DEPARTMENT OF HEALTH

Protecting, Maintaining and Improving the Health of All Minnesotans

January 18, 2018

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St. Paul, Minnesota 55155

Re: In The Matter of the Proposed Rules of the Department of Health Relating to the Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, part 7860 and part 7500; Revisor's ID Number R4396, Office of Administrative Hearings Docket No. 82-9000-34834:

Dear Librarian:

The Minnesota Department of Health (MDH) intends to adopt rules relating to Health Risk Limits for Groundwater. We plan to publish a Dual Notice of Intent to Adopt Rules in the January 22, 2018 in the *Minnesota State Register.*

MDH has prepared a Statement of Need and Reasonableness. As required by Minnesota Statutes, sections 14.131 and 14.23, the Department is sending the Library an electronic copy of the Statement of Need and Reasonableness at the same time we are mailing our Notice of Intent to Adopt Rules.

If you have questions, please contact me at 651-201-4923.

Sincerely,

Nancy Rice

Nancy Rice
Health Risk Assessment Unit
Division of Environmental Health
Minnesota Department of Health
P.O. Box 64975
St. Paul, MN 55164

Enclosure: Statement of Need and Reasonableness

STATE OF MINNESOTA

Minnesota Department of Health
In the Matter of the Proposed Rules
of the Minnesota Department of Health
Relating to Health Risk Limits for Groundwater,
Minnesota Rules, Chapter 4717, Part 7500 and Part 7860.
Revisor's ID Number: 04396

STATEMENT OF NEED AND REASONABLENESS

January 2018

1/5/2018___
Date

signed by Daniel Pollock, J.D.
Daniel Pollock, J.D.
Acting Commissioner
Minnesota Department of Health
P.O. Box 64975
St. Paul, MN 55164

Abbreviations and Acronyms

ADAF	Age-Dependent Adjustment Factor
$AF_{lifetime}$	Lifetime adjustment factor
BMD	Benchmark dose
BMDL	Benchmark dose lower-confidence limit
CEC	Contaminant of emerging concern
DAF	Dosimetric Adjustment Factors
DWEL	Drinking Water Equivalent Levels (issued by EPA)
(E)	Endocrine[1]
EPA	U.S. Environmental Protection Agency
HA	Health Advisory (issued by EPA)
HBV	Health-Based Value
HED	Human Equivalent Dose
HRA	Health Risk Assessment
HRL	Health Risk Limit
LOAEL	Lowest Observed Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
MCL	Maximum Contaminant Limit (created by the U.S. Environmental Protection Agency)
MDH	Minnesota Department of Health
MMB	Minnesota Management and Budget
NTP	National Toxicology Program
RfD	Reference Dose
RSC	Relative Source Contribution
SF	Slope Factor
SONAR	Statement of Need and Reasonableness

[1] See Glossary for further detail

MINNESOTA DEPARTMENT OF HEALTH

STATEMENT OF NEED AND REASONABLENESS

Proposed Amendments to the Rules on Health Risk Limits for Groundwater

(Minnesota Rules, Chapter 4717, parts 7500 and 7860)

About this Document

This Statement of Need and Reasonableness (SONAR) supports the Minnesota Department of Health's revision of its rules on the Health Risk Limits for Groundwater. The proposed rules are available at:

2016/2018 Proposed Rules Amendments
(http://www.health.state.mn.us/divs/eh/risk/rules/water/documents.html)

For questions or concerns regarding this document, please contact Nancy Rice at nancy.rice@state.mn.us or, call (651) 201-4923.

The Minnesota Department of Health (MDH) will publish the proposed rules in Minnesota's *State Register* at a later time. Subscribers of MDH's Groundwater Rules, Guidance and Chemical Review email subscription list will receive a notice of publication. For Minnesota's statutory procedure for adopting administrative rules, see Minnesota Statutes, section 14.001 et seq., and in particular, section 14.22.

Upon request, MDH can make this SONAR available in an alternative format. Contact Nancy Rice to make a request at the Minnesota Department of Health, Division of Environmental Health, 625 North Robert Street, PO Box 64975, St. Paul, MN 55164-0975, ph. (651) 201-4923, fax (651) 201-4606, or email: nancy.rice@state.mn.us.

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"It is the goal of the state that groundwater be maintained in its natural condition, free from any degradation caused by human activities."

Groundwater Protection Act, 1989, Minnesota Statutes, Chapter 103H

I. Introduction

About 75 percent of Minnesota's drinking water is from groundwater, making it an important resource for the state. In 1989, the Minnesota *Groundwater Protection Act* proclaimed its goal to maintain groundwater "in its natural condition, free from degradation caused by human activities" (Minnesota Statutes, section 103H.001). However, when groundwater quality monitoring shows that water quality has degraded, the *Groundwater Protection Act* authorizes the Minnesota Department of Health (MDH) to adopt rules that set health-protective limits, known as Health Risk Limits (HRLs), for contaminants found in groundwater that might be used for drinking (Minnesota Statutes, section 103H.201). An HRL value is a concentration of a groundwater contaminant, or a mixture of contaminants, that people can consume with little or no risk to health, and which has been adopted under rule. The value is expressed as micrograms of a chemical per liter of water (µg/L). MDH calculates HRL values for specific durations of exposure.

This project proposes to amend Minnesota Rules, Chapter 4717, by revising or adding HRLs for 22 groundwater contaminants. Specifically, the proposed amendments add new HRL values for four contaminants to part 4717.7860 (see Section IV.B.). The proposal will also repeal the outdated HRL values in parts 4717.7500 or 4717.7860, and add updated HRL values to 4717.7860 (see Section IV.C.) for 18 contaminants.

These proposed amendments build on MDH's 2009 rule revision and subsequent rulemaking.[2] Details on the 2009 HRL rule revision and subsequent rule adoption are presented in Section II. MDH will not be amending any other parts of the HRL rules in 2016/2018.

The *Minnesota Administrative Procedure Act* (APA) (Minnesota Statutes, section 14.131) requires MDH to justify the need to amend the existing HRL rules and the reasonableness of the amendments in a Statement of Need and Reasonableness (SONAR). This document fulfills that requirement.

[2] The current rules on the Health Risk Limits (Minnesota Rules, Chapter 4717, various parts) are available on the Minnesota Department of Health's website at Health Risk Limits Rules: (http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlrule.html).

The rules on Health Risk Limits (Minnesota Rules, Chapter 4717, various parts) are also available on the Minnesota Office of the Revisor of Statutes' website (https://www.revisor.mn.gov/rules/?id=4717)

This SONAR is divided into five sections. Section I is this introduction. Section II identifies MDH's statutory authority to adopt HRL rules and describes past HRL rule revisions. It explains the concept of HRL values and summarizes the methods MDH used to derive the HRL values. Section III includes the scope of the amendments MDH proposes in 2016/2018. Section IV analyzes each provision in the proposed rules. Section V discusses statutory requirements: the regulatory factors, the performance-based nature of the rules, the additional notice plan, and the impact of the proposed rules, all as required per Minnesota Statutes, section 14.131.

II. Background

This background information for MDH's guidance on groundwater contaminants:

- Describes the statutory authority to review, derive, adopt, and revise HRL values;
- Provides historical information about MDH's past rule revisions;
- Defines HRL values; and
- Discusses the methods MDH used to derive HRL values.

Note: A detailed description of the methods and the underlying principles is available in MDH's 2008/2009 SONAR (MDH, 2008. See Part IV, page 21).[3]

A. Statutory Authority

MDH derives its authority to propose and adopt HRLs for water contaminants from the following statutes:

1. THE GROUNDWATER PROTECTION ACT, 1989

The *Groundwater Protection Act* of 1989 (the 1989 Act) (Minnesota Statutes 2016, section 103H.201, subdivision (1)(a)) provides MDH with its statutory authority to adopt HRL values for groundwater contaminants. The 1989 Act states:

> "If groundwater quality monitoring results show that there is a degradation of groundwater, the commissioner of health may promulgate health risk limits under subdivision 2 for substances degrading the groundwater."

[3] MDH's 2008/2009 SONAR is available at: 2008 Statement of Need and Reasonableness (http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlsonar08.pdf)

The 1989 Act defines an HRL as (Minnesota Statutes 2016, section 103H.005, subdivision (3)):

> "a concentration of a substance or chemical adopted by rule of the commissioner of health that is a potential drinking water contaminant because of a systemic or carcinogenic toxicological result from consumption."

Minnesota Statutes, section 103H.201, subdivision (2)(a) states the authority to adopt HRL values:

> "(a) Health risk limits shall be adopted by rule."

The methods to derive HRL values are specified in Minnesota Statutes 2016, section 103H.201, subdivisions (1)(c) and (d):

> "(c) For systemic toxicants that are not carcinogens, the adopted health risk limits shall be derived using United States Environmental Protection Agency risk assessment methods using a reference dose, a drinking water equivalent, and a relative source contribution factor.
>
> "(d) For toxicants that are known or probable carcinogens, the adopted health risk limits shall be derived from a quantitative estimate of the chemical's carcinogenic potency published by the United States Environmental Protection Agency and determined by the commissioner to have undergone thorough scientific review."

MDH has specific authority to review and revise HRL values under Minnesota Statutes 2016, section 103H.201, subdivisions (3)(a) and (b):

> "(a) The commissioner shall review each adopted health risk limit at least every four years.
>
> "(b) The commissioner may revise health risk limits under subdivision 2."

2. HEALTH STANDARDS STATUTE, 2001

Additional authority is implicit under the 2001 *Health Standards Statute* (Minnesota Statutes 2016, section 144.0751), which applies to safe drinking water and air quality standards. Per this provision, safe drinking water standards must:

> "(1) be based on scientifically acceptable, peer-reviewed information; and
>
> "(2) include a reasonable margin of safety to adequately protect the health of infants, children, and adults by taking into consideration risks to each of the following health outcomes: reproductive development and

function, respiratory function, immunologic suppression or hyper-sensitization, development of the brain and nervous system, endocrine (hormonal) function, cancer, general infant and child development, and any other important health outcomes identified by the commissioner."

Under the provisions cited above, in cases of water degradation, MDH has the necessary statutory authority to review, develop, and adopt HRL values for water contaminants based on scientific methods to protect sensitive populations. Thus, MDH has the necessary authority to adopt the proposed rules.

B. Past MDH Rule Revisions

The 1989 Act authorized MDH to adopt HRL values for contaminants found in Minnesota groundwater. In 1993, MDH adopted methods to calculate HRL values and adopted HRL values for chemicals based on those methods. In 1994, MDH adopted additional HRL values based on 1993 methods (the 1993-1994 HRL values). The 1993-1994 HRL values were published in Minnesota Rules 4717.7500.

In 2001, MDH toxicologists and risk assessors evaluated the adequacy of the 1993 methods to calculate the HRL values. The review spanned seven years during which MDH hosted public meetings and invited stakeholder participation. MDH began formal rulemaking in 2008 by proposing an updated methodology to derive HRL values based on the United States Environmental Protection Agency's (U.S. EPA) risk-assessment guidelines.

In 2009, MDH adopted the new methods and the HRL values for 21 groundwater contaminants that it had derived using the updated methodology. The 2008/2009 SONAR (MDH SONAR, 2008) documents additional details on the nature and scope of MDH's 2009 HRL rule revision.

In 2007, the Minnesota Legislature enacted two laws to place certain water guidance values into rule. One law, Minnesota Session Laws 2007, chapter 37, section 1, directed MDH to adopt HRLs for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). MDH did this in August 2007 using the legislation's good-cause exemption authority for rulemaking. These values, which MDH later adopted via the full rulemaking process, appear as 2009 HRLs on the MDH website.

The second 2007 law concerned the Water Levels Standards: Minnesota Laws 2007, chapter 147, article 17, section 2, required MDH to set an HRL equal to the U.S. EPA Maximum Contaminant Level (MCL) value when the MCL value was more stringent (i.e., lower) than a Minnesota-derived HRL value. In response, MDH established 11 MCL values as HRLs in 2007, and adopted these HRLs into rule in 2009 along with the MCL for nitrate. These "MCL-HRLs," as they have been called, appeared in Minnesota Rules 4717.7850. MDH has been updating the MCL-HRL values using the methods

adopted in 2009, and replacing the outdated MCL-HRL values in rule. To date, six of the original 11 2009 MCL values remain in HRL rule.[4]

In 2011, MDH added HRL values for 22 contaminants to Minnesota Rules, part 4717.7860, and updated part 4717.7500 to reflect all repealed or updated values.

