Substance Overview

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

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

Recommendations

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

DHS recommends an enforcement standard of 100 micrograms per liter (µg/L) for thiamethoxam. The recommended standard is based on the United States Environmental Protection Agency's (EPA's) chronic oral reference dose for thiamethoxam.[1]

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

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

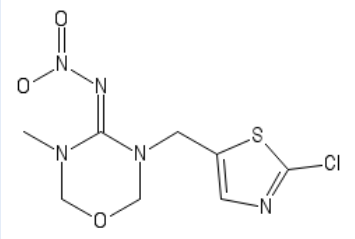
Recommended Standards	
Enforcement Standard:	100 µg/L
Preventive Action Limit:	10 µg/L

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standard

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

Standard Development

Federal Numbers

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

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A	

Acceptable Daily Intake

EPA Oral Reference Dose:	0.012 mg/kg-d	(2017)

Oncogenic Potential

EPA Cancer Slope Factor:	N/A	

Guidance Values

None available

Literature Search

Literature Search Dates:	2010 – 2019
Total studies evaluated:	Approximately 540
Key studies found?	Yes

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for thiamethoxam.[4]

Health Advisory

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

Drinking Water Concentrations at Specified Cancer Risk Levels

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for thiamethoxam.[7]

Acceptable Daily Intake

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

EPA Oral Reference Dose

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

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

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

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

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a Doses for 1998 study:

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

b Doses for 2004 study:

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

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

To set the oral reference dose for thiamethoxam, the EPA used combined data from both studies to give a NOAEL of 1.2 mg/kg-d. The EPA selected this value because the two studies used different terminology, criteria, and scoring for the histopathological evaluation leading to uncertainty in comparing the results across studies. The EPA selected a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). The EPA's chronic oral reference dose for thiamethoxam is of 0.01 mg/kg-d.

Oncogenic Potential

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

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

Cancer Classification

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

EPA Cancer Slope Factor

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

Additional Technical Information

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

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

Guidance Values

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

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

Literature Search

The most recent federal review on thiamethoxam was published in 2017 when the EPA's oral reference dose was established. Our literature review focused on the scientific literature published after the review by the EPA in 2017. A search on the National Institutes of Health's PubMed resource for articles published from January 2017 to February 2019 was carried out for studies related to thiamethoxam toxicity or its effects on a disease state in which information on thiamethoxam exposure or dose was included as part of the study.[c] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

Approximately 540 studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life, studies evaluating risk from non-mammalian species, studies using a product containing thiamethoxam, and monitoring studies from further review. After applying these exclusion criteria, we located one key study (Table A-1 contains a summary of this study). To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.[d] The key study did not meet the requirements to be considered a critical study (see Table A-2 for details on this evaluation).

Standard Selection

DHS recommends an enforcement standard of 100 µg/L for thiamethoxam.

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

Basis for Enforcement Standard

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

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

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

d Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect, and the BMD is an estimation of the dose that would cause a specific level of response (typically 5 or 10%).[8]

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

DHS recommends a preventive action limit of 10 µg/L for thiamethoxam.

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

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

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

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

Table A-2. Critical Study Selection

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity value identifiable?	Critical study?
El Okle, 2018	✓	✓	✓	1	✓	No

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

Imidacloprid | 2019

Substance Overview

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

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

Recommendations

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

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

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

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

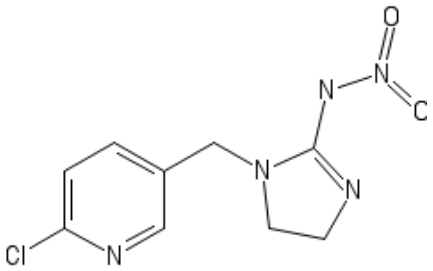
Recommended Standards	
Enforcement Standard:	0.2 µg/L
Preventive Action Limit:	0.02 µg/L

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standards

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

Standard Development

Federal Numbers		
Maximum Contaminant Level:	N/A	
Health Advisory:	N/A	
Drinking Water Concentration (Cancer Risk):	N/A	
State Drinking Water Standard		
NR809 Maximum Contaminant Level:	N/A	
Acceptable Daily Intake		
EPA Oral Reference Dose:	0.057 mg/kg-d	(2010)
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
None available		
Literature Search		
Literature Search Dates:	2010-2018	
Total studies evaluated:	Approximately 530	
Key studies found?	Yes	

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for imidacloprid.[14]

Health Advisory

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

Drinking Water Concentrations at Specified Cancer Risk Levels

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for imidacloprid.[16]

Acceptable Daily Intake

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

EPA Oral Reference Dose

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

Oncogenic Potential

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

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

Cancer Classification

The EPA and Joint FAO/WHO Meeting on Pesticide Residues (JMPR) have evaluated carcinogenic potential of imidacloprid and found that it did not show evidence of carcinogenicity in animal studies.[1,17] The international Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of imidacloprid.[18]

Cancer Slope Factor

The EPA has not established a cancer slope factor for imidacloprid.[19]

Additional Technical Information

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

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

Guidance Values

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

Literature Search

Our literature review focused on the scientific literature published since the risk assessment by EPA in 2010. We searched on the National Institutes of Health's PubMed database for articles published from January 2010 to October 2018 related to imidacloprid toxicity or its effects on a disease state in which information on imidacloprid exposure or dose was included as part of the study.[a] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

Approximately 530 studies were returned by the search engine. We excluded studies of short duration (< 60 days in rodents), studies on the effects on plant and aquatic life, studies evaluating risk from non-mammalians species, and monitoring studies from further review. After applying these exclusion criteria, we located 11 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.[b] Six of the studies met the criteria to be considered a critical study (see Table A-2 for details on the evaluation).

Critical Studies

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

b Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect, and the BMD is an estimation of the dose that would cause a specific level of response (typically 5 or 10%).[20]

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

General Toxicity

Bhardwaj et al, 2010

Bhardwaj et al evaluated the effects of exposure to imidacloprid on overall health in female rats.[21] Female rats were exposed to 5, 10, or 20 mg/kg-d of imidacloprid by gavage for 90 days. They found that the highest dose of imidacloprid decreased body weight, increased liver, kidney, and adrenal weights, altered clinical parameters, and decreased spontaneous locomotor activity.

We estimated an ADI of 0.03 mg/kg-d based on a NOAEL of 10 mg/kg-d and uncertainty factor of 300 to account for differences between people and research animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3).

Vohra et al, 2014

In their first study, Vohra et al evaluated the effects of exposure to imidacloprid on overall health in female rats.[22] Rats were exposed to 10 or 20 mg/kg-d of imidacloprid by gavage for 60 days. They found that imidacloprid reduced feed intake, heart and spleen weight, decreased acetylcholinesterase activity in plasma and brain.

We estimated an ADI of 0.003 mg/kg-d based on a Lowest Observed Adverse Effect Level (LOAEL) of 10 mg/kg-d and uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10).

Vohra et al, 2015

In their second study, Vohra et al evaluated the effects of exposure to imidacloprid on multiple generations of animals.[23] Female rats were exposed to 10 or 20 mg/kg-d of imidacloprid by gavage for 60 days and then mated with untreated males to obtain F1 and F2 generations and effects were evaluated in F2 animals. They found that the highest dose of imidacloprid reduced the average feed intake of females and increased the activity of alanine aminotransferase, alkaline phosphatase, and glucose 6-phosphate dehydrogenase in both sexes. Both doses of imidacloprid decreased acetylcholine esterase activity in plasma and brain in all treated animals and caused histopathological changes in the liver, kidney, and brain of females.

We estimated an ADI of 0.01 mg/kg-d based on a Lowest Observed Adverse Effect Level (LOAEL) of 10 mg/kg-d and uncertainty factor of 1000 to account for differences between people and research animals (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

Reproduction and Development

Bal et al, 2012a

In their first study, Bal et al evaluated the effects of exposure to imidacloprid on reproduction in developing male rats.[24] Rats were exposed to 0.5, 2, or 8 mg/kg-d of imidacloprid by gavage for 90 days. They found that imidacloprid decreased sperm concentration, reduced weight gain, and lowered testosterone and glutathione levels at all doses. We estimated an ADI of 0.0002 mg/kg-d based on a Lowest Observed Adverse Effect Level (LOAEL) of 0.5 mg/kg-d and uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10). This and the following study were the first peer-reviewed publications to evaluate the effects of imidacloprid on the male reproductive system.

Bal et al, 2012b

In their second study, Bal et al repeated the study in adult male rats.[8] They found that imidacloprid affected several reproductive parameters, reduced antioxidant levels, and disturbed fatty acid composition at all doses. For this study, we estimated an ADI of 0.0002 mg/kg-d based on a LOAEL of 0.5 mg/kg-d and an uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10). This and the previous study were the first peer-reviewed publications to evaluate the effects of imidacloprid on the male reproductive system.

Gawade et al, 2013

Gawade et al evaluated the effects of exposure to imidacloprid on reproduction and development.[25] Pregnant rats were exposed to 10, 30, or 90 mg/kg-d of imidacloprid by gavage during pregnancy (gestation days 6 to 20) to evaluate effects on maternal toxicity, fetal development, and the immune system. Additionally, a subset of the pups was exposed to imidacloprid by gavage until post-natal day 42 to evaluate effects on the immune system. They found that imidacloprid increased post-implantation loss, caused soft tissue abnormalities and skeletal alterations, and had adverse effects on immunity.

We estimated an ADI of 0.01 mg/kg-d based on a LOAEL of 10 mg/kg-d and uncertainty factor of 1000 to account for differences between people and research animals (10), differences among people (10), and use of a LOAEL rather than a NOAEL (10).

