Hexavalent Chromium | 2019

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

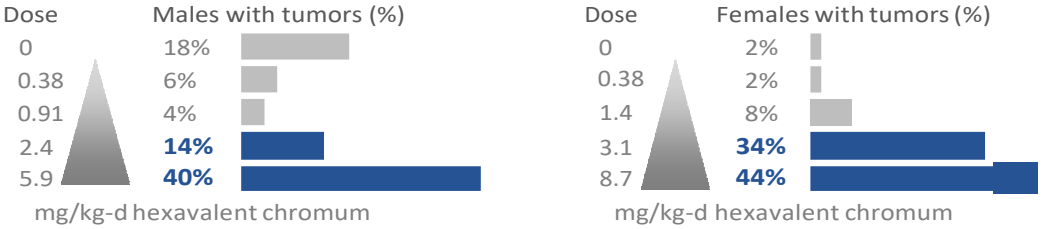
The EPA Office of Pesticide Programs (OPP) and Integrated Risk Information System (IRIS) have established or proposed cancer slope factors for hexavalent chromium.[9,12,13]

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 dehydrate in drinking water for two years. In rats, they found that the two highest doses caused adenoma and carcinoma in the small intestines (duodenum, jejunum, or ileum) of males and females. In mice, they found that the highest dose caused squamous cell carcinoma in the oral mucosa of males and females.

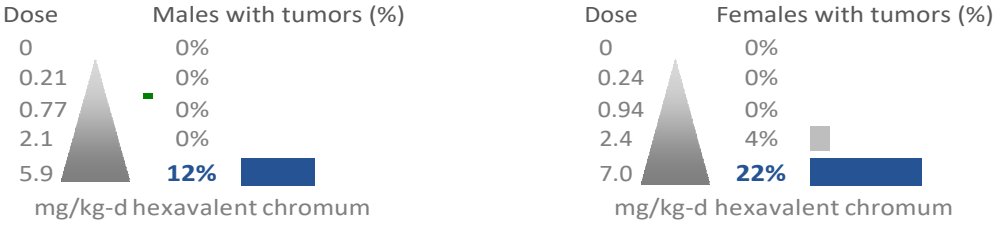
National Toxicology Program

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 for the male mouse data. Therefore, they determined that the female mouse data were 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

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a The following search terms were used in the literature review:
Title/Abstract: Hexavalent chromium
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]

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 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.

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]

Basis for Recommended Standard

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

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]

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.

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]

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]

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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: 0, 1.25, 12.5, 125 mg/kg-d	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. *Mixture caused more histopathology than	N/A	Sanchez-Martin, 2015 ([4])

						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 molecules, and organism-specific glucose transporters. Increase in serum insulin level in male progenies.	LOAEL: 8	Shobana, 2017 ([37])

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 Azoxymethane (AOM): 12.5 mg/kg	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 incidence, multiplicity, size, and grade and cell inflammatory response.	LOAEL: 1.3	Wang, 2012 ([5])
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,	✓	✓	✓	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 40(	
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.

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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%).[14]

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.

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]

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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.[6] 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.

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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.

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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%).[17]

Prepared by Curtis Hedman, Ph.D.

Wisconsin Department of Health Services

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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 | 2019

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 () for molybdenum is based the United States Environmental Protection Agency's (EPA's) Lifetime Health Advisory for molybdenum established in 1993.[1]

DHS recommends no change to the enforcement standard. DHS did not find any new significant technical information to indicate that a change is warranted.

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]

Current Standards	
Enforcement Standard:	40 µg/L
Preventive Action Limit:	8 µg/L
Year:	2006
Recommended Standards	
Enforcement Standard:	40 µg/L
Preventive Action Limit:	4 µg/L

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. [4,5] 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.[2,4]

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.[4,5] 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.[4,5] 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.[4,5] 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:	0.008 mg/kg-d	(2017)
Literature Search		
Literature Search Dates:	2013 – 2019	
Total studies evaluated:	Approximately 1500	
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 (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)).[3] 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

In 2013, DHS was asked by the Wisconsin Department of Natural Resources (DNR) to review the toxicity information on molybdenum and recommend whether any action on the existing NR140 groundwater standards should be considered. DHS did not identify significant technical information that was scientifically valid and not considered by EPA when the federal number (i.e,. the Lifetime Health Advisory) was established, which is required by statute in order to recommend a groundwater enforcement standard different than the federal number. As such, DHS concluded that it was not appropriate to revise the existing groundwater standard for molybdenum at the time. During the review, DHS was made aware that the EPA was reviewing the Lifetime Health Advisory for

molybdenum.[a] DHS concluded that the available technical information suggested that a different molybdenum concentration in water could be used as an interim health advisory level for the purposes of issuing individual drinking water advisories to Wisconsin well-owners until the EPA review was completed.