In 2013, MDH added HRL values to Minnesota Rules, part 4717.7860 for six chemicals not previously in the HRL rules, and repealed and replaced outdated HRL values for six chemicals. In total, MDH adopted new or updated HRL values for 12 chemicals in 2013.

In 2015, MDH proposed new HRL values for eight chemicals that had not previously appeared in the HRL Rules. MDH also proposed to repeal outdated HRL values for three more chemicals in Minnesota Rules, part 4717.7500, and replace the repealed values with updated guidance in part 4717.7860. Further, outdated HRL values for three chemicals already in Minnesota Rules part 4717.7860 were repealed and replaced with new values in this part. In total, MDH adopted new or updated HRL values for 14 chemicals in 2015.

MDH is proposing to adopt new or updated HRL values for 22 contaminants in 2018. Of these, 18 contaminants have values that were previously adopted into rule in 1993, 2009, or 2011. Under the proposed rule amendments, MDH would repeal the 18 outdated 1993, 2009, and 2011 values from Minnesota Rules, parts 4717.7500 or 4717.7860, and add the updated values to, or update them in, Minnesota Rules, part 4717.7860. Likewise, MDH would add four additional new values to Minnesota Rules, part 4717.7860.

The table below summarizes the new and updated HRLs adopted into rule since 2007. Some HRLs have been updated more than once.

Table 1. Number of Health Risk Limit (HRL) updates by year

Year	Number of new HRLs	Number of updated HRLs	Total Number of Chemicals with new or updated HRLs
2007	2	12	14
2009	6	15	21
2011	14	8	22
2013	6	6	12

[4] Minnesota Rules, part 4717.7850 (https://www.revisor.mn.gov/rules/?id=4717.7850)

Year	Number of new HRLs	Number of updated HRLs	Total Number of Chemicals with new or updated HRLs
2015	8	6	14
2018 (proposed)	4	18	22
Total	**40**	**65**	**105**

C. Defining Health Risk Limits (HRLs)

HRL values are a type of health-protective guidance MDH developed for groundwater contaminants that pose a potential threat to human health if consumed in drinking water. The 1989 Act (Minnesota Statutes 2016, section 103H.005, subdivision (3)) defines an HRL as:

> "…a concentration of a substance or chemical adopted by rule of the commissioner of health that is a potential drinking water contaminant because of a systemic or carcinogenic toxicological result from consumption."

MDH has defined an HRL more precisely as a concentration of a groundwater contaminant, or a mixture of contaminants, that is likely to pose little or no health risk to humans, including vulnerable subpopulations, and has been adopted into rule. MDH first calculates a value called a health-based water guidance value (HBV), for specific durations of exposure, which may be later adopted into rule. An HRL is expressed as micrograms of a chemical per liter of water (µg/L).

In calculating water guidance values, MDH assumes people could drink the water containing the contaminant. This is consistent with Minnesota Statutes 2016, section 115.063, subdivision 2, that "the actual or potential use of the waters of the state for potable water supply is the highest priority use of that water and deserves maximum protection by the state…" Further, the stated statutory intent is to prevent degradation (Minnesota Statutes 2016, section 103H.001) and to protect the waters of the state (Minnesota Statutes 2016, section 115.063, subdivision (1)).

Risk managers in partner state agencies, such as the Minnesota Department of Agriculture (MDA) and the Minnesota Pollution Control Agency (MPCA), request and apply HRL values in their respective risk-abatement and contamination-response programs. In addition, MDH's Site Assessment and Consultation Unit, Drinking Water Protection, and Well Management programs use HRL values to provide advice.

Except for the requirements for water resources protection (specified in Minnesota Statutes 2016, section 103H.275, subdivision 1(c)(2)), neither Minnesota statute nor current HRL rule (Minnesota Rules, Chapter 4717) specifies how HRL values should be used. In issuing guidance, MDH assumes risk managers consider several principles when applying HRL values. MDH-derived HRL values:

- Specify a water quality level acceptable for human consumption;
- Should not be interpreted as acceptable degradation levels;
- Do not address non-ingestion pathways of exposure to contaminants in water (e.g., dermal or inhalation), except in apportioning exposure through the use of a Relative Source Contribution (RSC) factor[5];
- Do not account for economic or technological factors such as the cost or feasibility of treatment; and
- Do not account for the potential impact on the environment outside the realm of drinking water, or the health of non-human species.

MDH cannot anticipate all the situations for which HRL values might provide meaningful guidance. Nor can MDH anticipate all the factors that might determine whether applying an HRL value is appropriate. As mentioned before, HRL values are but one of several sets of criteria that state groundwater, drinking water, and environmental protection programs may use to evaluate water contamination. Each program must determine whether to apply an HRL or whether site-specific characteristics justify deviation from HRL values.

D. MDH-derived Health Risk Limit (HRL) Algorithm

The MDH Health Risk Assessment (HRA) Unit derives water guidance values. MDH HRA does not enforce or regulate the use of health-based guidance, but provides recommended values for risk assessors and risk managers to use in making decisions and evaluating health risks. MDH health-based guidance is only one set of criteria that state groundwater and environmental protection programs use to evaluate contamination. In addition, there are federal requirements for permissible levels of some drinking-water contaminants called the Maximum Contaminant Levels (MCLs). Legally enforceable under the National Primary Drinking Water Regulations, they apply only to public water systems. More information about MCLs is available in Section V.C.7, below.

As stated above, MDH derives HRL values using the methods MDH adopted in 2009 (Minnesota Rules, part 4717.7810 through part 4717.7900). The calculation used to

[5] For more information on RSC, see the 2008/2009 SONAR [Part IV.E.1, page 51] at http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlsonar08.pdf (PDF) and Minnesota Rules, part 4717.7820, subpart 22

develop an HRL value is a function of how toxic a chemical is (that is, the minimum quantity that will cause health effects), the duration of exposure, and the amount of water individuals drink (intake rates) during the exposure period.

MDH's approach for developing non-cancer HRL values (nHRL) for effects other than cancer is specified in rule (Minnesota Rules, part 4717.7830, subpart 2). MDH also uses this approach for chemicals that cause cancer only after a known dose level is exceeded (e.g., threshold carcinogens). The algorithms and explanation of concepts used to derive HRL values are presented in Appendix C of this SONAR.[6]

In 2016, MDH updated the intake rates used to calculate the water guidance for each duration to match EPA's intake rates in the most recent (2011) Exposure Factors Handbook (EPA, 2011a). Previously, MDH was using draft intake rate values for ages of less than one year, and intake rates from the 2004 EPA Per Capita report (EPA, 2004c) for all other ages. These values were available at the time MDH was conducting rulemaking in 2008. EPA finalized the intake rates for all ages in the 2011 Exposure Factors Handbook.

Going forward, MDH will use the 2011 EPA intake values, as announced by a GovDelivery message sent on June 15, 2016. The new intake rates are below:

Table 2. Comparison of Draft and Finalized Intake Rates

Duration	**2008 Intake Rate**	**2011 Intake Rate**
Acute/Short-term	0.289	0.285
Subchronic	0.077	0.070
Chronic	0.043	0.044
Cancer: Age-Dependent Adjustment Factor (ADAF)	<2 yrs - 0.137 2 - < 16yrs - 0.047 16 yrs & over - 0.039	<2 yrs - 0.125 2 - < 16yrs - 0.045 16 yrs & over - 0.041
Cancer: lifetime adjustment factor ($AF_{lifetime}$)	0.043	0.044

[6] Additional information is available in MDH's 2008/2009 SONAR (http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlsonar08.pdf) (PDF) (MDH, 2008. See Part IV).

Duration	2008 Intake Rate	2011 Intake Rate
Pregnant Women	0.043	0.043

III. 2016/2018 Proposed Rules

This section describes the proposed rules' scope and the basis for contaminants considered in the amendments.

A. Scope

The 2016/2018 proposed rule amendments are limited to Minnesota Rules, parts 4717.7500 and 4717.7860 as noted below. MDH is not amending other parts of the HRL rules. Through the proposed rules, MDH intends to:

- Adopt into rule HRL values for 22 groundwater contaminants with guidance developed using the 2009 methodology. Of these 22 contaminants, four contaminants have not had previously adopted values in HRL rule. The proposed HRL values will be added to Minnesota Rules, part 4717.7860 (see Table 3 and Section V for details); and

- Repeal outdated guidance in Minnesota Rules, parts 4717.7500 for five contaminants for which an HRL was adopted in 1993, 10 contaminants with HRL values adopted in 2009, and 3 contaminants with HRL values adopted in 2011 (see Table 3 and Section V for details). The repealed values will be replaced with values added in Minnesota Rules, parts 4717.7860, as noted above.

Table 3. Contaminants included in the 2016/2018 proposed HRL amendments

Chemical Abstract Service (CAS) Number	**Chemical Name**	**Previously adopted values in HRL Rule? (year adopted)**
83-32-9	Acenaphthene	Yes (1993)
34256-82-1	Acetochlor	Yes (2009)
187022-11-3	Acetochlor ESA	Yes (2011)
194992-44-4	Acetochlor OXA	Yes (2011)
15972-60-8	Alachlor	Yes (2009)
67-66-3	Chloroform	Yes (2009)
210880-92-5 (Formerly 205510-53-8)	Clothianidin	No
21725-46-2	Cyanazine	Yes (2009)
159-59-2	cis-1,2-Dichloroethene	Yes (2009)
94-75-7	2,4-Dichlorophenoxyacetic acid (2,4-D)	Yes (1993)
60-57-1	Dieldrin	Yes (2009)

Chemical Abstract Service (CAS) Number	Chemical Name	Previously adopted values in HRL Rule? (year adopted)
88-85-7	Dinoseb	No
759-94-4	S-Ethyl-N,N-dipropylthiocarbamate (EPTC)	Yes (1993)
206-44-0	Fluoranthene	Yes (1993)
375-22-4	Perfluorobutyrate (PFBA)	Yes (2011)
335-67-1 (and others)	Perfluorooctanoic Acid (PFOA) and Salts	Yes (2009)
1763-23-1 (and others)	Perfluorooctane Sulfonate (PFOS) and Salts	Yes (2009)
129-00-0	Pyrene	Yes (1993)
109-99-9	Tetrahydrofuran	No
153719-23-4	Thiamethoxam	No
71-55-6	1,1,1-Trichloroethane	Yes (2009)
75-01-4	Vinyl Chloride	Yes (2009)

B. Selection of Contaminants for Review

MDH selected the contaminants for the 2016/2018 amendments based on two separate nominating processes, described below. Each year, MDH uses these two processes to create work plans to assess chemicals for health risks and to develop and issue guidance (see Appendix D).

In one process MDH holds an annual interagency meeting for representatives of MDA, MPCA, MDH, and other agencies to discuss their concerns about specific contaminants, and to rank a list of chemicals according to each agency's need for new or updated water guidance. A final list of priority chemicals is generated from this process.

In the second process, anyone, including members of the public, may nominate chemicals through the MDH Contaminants of Emerging Concern (CEC) program's website or by contacting MDH. MDH then screens these chemicals for toxicity and exposure potential and ranks them for review priority.

In addition, MDH continues to carry out its plan to routinely re-evaluate previously adopted HRLs. Nine contaminants that were adopted in 2009 and 15 that were adopted in 2011 were eligible for review in 2016 and 2017, respectively, under this plan.

As MDH reviewed each chemical, it posted the following information on MDH's Chemicals Under Review[7] webpage: the chemical's name, its Chemical Abstracts Service (CAS) Registry Number, and the date it was posted. After completing each review, MDH posted the guidance values and the chemical-specific summary sheets on the Human Health Based Water Guidance[8] webpage. MDH also notified subscribers to MDH HRL Rules, Guidance and Chemical Review email notification account[9] about the updated guidance's availability.

IV. Applying MDH-derived Methods

MDH derived the proposed HRL values using the methods it adopted in 2009. The 2009 methods follow current scientific risk-assessment principles. MDH is not proposing any changes to these methods in the 2016/2018 proposed amendments. MDH has begun, however, to use the water-intake rates that EPA updated and finalized in 2011.