Glucose Regulation

Sun et al, 2016

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

DHS considers this study a critical study because it is of a longer-term duration (more than 60 days), it evaluated more than one dose, and it found significant health effects. The estimated ADI from this study is 0.00002 mg/kg-d. The ADI is based on a LOAEL of 0.06 mg/kg-d and an uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10). This study was one of the first peer-reviewed publications to evaluate the effects of imidacloprid on glucose regulation and obesity. Some of the observed effects on high-fat diet induced weight gain, insulin resistance, and glucose levels occurred at doses lower than the EPA's oral reference dose.

Sun et al, 2017

In 2017, Sun et al repeated their experiment in female mice.[11] Females were less sensitive to the effects of imidacloprid. They found that only the middle dose (0.6 mg/kg-d) enhanced high fat diet-induced weight gain and adiposity. They also found that only the highest dose of imidacloprid (6 mg/kg-d) increased insulin levels and did so without an effect on glucose levels. The authors hypothesized that estrogens may be responsible for the increased resistance to high fat-diet induced glucose intolerance and insulin resistance observed in the female mice compared to male mice. They theorized that it might take longer for female mice to develop the same effects as the male mice.

We estimated an ADI of 0.0002 mg/kg-d based on a NOAEL of 0.06 and uncertainty factor of 300 to account for account for differences between people and research animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3). This study was one of the first peer-reviewed publications to evaluate the effects of imidacloprid on glucose regulation and obesity.

Neurology

Kara et al, 2015

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

Because this study is of a longer-term duration, evaluated more than one dose, and found significant health effects, DHS considers it a critical study. This study evaluated the effect of imidacloprid on spatial learning and memory at levels below EPA's NOAEL. This study found that imidacloprid affected learning in a dose-dependent manner in infants and decreased cognitive function in infants and adults making a critical study. The estimated ADI from this study is 0.00002 mg/kg-d. The ADI is based on a NOAEL of 0.5 mg/kg-d and an uncertainty factor of 300 to account for differences between people and research

animals (10), differences among people (10), and use of a shorter term study to protect against effects from long-term exposures (3).

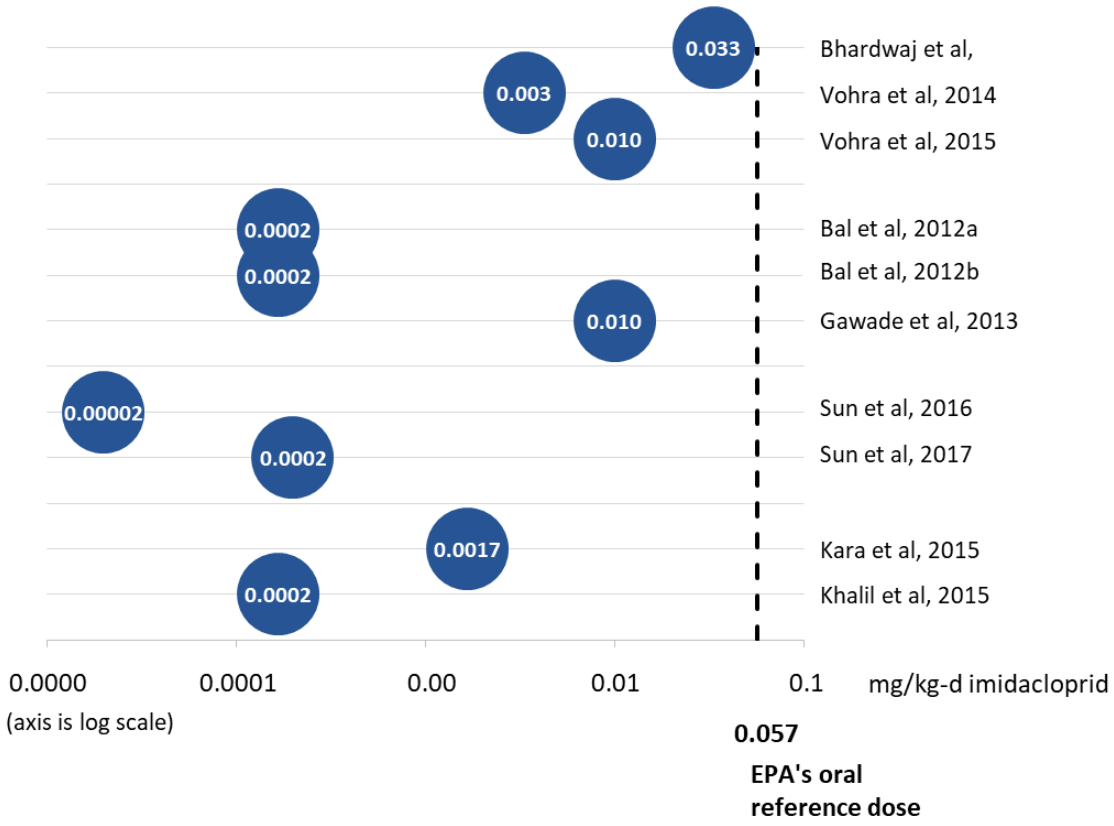
Kahlil et al, 2017

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

DHS considers this study a critical study because it is of a longer-term duration, evaluated more than one dose, and found significant health effects. The results from this study are consistent with results from other critical studies – more specifically, the effects on insulin and glucose regulation are consistent with the results of the studies by Sun et al and the effects on neurological parameters are consistent with results by Kara et al The estimated ADI from this study is 0.0002 mg/kg-d. The ADI is based on a LOAEL of 0.5 mg/kg-d and uncertainty factor of 3000 to account for differences between people and research animals (10), differences among people (10), use of a shorter term study to protect against effects from long-term exposures (3), and use of a LOAEL rather than a NOAEL (10).

Summary

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



Data from recent studies suggest that the ADI used to set the groundwater standard **should be lower than EPA's oral reference dose**.

Standard Selection

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

Basis for Enforcement Standard

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

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

To calculate the ADI as specified in s. 160.13, Wisc. Statute, DHS selected the 2016 study by Sun et al as the critical study. We selected a LOAEL of 0.06 mg/kg-d because effects on weight gain, adipose cell size, kidney weight, and glucose level were observed at this dose. We selected a total uncertainty factor of

3000 to account for differences among people and research animals, differences among people, using data from a short-term study to protect against effects from long-term exposures, and having to use a LOAEL rather than a NOAEL in these calculations. To determine the recommended enforcement standard, DHS used the ADI, and, as required by Ch. 160, Wis. Stats., a body weight of 10 kg, a water consumption rate of 1 L/d, and a relative source contribution of 100%.

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

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

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

Table A-1. Imidacloprid Toxicity Studies from Literature Review

Study Type	Species	Duration	Doses (mg/kg-d)	Route	Endpoints	Toxicity Value (mg/kg-d)	Reference
Reproduction	Rat (male)	65 d	Males: 1	Gavage	Serious abnormalities in sperm morphology and concentration, imbalance of sexual hormones	LOAEL: 1	Abdel-Rahman et al, 2017 ([26])
Short-term	Mice (male)	15 d	Males: 5, 10, 15	Gavage	Decreased body weight, elevated serum chemistry, liver and kidney toxicity	NOAEL: 10 LOAEL: 15	Arfat et al, 2014 ([27])
Short-term	Mice (female)	28 d	Females: 2.5, 5, 10	Gavage	Suppressed cell-mediated immune response, alterations to the spleen and liver, delayed type hypersensitivity response	NOAEL: 2.5 LOAEL: 5	Badgujar et al, 2013 ([28])
Short-term	Mice (both)	7, 14 and 28 d	Males: 5.5, 11, 22	Gavage	Sperm head abnormality, mutagenic effects at spermatogonial stage	LOAEL: 5.5	Bagri et al, 2015 ([3])
Short-term	Mice (female)	7, 14 and 28 d	Females: 5.5, 11, 22	Gavage	Dose and time-dependent increase in frequencies of micronuclei per cell and chromosomal aberrations in bone marrow cells	NOAEL: 11 LOAEL: 22	Bagri et al, 2016 ([4])
Longer-term	Rat (female)	90 d	Males: 0.5, 2, 8	Gavage	Decreased sperm concentration, weight gain, testosterone, and glutathione levels	LOAEL: 0.5	Bal et al, 2012a ([7])
Longer-term	Rat (male)	90 d	Males: 0.5, 2, 8	Gavage	Deterioration of sperm parameters, testosterone levels, increased apoptosis of germ cells, seminal DNA fragmentation, depletion of antioxidants, and disturbance of fatty acid composition	LOAEL: 0.5	Bal et al, 2012b ([8])
Longer-term	Rat (female)	90 d	Females: 5, 10, 20	Gavage	Decreased body weight, increased liver, kidney, and adrenal weight; altered clinical parameters; decreased spontaneous locomotor activity	NOAEL: 10 LOAEL: 20	Bhardwaj et al, 2010 ([21])