In addition to this interim health advisory, we searched for values that were published since 2013 when the EPA published their latest IRIS review. We found relevant guidance values from the Agency for Toxic Substances and Disease Registry (ATSDR).

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 (draft)

In 2017, the Agency for Toxic Substances and Disease Registry (ATSDR) recommended a draft intermediate-duration oral minimal risk level (MRL) of 0.008 mg/kg-d for molybdenum.[4] The ATSDR also selected the study by Fungwe et al. as their critical study. Instead of using the NOAEL of 0.9 mg/kg-d presented in the study, ATSDR calculated a NOAEL of 0.76 mg/kg-d. This difference comes from using an average water intake rate and an average body weight for rats as recommended by the EPA instead of values from the study.[14] The ATSDR applied a total uncertainty value of 100 to account for differences between people and research animals (10) and differences among people (10).

Literature Search

The DHS reviewed the literature on molybdenum toxicity published since 1993 (the year when EPA published their health advisory level). We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from 1993 to May 2019 for studies related to molybdenum toxicity or its effects on a disease state in which information on exposure or dose was

a As of June 2019, EPA has not completed its review of the Lifetime Health Advisory for molybdenum.

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 1,500 studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life, studies not evaluating health risks, and studies evaluating risk from non-mammalians species from further review. After applying these exclusion criteria, we located seven 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.[c] Two of the studies met the criteria to be considered a critical study (see Table A-2 for details on the evaluation).

Critical Studies

To compare results between studies, we calculated acceptable daily intake (ADI) values for each study/effect. The ADI is the estimated amount of molybdenum 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.

Pandey and Singh, 2002

Pandey and Singh examined the reproductive toxicity of molybdenum in rats.[16] In this study, the researchers exposed adult male rats to different concentrations of sodium molybdate (0, 4.7, 14 or 24 mg molybdenum/kg-d) in the diet for 60 days and evaluated the effects on sperm count, sperm motility, and sperm abnormalities. The researchers identified a NOAEL of 4.7 mg/kg-d for molybdenum based on a decrease in sperm count, sperm motility, increase in sperm abnormalities, and degeneration of seminiferous tubules.

We estimated an ADI of 0.016 mg/kg-d based on a NOAEL of 4.7 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). The calculated ADI is higher than ADIs identified in other studies on reproductive effects and the ADI (0.005 mg/kg-d) used to set the existing federal number for molybdenum.

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b The following search terms were used in the literature review:
Title/Abstract: Molybdenum
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%).[15]

Lyubimov et al., 2004

Lyubimov et al. examined the reproductive toxicity of molybdenum in rats.[17] In this study, the researchers exposed adult rats to different concentrations of ammonium tetrathiomolybdate (0, 0.4, 1.5, or 4.4 mg molybdenum/kg-d) with copper supplementation (110 mg/kg of diet) by gavage for 60 days and evaluated the reproductive endpoints in both males and females. The researchers identified a NOAEL of 1.5 mg/kg-d for molybdenum based on a decrease in sperm motility and sperm count, histological alteration in spermatogenesis, and increased sperm morphological alterations in males. No adverse effects were observed at any dose level on reproductive endpoints in females.

We estimated an ADI of 0.005 mg/kg-d based on a NOAEL of 1.5 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). The calculated ADI is the same as the ADI (0.005 mg/kg-d) used to set the existing federal number for molybdenum.

Standard Selection

DHS recommends no change to the enforcement standard for molybdenum.

The current enforcement standard for molybdenum is based on the most recent federal number, EPA's lifetime health advisory of 40 µg/L.

Basis for Enforcement Standard

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

DHS has discretion to recommend an enforcement standard different than a federal number if the following two criteria are met:

- There is significant technical information that is scientifically valid and was not considered when the federal number was established.[d]
- The department concludes with reasonable scientific certainty that a different standard is justified.

The Fungwe study used by DHS to develop an interim health advisory level in 2013 was considered by the EPA when the lifetime health advisory level was established.