When MDH proposed updated water-guidance methods in 2008, EPA was planning to revise the U.S. water-consumption intake rates, but the updated intake rates were not yet available. EPA later published the final updated values, which MDH is now using for calculating water guidance. (See Section II. D. for more information.)

Applying the 2009 methods or updated water intake rates to previously adopted HRL values yields new HRL values that, if they changed, may be higher or lower than the previous values. These fluctuations are related to several factors, such as:

- Extent and quality of toxicity data for a chemical;
- Application of DAFs (dosimetric adjustment factors) to derive HEDs (human equivalency doses)[10];
- Changes in water intake rates within the guidance algorithms to consider the effect on sensitive subpopulations (e.g., infants and children); and
- Age-dependent adjustment factors used within the algorithms.

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[7] The Chemicals Under Review webpage is available at: Chemicals Under Review (http://www.health.state.mn.us/divs/eh/risk/review/index.html)

[8] See the Human-Health Based Water Guidance Table (http://www.health.state.mn.us/divs/eh/risk/guidance/gw/table.html). All health-based guidance values for water are summarized in this table, including those that have not been adopted into rule.

[9] Electronic subscriptions to this account may be requested at https://public.govdelivery.com/accounts/MNMDH/subscriber/new?topic_id=MNMDH_39

[10] DAF and HED are used to estimate the amount of chemical a human would need to ingest to have the same exposure the tested animal.

Among the 22 chemicals included in this 2016/2018 proposed rule, 18 currently have HRL values. Of these, five were adopted in 1993, ten were adopted in 2009, and three were adopted in 2011. The table below shows the current lowest HRL values and proposed new HRL values.

Table 4. Comparison of Lowest Current Health Risk Limit (HRL) and Lowest Proposed HRL, by Chemical

Chemical Abstract Service number	Chemical Name	Current Lowest HRL (µg/L)	Proposed Lowest HRL (µg/L)
83-32-9	**Acenaphthene**	400 (1993 HRL)	100
34256-82-1	**Acetochlor**	9 (2009 HRL)	20
187022-11-3	**Acetochlor ESA**	300 (2011 HRL)	300
194992-44-4	**Acetochlor OXA**	100 (2011 HRL)	90
15972-60-8	**Alachlor**	5 (2009 HRL)	9
67-66-3	**Chloroform**	30 (2009 HRL)	20
21725-46-2	**Cyanazine**	1 (2009 HRL)	1
159-59-2	**cis-1,2-Dichloroethene**	50 (2009 HRL)	6
94-75-7	**2,4-Dichlorophenoxyacetic acid**	70 (1993 HRL)	30
60-57-1	**Dieldrin**	0.006 (2009 HRL)	0.006
759-94-4	**S-Ethyl-N,N-dipropylthiocarbamate (EPTC)**	200 (1993 HRL)	40
206-44-0	**Fluoranthene**	300 (1993 HRL)	70
375-22-4	**Perfluorobutyrate (PFBA)**	7 (2011 HRL)	7
335-67-1 (and others)	**Perfluorooctanoic Acid (PFOA) and Salts**	0.3 (2009 HRL)	0.035
1763-23-1 (and others)	**Perfluorooctane Sulfonate (PFOS) and Salts**	0.3 (2009 HRL)	0.027
129-00-0	**Pyrene**	200 (1993 HRL)	50

Chemical Abstract Service number	Chemical Name	Current Lowest HRL (µg/L)	Proposed Lowest HRL (µg/L)
71-55-6	**1,1,1-Trichloroethane**	9,000 (2009 HRL)	5,000
75-01-4	**Vinyl Chloride**	0.2 (2009 HRL)	0.2

For more information about the algorithms used in calculating guidance, please see Appendix C.

MDH has two methods to derive HRL values depending on whether a dose can be found that causes no harm in animals or people. Historically, these methods were applied according to the type of health effect that the chemical exposure caused and were termed 'non-cancer' and 'cancer' methods. The scientific community, however, now recognizes that chemicals are better assessed according to what is known about finding a dose that causes no harm, regardless of the health effect.

In most toxicity studies, there is a low dose or exposure at which the chemical does no harm or has no effect on the animal tested. A dose that does not appear to cause harm (with all higher doses causing harm) is called "the threshold." Many carcinogens cause cancer only after exposure to high doses. These carcinogens might also have a threshold dose for effects other than cancer. That is, at a dose lower than the threshold dose, the chemical will not cause cancer or other health effects. MDH's threshold method, historically called a "non-cancer method," has been used by MDH for any chemical that exhibits a threshold, including many carcinogens.

Some carcinogens (and some neurotoxicants such as lead) have no apparent threshold because every dose tested appears to cause some potentially harmful effect. MDH uses a method that presumes even the lowest potential exposure has some small risk of harm. This method is based on carcinogenic potency and is described in the 2008/2009 SONAR (MDH, 2008). MDH's non-threshold method, historically called a "cancer method," has only been used by MDH for carcinogens that do not show a threshold. (See also Appendix C for more information.)

Among the 22 chemicals for which HRL values are proposed during this 2016/2018 rulemaking, there are five carcinogenic chemicals.[11] Three of the five are considered to be threshold carcinogens (acetochlor, alachlor, and chloroform) and the chronic non-cancer values are considered protective of public health. The remaining two are not considered to have thresholds, and therefore a cancer HBV value has been derived.

[11] See Carcinogen in Glossary

Also, three contaminants included here are polycyclic aromatic hydrocarbons (PAHs). Most PAHs are usually found in mixtures which include a variety of PAHs. Please refer to the MDH guidance "Polycylic Aromatic Hydrocarbons: Methods for Estimating Health Risks from Carcinogen PAHs": http://www.health.state.mn.us/divs/eh/risk/guidance/pahmemo.html for the potency equivalency factors to estimate risks for carcinogenic PAHs.

V. Rule-by-Rule Analysis

This section explains the Health Risk Limits Table (Minnesota Rules, part 4717.7860) and discusses each provision of the rules proposed by MDH. It also lists the chemicals MDH proposes to repeal from part 4717.7500.

A. EXPLAINING THE HEALTH RISK LIMITS TABLE (Minnesota Rules, part 4717.7860)

The Health Risk Limits table in Minnesota Rules, part 4717.7860 lists the HRL values derived for chemicals found in Minnesota's groundwater. As noted before, an HRL value represents the health-protective limit of the concentration of a contaminant in groundwater that poses little or no risk to human health, including vulnerable subpopulations, based on current scientific knowledge. HRL values are derived using the methodology specified in Minnesota Rules, parts 4717.7830 and 4717.7840 (see Appendix C for detailed explanations and definitions of the technical terms that follow).

For each chemical and its proposed HRL value(s), MDH provides the following information in a table, as shown in Figure 1 below:

Figure 1.

Example of table showing proposed rule

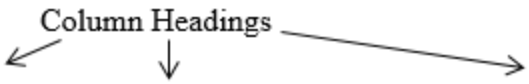
Subp. XX Chemical name. Heading Section

CAS number[12]: XXX-XX-X (identifies the chemical)

Year Adopted: 2018

Volatility: XX

[12] Chemical Abstract Service number for assigning a unique number to chemicals. (*See glossary in Appendix A)*



	Acute	Short-Term	Subchronic	Chronic	Cancer
HRL (µg/L)					
RfD (mg/kg-day)					
RSC					
SF (per mg/kg-day)					
ADAF or $AF_{lifetime}$					
Intake Rate (L/kg-day)					
Endpoints					

Row headings

Heading section:

- The chemical name;
- The CAS Registry Number that uniquely identifies each chemical;
- The year the rule will be adopted (estimated); and
- The chemical's volatility classification (nonvolatile, low, moderate, or high).

Row headings:

- **HRL (µg/L):** The Health Risk Limit value shown in micrograms per liter;

- **RfD (mg/kg-day):** The duration-specific reference dose (RfD) is an estimate of a dose level that is likely to be without an appreciable risk of adverse effects and includes uncertainty factors. See the glossary in Appendix A, chemical summary sheets in Appendix E, or Minnesota Rules 4717.7820 (https://www.revisor.mn.gov/rules/?id=4717.7820) for more information.
- **RSC:** Relative source contribution (RSC) is a portion of the reference dose that is allocated to drinking water;
- **SF (per mg/kg-day):** Slope factor (SF) is an upper-bound estimate of cancer risk per increment of dose, usually expressed in units of cancer incidence per milligram of chemical per kilogram of body weight per day (per [mg/kg-day] or $[mg/kg\text{-}day]^{-1}$). It reflects increased risks as the dose increases. The steeper the slope, the more potent the carcinogen.
- **Age-Dependent Adjustment Factors (ADAF) or Lifetime Adjustment Factor ($AF_{lifetime}$):** A multiplier of the cancer slope factor that adjusts for the increased susceptibility to cancer from early-life exposures to linear carcinogens.
- **Intake Rate (IR) (L/kg-day):** The amount of water, on a per body weight basis, ingested on a daily basis (liters per kg body weight per day or L/kg-day) for a given duration. MDH uses a time-weighted average of the 95th percentile intake rate for the relevant duration.
- **Endpoint:** Endpoint refers to the organ systems that are most susceptible to harm (or in the case of the endocrine system otherwise involved [see Endocrine (E) in the glossary for more information]) and that should be grouped together for evaluation when more than one chemical is present (additivity endpoint).

Column headings:

Guidance values are developed for specific time durations or cancer endpoints, as follows:

- **Acute:** A period of 24 hours or less.
- **Short-Term:** A period of more than 24 hours, up to 30 days.
- **Subchronic:** A period of more than 30 days, up to approximately 10 percent of the life span in humans (more than 30 days up to approximately 90 days is typically used mammalian laboratory animal species).
- **Chronic:** A period of more than approximately 10 percent of the life span in humans (more than approximately 90 days to 2 years in typically used mammalian laboratory animal species).
- **Cancer:** The duration used for cancer is 70 years.

In addition, the following notations are used within the tables:

- "--" means not relevant
- "NA" means not applicable. "NA" in the cancer column means that the chemical has not been classified as a linear (non-threshold) carcinogen
- "ND" means not derived due to absence or paucity of toxicity information
- "None" means that the HRL value is based on a general adverse effect (e.g., reduced adult body weight) not attributable to a specific organ system. This endpoint is therefore not included in the calculation of a health risk index, which is used in determining the risk of exposure to multiple chemicals in water.

Where noted and so that HRL values for longer durations of exposure are adequately protective of shorter durations of exposure:

- "(1)" indicates the calculated HRL value is greater than the acute value, the HRL is set to equal the acute HRL value;
- "(2)" indicates the calculated HRL value is greater than the short-term HRL value, the HRL is set equal to the short-term HRL value; and
- "(3)" indicates the calculated HRL is greater than the subchronic HRL, the HRL is set to equal the subchronic HRL value.

More information about each parameter can be found in Appendix C and in the 2008/2009 SONAR (http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlsonar08.pdf) (PDF) (MDH, 2008).

B. PROPOSED RULES: THE HEALTH RISK LIMITS TABLE (Minnesota Rules, part 4717.7860)

1. Proposed HRL Rules Amendments for New or Updated Guidance

The following pages describe HRL Rules amendments proposed for 22 substances with new or updated guidance values:

Subp. 2a. Acenaphthene

CAS number: 83-32-9
Year Adopted: 2018
Volatility: Moderate

Acute duration.
Not derived because of insufficient data.

Short-term duration.
Not derived because of insufficient data.

Subchronic duration.
The proposed subchronic duration nHRL is 200 µg/L. The RfD is 0.070 mg/kg-d and the intake rate is 0.070 L/kg-d. The Relative Source Contribution (RSC) is 0.2. The point of departure (POD) is the Benchmark Dose Level ($BMDL_{10}$) of 162 mg/kg-d. The Dose Adjustment Factor (DAF) is 0.13. The POD times the DAF (162 mg/kg-d × 0.13) is equal to the Human Equivalent Dose (HED) of 21 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 10 for database uncertainty due to a lack of reproductive/developmental studies and a lack of testing in a second species). Critical effects are increased relative liver weight in female mice. Co-critical effects are decreased relative adrenal weight. The additivity endpoints are adrenal and hepatic (liver) system.

