8] *Citrobacter* can cause sepsis and meningitis in infants and may cause pneumonia in immunocompromised people or infants.

a The following search terms were used in the literature review:
Title/abstract: (coliforms OR microbial) AND (groundwater OR "drinking water")
Language: English

- *Enterobacter* species can be found in feces or the environment.[9] *Enterobacter* are opportunistic pathogens and the cause of many hospital-borne infections. They can cause brain abscesses, pneumonia, meningitis, and septicemia (blood infection).

A handful of studies have examined the correlation between total coliform, *E. coli*, and pathogens in groundwater. Locas et al. evaluated the occurrence of pathogen indicators (enterococci, *E. coli*, total coliforms, coliphages) and pathogenic viruses (human enteric viruses and norovirus) in groundwater samples from 12 sites in Canada in two studies.[10,11] They detected human enteric viruses in two samples in which total coliforms were present but *E. coli* was absent. While this scenario is likely rare, it suggests that the absence of *E. coli* is not a conclusive indication that the water is pathogen free. In fact, Locas et al found that total coliforms were the only microorganism always present simultaneously with culturable viruses. In another study, Abbaszadegan et al. looked at the correlation between total coliform and E. coli and pathogenic viruses in groundwater.[12] They found that total coliform is a slightly more sensitive test for the occurrence of viruses than *E. coli*.

Our literature search has shown that members of the total coliform family can be pathogenic and that total coliforms can be valuable indicators for the presence (or absence) of pathogens in drinking water and groundwater.

Standard Selection

DHS recommends an enforcement standard of 0 for total coliform.

Basis for Enforcement Standard
- ☑ Federal Number
- ☐ Cancer Potential
- ☐ EPA Acceptable Daily Intake
- ☐ Technical information

Chapter 160 of State Statute requires that DHS recommend adoption of a federal number unless there is new information not considered by the EPA when this level was adopted. Federal numbers include maximum contaminant levels or drinking water standards from the EPA. For total coliform, EPA replaced the maximum contaminant level with a treatment technique. For some systems, this technique is triggered when total coliform is present (levels are more than zero). DHS considers this trigger as a federal number.

While total coliforms are not a direct indicator of fecal contamination and not all coliform bacteria are pathogenic, they can be used to evaluate the potential for infection associated with a water supply. The detection of total coliform in a well indicates that the well is compromised in some way and vulnerable to contamination by pathogens until the sanitary defect is identified and repaired.

Wisconsin's groundwater is used as a drinking water source in private wells and many public water systems. Unlike public systems, private well owners are not required to have their wells inspected and repaired following detection of total coliform, making them more at risk for the potential health effects described above. Furthermore, private well users include many sensitive subpopulations, including pregnant women, infants, and immunocompromised individuals. Therefore, DHS recommends an enforcement standard of zero for total coliform.

DHS recommends a preventive action limit of 0 for total coliform.

Because DHS recommends an enforcement standard of zero for total coliform, the recommended preventive action limit is also zero.

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