Longer-term	Rat (male)	90 d	Males: 0.5, 2, 8	Gavage	Diminished learning activities	NOAEL: 0.5 LOAEL: 2	Kara et al, 2015 ([9])
Developmental imunotoxicity	Rat (female)	Gestation Lactation Growth	Females: 10, 30, 90	Gavage	Increased post-implantation loss, soft tissue abnormalities, skeletal alterations, adverse effects on immunity	LOAEL: 10	Gawade et al, 2013 ([25])
Longer-term	Rat (male)	60 d	Males: 0.5, 1.0	Gavage	Altered cortisone and catecholamine levels; behavioral deficits; hyperglycemic effect; altered mRNA level of glucose transporters; structural perturbations in the pancreas; decreased expression of insulin and GLUT4	LOAEL: 0.5	Khalil et al, 2017 ([10])
Co-exposure with arsenic	Rat (both)	28 d	Imidacloprid: 16.9 Arsenic: 50, 100, 150 µg/L	Imid: gavage As: water	Imidacloprid alone increased markers of oxidative stress and reduced antioxidant levels in the liver. Co-administration with arsenic increased the severity of these effects.	N/A	Mahajan et al, 2018a ([6])
Co-exposure with arsenic	Rat (male)	28 d	Imid: 16.9 As: 50, 100, 150 µg/L	Imid: gavage As: water	Imidacloprid alone increased markers of oxidative stress and reduced antioxidant levels in the testes. Co-administration with arsenic increased the severity of these effects.	N/A	Mahajan et al, 2018b ([5])
Immune challenge	Mice (male)	30 d	6.55	Gavage	Animals challenged with E. *coli* lipopolysaccharides had increased total cell and neutrophil counts	LOAEL: 6.55	Pandit et al, 2016 ([29])
Longer-term	Mice (male)	84 d	Males: 0.06, 0.6, 6	Diet	Enhanced high fat diet-induced weight gain and adiposity, increased serum insulin levels, inhibited AMPK-alpha	LOAEL: 0.06	Sun et al, 2016 ([2]) **Used by DHS for ADI**
Longer-term	Mice (female)	84 d	Females: 0.06, 0.6, 6	Diet	Enhanced high fat diet-induced weight gain and adiposity, increased serum insulin levels, inhibited AMPK-alpha	NOAEL: 0.06 LOAEL: 0.6	Sun et al, 2017 ([11])

Longer-term	Rat (female)	60 d	Females: 10, 20	Gavage	Reduced feed intake, heart and spleen weight, decreased acetylcholinesterase activity in plasma and brain	LOAEL: 10	Vohra et al, 2014 ([22])
Generational	Rat (female)	3 generations	Females: 10, 20	Gavage	Significantly reduced food intake in F2 females; altered biochemistry parameters	LOAEL: 10	Vohra et al, 2015 ([23])

Table A-2. Critical Study Selection

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Dose-response relationship?	Toxicity value identifiable?	Critical study?
Abdel-Rahman et al, 2017	✓	✓	✓	⦸	✓	No
Bal et al, 2012a	✓	✓	✓	✓	✓	**Yes**
Arfat et al, 2014	⦸	✓	✓	✓	✓	No
Badgujar et al, 2013	⦸	✓	✓	✓	✓	No
Bagri et al, 2015	⦸	✓	✓	✓	✓	No
Bagri et al, 2016	⦸	✓	✓	✓	✓	No
Bal et al, 2012b	✓	✓	✓	✓	✓	**Yes**
Bhardwaj et al, 2010	✓	✓	✓	✓	✓	**Yes**
Kara et al, 2015	✓	✓	✓	✓	✓	**Yes**
Gawade et al, 2013	✓	✓	✓	✓	✓	**Yes**
Khalil et al, 2017	✓	✓	✓	✓	✓	**Yes**
Mahajan et al, 2018a	⦸	⦸	✓	⦸	⦸	No
Mahajan et al, 2018b	⦸	⦸	✓	⦸	⦸	No
Pandit et al, 2016	✓	✓	✓	⦸	✓	No
Sun et al, 2016*	✓	✓	✓	✓	✓	**Yes**
Sun et al, 2017	✓	✓	✓	✓	✓	**Yes**
Vohra, 2014	✓	✓	✓	✓	✓	**Yes**
Vohra, 2015	✓	✓	✓	✓	✓	**Yes**

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

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

Clothianidin | 2019

Substance Overview

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

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

Recommendations

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

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

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

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

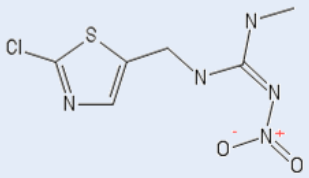
Recommended Standards	
Enforcement Standard:	1,000 µg/L
Preventive Action Limit:	200 µg/L

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standards

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

Standard Development

Federal Numbers

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

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A	

Acceptable Daily Intake

EPA Oral Reference Dose:	0.098 mg/kg-d	(2012)

Oncogenic Potential

EPA Cancer Slope Factor:	N/A	

Guidance Values

None available

Literature Search

Literature Search Dates:	2012 – 2018
Total studies evaluated:	Approximately 260
Key studies found?	Yes

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for clothianidin.[5]

Health Advisory

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

Drinking Water Concentration (Cancer Risk)

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for clothianidin.[8]

Acceptable Daily Intake

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

EPA Oral Reference Dose

In 2012, the EPA Office of Pesticide Programs conducted a Human Health Risk Assessment as part of the registration of clothianidin.[2] In their assessment, the EPA reviewed a number of studies on the toxicity of clothianidin. They selected a 2-generation reproduction study in rats as the critical study (MRID: 45422715). In this study, 2 generations of rats were exposed to different concentrations of clothianidin in their diet before mating, during mating, and during gestation and lactation: 0, 9.8, 31.2, or 163.4 milligrams per kilogram body weight per day (mg/kg-d) in males and 0, 10.7, 34.3, or 188.8 mg/kg-d in females. Clothianidin affected parental body and thymus weights at the highest dose. Clothianidin also decreased body and thymus weights, delayed sexual maturation, and increased stillbirths in offspring at the two highest doses. The No Observable Adverse Effect Level (NOAEL) from this study was 9.8 mg/kg-d based on effects to the offspring. The EPA selected a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). The EPA's chronic oral reference dose for clothianidin is 0.098 mg/kg-d.

Oncogenic Potential

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

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

Cancer Classification

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

EPA Cancer Slope Factor

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

Additional Technical Information

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

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

Guidance Values

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

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2012. We conducted a search on the National Institutes of Health's PubMed resource for articles published from January 2012 to August 2018 out for studies related to clothianidin toxicity or its effects on a disease state in which information on clothianidin exposure or dose was included as part of the study.[a] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

Approximately 260 studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life, studies evaluating risk from non-mammalian species, and monitoring studies from further review. After applying these exclusion criteria, we located four key studies (Table A-1 contains a summary of these studies). To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value. [b] None of the studies met the requirements to be considered a critical study (see Table A-2 for details on the evaluation).

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

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

Standard Selection

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

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

Basis for Enforcement Standard

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

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

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

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

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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Appendix A. Toxicity Data

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

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

Table A-2. Critical Study Selection

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity value identifiable?	Critical study?
Hirano, 2015	✓	✓	✓	**3**	✓	No
Tanaka, 2012a	✓	✓	✓	**3**	⦸	No
Tanaka, 2012b	✓	✓	✓	**3**	⦸	No
Yanai, 2017	✓	⦸	⦸	**2**	✓	No

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

Isoxaflutole | 2019

Substance Overview

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

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

Recommendations

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

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

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

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

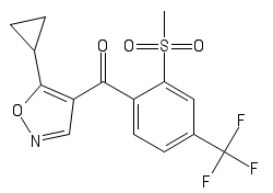
DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for isoxaflutole and isoxaflutole diketonitrile be set at 10% of the enforcement standard because the EPA has classified isoxaflutole as a likely human carcinogen and the likelihood that isoxaflutole diketonitrile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

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standards

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

Standard Development

Federal Numbers		
Maximum Contaminant Level:	N/A	
Health Advisory:	N/A	
Drinking Water Concentration (Cancer Risk):	N/A	
State Drinking Water Standard		
NR809 Maximum Contaminant Level:	N/A	
Acceptable Daily Intake		
EPA Oral Reference Dose:	0.02 mg/kg-d	(2011)
Oncogenic Potential		
EPA Cancer Slope Factor:	0.0114 $(mg/kg\text{-}d)^{-1}$	(2011)
Guidance Values		
JMPR Average Daily Intake:	0.2 mg/kg-d	
Literature Search		
Search Dates:	2011 – 2018	
Total studies evaluated:	Approximately 10	
Key studies found?	No	

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for isoxaflutole.[7]

Health Advisory

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

Drinking Water Concentrations at Specified Cancer Risk Levels

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for isoxaflutole.[10]

Acceptable Daily Intake

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

EPA Oral Reference Dose

In 2011, EPA conducted a Human Health Risk Assessment (HHRA) as part of the Registration of Isoxaflutole for use on Soybeans.[1] In their assessment, EPA reviewed a number of studies on the toxicity of isoxaflutole. The EPA selected a chronic/carcinogenicity study in rats described above as the principal study (MRID: 43904806). In addition to cancer effects described above, liver, thyroid, ocular, and nervous system effects were observed at levels at and above 20 mg/kg-d. The EPA selected a NOAEL of 2 mg/kg-d and applied a total uncertainty factor of 100 to account for differences between people and research animals (10) and differences among people (10). The EPA's chronic oral reference dose for isoxaflutole is 0.2 mg/kg-d.

Oncogenic Potential

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

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

Cancer Classification

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

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

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

EPA Cancer Slope Factor

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

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

Additional Technical Information

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

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

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

Guidance Values

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

JMPR Average Daily Intake

The JMPR recommended a chronic oral reference dose of 0.2 mg/kg-d in 2013 as part of their review of the human health toxicity information for isoxaflutole.[2,3] They based this value on the same study and effects used by the EPA to establish their oral reference dose.

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2012. We conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2011 to August 2018 related to isoxaflutole toxicity or its effects on a disease state in which information on exposure or dose was included as part of the study.[b] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

Approximately 10 studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life and studies not evaluating health risks from further review. After applying these exclusion criteria, we did not locate any key studies.