Chronic duration.
The proposed chronic nHRL is 100 µg/L. The RfD is 0.021 mg/kg-d and the intake rate is 0.044 L/kg-d. The RSC is 0.2. The $BMDL_{10}$ is 162 mg/kg-d and the HED is 21 mg/kg-d, calculated by multiplying the POD of 162 mg/kg-d by the DAF of 0.13. The uncertainty factor is 1000 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 3 for extrapolation from a subchronic to a chronic study, and 10 for database uncertainty due to a lack of reproductive/developmental studies and a lack of testing in a second species). The critical effect is an increased relative liver weight in female mice. The co-critical effect is decreased relative adrenal weight. The additivity endpoints are adrenal and hepatic (liver) system.

Cancer.
Not applicable.

Acenaphthene

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	200	100	NA
RFD (mg/kg-day)	--	--	0.070	0.021	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	0.070	0.044	--
Endpoints	--	--	adrenal, hepatic (liver) system	adrenal, hepatic (liver) system	--

Subp. 3. Acetochlor

CAS number: 34256-82-1
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 30 µg/L. The RfD is 0.016 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The point of departure is a (NOAEL) of 22.4 mg/kg-d, the DAF is 0.22, and the HED is 4.93 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability, and 10 for database uncertainty, which includes lack of developmental neurotoxicity studies and lack of short-term study in sensitive species [dog]). The critical effects are decreased pup body weight, decreased number of pups per litter, decreased pup spleen and brain weight. The co-critical effects are decreased mean pup body weight, increased uridine diphosphate glucuronosyltransferase (UDGPT) activity, increased T4, and decreased T3. The additivity endpoints are developmental, hepatic (liver) system, thyroid (E).

Subchronic duration.
The proposed subchronic duration nHRL is 30 µg/L. The RfD is 0.012 mg/kg-d and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The POD is the NOAEL of 2 mg/kg-d. The DAF is 0.59. The HED is of 1.18 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty [for lack of developmental neurotoxicity studies]). Critical effects are increased salivation, increased incidence of renal interstitial nephritis, testicular histopathology (testicular degeneration and hypospermia), liver glycogen depletion. There are no co-critical effects(s). The additivity endpoints are hepatic (liver) system, male reproductive system, nervous system, renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 20 µg/L. The RfD is 0.0039 mg/kg-d and the intake rate is 0.044 L/kg-d. The RSC is 0.2. The HED is 1.18 mg/kg-d, calculated by multiplying the POD NOAEL of 2 mg/kg-d by the DAF of 0.59. The uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 10 for extrapolation from a subchronic to a chronic study). The critical effects are increased salivation, increased incidence of renal interstitial nephritis and chronic vasculitis, testicular histopathology (testicular degeneration and hypospermia), liver glycogen depletion. The co-critical effect an increased incidence of bronchiolar hyperplasia and renal tubular hyperplasia and decreased body weight gain. The additivity endpoints are hepatic (liver) system, male reproductive system, nervous system, renal (kidney) system, respiratory system.

Cancer.
Not applicable.

Acetochlor

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	30	30	20	NA
RFD (mg/kg-day)	--	0.016	0.012	0.0039	--
RSC	--	0.5	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Intake Rate (L/kg-day)	--	0.285	0.070	0.044	--
Endpoints	--	developmental, hepatic (liver) system, thyroid (E)	hepatic (liver) system, male reproductive system, nervous system, renal (kidney) system	hepatic (liver) system, male reproductive system, nervous system, renal (kidney) system, respiratory system	--

Subp. 3a. Acetochlor ESA

CAS number: 187022-11-3
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 500 µg/L. The RfD is 0.29 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The point of departure is a (LOAEL) of 374.6 mg/kg-d, the DAF is 0.23, and the HED is 86.2 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 3 for extrapolation from a LOAEL to a NOAEL, and 3 for database uncertainty, which includes lack of developmental or multigenerational reproductive studies). The critical effect is increased free thyroxine (T4). The co-critical effects are increased thyroid stimulating hormone (TSH). The additivity endpoint is thyroid (E).

Subchronic duration.
The proposed subchronic duration nHRL is 500 µg/L. The RfD is 0.19 mg/kg-d and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The POD is the NOAEL of 225.4 mg/kg-d. The DAF is 0.25, resulting in a HED of 56.4 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 10 for database uncertainty, which includes the lack of two-generation study, lack of sensitive endpoint testing [thyroid], and lack of second species [based on parent

compound, dog appears to be more sensitive]). Critical effects are decreased body weight, decreased body weight gain, and decreased food utilization. The co-critical effects are increased thyroid stimulating hormone (TSH), increased free thyroxine (T4), increased free triiodothyronine (T3), and increased relative testes weight. The additivity endpoints are male reproductive system and thyroid (E).

Chronic duration.
The proposed chronic nHRL is 300 µg/L. The RfD is 0.056 mg/kg-d and the intake rate is 0.044 L/kg-d. The RSC is 0.2. The DAF is 0.25 and the HED of 56.4 mg/kg-d. The uncertainty factor is 1000 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 3 for subchronic to chronic extrapolation, and 10 for database uncertainty, which includes lack of two-generation study, lack of sensitive endpoint testing [thyroid], and lack of second species [based on parent compound, dog appears to be more sensitive]. The critical effects are decreased body weight, decreased body weight gain, and decreased food utilization. The co-critical effects are increased thyroid stimulating hormone (TSH), increased free thyroxine (T4), increased free triiodothyronine (T3), and increased relative testes weight. The additivity endpoints are male reproductive system and thyroid (E).

Cancer.
Not applicable.

Acetochlor ESA

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	500	500	300	NA
RFD (mg/kg-day)	--	0.29	0.19	0.056	--
RSC	--	0.5	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	0.070	0.044	--
Endpoints	--	thyroid (E)	male reproductive system, thyroid (E)	male reproductive system, thyroid (E)	--

Subp. 3b. Acetochlor OXA

CAS number: 184992-44-4
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 100 µg/L. The RfD is 0.081 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The point of departure is a (LOAEL) of 367.2 mg/kg-d, the DAF is 0.22, and the HED is 80.8 mg/kg-d. The total uncertainty factor is 1000 (3 for interspecies differences [for toxicodynamics]; 10 for intraspecies variability; 10 for extrapolation from a LOAEL to a NOAEL, and 3 for database uncertainty [lack of multigenerational reproductive study]). The critical effects are decreased thyroid stimulating hormone (TSH). The co-critical effects are decreased body weight gain, decreased total triiodothyronine (tT3), increased relative thyroid weight. The additivity endpoint is thyroid (E).

Subchronic duration.
The proposed subchronic nHRL is 100 µg/L. The subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 100 µg/L. The additivity endpoint is thyroid (E).

Chronic duration.
The proposed chronic nHRL is 90 µg/L. The RfD is 0.019 mg/kg-d and the intake rate is 0.044 L/kg-d. The RSC is 0.2. The DAF is 0.24 and the HED of 18.5 mg/kg-d. The uncertainty factor is 1000 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 3 for subchronic to chronic extrapolation, and 10 for database uncertainty which includes lack of multigenerational reproductive study, lack of studies in a second species [based on parent compound, dog appears to be more sensitive], lack of studies showing thyroid and motor activity effects [sensitive endpoints for parent compound, acetochlor]). The critical effects are decreased body weight, decreased body weight gain, and decreased food utilization. The co-critical effect is decreased thyroid stimulating hormone (TSH). The additivity endpoint is thyroid (E).

Cancer.
Not applicable.

Acetochlor OXA

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	100	100 (2)	90	NA

	Acute	Short-term	Subchronic	Chronic	Cancer
RFD (mg/kg-day)	--	0.29	(2)	0.019	--
RSC	--	0.5	(2)	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	(2)	0.044	--
Endpoints	--	thyroid (E)	thyroid (E)	thyroid (E)	--

Subp. 4. Alachlor

CAS number: 15972-60-8
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 100 µg/L. The RfD is 0.077 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The point of departure is a NOAEL of 10 mg/kg-d, the DAF is 0.23, and the HED is 2.3 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effects are decreased kidney weight in pups and adult animals, nephritis, and kidney damage. There are no co-critical effects. The additivity endpoints are developmental and renal (kidney) system.

Subchronic duration.
The proposed subschronic nHRL is 60 µg/L. The RfD is 0.020 mg/kg-d and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The point of departure is a NOAEL of 1 mg/kg-d, the DAF is 0.61, and the HED is 0.61 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effect is hemosiderosis of the kidney and spleen. The co-critical effect is increased liver weight. The additivity endpoints are hematological (blood) system, hepatic (liver) system, and renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 9 µg/L. The RfD is 0.0020 mg/kg-d and the intake rate is 0.044 L/kg-d. The RSC is 0.2. The HED is 0.61 mg/kg-d, calculated by multiplying the POD NOAEL of 1 mg/kg-d by the DAF of 0.61. The uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 10 for extrapolation from a subchronic to a chronic study). The critical effect is hemosiderosis of the kidney and spleen. The co-critical effect is increased liver weight. The additivity endpoints are hematological (blood) system, hepatic (liver) system, renal (kidney) system.

Cancer.
Not applicable.

Alachlor

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	100	60	9	NA
RFD (mg/kg-day)	--	0.077	0.020	0.0020	--
RSC	--	0.5	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	0.070	0.044	--
Endpoints	--	developmental, renal (kidney) system	hematological (blood) system, hepatic (liver) system, renal (kidney) system	hematological (blood) system, hepatic (liver) system, renal (kidney) system	--

Subp. 7. Chloroform

CAS number: 67-66-3
Year Adopted: 2018
Volatility: High

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 20 µg/L. The RfD is 0.022 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.2. The point of departure is a LOAEL of 50 mg/kg-d, the DAF is 0.13, and the HED is 6.5 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability, and 10 for extrapolation from a LOAEL to a NOAEL. The critical effect is suppression of the humoral immune system (antigen forming cells). The co-critical effects are increased liver weight, liver lesions, decreased body weight gain in pups, increased frequency of incomplete skull ossification in fetuses. The additivity endpoints are developmental, hepatic (liver) system, and immune system.

Subchronic duration.
The proposed subchronic nHRL is 20 µg/L. The subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 20 µg/L. The additivity endpoints are developmental, hepatic (liver) system, and immune system.

Chronic duration.
The proposed subchronic nHRL is 20 µg/L. The chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the proposed chronic nHRL is set equal to the proposed short-term nHRL of 20 µg/L. The additivity endpoints are developmental, hepatic (liver) system and immune system.

Cancer.
Not applicable.

Chloroform

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	20	20 (2)	20 (2)	NA
RFD (mg/kg-day)	--	0.022	(2)	(2)	--

	Acute	Short-term	Subchronic	Chronic	Cancer
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	(2)	(2)	--
Endpoints	--	developmental, hepatic (liver) system, immune system	developmental, hepatic (liver) system, immune system	developmental, hepatic (liver) system, immune system	--

Subp. 7a. Clothianidin

CAS number: 210880-92-5 (former CAS number: 205510-53-8)
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 200 µg/L. The RfD is 0.093 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The point of departure is a NOAEL of 12 mg/kg-d, the DAF is 0.23, and the HED is 2.8 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effect is decreased pup body weight gain. The co-critical effect is decreased body weight gain in pregnant adult rats. The additivity endpoint is developmental.

Subchronic duration.
The proposed subchronic nHRL is 200 µg/L. The subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 200 µg/L. The additivity endpoint is developmental.

Chronic duration.
The proposed chronic nHRL is 200 µg/L. Because the chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period, the proposed chronic nHRL is set equal to the proposed short-term nHRL of 200 µg/L. The additivity endpoint is developmental.

Cancer.
Not applicable.

Clothianidin

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	200	200 (2)	200 (2)	NA
RFD (mg/kg-day)	--	0.093	(2)	(2)	--
RSC	--	0.5	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--

	Acute	Short-term	Subchronic	Chronic	Cancer
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	(2)	(2)	--
Endpoints	--	developmental	developmental	developmental	--

Subp. 8. Cyanazine

CAS number: 21725-46-2
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
The proposed acute nHRL is 3 µg/L. The RfD is 0.0015 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The point of departure is a NOAEL of 1.0 mg/kg-d, the DAF is 0.46, and the HED is 0.46 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability and 10 for database uncertainty [neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed]). The critical effect is increased post-implantation loss. There are no co-critical effects. The additivity endpoints are developmental and female reproductive system.