In the current literature review, we identified two critical studies published since the year when EPA published their health advisory level. Both studies observed effects on the reproductive system that are

d Per s. 160.07 (4) (e), Wis. Stats., when DHS is evaluating evidence for establishing an enforcement standard different than a federal number, the department will consider the extent to which the evidence was developed in accordance with scientifically valid analytical protocols and may consider whether the evidence was subjected to peer review, resulted from more than one study, and is consistent with other credible medical or toxicological evidence.

consistent with other studies. The technical information identified in the present review observed effects at doses similar or higher than the existing lifetime health advisory. As a result, DHS concludes that the information identified does not meet the criteria described above. Therefore, DHS recommends no change to the enforcement standard for molybdenum.

DHS recommends a preventive action limit of 4 µg/L for molybdenum.

DHS recommends that the preventive action limit for molybdenum be set at 10% of the enforcement standard because new studies have shown that molybdenum can cause teratogenic and interactive effects.[2-4] Molybdenum has not been shown to have carcinogenic or mutagenic effects.[4]

Prepared by Clara Jeong, Ph.D.

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. Molybdenum Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Form	Endpoints	Toxicity Value (mg/kg-d)	Reference
Short-term	Rabbit (male)	14 d	0.58	Diet	Ammonium heptamolybdate	No histological alterations in the liver or alterations in serum clinical chemistry parameters. Reduction in germ cells and mature spermatocytes (incidence and statistical significance were not reported)	LOAEL: 0.58	Bersenyi et al. 2008 ([18])
Short-term	Rabbit (female)	14 d	1.2	Diet	Ammonium heptamolybdate	A 60% increase in serum triglyceride levels was found; no significant alterations in liver or kidney histopathology.	LOAEL: 1.2	Bersenyi et al. 2008 ([18])
Short-term	Mouse	14 d	1.2	Diet	Ammonium heptamolybdate	No histological alterations observed in the ovaries	NOAEL: 1.2	Bersenyi et al. 2008 ([18])
Longer-term	Rat	59 – 61 d (male)	0.4, 1.5, 4.4	Gavage	Ammonium tetrathiomolybdate	Decreases in body weight gain in males starting at day 50. Decreases in erythrocyte count, hemoglobin concentration, and hematocrit in males. Decreases in sperm motility and sperm count, and increased sperm morphological alterations; histological alterations in spermatogenesis in all males.	NOAEL: 1.5 LOAEL: 4.4	Lyubimov et al., 2004 ([17])
Longer-term	Rat	22 – 35 d (female)	0.4, 1.5, 4.4	Gavage	Ammonium tetrathiomolybdate	No effect on body weight gain, clinical, reproductive, or developmental parameters.	NOAEL: 4.4	Lyubimov et al., 2004 ([17])
Chronic Reproductive	Rat	90 d	5, 17, 60	Diet	Sodium molybdate	No change in estrous cycle, sperm counts, motility, and morphology Decreased body weight, food consumption, water consumption.	NOAEL: 17 LOAEL: 60	Murray et al., 2014a ([19])

						Renal histopathology.		
Short-term Developmental	Rat	Gestation days 6 to 20	3, 10, 20, 40	Diet	Sodium molybdate	No change in embryo fetal survival and fetal body weight No developmental malformation	NOAEL: 40	Murray et al. , 2014b ([20])
Chronic Reproductive	Rat	2 generations	5, 17, 40	Diet	Sodium molybdate	No effects on estrus cycles, sperm parameters, mating, fertility, gestation, litter size, pup survival, growth or postnatal development. Decreased body weight and food consumption. Mild degeneration of seminiferous tubules at high doses.	Reproductive NOAEL: 40 Systemic NOAEL: 17	Murray et al. , 2019 ([21])
Longer-term	Rat	60 d	4.7, 14, 24	Gavage	Sodium molybdate	No significant alterations in body weight gain. Decreases in sperm count and sperm motility and increases in sperm abnormalities were observed at 24 mg/kg mg/kg and higher. Degeneration of seminiferous tubules were observed in the testes at 24 mg/kg (incidence and statistical significance were not reported)	NOAEL: 4.7 LOAEL: 14	Pandey and Singh, 2002 ([16])
Longer-term	Rat	60 d	14	Gavage	Sodium molybdate	Decrease in fertility (60% versus control). Increased post-implantation losses, increased resorptions, decreased number of live fetuses, and decreases in fetal weight and crown-rump length in males mated with unexposed females.	LOAEL: 14	Pandey and Singh, 2002 ([16])
Longer-term	Rat	63 d	100	Water	Sodium molybdate	Slight decrease (approximately 4%) systolic blood pressure. No significant alterations in blood triglyceride, glucose, or insulin	NOAEL: 100	Peredo et al., 2013 ([22])

						levels		
Short-term	Mouse	14 d	3, 6, 12, 25, 49	?	Sodium molybdate	Significant decreases in relative epididymis weight, sperm concentration, and sperm motility and increase in rate of sperm abnormalities.	NOAEL: 12 LOAEL: 25	Zhai et al., 2013 ([23])
Short-term	Mouse	14 d	0.76, 1.5, 3, 6	Water	Sodium molybdate	Decreased ovary weight Increased abnormal oocyte	LOAEL: 3	Zhang et al., 2013 ([24])