Standard Selection

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

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

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

Therefore, DHS recommends using EPA's cancer slope

Basis for Enforcement Standard

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

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

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

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

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

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

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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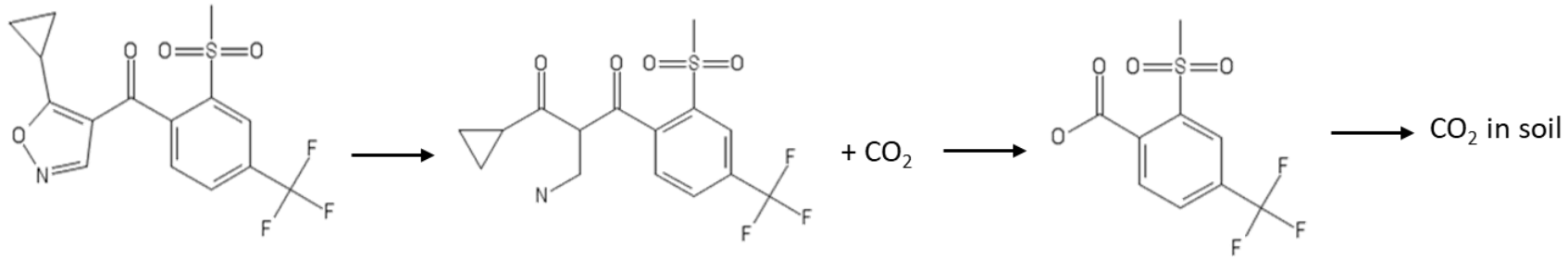
Appendix A: Isoxaflutole Degradation

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



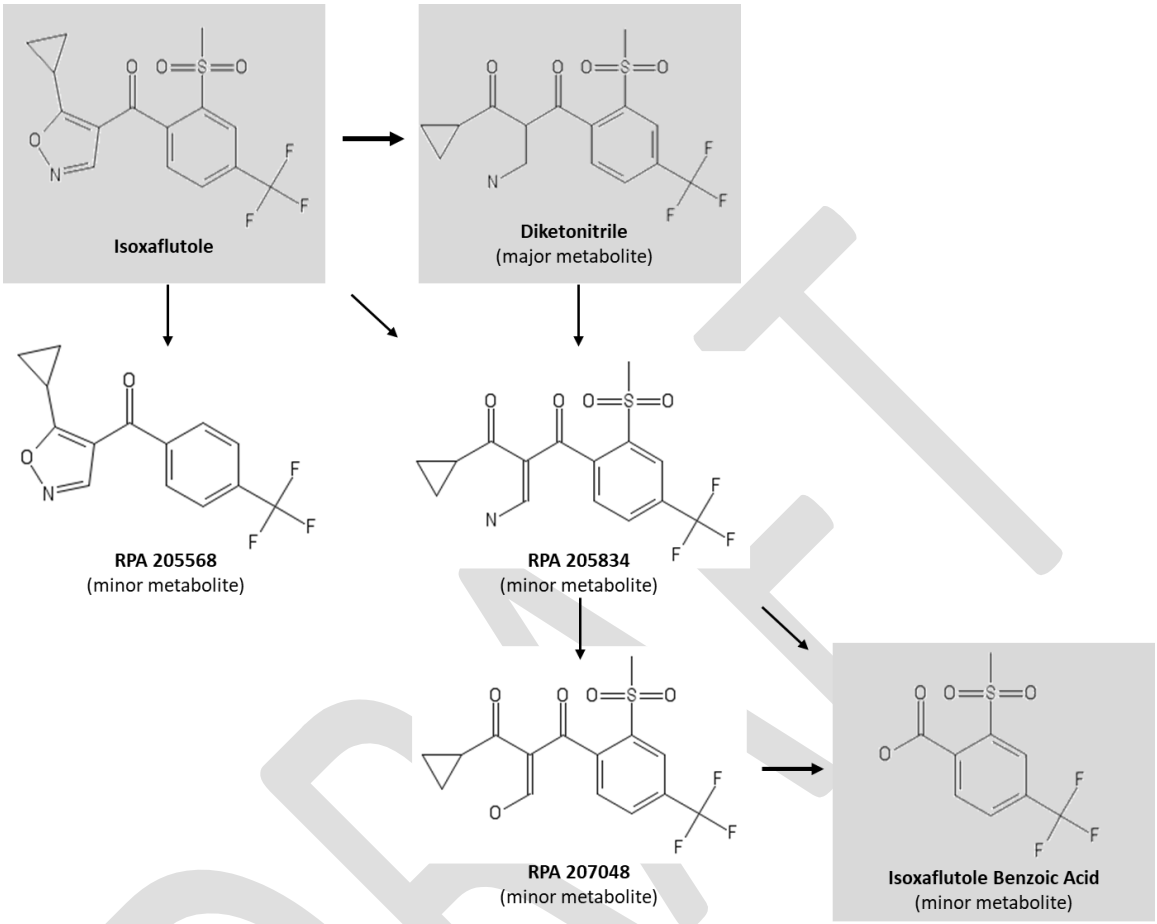
Isoxaflutole
(Pro-Herbicide)

Diketonitrile
(Herbicide)

Isoxaflutole
Benzoic Acid

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

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



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

Isoxaflutole Diketonitrile | 2019

Substance Overview

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

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

Recommendations

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

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

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

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

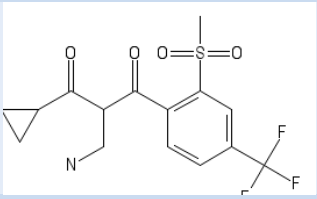
DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for isoxaflutole and isoxaflutole diketonitrile be set at 10% of the enforcement standard because the EPA has classified isoxaflutole as a likely human carcinogen and the likelihood that isoxaflutole diketonitrile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

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standards

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

Standard Development

Federal Numbers	
Maximum Contaminant Level:	N/A
Health Advisory:	N/A
Drinking Water Concentration (Cancer Risk):	N/A
State Drinking Water Standard	
NR809 Maximum Contaminant Level:	N/A
Acceptable Daily Intake	
EPA Oral Reference Dose:	N/A
Oncogenic Potential	
EPA Cancer Slope Factor:	N/A
Guidance Values	
JMPR Average Daily Intake:	N/A
Literature Search	
Search Dates:	2011 – 2018
Total studies evaluated:	5
Key studies found?	No

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for isoxaflutole diketonitrile.[7]

Health Advisory

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

Drinking Water Concentrations at Specified Cancer Risk Levels

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for isoxaflutole diketonitrile.[10]

Acceptable Daily Intake

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

EPA Oral Reference Dose

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

Oncogenic Potential

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

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

Cancer Classification

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

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

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

EPA Cancer Slope Factor

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

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

Additional Technical Information

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

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

Guidance Values

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

JMPR Average Daily Intake

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

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2011. We conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2011 to August 2018 related to isoxaflutole diketonitrile toxicity or its effects on a disease state in which information on exposure or dose was included as part of the study.[b] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

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

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

Standard Selection

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

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

Basis for Enforcement Standard

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

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

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

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

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

Prepared by Sarah Yang, Ph.D.

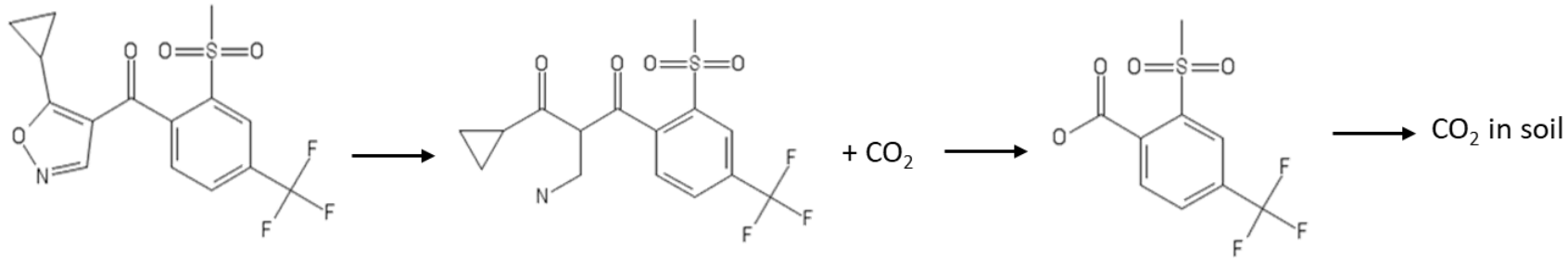
Wisconsin Department of Health Services

References

1. USEPA. Isoxaflutole. Section 3 Registration for Use on Soybeans. Human-Health Risk Assessment. In: Preventation OoCSaP, ed. Vol EPA-HQ-OPP-2010-08452011.
2. JMPR. Isoxaflutole - Tox Monograph. In: Residues JFWMoP, ed2013.
3. JMPR. Isoxaflutole. In: (JMPR) JFWMoPR, ed2013.
4. DATCP. Pesticide Database Searches. 2016; https://www.kellysolutions.com/wi/pesticideindex.asp.
5. MDA. Isoxaflutole. In: Agriculture MDo, ed2015.
6. WIDNR. Groundwater Quality. In: Resources WDoN, ed. *Chapter NR 140*2017.
7. USEPA. National Primary Drinking Water Regulations. 2018; https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations.
8. USEPA. Drinking Water Contaminant Human Health Effects Information. 2019; https://www.epa.gov/dwstandardsregulations/drinking-water-contaminant-human-health-effects-information#hh1.
9. USEPA. IRIS Assessments. 2019; https://cfpub.epa.gov/ncea/iris_drafts/AtoZ.cfm.
10. WIDNR. Safe Drinking Water In: Resources WDoN, ed. *Chapter NR 809*2018.
11. IARC. List of Classification, Volumes 1-123. 2018; https://monographs.iarc.fr/list-of-classifications-volumes/. Accessed May 17, 2019.
12. USEPA. EPA's Exposure Factors handbook. 2019; https://www.epa.gov/expobox/about-exposure-factors-handbook?_sm_au_=iHV5B5HjsMP7lBnr.