Short-term duration.
The proposed short-term nHRL is 3 µg/L. The RfD is 0.0015 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The point of departure is a NOAEL of 1.0 mg/kg-d, the DAF is 0.46, and the HED is 0.46 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability and 10 for database uncertainty [neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed]). The critical effect is alterations in fetal ossification sites and decreased litter size. The co-critical effects are increased post implantation loss, altered fetal skeletal ossification, increased relative brain weight and decreased relative kidney weight in weanlings, decreased adult body weight gain and food intake. The additivity endpoints are developmental and female reproductive system.

Subchronic duration.
The proposed subchronic nHRL is 3 µg/L. The RfD is 0.0012 mg/kg-d and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The point of departure is a NOAEL of 0.625 mg/kg-d, the DAF is 0.59, and the HED is 0.37 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 10 for database uncertainty [neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed]). The critical effects are decreased adult body weight

and body weight gain, and increased relative liver and kidney weights in adults. The co-critical effects are increased post implantation loss, altered fetal skeletal ossification, increased relative brain weight and decreased relative kidney weight in weanlings, and decreased adult body weight gain and food intake. The additivity endpoints are developmental, female reproductive system, hepatic (liver) system, and renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 1 µg/L. The RfD is 0.00022 mg/kg-d and the intake rate is 0.044 L/kg-d. The RSC is 0.2. The HED is 0.067 mg/kg-d, calculated by multiplying the POD NOAEL of 0.259 mg/kg-d by the DAF of 0.26. The uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 10 for database uncertainty [neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed]). The critical effects are significant decrease in adult mean body weight and body weight gain, and decreased food consumption and food efficiency. The co-critical effects are decreased body weight gain in adults, and reduced growth and food consumption. There are no additivity endpoints.

Cancer.
Not applicable.

Cyanazine

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	3	3	3	1	NA
RFD (mg/kg-day)	0.0015	0.0015	0.0012	0.00022	--
RSC	0.5	0.5	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.285	0.285	0.070	0.044	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Endpoints	developmental, female reproductive system	developmental, female reproductive system	developmental, female reproductive system, hepatic (liver) system, renal (kidney) system	None	--

Subp. 9. *cis*-1,2-Dichloroethylene

CAS number: 156-59-2
Year Adopted: 2018
Volatility: High

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 20 µg/L. The RfD is 0.033 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.2. The $BMDL_{10}$ is 43.3 mg/kg-d, the DAF is 0.23, and the HED is 9.9 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 10 for database uncertainty related to a lack of reproductive, developmental, neurological, or immune testing, as well as a lack of testing in species other than the rat). Critical effects are increased liver weights in females. There are no co-critical effects. The additivity endpoint is hepatic (liver) system.

Subchronic duration.
The proposed subchronic nHRL is 10 µg/L. The RfD is 0.0043 mg/kg-d and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The $BMDL_{10}$ is 5.1 mg/kg-d, the DAF is 0.25, and the HED is 1.28 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 10 for database uncertainties related to a lack of reproductive, developmental, neurological, or immune testing, as well as a lack of testing in species other than the rat). Critical effects are increased kidney weights in males. There are no co-critical effects. The additivity endpoint is renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 6 µg/L. The RfD is 0.0013 mg/kg-d and the intake rate is 0.044 L/kg-d. The RSC is 0.2. The $BMDL_{10}$ is 5.1 mg/kg-d, the DAF is 0.25, and the HED is 1.28 mg/kg-d. The total uncertainty factor is 1000 (3 for interspecies differences

[for toxicodynamics], 10 for intraspecies variability, 3 for extrapolation from a subchronic study to a chronic study, and 10 for database uncertainties related to a lack of reproductive, developmental, neurological, or immune testing, as well as a lack of testing in species other than the rat). The critical effect is increased kidney weights in males. There are no co-critical effects. The additivity endpoint is renal (kidney) system.

Cancer.
Not applicable.

***cis*-1,2-Dichloroethylene**

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	20	10	6	NA
RFD (mg/kg-day)	--	0.033	0.0043	0.0013	--
RSC	--	0.2	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	0.070	0.044	--
Endpoints	--	hepatic (liver) system	renal (kidney) system	renal (kidney) system	--

Subp. 10a. 2,4-Dichlorophenoxyacetic acid (2,4-D)

CAS number: 94-75-7
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 30 µg/L. The RfD is 0.048 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 21 mg/kg-d, the DAF is 0.23, and the HED is 4.8 mg/kg-d. The total uncertainty factor is 100 (10 for interspecies differences [for toxicokinetic portion retained after DAF application due to remaining uncertainty] and 10 for intraspecies variability). Critical effects are increased thyroid stimulating hormone in pregnant rats and decreased adrenal weight and thyroxine in offspring. Co-critical effects are increased skeletal abnormalities in offspring and decreased offspring body weight. The additivity endpoints are adrenal, developmental, and thyroid (E).

Subchronic duration.
The proposed subchronic nHRL is 30 µg/L. The subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 30 µg/L. The additivity endpoints are adrenal, developmental and thyroid (E).

Chronic duration.
The proposed chronic nHRL is 30 µg/L. Because the chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period, the proposed chronic nHRL is set equal to the proposed short-term nHRL of 30 µg/L. The additivity endpoints are adrenal, developmental and thyroid (E).

Cancer.
Not applicable.

2,4-Dichlorophenxoyacetic acid

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	--	30	30 (2)	30 (2)	NA
RFD (mg/kg-day)	--	0.048	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--

	Acute	Short-term	Subchronic	Chronic	Cancer
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	(2)	(2)	--
Endpoints	--	adrenal, developmental, thyroid (E)	adrenal, developmental, thyroid (E)	adrenal, developmental, thyroid (E)	--

Subp. 11. Dieldrin

CAS number: 60-57-1
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 0.2 µg/L. The RfD is 0.00011 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The POD is a NOAEL of 0.01 mg/kg-d, the DAF is 0.32, and the HED is 0.0032 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effect is impaired learning. Co-critical effects are decreased pup viability, increased preweaning pup mortality, decreased antigen processing by alveolar macrophages, decreased tumor cell-killing ability. The additivity endpoints are developmental, immune system, and nervous system.

Subchronic duration.
The proposed subchronic nHRL is 0.2 µg/L. The subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 0.2 µg/L. The additivity endpoints are developmental, immune system, and nervous system.

Chronic duration.
The proposed chronic nHRL is 0.2 µg/L. The RfD is 0.000043 mg/kg-d and the intake rate is 0.044 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 0.005 mg/kg-d, the DAF is 0.26, and the HED is 0.0013 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability). The critical effect is increased relative liver weight. The co-critical effects are cerebral edema and small foci degeneration, decreased litter size, increased relative liver weight, decreased

antigen processing by alveolar macrophages, and decreased tumor cell-killing ability. The additivity endpoints are developmental, hepatic (liver) system, immune system, and nervous system.

Cancer.
The proposed cHRL value is 0.006 µg /L. The cancer classification is Group B2, probable human carcinogen. The cancer slope factor is 16 $(mg/kg\text{-}d)^{-1}$ based on a 1993 EPA assessment. The Lifetime Adjustment Factor is 2.5, and the intake rate is 0.044 L/kg-day. The tumor site is the liver.

Dieldrin

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	0.2	0.2 (2)	0.2	0.006
RFD (mg/kg-day)	--	0.00011	(2)	0.000043	--
RSC	--	0.5	(2)	0.2	--
SF (per mg/kg-day)	--	--	--	--	16
ADAF or $AF_{lifetime}$	--	--	--	--	2.5
Intake Rate (L/kg-day)	--	0.285	(2)	0.044	0.044
Endpoints	--	developmental, immune system, nervous system	developmental, immune system, nervous system	developmental, hepatic (liver) system, immune system, nervous system	cancer

Subp. 11f. Dinoseb

CAS number: 88-85-7
Year Adopted: 2018
Volatility: Moderate

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 8 µg/L. The RfD is 0.0048 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The POD is a LOAEL of 6.52 mg/kg-d, the DAF is 0.22, and the HED is 1.43 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicokinetics],10 for intraspecies variability, 3 for the use of a LOAEL instead of a NOAEL, and 3 for database uncertainty for lack of an adequate multigenerational study and because the current studies were unable to identify a NOAEL). Critical effects are increased number of fetuses with skeletal variations and short supernumerary ribs. Co-critical effects are decreased pup survival at birth, decreased maternal body weight, decreased fetal body weight, decreased body weight gain during pregnancy, decreased body weight of live fetuses, increased number of fetuses with external malformations, increased incidence of micropthalmia, increased number of skeletal malformations, and decreased placenta weight. The additivity endpoint is developmental.

Subchronic duration.
The proposed subchronic nHRL is 8 µg/L. Because the subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 8 µg/L. The additivity endpoint is developmental.

Chronic duration.
The proposed chronic nHRL is 8 µg/L. Because the chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period, the proposed chronic nHRL is set equal to the proposed short-term nHRL of 8 µg/L. The additivity endpoint is developmental.

Cancer.
Not applicable.

Dinoseb

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	8	8 (2)	8 (2)	NA

	Acute	Short-term	Subchronic	Chronic	Cancer
RFD (mg/kg-day)	--	0.0048	(2)	(2)	--
RSC	--	0.5	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	(2)	(2)	--
Endpoints	--	developmental	developmental	developmental	--

Subp. 12b. *S*-Ethyl-*N*,*N*-dipropylthiocarbamate (ETPC)

CAS number: 759-94-4
Year Adopted: 2018
Volatility: Moderate

Acute duration.
The proposed acute duration nHRL is 300 µg/L. The RfD is 0.16 mg/kg-d and the intake rate is 0.285 L/kg-d. The POD is a LOAEL of 200 mg/kg-d, DAF is 0.16, and the HED is 48 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies extrapolation [for toxicodynamics], 10 for intraspecies variability, 10 for extrapolation from a LOAEL to a NOAEL due to the severity of the effect [brain necrosis]). The critical effect is necrosis of the pyriform/entorhinal cortex and/or dentate gyrus of the brain. There are no co-critical effects. The additivity endpoint is nervous system.

Short-term duration.
The proposed short-term nHRL is 300 µg/L. The RfD is 0.16 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The POD is a NOAEL of 21.9 mg/kg-d, the DAF is 0.22, and the HED is 4.8 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies extrapolation [for toxicodynamics] and 10 for intraspecies variability). Critical effects are decreased pup weight at postnatal day 1, clinical signs of neurotoxicity in dams at

parturition and increased whole litter losses. Co-critical effects are decreased pup body weight and decreased pup body weight gain. The additivity endpoints are developmental, female reproductive system, and nervous system.

Subchronic duration.
The proposed subchronic nHRL value is 90 µg/L. The RfD is 0.033 mg/kg-d and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The POD for females is a NOAEL of 5 mg/kg-d, and for males the POD is a NOAEL is 4 mg/kg-d. The DAF is 0.22 and 0.24 for females and males, respectively. The HED is calculated by taking one half of the sum of both the female and male HEDs. (That is: ((female POD × female DAF) + (male POD × male DAF))÷2). The HED is 1.0 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effect is myocardial degeneration. There are no co-critical effects. The additivity endpoint is cardiovascular system.

Chronic duration.
The proposed chronic nHRL value is 40 µg/L. The RfD is 0.0083 mg/kg-d. The POD is a LOAEL of 9 mg/kg-d, the DAF is 0.28, and the HED is 2.5 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies extrapolation [for toxicodynamics], 10 for intraspecies variability, 10 for extrapolation from LOAEL to NOAEL because the effects were severe). The critical effect is cardiomyopathy and the co-critical effect is myocardial degeneration. Additivity endpoint is cardiovascular system.

Cancer.
Not applicable.

***S*-Ethyl-*N*,*N*-dipropylthiocarbamate (EPTC)**

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	300	300	90	40	NA
RFD (mg/kg-day)	0.16	0.16	0.033	0.0083	--
RSC	0.5	0.5	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.285	0.285	0.070	0.044	--
Endpoints	nervous system	developmental, female reproductive system, nervous system	cardiovascular system	cardiovascular system	--

Subp. 12d. Fluoranthene

CAS number: 206-44-0
Year Adopted: 2018
Volatility: Low

Acute duration.
Not derived because of insufficient data.

Short-term duration.
Not derived because of insufficient data.