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?
Bersenyi et al. 2008 (rabbit - males)	⦸	✓	✓	1	✓	No
Bersenyi et al. 2008 (rabbit - females)	⦸	✓	✓	1	✓	No
Bersenyi et al. 2008 (mouse)	⦸	⦸	⦸	1	✓	No
Lyubimov et al., 2004 (males)	✓	✓	✓	**3**	✓	**Yes**
Lyubimov et al., 2004 (females)	⦸	⦸	⦸	**3**	✓	No
Murray et al., 2014a	✓	See note	✓	**3**	✓	No
Murray et al., 2014b	✓	See note	✓	**4**	✓	No
Murray et al., 2019	✓	See note	✓	**3**	✓	No
Pandey and Singh, 2002	✓	✓	✓	**3**	✓	**Yes**
Pandey and Singh, 2002	✓	✓	✓	1	✓	No
Peredo et al., 2013	✓	⦸	✓	1	✓	No
Zhai et al., 2013	⦸	✓	✓	**5**	✓	No
Zhang et al., 2013	⦸	✓	✓	**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.

Note: Murray et al. examined the reproductive and developmental toxicity of molybdenum in rats. However, all three studies did not observe any effects related to reproductive or developmental toxicity endpoints at any doses. In these studies, the systemic toxicity NOAELs were lower than the NOAELs of reproductive or developmental toxicity. This is inconsistent with the findings from other studies where such effects were observed (i.e. altered estrous cycles, decreased sperm count, motility, and morphology) in similar or lower doses of molybdenum.

Aluminum | 2019

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 and Preventive Action Limit for 1,1-dichloroethane. DHS found new technical information that is consistent with the data used to set the current standard.

Current Standards	
Enforcement Standard:	200 µg/L
Preventive Action Limit:	20 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 10%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 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.

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

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%).[13]

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.

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).

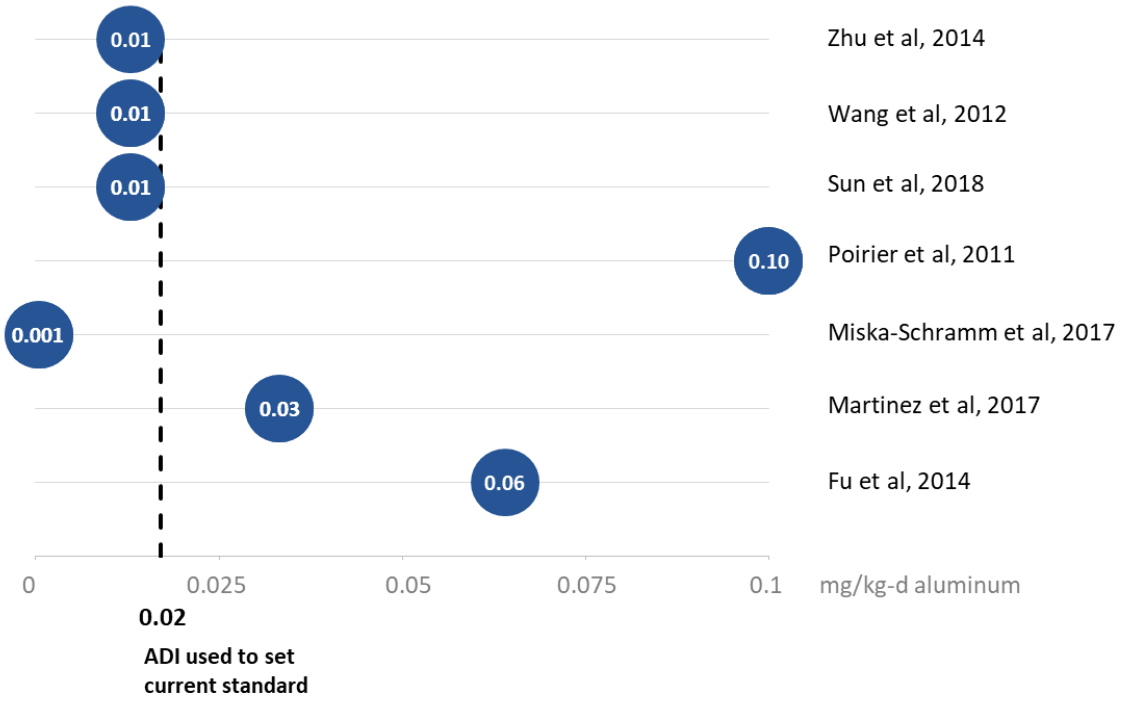
Zhu et al, 2014

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 no change to preventive action limit for aluminum.