Appendix A: Isoxaflutole Degradation

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



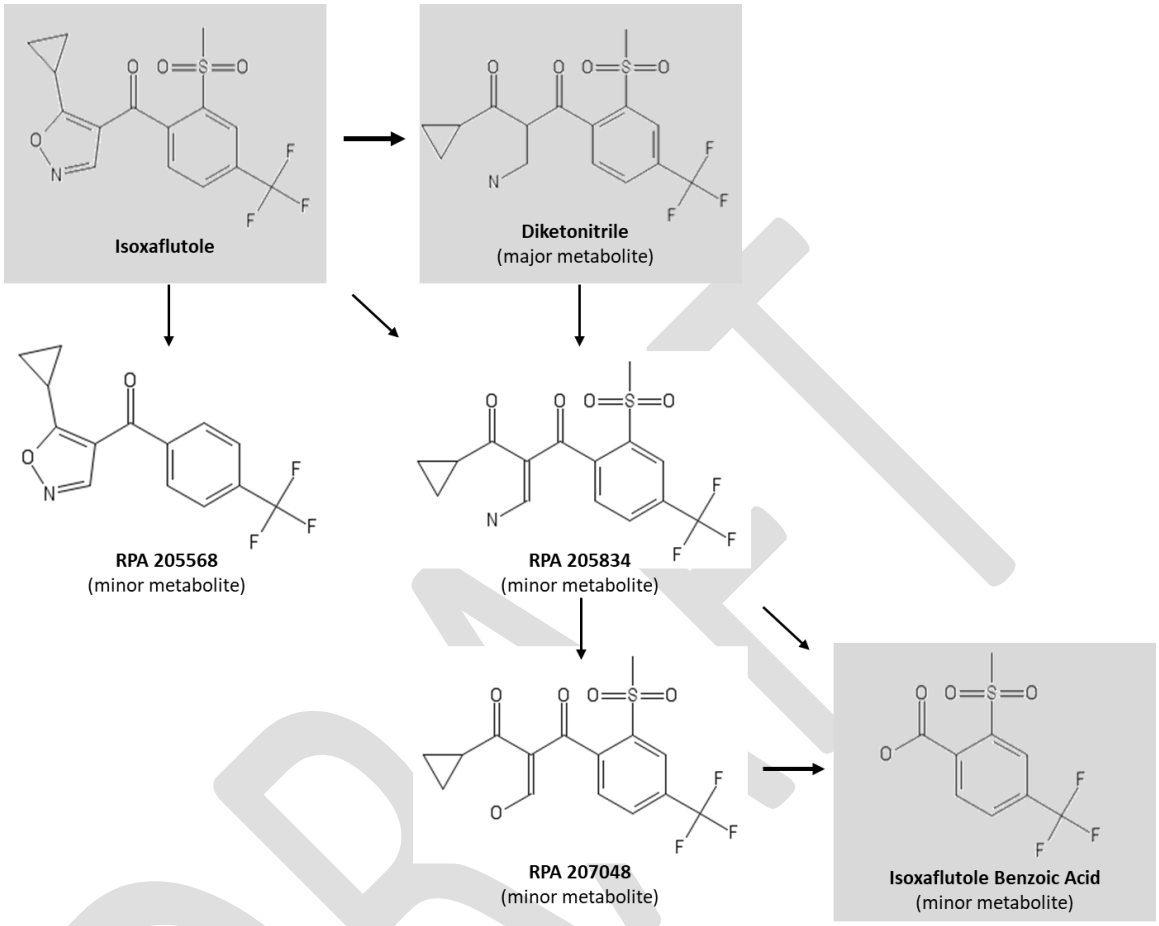
Isoxaflutole
(Pro-Herbicide)

Diketonitrile
(Herbicide)

Isoxaflutole
Benzoic Acid

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

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



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

Isoxaflutole Benzoic Acid | 2019

Substance Overview

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

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

Recommendations

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

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

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

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

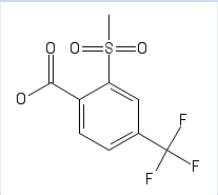
Recommended Standards	
Enforcement Standard:	800 µg/L
Preventive Action Limit:	160 µg/L
(Applies to isoxaflutole benzoic acid)	

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standards

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

Standard Development

Federal Numbers

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

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A

Acceptable Daily Intake

EPA Oral Reference Dose:	N/A

Oncogenic Potential

EPA Cancer Slope Factor:	N/A

Guidance Values

JMPR Average Daily Intake:	N/A

Literature Search

Search Dates:	2011 – 2018
Total studies evaluated:	2
Key studies found?	No

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for isoxaflutole benzoic acid.[7]

Health Advisory

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

Drinking Water Concentrations at Specified Cancer Risk Levels

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for isoxaflutole benzoic acid.[10]

Acceptable Daily Intake

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

EPA Oral Reference Dose

The EPA does not have an oral reference dose for isoxaflutole benzoic acid.[1]

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

Oncogenic Potential

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

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

Cancer Classification

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

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

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

EPA Cancer Slope Factor

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

Additional Technical Information

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

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

Guidance Values

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

JMPR Average Daily Intake

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

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2011. We conducted a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2011 to August 2018 related to isoxaflutole diketonitrile toxicity or its effects on a disease state in which information on exposure or dose was included as part of the study.[a] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans. Two studies were returned by the search engine. We excluded studies on the effects on plant and aquatic life and studies not evaluating health risks from further review. After applying these exclusion criteria, we did not locate any key studies.

We also evaluated the four studies that EPA and JMPR considered in their human risk assessment using these same criteria (as described in the *EPA Oral Reference Dose* and *JMPR Average Daily Intake* sections above). To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.[b]

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

b Appropriate toxicity values include the no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL), and benchmark dose (BMD). The NOAEL is the highest dose tested that did not cause an

Critical Study

Repetto-Larsay, 1999

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

Standard Selection

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

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

Basis for Enforcement Standard

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

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

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

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adverse effect, the LOAEL is the lowest dose tested that caused an adverse effect, and the BMD is an estimation of the dose that would cause a specific level of response (typically 5 or 10%).[12]

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

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

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

References

1. USEPA. Isoxaflutole. Section 3 Registration for Use on Soybeans. Human-Health Risk Assessment. In: Preventation OoCSaP, ed. Vol EPA-HQ-OPP-2010-08452011.
2. JMPR. Isoxaflutole - Tox Monograph. In: Residues JFWMoP, ed2013.
3. JMPR. Isoxaflutole. In: (JMPR) JFWMoPR, ed2013.
4. DATCP. Pesticide Database Searches. 2016; https://www.kellysolutions.com/wi/pesticideindex.asp.
5. MDA. Isoxaflutole. In: Agriculture MDo, ed2015.
6. WIDNR. Groundwater Quality. In: Resources WDoN, ed. *Chapter NR 140*2017.
7. USEPA. National Primary Drinking Water Regulations. 2018; https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations.
8. USEPA. Drinking Water Contaminant Human Health Effects Information. 2019; https://www.epa.gov/dwstandardsregulations/drinking-water-contaminant-human-health-effects-information#hh1.
9. USEPA. IRIS Assessments. 2019; https://cfpub.epa.gov/ncea/iris_drafts/AtoZ.cfm.
10. WIDNR. Safe Drinking Water In: Resources WDoN, ed. *Chapter NR 809*2018.
11. IARC. List of Classification, Volumes 1-123. 2018; https://monographs.iarc.fr/list-of-classifications-volumes/. Accessed May 17, 2019.
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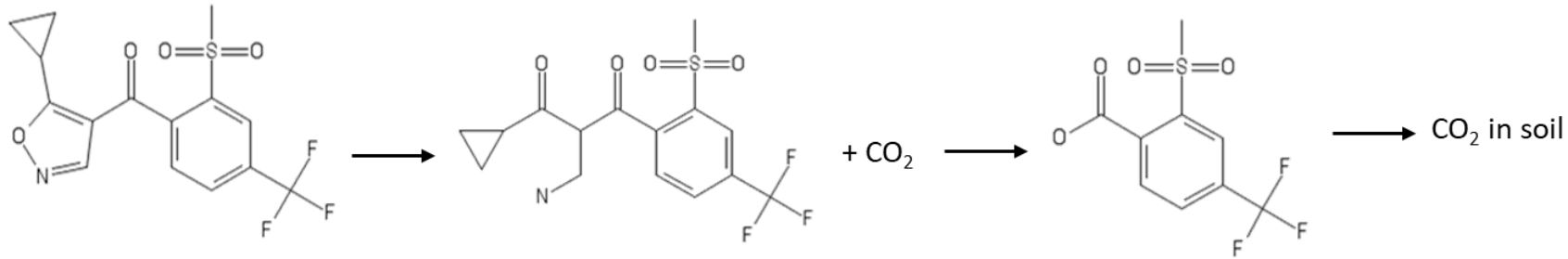
14. Dange M. 28-day toxicity study in the rat by dietary administration – RPA 203328 (a metabolite of RPA 201772). In. Sophia Antipolis, France: Rhône-Poulenc Agrochimie Centre de Recherche,; 1995:MIRD: 43904813.
15. Bigot D. SRPA 203328: 90-day toxicity study in the rat by dietary administration. In. *Rhone-Poulenc Agrochimie*. Sophia Antipolis Cedex, France1998:MRID: 45655903.
16. Dange M. RPA 203328 – exploratory 14-day toxicity study in the rat by gavage. In: Recherche R-PSACd, ed. Sophia Antipolis, France1994.