Subchronic duration.
The proposed subchronic nHRL value is 200 µg/L. The RfD is 0.053 mg/kg-d and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{10}$ of 124 mg/kg-d, the DAF is 0.13, and the HED is 16 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 10 for database uncertainty due to lack of reproductive and developmental studies). The critical effect is nephropathy. The co-critical effects are increased relative liver weight and increased serum glutamic-pyruvic transaminase (SGPT). The additivity endpoints are hepatic (liver) system and renal (kidney) system.

Chronic duration.
The proposed chronic nHRL value is 70 µg/L. The RfD is 0.016 mg/kg-d and the intake rate is 0.044 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{10}$ of 124 mg/kg-d, based on a U.S. Environmental Protection Agency subchronic study. The DAF is 0.13 and the HED is 16 mg/kg-d. The total uncertainty factor is 1000 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 3 for extrapolation from a subchronic to chronic study, and 10 for database uncertainty due to lack of reproductive and developmental studies). The critical effect is nephropathy. The co-critical effects are increased relative liver weight and increased SGPT. The additivity endpoint is hepatic (liver) system and renal (kidney) system.

Cancer.
Not applicable.

Fluoranthene

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	200	70	NA
RFD (mg/kg-day)	--	--	0.053	0.016	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--

	Acute	Short-term	Subchronic	Chronic	Cancer
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	0.070	0.044	--
Endpoints	--	--	hepatic (liver) system, renal (kidney) system	hepatic (liver) system, renal (kidney) system	--

Subp. 14b. Perfluorobutyrate

CAS number: 375-22-4
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 7 µg/L. The RfD is 0.0038 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The POD is a $BMDL_{10}$ of 3.01 mg/kg-d, the DAF is a chemical-specific toxicokinetic adjustment of 8. The HED is 0.38 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies extrapolation [for toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty [study did not identify a NOAEL or acceptable BMDL10 for thyroid effects. A multigeneration reproductive study has not been conducted, however the database does include an extended one generation developmental study]). The critical effect is decreased cholesterol. Co-critical effects are increased relative thyroid weight, decreased serum total thyroxine (TT4), and decreased dialysis free thyroxine (dFT4). The additivity endpoints are hepatic (liver) system and thyroid (E).

Subchronic duration.
The proposed subchronic nHRL value is 7 µg/L. The subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 7 µg/L. The additivity endpoints are hepatic (liver) system and thyroid (E).

Chronic duration.
The proposed chronic nHRL value is 7 µg/L. The chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the proposed chronic nHRL is set equal to the proposed short-term nHRL of 7 µg/L. The additivity endpoints are hepatic (liver) system and thyroid (E).

Cancer:
Not applicable.

Perfluorobutyrate

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	7	7 (2)	7 (2)	NA
RFD (mg/kg-day)	--	0.0038	(2)	(2)	--
RSC	--	0.5	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	(2)	(2)	--
Endpoints	--	hepatic (liver) system, thyroid (E)	hepatic (liver) system, thyroid (E)	hepatic (liver) system, thyroid (E)	--

Subp. 15. Perfluorooctane Sulfonate (PFOS) and Salts

CAS number: 1763-23-1; 29081-56-9; 70225-14-8; 2795-39-3; 29457-72-5
Year Adopted: 2018
Volatility: Nonvolatile

Note: PFOS bioaccumulates in serum, crosses the placenta, and is excreted into breastmilk. Serum concentrations are the best measure of internal dose and are therefore considered to be the most appropriate basis for deriving an RfD that is protective of potential health effects. Further, research has shown that for infants whose only source of milk is breastmilk (i.e., a breastfed infant), breastmilk can be a major source of exposure to PFOS, resulting in infant serum concentrations that are higher than maternal concentrations. To ensure that MDH's revised health-based water guidance values were adequately protective of infants, a one-compartment toxicokinetic (TK) model was developed to predict serum concentrations.

The TK model used the same parameters as the standard equation: RfD (represented by the internal measure, an estimated serum concentration associated with the RfD), an RSC, and an upper-end fluid intake rate. The model predicted serum concentrations from birth through attainment of steady-state conditions (rate of intake reached equilibrium with rate of elimination) at a given water level. The model was run in an iterative manner until a water level that resulted in serum concentrations at or below the portion allotted to drinking water (i.e., RSC x serum concentration associated with the RfD).

Acute duration.
Not applicable.

Short-term duration.
The proposed short-term nHRL value is 0.037 µg/L. The RfD is 0.0000051 mg/kg-d (corresponding serum concentration is 0.063 mg/L). In keeping with MDH's practice, 95th percentile water intake rates (Table 3-1 and 3-3, USEPA 2011) or upper percentile breastmilk intake rates (Table 15-1, USEPA 2011) were used. Breastmilk concentrations were calculated by multiplying the maternal serum concentration by a PFOS breastmilk transfer factor of 1.3%. For the breast-fed infant exposure scenario, a period of exclusive breastfeeding for one year was used as representative of a reasonable maximum exposure scenario. The RSC is 0.5. The POD is a NOAEL of 6.26 mg/L serum concentration, the DAF is 0.000081 L/kg, and the HED is 0.00051 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty [additional studies regarding immunotoxicity are warranted]). The critical effects are decreased pup body weight. The co-critical effects in offspring exposed during development are delayed eye opening, increased sternal defects, changes in lung development, decreased glucose tolerance, increased motor activity and decreased habituation, decreased levels of thyroxine (T4), and decreased survival. In adult animals the co-critical effects liver weight changes accompanied by changes in cholesterol levels and histology; decreased levels of thyroxine (T4); decreased SRBC response, increased NK cell activity, decreased spleen and thymus weight and cellularity. The additivity endpoint are developmental, hepatic (liver) system, immune system, thyroid (E).

Subchronic and Chronic durations.
PFOS is a bioaccumulative chemical. Since short-term exposures have the potential to stay in the body for an extended period of time, a single nHRL value of 0.037 µg/L has been proposed for short-term, subchronic, and chronic durations.

Cancer:
Not applicable.

Perfluorooctane Sulfonate (PFOS) and Salts

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	NA	0.027	0.027	0.027	NA
RFD (mg/kg-day)	--	0.0000051	0.0000051	0.0000051	--
RSC	--	0.5	0.5	0.5	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Intake Rate (L/kg-day)	--	*	*	*	--
Endpoints	--	developmental, hepatic (liver) system, immune system, thyroid (E)	developmental, hepatic (liver) system, immune system, thyroid (E)	developmental, hepatic (liver) system, immune system, thyroid (E)	--

* 95th percentile water intake rates (Tables 3-1 and 3-3, EPA, 2011a) or upper percentile breastmilk intake rates (Table 15-1, EPA, 2011a), and MDH background information

Subp. 16. Perfluorooctanoic Acid (PFOA) and Salts

CAS number: 335-67-1; 335-66-0; 3825-26-1; 2395-00-8; 335-93-3; 335-95-5
Year Adopted: 2018
Volatility: Nonvolatile

Note: PFOA bioaccumulates in serum, crosses the placenta, and is excreted into breastmilk. Serum concentrations are the best measure of internal dose and are therefore considered to be the most appropriate basis for deriving an RfD that is protective of potential health effects. Further, research has shown that for infants whose only source of milk is breastmilk (i.e., a breastfed infant), breastmilk can be a major source of exposure to PFOA, resulting in infant serum concentrations that are higher than maternal concentrations. To ensure that MDH's revised health-based water guidance values were adequately protective of infants, a one-compartment toxicokinetic (TK) model was developed to predict serum concentrations.

The TK model used the same parameters as the standard equation: RfD (represented by the internal measure, an estimated serum concentration associated with the RfD), an RSC, and an upper-end fluid intake rate. The model predicted serum concentrations from birth through attainment of steady-state conditions (rate of intake reached equilibrium with rate of elimination) at a given water level. The model was run in an iterative manner until a water level that resulted in serum concentrations at or below the portion allotted to drinking water (i.e., RSC x serum concentration associated with the RfD).

Acute duration.
Not applicable.

Short-term duration.
The proposed short-term nHRL value is 0.035 µg/L. The RfD is 0.000018 mg/kg-d (corresponding serum concentration is 0.13 mg/L). In keeping with MDH's practice, 95th percentile water intake rates (Table 3-1 and 3-3, EPA, 2011a) or upper percentile breastmilk intake rates (Table 15-1, EPA, 2011a) were used. Breastmilk concentrations

were calculated by multiplying the maternal serum concentration by a PFOA breastmilk transfer factor of 5.2%. The intake rates and breastfeeding period of one year were used as representative of a reasonable maximum exposure scenario. The RSC is 0.5. The POD is a LOAEL of 38 mg/L serum concentration, the DAF is 0.00014 L/kg, and the HED is 0.0053 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], and 10 for intraspecies variability. With the exception of accelerated preputial separation (PPS), the effects observed at the LOAEL were mild. A LOAEL-to-NOAEL uncertainty factor of 3 was used, along with a database uncertainty factor of 3 [for the lack of an acceptable 2-generation study]). The critical effects are delayed ossification, accelerated PPS in male offspring, trend for decreased pup body weight, and increased maternal liver weight. The co-critical effects in offspring exposed during development are changes in liver weight, histology, and triglycerides, and delayed mammary gland development. The co-critical effects in adult animals are liver weight changes accompanied by changes in liver enzyme levels, changes in triglyceride and cholesterol levels, and microscopic evidence of cellular damage, decreased spleen weight, decreased spleen lymphocytes, and decreased IgM response, and kidney weight changes. The additivity endpoint are developmental, hepatic (liver) system, immune system, and renal (kidney) system.

Subchronic and Chronic durations.
PFOS is a bioaccumulative chemical. Since short-term exposures have the potential to stay in the body for an extended period of time a single nHRL value of 0.037 µg/L has been proposed for short-term, subchronic, and chronic durations.

Cancer:
Not applicable.

Perfluorooctanoic Acid (PFOA) and Salts

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	NA	0.035	0.035	0.035	NA
RFD (mg/kg-day)	--	0.000018	0.000018	0.000018	--
RSC	--	0.5	0.5	0.5	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	*	*	*	--
Endpoints	--	developmental, hepatic (liver) system, immune	developmental, hepatic (liver) system, immune	developmental, hepatic (liver) system, immune	--

	Acute	Short-term	Subchronic	Chronic	Cancer
		system, renal (kidney) system	system, renal (kidney) system	system, renal (kidney) system	

* 95th percentile water intake rates (Tables 3-1 and 3-3, EPA, 2011a) or upper percentile breastmilk intake rates (Table 15-1, EPA, 2011a), and MDH background information.

Subp. 16a. Pyrene

CAS number: 129-00-0
Year Adopted: 2018
Volatility: Moderate

Acute duration.
Not derived because of insufficient data.

Short-term duration.
Not derived because of insufficient data.

Subchronic duration.
The proposed subchronic nHRL value is 90 µg/L. The RfD is 0.033 mg/kg-d, and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 75 mg/kg-d, the DAF is 0.13, and the HED is 10 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 10 for database uncertainty due to lack of reproductive/developmental studies and a lack of studies in a second species). The critical effects are nephropathy in female mice and decreased kidney weight. There is no co-critical effect. The additivity endpoint is renal (kidney) system.

Chronic duration.
The proposed chronic nHRL value is 50 µg/L. The RfD is 0.010 mg/kg-d, and the intake rate is 0.044 L/kg-d. The POD is a NOAEL of 75 mg/kg-d. The DAF is 0.13 and HED is 10 mg/kg-d. The RSC is 0.2.The total uncertainty factor is 1000 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 3 for extrapolation from a subchronic study to a chronic study [due to the lack of severity of the critical effect], 10 for database uncertainty [for lack of reproductive and developmental studies and a lack of studies in a second species]). The critical effects are nephropathy in female mice and decreased kidney weight. There is no co-critical effect. The additivity endpoint is renal (kidney) system.

Cancer:
Not applicable.

Pyrene

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	90	50	NA
RFD (mg/kg-day)	--	--	0.033	0.010	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	0.070	0.044	--
Endpoints	--l	--	renal (kidney) system	renal (kidney) system	--

Subp. 18a. Tetrahydrofuran

CAS number: 109-99-9
Year Adopted: 2018
Volatility: Moderate

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 600 µg/L. The RfD is 0.82 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 371 mg/kg-d, the DAF is 0.22, and the HED is 82 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies extrapolation [for toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty [oral data gaps include assessment of neurological effects and evaluation in a second species as limited oral data suggest rat may not be the most sensitive species]). Critical effects are decreased pup body weight gain and delayed eye opening. Co-critical effects are decreased pup body weight gain and decreased maternal body weight gain during gestation. The additivity endpoint is developmental.