The current preventive action limit for aluminum is set at 10% of the enforcement standard because two studies have shown possible carcinogenic effect in animals.[3,4] As part of our review, we did not find any evidence to suggest that a different preventive action limit is appropriate. Therefore, DHS recommends no change to the preventive action limit for aluminum.

Prepared by Robert Thiboldeaux, Ph.D. and Sarah Yang, Ph.D.

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	LOAEL: 300	Dong et al, 2016 ([25])

					P450scc protein expression		
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-	LOAEL: 13	Sun et al, 2011 ([18])

					dependent manner		
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

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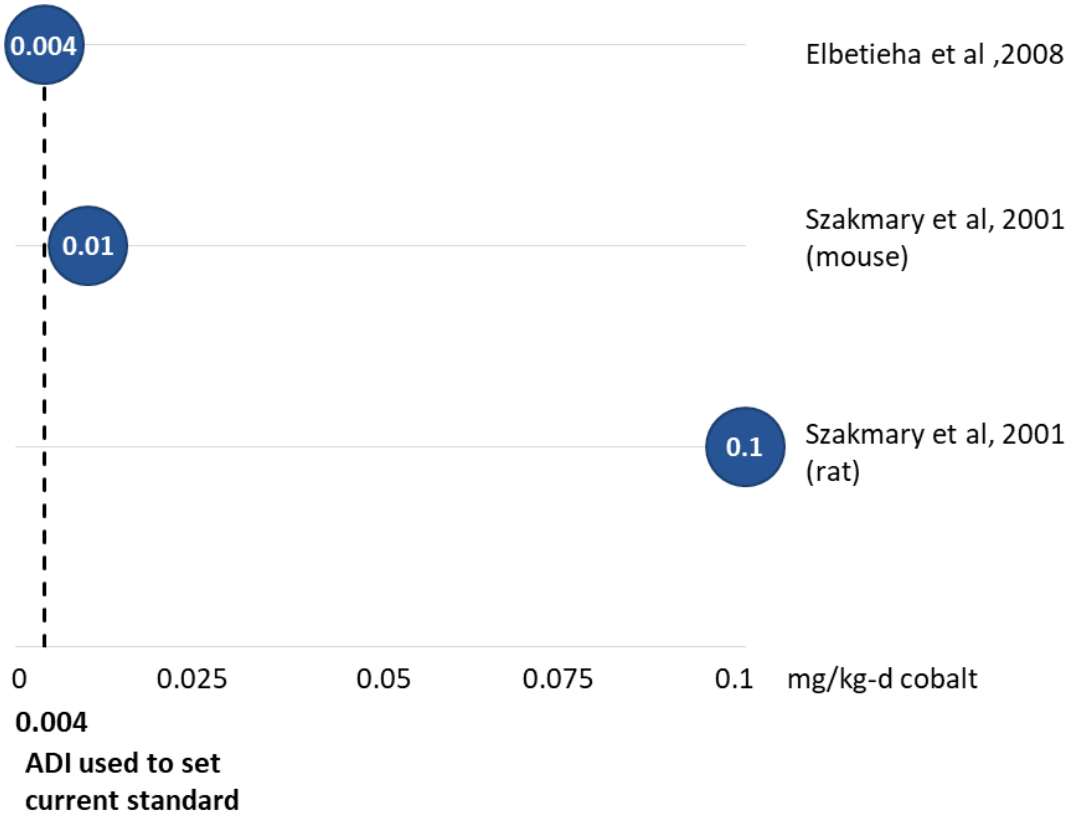
a Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect,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

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 2,000 µg/L (equal to 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:	2,000 µg/L
Preventive Action Limit:	400 µg/L
Year:	2005

Recommended Standards	
Enforcement Standard:	2,000 µg/L
Preventive Action Limit:	400 µg/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.

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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 2,000 µg/L (equal to 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.