Appendix A: Isoxaflutole Degradation

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



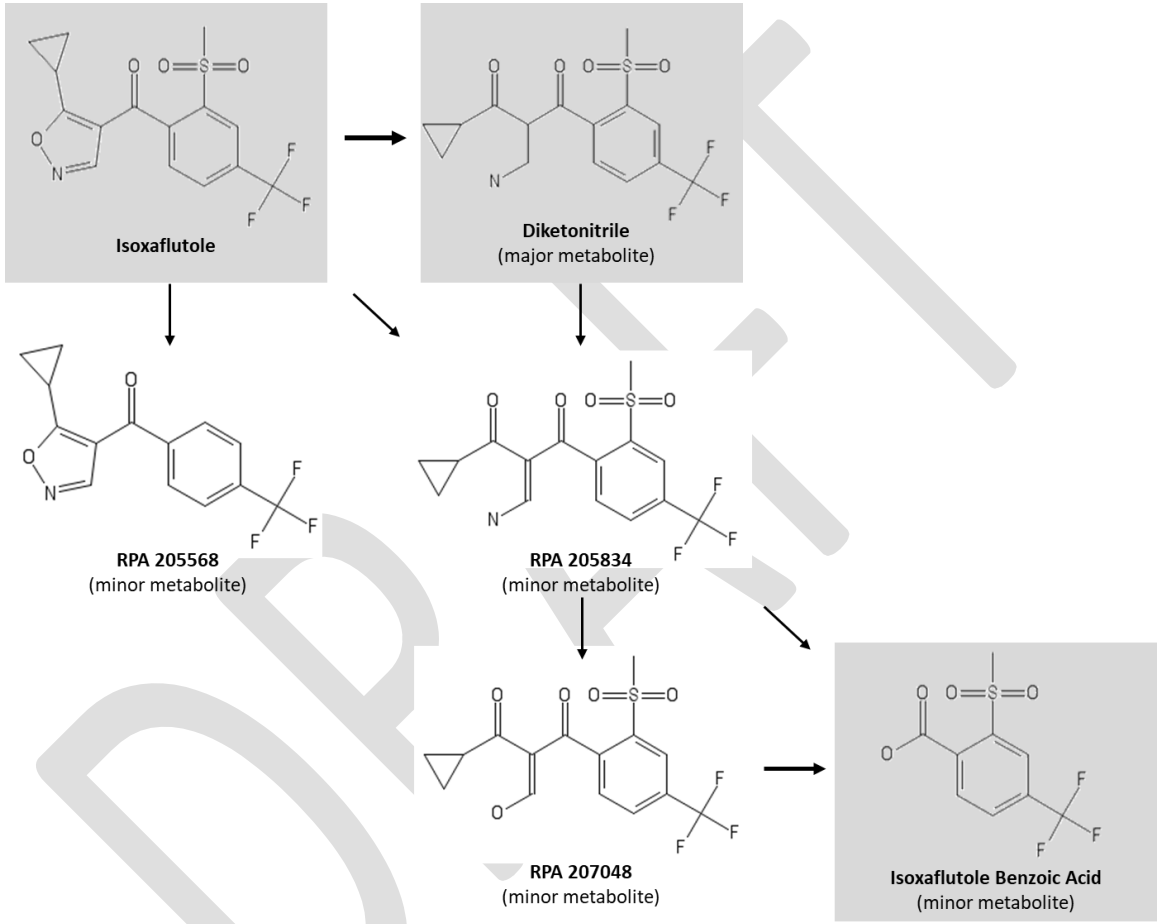
Isoxaflutole
(Pro-Herbicide)

Diketonitrile
(Herbicide)

Isoxaflutole
Benzoic Acid

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

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



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

Appendix B: Isoxaflutole Benzoic Acid Toxicity

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

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

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

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

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

Thiencarbazone-methyl | 2019

Substance Overview

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

Recommendations

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

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

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

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

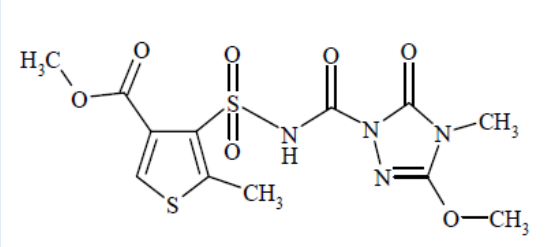
Recommended Standards	
Enforcement Standard:	10 mg/L
Preventive Action Limit:	2 mg/L

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standard

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

Standard Development

Federal Numbers

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

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A	

Acceptable Daily Intake

EPA Oral Reference Dose	1.17 mg/kg-d	(2008)

Oncogenic Potential

EPA Cancer Slope Factor:	N/A	

Guidance Values

None available

Literature Search

Search Dates:	2008 – 2019
Total studies evaluated:	5
Key studies found?	No

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for thiencarbazone-methyl.[3]

Health Advisory:

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

Drinking Water Concentration (Cancer Risk)

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for thiencarbazone-methyl.[5]

Acceptable Daily Intake

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

EPA Oral Reference Dose

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

Oncogenic Potential

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

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

Cancer Classification

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

EPA Cancer Slope Factor

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

Additional Technical Information

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

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

Guidance Values

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

EFSA Acceptable Daily Intake

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

Literature Search

The most recent federal number for thiencarbazone-methyl is the EPA's oral reference dose which was published in 2008. Therefore, our literature review focused on the scientific literature published after the review by the EPA in 2008. A search on the National Institutes of Health's PubMed resource for articles published from January 2008 to February 2019 was carried out looking for studies related to thiencarbazone-methyl toxicity or its effects on a disease state in which information on thiencarbazone-methyl exposure or dose was included as part of the study.[1] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses.

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

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

Standard Selection

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

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

Basis for Enforcement Standard

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

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

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

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

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

References

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

Monomethyl Tetrachloroterephthalic Acid | 2019

Substance Overview

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

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

Recommendations

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

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

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

Current Standards

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

(Applies to dacthal only)

Recommended Standards

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

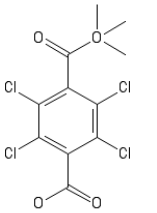
(Applies to dacthal, MTP, and TPA)

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standard

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

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

Standard Development

Federal Numbers

Maximum Contaminant Level:	N/A	
Lifetime Health Advisory:	70 µg/L	(2008)
Drinking Water Concentration (Cancer Risk):	N/A	

State Drinking Water Standard

NR809 Maximum Contaminant Level:	N/A

Acceptable Daily Intake

EPA Oral Reference Dose:	N/A

Oncogenic Potential

EPA Cancer Slope Factor:	N/A

Guidance Values

None available

Literature Search

Literature Search Dates:	2008 – 2018
Total studies evaluated:	None
Key studies found?	No

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for MTP or dacthal.[7]

Health Advisories

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

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

Drinking Water Concentrations at Specified Cancer Risk Levels

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for MTP or dacthal.[8]

Acceptable Daily Intake

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

Oral Reference Dose

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

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

Oncogenic Potential

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

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

Cancer Classification

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

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

EPA Cancer Slope Factor

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

Additional Technical Information

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

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

Guidance Values

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

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2008. We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2008 to April 2018 related to MTP toxicity or effects on a disease state in which information on MTP exposure or dose was included as part of the study.[a] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans. No studies were returned by the search engine.

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

Standard Selection

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

Basis for Enforcement Standard

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

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

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

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

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

References

1. USEPA. Drinking Water Health Advisory For Dacthal and Dacthal Degradates: Tetrachloroterephthalic acid (TPA) and Monomethyl Tetrachloroterephthalic acid (MTP). In:2008.
2. USEPA. Reregistration Eligibility Decision (RED) DCPA. In:1998.
3. USEPA. Health Effects Support Document for Dacthal Degradates: Tetrachloroterephthalic Acid (TPA) and Monomethyl Tetrachloroterephthalic Acid (MTP). 2008(822-R-08-005).
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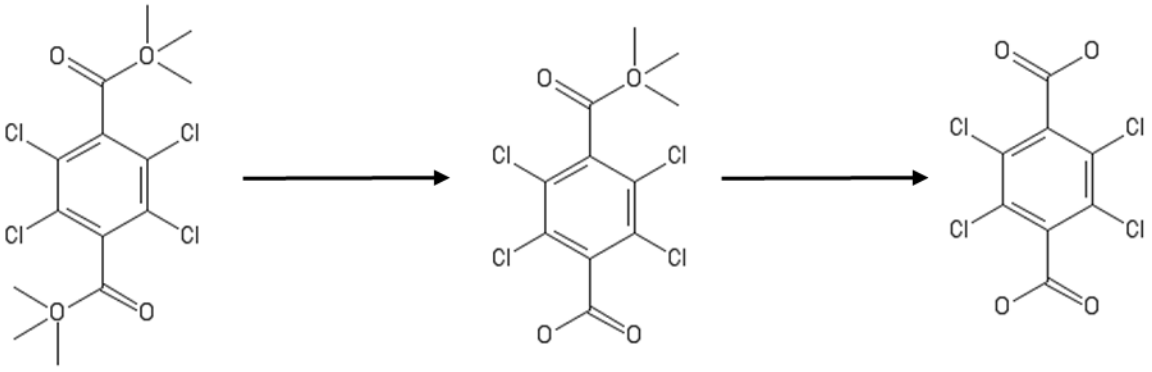
14. ISK. A 28-Day Feeding Study in Rats with Technical DCPA. In: Corporation IB, ed. Washington, DC 20460: EPA; 1990:HED Doc. No. 0084008.
15. ISK. A 90-Day Feeding Study in Rats with Technical DCPA. In: Corporation IB, ed. Washington, DC 20460: EPA; 1991:HED Doc. No. 0084008.
16. ISK. In: Corporation IB, ed1993:HED Doc. No. 010513.