Subchronic duration.
The proposed subchronic nHRL is 600 µg/L. The subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 600 µg/L. The additivity endpoint is developmental.

Chronic duration.
The proposed chronic nHRL is 600 µg/L. Because the chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period, the proposed chronic nHRL is set equal to the proposed short-term nHRL of 600 µg/L. The additivity endpoint is developmental.

Cancer:
Not derived.

Tetrahydrofuan

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	600	600 (2)	600 (2)	NA
RFD (mg/kg-day)	--	0.82	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	(2)	(2)	--
Endpoints	--	developmental	developmental	developmental	--

Subp. 18b. Thiamethoxam

CAS number: 153719-23-4
Year Adopted: 2018
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 400 µg/L. The RfD is 0.25 mg/kg-d and the intake rate is 0.285 L/kg-d. The RSC is 0.5. The POD is a NOAEL of 34.5 mg/kg-d, the DAF is 0.22, and the HED is 7.6 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies extrapolation [for toxicodynamics] and 10 for intraspecies variability). Critical effects are reduced pup body weight. Co-critical effects are hepatocyte hypertrophy, maternal death during pregnancy accompanied by hemorrhage of the uterus and bloody discharge in the perineal area, decreased number of animals with live fetuses, decreased fetal body weight, and increased fetal skeletal anomalies (fused sternebrae). The additivity endpoints are developmental, female reproductive system, and hepatic (liver) system.

Subchronic duration.
The proposed subchronic nHRL value is 200 µg/L. The RfD is 0.057 mg/kg-d, and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 4.05 mg/kg-d, the DAF is 0.43, and the HED is 1.7 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effects are seminiferous tubule atrophy. There is no co-critical effect. The additivity endpoint is male reproductive system.

Chronic duration.
The proposed chronic nHRL is 200 µg/L. Because the chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period, the proposed chronic nHRL is set equal to the proposed subchronic nHRL of 200 µg/L. The additivity endpoint is male reproductive system.

Cancer:
Not applicable.

Thiamethoxam

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	400	200	200 (3)	NA
RFD (mg/kg-day)	--	0.25	0.057	(3)	--
RSC	--	0.5	0.2	(3)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.285	0.070	(3)	--
Endpoints	--	developmental, female reproductive system, hepatic (liver) system	male reproductive system	male reproductive system	--

Subp. 19. 1,1,1-Trichloroethane

CAS number: 71-55-6
Year Adopted: 2018
Volatility: High

Acute duration.
Not derived because of insufficient information.

Short-term duration.
Not derived because of insufficient information.

Subchronic duration.
The proposed subchronic nHRL value is 9,000 µg/L. The RfD is 3.0 mg/kg-d, and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{10}$ of 2,155 mg/kg-d, the DAF is 0.14, and the HED is 302 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability and 3 for database uncertainty [inadequate evaluation of neurological endpoint {identified as critical endpoint in inhalation studies}]). The critical effect is decreased adult body weight. The co-critical effects are decreased adult body weight/weight gain, decreased relative liver weight and decreased epididymal spermatozoal concentration. The additivity endpoint are hepatic (liver) system and male reproductive system.

Chronic duration.
The proposed chronic nHRL value is 5,000 µg/L. The RfD is 1.0 mg/kg-d, and the intake rate is 0.044 L/kg-d. The POD is a $BMDL_{10}$ of 2,155 mg/kg-d. The DAF is 0.14 and HED is 302 mg/kg-d. The RSC is 0.2.The total uncertainty factor is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, 3 for sub-chronic to chronic extrapolation, and 3 for database uncertainty [inadequate evaluation of neurological endpoint {identified as critical endpoint in inhalation studies}]). The critical effect is decreased adult body weight. The co-critical effects are decreased adult body weight/weight gain, decreased relative liver weight, and decreased epididymal spermatozoal concentration. The additivity endpoints are hepatic (liver) system and male reproductive system.

Cancer.
Not applicable.

1,1,1-Trichloroethane

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	9,000	5,000	NA
RFD (mg/kg-day)	--	--	3.0	1.0	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--

	Acute	Short-term	Subchronic	Chronic	Cancer
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	0.070	0.044	--
Endpoints	--	--	hepatic (liver) system, male reproductive system.	hepatic (liver) system, male reproductive system.	--

Subp. 23. Vinyl Chloride

CAS number: 75-01-4
Year Adopted: 2018
Volatility: High

Acute duration.
Not derived because of insufficient information.

Short-term duration.
Not derived because of insufficient information.

Subchronic duration.
The proposed subchronic nHRL value is 90 µg/L. The RfD is 0.033 mg/kg-d and the intake rate is 0.070 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 10 ppm and the HED is 1 mg/kg-d based on chemical-specific PBPK modeling. The total uncertainty factor is 30 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effects are increased liver weight, hypertrophy, and hepatocellular foci. The co-critical effect is increased liver weight. The additivity endpoint is hepatic (liver) system.

Chronic duration.
The proposed chronic nHRL value is 10 µg/L. The RfD is 0.0030 mg/kg-d and the intake rate is 0.044 L/kg-d. The POD is a NOAEL of 0.13 mg/kg-d. The HED is 0.09 mg/kg-d based on chemical-specific PBPK modeling. The RSC is 0.2.The total uncertainty factor is 30 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability).

The critical effects are liver cell polymorphism and liver cyst formation. The co-critical effect is increased liver weight. The additivity endpoint is hepatic (liver) system.

Cancer.
The proposed cHRL value is 0.2 µg /L. The cancer classification is Known Human Carcinogen by EPA 2000. The cancer slope factor is 1.4 $(mg/kg\text{-}d)^{-1}$. This is based on total of liver angiosarcoma, hepatocellular carcinoma, and neoplastic nodules - adjusted for continuous lifetime exposure from birth in female Wistar rats reported by (Feron et al. 1981). The lifetime Adjustment Factor is 1. The intake rate is 0.044 L/kg-day. The tumor site is (hepatic) liver.

Vinyl Chloride

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	90	10	0.2
RFD (mg/kg-day)	--	--	0.033	0.0030	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)					1.4
ADAF or $AF_{lifetime}$	--	--	--	--	1
Intake Rate (L/kg-day)	--	--	0.070	0.044	0.044
Endpoints	--	--	hepatic (liver) system	hepatic (liver) system	cancer

2. Proposed Deletions: Health Risk Limits (Minnesota Rules, *parts 4717.7500 and 4717.7860*)

Based on MDH's recent review of health-based guidance values listed in Minnesota Rules, parts 4717.7500 and 4717.7860, MDH intends to repeal five outdated HRLs adopted into rule in 1993-1994, 10 of the HRLs adopted into rule in 2009, and 3 HRLs adopted into rule in 2011. The specific subparts to be repealed are noted below:

Subparts to be repealed from part 4717.7500. (updated values for this chemical, shown in Section V B. of this SONAR, will be added to part 4717.7860):

Subp. 2. Acenaphthene

Subp. 45. 2,4-Dichlorophenoxyacetic acid (2,4-D)

Subp. 51. S-Ethyl-N,N-dipropylthiocarbamate (EPTC)

Subp. 53. Fluoranthene

Subp. 75. Pyrene

Subparts to be repealed from part 4717.7860. Repealed guidance values will be replaced with updated guidance values (updated values for this chemical, shown in Section V B. of this SONAR, will be added back to part 4717.7860):

Subp. 3. Acetochlor

Supb. 3a. Acetochlor ESA

Supb. 3b. Acetochlor OXA

Subp. 4. Alachlor

Subp. 7. Chloroform

Subp. 8. Cyanazine

Subp. 9. cis-1,2-Dichloroethylene

Subp. 11. Dieldrin

Subp. 14b. Perfluorobutyrate (PFBA)

Subp. 15. Perfluorooctane sulfonate (PFOS) and salts.

Subp. 16. Perfluorooctanoic acid (PFOA) and salts

Subp. 19. 1,1,1-Trichloroethane

Subp. 23. Vinyl Chloride

C. REGULATORY ANALYSIS

This section discusses the regulatory factors, the performance-based rules, the additional notice plan, and the impact of the proposed rules, as required by Minnesota Statutes, section 14.131.

Minnesota Statutes, section 14.131, sets out eight factors for regulatory analysis that agencies must include in the SONAR. This section discusses each of the factors.

1. Classes of persons probably affected by the proposed rules, including classes that will bear the costs and classes that will benefit

Because the subject of these rules is the quality of groundwater used as drinking water in Minnesota, the proposed amendments could potentially affect nearly all persons in Minnesota. Those affected depends on how state agencies charged with protecting Minnesota's environment and water resources apply HRL values.

Generally, HRLs serve as benchmarks in state water-monitoring and contamination-response programs that protect all Minnesotans' health. In addition, HRL values and related chemical data are incorporated into other state rules that also protect Minnesota's water resources (e.g., MPCA's solid waste and surface water rules), thus benefitting the entire state.

More specifically, the amendments can affect individuals or populations when a public or private water supply becomes contaminated and federal MCLs are unavailable. In these instances, the responding agency estimates the risks from consuming contaminated water using HRL values, and advises the regulated party, the responsible governmental unit, the water operator, or the public on how to eliminate or reduce risk.

Monetary costs for applying the HRLs could affect those found responsible for contaminating or degrading groundwater, or communities that use public funds to remediate contaminated water.

The proposed amendments provide protection to human life stages that are sensitive or highly exposed. Risk managers have the option of applying HRL values to the general population, or adjusting them for smaller groups or "sub-populations."

2. The probable costs of implementation and enforcement and any anticipated effect on state revenues

The proposed amendments *do not* have any direct impact on state revenues. There are no fees associated with the rules. The amendments simply provide health-based levels for certain water contaminants. Agencies that apply HRL values will need to determine costs on a case-by-case basis.

3. A determination of whether there are less costly or less intrusive methods for achieving the purpose of the proposed rule

AND

4. A description of any alternative methods for achieving the purpose of the proposed rule that were seriously considered by the agency and the reasons why they were rejected in favor of the proposed rule

Minnesota Rules, parts 4717.7500, 4717.7850 and 4717.7860 establish HRL values, which are uniform, science-based values that protect the health of people who drink groundwater.

Unlike other rules that regulate citizen or industry activities, this HRL rules revision applies the specific methodology previously adopted to identified contaminants and calculates and adopts the calculated values themselves. As described in Section II. A. above, Minnesota Statutes, section 103H.201, subdivision 1, prescribes the methods that

the Commissioner must use in deriving HRL values. In paragraph (c) the statute requires that the Commissioner establish HRLs for contaminants that are not carcinogens, "using United States Environmental Protection Agency risk assessment methods using a reference dose, a drinking water equivalent, and a relative source contribution factor."

Likewise, in paragraph (d) the Commissioner must derive HRL values for contaminants that are known or probable carcinogens "from a quantitative estimate of the chemical's carcinogenic potency published by the United States Environmental Protection Agency and determined by the commissioner to have undergone thorough scientific review."

In addition, Minnesota Statutes, section 144.0751, provides further direction. Per this provision, safe drinking water standards must "be based on scientifically acceptable, peer-reviewed information" and "include a reasonable margin of safety to adequately protect the health of infants, children, and adults…" The section also lists risks to specific health outcomes that the commissioner must consider.

Thus the statutes limit MDH's discretion about how it may determine allowable amounts of water contaminants. In 2009, the Commissioner adopted the methodology for carrying these directives out, which is now contained in Minnesota Rules, parts 4717.7820 and 4717.7830. This rulemaking project adds new values or repeals old values by applying the methodology adopted in 2009, which is not under review at present. MDH regularly adopts the specific HRL values through a process designed to inform and engage the public. MDH currently follows an approximately two-year cycle for developing and adopting updated or new HRL values and repealing outdated values. MDH uses this schedule to ensure the HRL values reflect the most up-to-date toxicity information.

Because of the specific nature of these rules, the method for achieving the proposed rules' purpose has already been established by the 2009 rulemaking. There are no less costly or less intrusive methods for adopting these new chemical values. Similarly, the fact that the method was set in the 2009 rulemaking precludes alternative methods for achieving the purpose of the proposed rule. The only choices that the agency considered were the selection of the specific chemicals for this round of revisions.