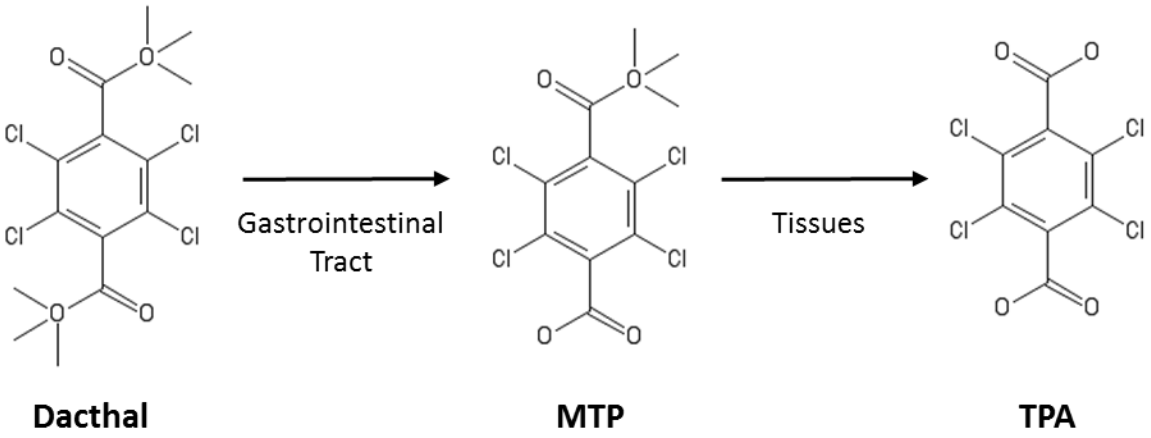
Appendix A

Figure A-1. Dacthal Degradation in the Environment



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

Figure A-2. Metabolism of Dacthal in the Body



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

Appendix B. Health Advisories

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

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

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

Tetrachloroterephthalic Acid | 2019

Substance Overview

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

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

Recommendations

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

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

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

Current Standards

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

(Applies to dacthal only)

Recommended Standards

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

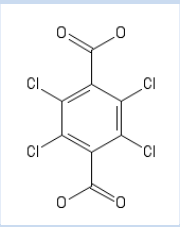
(Applies to dacthal, MTP, and TPA)

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standard

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

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

Standard Development

Federal Numbers		
Maximum Contaminant Level:	N/A	
Health Advisory Levels		
10-day Child:	100,000 µg/L	(2008)
Longer-term Child:	50,000 µg/L	(2008)
Longer-term Adult:	200,000 µg/L	(2008)
Lifetime:	70 µg/L	(2008)
Drinking Water Concentration (Cancer Risk):	N/A	
State Drinking Water Standard		
NR809 Maximum Contaminant Level:	N/A	
Acceptable Daily Intake		
EPA Oral Reference Dose:	N/A	
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
None available		
Literature Search		
Literature Search Dates:	2008 – 2019	
Total studies evaluated:	5	
Key studies found:	No	

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for TPA or dacthal.[7]

Health Advisories

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

10-day Child

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

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

Longer-term Child

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

Longer-term Adult

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

Lifetime

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

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

Drinking Water Concentrations at Specified Cancer Risk Levels

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for TPA or dacthal.[11]

Acceptable Daily Intake

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

part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Assessment System (IRIS) program.

Oral Reference Dose

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

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

Oncogenic Potential

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

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

Cancer Classification

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

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

EPA Cancer Slope Factor

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

Additional Technical Information

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

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

Guidance Values

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

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2008. We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from January 2008 to May 2019 related to TPA toxicity or effects on a disease state in which information on TPA exposure or dose was included as part of the study.[a] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

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

Standard Selection

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

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

Basis for Enforcement Standard

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

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

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

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

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

Prepared by Sarah Yang, Ph.D.

Wisconsin Department of Health Services

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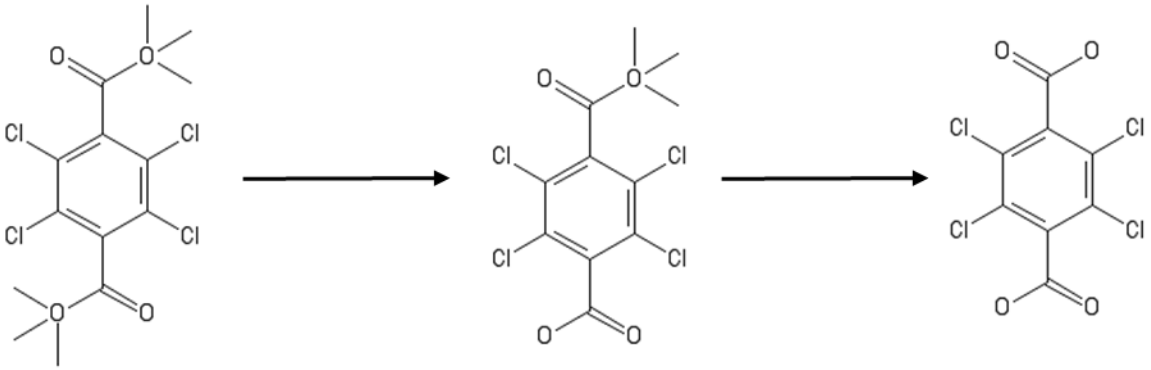
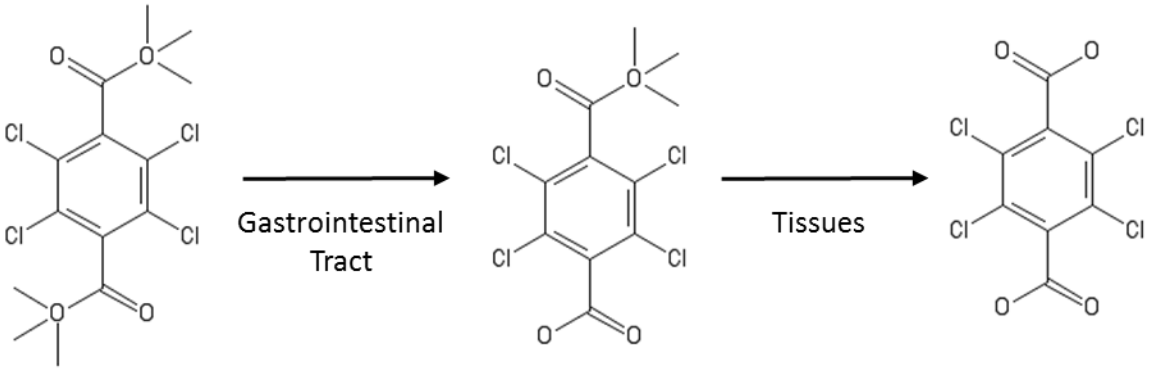
Appendix A

Figure A-1. Dacthal Degradation in the Environment



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

Figure A-2. Metabolism of Dacthal in the Body



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

Appendix B. Health Advisories

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

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

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

Glyphosate | 2019

Substance Overview

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

Recommendations

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

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

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

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

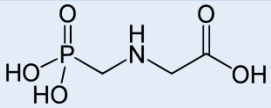
Recommended Standards	
Enforcement Standard:	10 mg/L
Preventive Action Limit:	1 mg/L

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standard

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

Standard Development

Federal Numbers		
Maximum Contaminant Level (MCL):	700 µg/L	(1994)
Health Advisories		
10-Day child:	20 mg/L	(1989)
Lifetime Health Advisory:	800 µg/L	(1989)
Drinking water concentration (cancer risk):	N/A	
State Drinking Water Standard		
NR809 Maximum Contaminant Level:	700 µg/L	(2016)
Acceptable Daily Intake		
EPA Oral Reference Dose (IRIS):	0.1 mg/kg-d	(1987)
EPA Draft Oral Reference Dose (OPP):	1 mg/kg-d	(2017)
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
ATSDR Draft Chronic Oral Minimum Risk Level:	1 mg/kg-d	(2019)
Literature Search		
Literature Search Dates:	2019	
Total studies evaluated:	Approximately 40	
Key studies found?	No	

Federal Numbers

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

Maximum Contaminant Level

The EPA established a Maximum Contaminant Level (MCL) for glyphosate of 700 micrograms per liter (µg/L) in 1994.[8] The EPA reviewed the MCL in 2002 as part of the first six-year review.[9] They determined that the MCL was not appropriate for revision because it was currently undergoing an EPA health risk assessment.

Health Advisories

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

10-Day Health Advisory

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

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

Lifetime Health Advisory

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

As of March 2016, Wisconsin has a maximum contaminant level of 700 µg/L for glyphosate.[11] This value is based on the EPA's MCL from 1994.

Acceptable Daily Intake

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

EPA Oral Reference Dose (IRIS)

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

EPA Draft Oral Reference Dose (Office of Pesticide Programs)

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

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

Oncogenic Potential

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

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

Cancer Classification

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

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

EPA Cancer Slope Factor

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

Additional Technical Information

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

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

Guidance Values

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

ATSDR Draft Chronic Oral Minimum Risk Level

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

Literature Search

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

Approximately 40 studies were returned by the search engine. We excluded studies that did not evaluate health effects, studies from non-mammalian species, and studies for plants from further review. After applying these exclusion criteria, we did not locate any key studies.

Standard Selection

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

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

Basis for Enforcement Standard

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

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

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

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

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

Prepared by Clara Jeong, Ph.D.

Wisconsin Department of Health Services

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Appendix A. Carcinogenic Potential of Glyphosate

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

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

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

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

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

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

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

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

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

Species	Duration	Dose (mg/kg-d)	Route	Endpoints	Reference	Reviewed by IARC?	Reviewed by EPA?
Rat	26 months	Males: 0, 3.05, 10.3, 31.49 Females: 0, 3, 11, 34	diet	Increased incidence of testicular interstitial tumors.	Lankas 1981 MRID: 00093879	Yes	Yes
Rat	24 months	Males: 0, 89, 362, 940 Females: 0, 113, 457, 1183	diet	Increased incidence of liver adenoma. Increased incidence of thyroid adenomas and combined adenomas/carcinomas in females. Thyroid C-cell hyperplasia observed. No evidence of progression from adenoma to carcinoma in pancreas, liver, and thyroid	Stout and Ruecker 1990 MRIDs: 41643801 41728701	Yes	Yes
Rat	104 weeks	Males: 0, 11, 112, 320, 1147 Females: 0, 12, 109, 347, 1134	diet	No histopathological changes.	Atkinson 1993a MRID: 49631701	No	Yes
Rat	24 months	Males: 0, 121, 361, 1214 Females: 0, 145, 437, 1498	diet	No treatment-related non-neoplastic lesions. Increased incidence of liver adenomas in males.	Brammer 2001 MRID: 49704601	No	Yes
Rat	2 years	Males: 0, 4.2, 21.2, 41.8 Females: 0, 5.4, 27, 55.7	diet (sulfosate, 56.2% pure)	No histopathological changes.	Pavkov and Wyand 1987 MRIDs: 40214007 41209905 41209907	Yes	Yes
Rat	24 months	Males: 0, 6.3, 59.4, 595.2 Females: 0, 8.6, 88.5, 886	diet	No histopathological changes.	Suresh 1996 MRID: 49987401	Yes	Yes
Rat	24 months	Males: 0, 104, 354, 1127	diet	No histopathological changes.	Enemoto 1997 MRIDs: 50017013	Yes	Yes

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

Aminomethylphosphonic Acid (AMPA) | 2019

Substance Overview

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

Recommendations

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

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

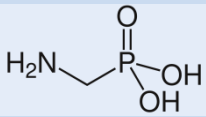
DHS recommends that the NR140 Groundwater Quality Public Health Preventive Action Limit for AMPA be set at 20% of the enforcement standard because AMPA has not been shown to have carcinogenic, mutagenic, teratogenic, or interactive effects.

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

Health Effects

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

Chemical Profile

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

Exposure Routes

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

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

Current Standard

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

Standard Development

Federal Numbers		
Maximum Contaminant Level:	N/A	
Health Advisory	N/A	
Drinking water concentration (cancer risk):	N/A	
State Drinking Water Standard		
NR809 Maximum Contaminant Level:	N/A	
Acceptable Daily Intake		
EPA Oral Reference Dose:	N/A	
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
JMPR (sum of AMPA and glyphosate)	1 mg/kg-d	(2016)
Literature Search		
Literature Search Dates:	2017 – 2019	
Total studies evaluated:	Approximately 60	
Key studies found?	Yes	

Federal Numbers

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

Maximum Contaminant Level

The United States Environmental Protection Agency (EPA) does not have a maximum contaminant level for AMPA.[4]

Health Advisories

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

As of March 2016, Wisconsin has not established a state maximum contaminant level for AMPA.[5,6]

Acceptable Daily Intake

If a federal number and a state drinking water standard are not available, ch. 160, Wis. Stats. requires that DHS use an acceptable daily intake (ADI) from the EPA to develop the recommendation. Statute allows DHS to recommend a different value if an ADI from the EPA does not exist or if there is significant

technical information that is scientifically valid, was not considered when the federal ADI was set, and indicates a different number should be used. The EPA provides ADIs, termed oral reference doses, as part of a health advisory, human health risk assessment for pesticides, or for use by the Integrated Risk Assessment System (IRIS) program.

EPA Oral Reference Dose (Office of Pesticide Program)

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

Oncogenic Potential

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

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

Cancer Classification

The EPA has not determined the cancer classification for AMPA.

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

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

Additional Technical Information

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

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

Guidance Values

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

JMPR Acceptable Daily Intake

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

Literature Search

Our literature review focused on the scientific literature published after the review by the EPA Office of Pesticide Programs in 2017.[2] We carried out a search on the National Institutes of Health's PubMed resource for relevant articles published from 2017 to May 2019 for studies related to AMPA toxicity or its effects on a disease state in which information on exposure or dose was included as part of the study.[a] Ideally, relevant studies used in vivo (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans. Approximately 60 studies were returned by the search engine. We excluded studies on effects on plants and non-mammalian species, as well as non-toxicity related articles. After applying these exclusion criteria, no key studies were identified.

We also evaluated the three studies that EPA and JMPR considered in their human risk assessment using these same criteria. To be considered a critical study, the study must be of an appropriate duration (at least 60 days or exposure during gestation), have identified effects that are consistent with other studies and relevant for humans, have evaluated more than one dose, and have an identifiable toxicity value.

Critical Studies

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

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

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

Estes et al, 1979 (MRID: 00241351)

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

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

Holson et al, 1979 (MRID: 43334705)

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

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

Summary

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

Standard Selection

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

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

Basis for Enforcement Standard

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

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

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

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

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

Prepared by Clara Jeong, Ph.D.

Wisconsin Department of Health Services

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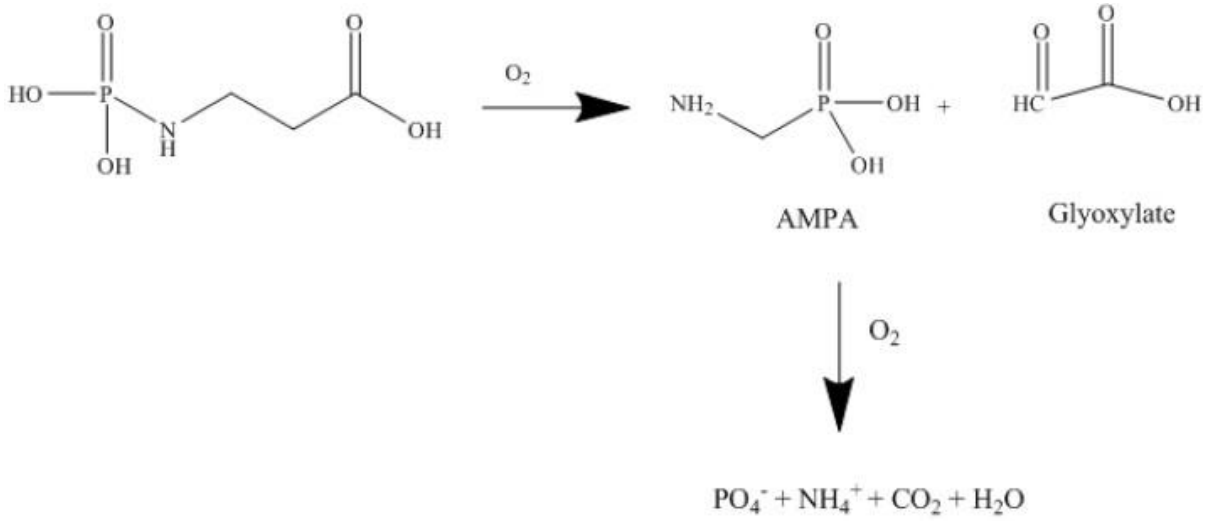
Appendix A: Glyphosate Degradation

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

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



Source: Schuette 1998

Appendix B. Toxicity Data

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

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

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

Reference	Appropriate duration?	Effects consistent with other studies?	Effects relevant to humans?	Number of doses	Toxicity value identifiable?	Critical study?
Estes et al. (1979) [9] MRID: 00241351	✓	✓	✓	**4**	✓	**Yes**
Holson et al. (1991)[10] MRID: 43334705	✓	✓	✓	**4**	✓	**Yes**
Tompkins et al. (1991) [12] MRID: 43334702	✓	⦸	⦸	**4**	✓	No

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

Sulfentrazone | 2019

Substance Overview

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

Recommendations

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

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

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

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

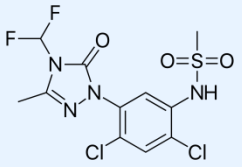
Recommended Standards	
Enforcement Standard:	1,000 µg/L
Preventive Action Limit:	100 µg/L

Health Effects

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

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

Chemical Profile

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

Exposure Routes

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

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

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

Current Standard

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

Standard Development

Federal Numbers		
Maximum Contaminant Level:	N/A	
Health Advisory:	N/A	
Drinking Water Concentration (Cancer Risk):	N/A	
State Drinking Water Standard		
NR809 Maximum Contaminant Level:	N/A	
Acceptable Daily Intake		
EPA Oral Reference Dose:	0.14 mg/kg-d	(2014)
Oncogenic Potential		
EPA Cancer Slope Factor:	N/A	
Guidance Values		
None available		
Literature Search		
Literature Search Dates:	2014 – 2018	
Total studies evaluated:	15	
Key studies evaluated:	None	
Key studies found?	No	

Federal Numbers

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

Maximum Contaminant Level

The EPA does not have a maximum contaminant level for sulfentrazone.[5]

Health Advisory

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

Drinking Water Concentration (Cancer Risk)

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

State Drinking Water Standard

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

NR 809 Maximum Contaminant Level

Wisconsin does not have a state drinking water standard for sulfentrazone.[7]

Acceptable Daily Intake

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

EPA Oral Reference Dose

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

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

Oncogenic Potential

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

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

Cancer Classification

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

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

EPA Cancer Slope Factor

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

Additional Technical Information

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

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

Guidance Values

For sulfentrazone, we searched for values that been published since 2014 when the EPA published their human health risk assessment. We did not find any relevant guidance values from the EPA, Agency for Toxic Substances and Disease Registry (ATSDR), or World Health Organization (WHO).

Literature Search

Our literature review focused on the scientific literature published after the review by EPA in 2014. We conducted a search on the National Institutes of Health's PubMed resource for articles published from January 2014 to August 2018 out for studies related to sulfentrazone toxicity or its effects on a disease state in which information on sulfentrazone exposure or dose was included as part of the study.[1] Ideally, relevant studies used *in vivo* (whole animal) models and provided data for multiple doses over an exposure duration proportional to the lifetime of humans.

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

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

Standard Selection

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

Basis for Enforcement Standard

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

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

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

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

Prepared by Clara Jeong, Ph.D.

Wisconsin Department of Health Services

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