HRL values, before being adopted into rule, are often initially derived at other agencies' request. MDH derives this guidance, known as a Health-Based Value (HBV), using the same methodology as an HRL. While all HRL values were initially HBV values, not all HBV values are adopted into rule as HRLs.

The HBV values may be less costly because the agency has not used resources adopt them into rule. In practice, risk managers may use HBV values in the same way as HRL values. However, because HBV values have not been adopted into rule, state agencies and the regulated community may consider them to be transient in nature and therefore not give them the same weight they would give adopted HRLs. Both regulators and risk managers consider HRLs values more useful in long-term planning because they are

considered more permanent. Adopting the guidance into rule standardizes the use of guidance statewide, and provides the authority and uniformity of rule.

HBVs for groundwater contaminants that MDH has derived through the HRL standard methodology are eligible for rule adoption. MDH rejects the possibility of leaving the proposed chemicals in their outdated or HBV status.

5. The probable costs of complying with the proposed rule

Because the HRL rules must establish limits for contaminants, rather than specify how to apply the health-protective numbers, MDH does not apply or enforce them. While MDH cannot quantifying probable costs of complying with the proposed amendments, MDH can describe generally how applying its HRLs can lead to costs for parties regulated by other agencies.

HRL values are only one set of criteria that agency risk managers use to evaluate whether a contaminant's concentration in groundwater poses a risk to health. HRL values are not intended to be bright lines between "acceptable" and "unacceptable" concentrations. MDH derives HRL values using conservative methods so that exposures below an HRL value would present minimal, if any, risk to human health. Similarly, a contaminant concentration above an HRL value, without considering other information, might not indicate a public health problem. However, because the lowest proposed HRL values for eight of the contaminants are lower than the 1993/1994 or 2009 HRL values (i.e., acenaphthene, chloroform, cis-1,2-dichloroethene, 2,4-dichlorophenoxyacetic acid (2,4-D), S-ethyl-N,N-dipropylthiocarbamate (EPTC), fluoranthene, pyrene, 1,1,1-trichloroethane), the cost of remediating or preventing water contamination might increase. The proposed HRL values for the chemicals that lack 1993/1994 or 2009 HRL values are new HRL values. Costs associated with implementation any of these new values are likewise indeterminate for MDH, and must also be evaluated on a case-by-case basis in enforcement circumstances faced by MDH's partners. For these reasons, MDH can merely describe these probable costs for complying in these general terms.

6. The probable costs or consequences of not adopting the proposed rule

Not adopting the proposed amendments would impose immeasurable costs or consequences affecting water. As stated above, Minnesota's groundwater is a primary source of drinking water for many Minnesotans, making the need to protect these waters obvious and imperative. A failure to revise the rules would ignore legislative directives and leave an outdated set of standards in place, providing only limited options for protecting some segments of the population.

Though the state's goal is to prevent water degradation, adopting and applying the new HRLs proposed does not in and of themselves prevent degradation. Some water resources

have already been unintentionally contaminated by releases—by activities that occurred before the source waters' vulnerability to contamination was known; by activities that occurred before certain chemicals were identified as toxic; or before regulations prohibiting releases had been implemented. HRL values allow authorities to evaluate drinking water sources to ensure that there is minimal risk to human health from using them for drinking. A reliable source of water that is safe for human consumption is essential to a state's ability to safeguard a high standard of living for its citizens.

7. Differences between the proposed rule and existing federal regulations, and the need for and reasonableness of each difference

U.S. EPA's Office of Water publishes several sets of drinking water-related standards and health advisories such as Maximum Contaminant Level Goals (MCLGs), MCLs, and lifetime Health Advisories (HAs). While these are similar to MDH-derived HRL values in some respects, they differ in important ways noted below. Furthermore, for any given chemical, the U.S. EPA may have developed all, several, one, or none of these standards and advisories.

MDH-derived HRL values differ from existing federal regulations and advisory values in several ways:

- HRL values are based strictly on human health;
- MDH derives guidance for chemicals that are of high importance specifically to Minnesota;
- MDH has developed more exposure time durations than U.S. EPA;
- MDH derives HRL values explicitly, including a reasonable margin of safety for vulnerable sub-populations (e.g., infants and children, who are potentially at higher risk than adults); and
- In general, MDH can derive guidance more expediently.

While some federal regulations or advisory values might adhere to one or two of the conditions above, none adheres to all conditions.

EPA-derived Maximum Contaminant Level Goals (MCLGs) are advisory values based solely on considerations of human health. However, by definition, the MCLG for any chemical that causes cancer is zero. Because restoring contaminated groundwater to a pristine condition might not be possible, MCLGs do not provide meaningful practical values for MDH's partners to apply to groundwater contaminated by carcinogens.

EPA-derived MCLs are federal standards adopted for the regulation of *public* drinking water in Minnesota. However, MCLs consider the costs required to reduce contaminant

concentrations to a given level and the technological feasibility of reaching that level. The factors that determine economic and technological feasibility for public drinking water systems might not be relevant to *private* drinking water wells or to other sites affected by contamination. The U.S. EPA has developed MCLs for 91 chemicals, with the most recent value developed in 2001. As a result, most MCLs were developed using outdated methods based only on adult intakes and body weight.

EPA-derived Drinking Water Equivalent Levels (DWELs) and Health Advisories (HAs) are estimates of acceptable drinking water levels of non-carcinogens or carcinogens based on health effects information. DWELs and HAs serve as non-regulatory technical guidance for federal, state, and local officials. DWELs assume that all of an individual's exposure to a contaminant is from drinking water. HRL values and lifetime HAs take into account people's exposure via routes other than drinking water, and allocate to drinking water only a portion of an individual's allowable exposure (i.e., incorporate the relative source contribution (RSC) factor). HAs might be derived for exposure durations of one day, ten days, or a lifetime. One-day and ten-day HAs incorporate intake and body-weight parameters appropriate for children but do not incorporate an RSC.

Importantly, the chemicals for which MDH develops guidance are those that MDH and its partners have deemed to be priorities in Minnesota. At the federal level, guidance is developed based on nationwide priorities. At times, because of varying geographic and historical factors, including usage of chemicals, chemicals important nationally may not be as high in priority for Minnesota, and chemicals important to Minnesotans may not be ranked as high nationally. Guidance developed by MDH, however, is often based on requests from Minnesota risk managers who have detected a chemical at locations within the state, or from members of the public who have concerns about specific known or potential contaminants in Minnesota waters.[13]

MDH reviews and prioritizes the Contaminants of Emerging Concern (CEC) nominations to determine which nominated contaminants have the highest impact on Minnesota's drinking water. Those with the highest priority and available toxicity information are selected for full review. In addition, the HRL program within the Health Risk Assessment unit receives nominations from Minnesota state agencies for contaminants that staff find in Minnesota groundwater during monitoring or remediation efforts. Staff from several state agencies prioritize these nominations during an annual meeting. As a result of the input from these other agencies, there are Minnesota HRL values for 141 chemicals that have been found in Minnesota groundwater; there are 91 chemicals for which U.S. EPA has MCLs. This proposed update for 18 existing HRL values and addition of four new HRL values will bring HRLs to a total of 145 chemicals in Minnesota.

[13] Nominations may be submitted via the MDH website at Nominate Chemicals (http://www.health.state.mn.us/divs/eh/risk/guidance/dwec/nominate.cfm). Anyone may submit a nomination.

Minnesota's water guidance also protects more sensitive populations, especially infants and children. The EPA currently derives guidance values primarily for subchronic (from 30 days to 10% of a lifetime) and chronic (more than 10% of a lifetime) duration while MDH derives guidance for acute (one day) and short-term (between one and 30 days) durations in addition to subchronic and chronic durations. Providing guidance for less than subchronic durations helps ensure that risk management decisions protect all exposed individuals.

Further, Minnesota-developed guidance is often available more quickly than guidance developed by U.S. EPA. At times, the EPA's issuance of new guidance can be delayed for various reasons. When Minnesota state agencies or the public requests an HRL guidance value, groundwater contaminants have often already been detected in the state, with potential for human exposure. This obviously increases the need for timely updated or new guidance.

8. An assessment of the cumulative effect of the rule with other federal and state regulations related to the specific purpose of the rule.

As stated in item 7 above, there are no other state and federal rules devoted to the specific purpose of setting allowable water contaminant values for groundwater. The amendments proposed here only build on the regulatory results already established. MDH is not proposing enforceable standards but adopting further guidance for risk managers and our partners to use in their evaluation and mitigation work.

The amendments have no direct regulatory impact because the HRA Unit at MDH does not enforce or regulate the use of health-based guidance. MDH provides recommended values for use by risk assessors and risk managers in making decisions and evaluating health risks. Other programs within MDH or other agencies may independently adopt these health-based values and incorporate them within enforceable requirements related to permitting or remediation activities.

MDH cannot anticipate all the situations in which HRL values might provide meaningful guidance. Nor can MDH anticipate all the factors that its partners might weigh to determine whether applying an HRL value is appropriate. Each agency or program must decide whether to apply an HRL value or whether site-specific characteristics justify deviation from HRL values.

Health-based guidance is only one set of criteria that state water and environmental protection programs use to evaluate contamination. Other state and federal health or environmentally-based rules, laws, or considerations may apply. For example, the federally-implemented MCLs for drinking water are applicable to public water systems. MCL values are legally enforceable under the National Primary Drinking Water Regulations. Further, MCLs are not applicable to private water supplies. Those who consume or work to protect the water from a private well may seek to comply with an HRL or MCL value in the interest of protecting health.

Overall, the cumulative effect of these rules is incremental and will vary on a case-by-case basis, depending on the type of contamination present, the level of threat to human health or the environment, and the requirements of the responsible governmental agency. In some situations the rules may have little or no effect, especially when other laws take precedence or when contamination is already below the HRL value. In another case where an HRL value is exceeded, an agency might invoke its requirement that the responsible party bring the contaminant concentration down to a safe level for consumption. Thus the proposed HRL values will work with those HRLs already adopted to serve as another important evidence-based resource for other agencies to apply when assessing how best to protect Minnesota's drinking water from further degradation, thus protecting the health of all its citizens.

D. PERFORMANCE-BASED RULES

The proposed amendments allow risk managers and stakeholders flexibility in determining how best to protect the public from potentially harmful substances in our groundwater. HRL values provide a scientific and policy context within which the risks posed by a particular situation may be analyzed. Following the risk analysis, risk managers and stakeholders, including other regulatory agencies, may examine the options and make decisions on a course of action. After implementation, they may evaluate outcomes.

E. ADDITIONAL NOTICE

In addition to the notice requirements specified by the Minnesota Administrative Procedures Act (APA) (Minnesota Statutes, sections 14.001 *et seq*.) for the publication of official notices in the *State Register* and related procedures, described below, MDH has or will complete additional notice activities, as follows:

- Before beginning rulemaking, MDH sent a notice on April 7, 2016, via its GovDelivery Water Rules, Guidance and Chemical Review Account, to notify subscribers that MDH was considering HRL rulemaking. The message included a link to a webpage with a list of eligible contaminant guidance values. Comments were encouraged. This email was sent to 3,036 subscribers.

- Request for Comments: On July 28, 2016, two business days before to the Request for Comments publication, MDH made phone calls or sent emails to ten individuals, environmental advocacy organization staff, or trade organization staff who had requested notice about MDH HRL rulemaking activity. The same day, MDH also sent emails to three staff members of other State agencies about the pending Request for Comments. Per request from Minnesota Department of Agriculture (MDA), three additional MDA staff were notified on August 1, 2016. The notices provided information about pending publication of the Request for

Comments, and links to MDH's Rules webpage that contained information about each chemical with water guidance eligible for rulemaking.

MDH published the "Request for Comments" notice in the *Minnesota State Register* on August 1, 2016. The notice provided an overview of possible amendments to the current HRL rules and invited public comment. The notice is available in the *Minnesota State Register*, August 1, 2016 issue: (https://mn.gov/admin/assets/SR41_5 - Accessible_tcm36-263465.pdf) (PDF) The day of the publication, MDH sent out a GovDelivery notice to the 3,052 subscribers of the Water Rules, Guidance and Chemical Review account to provide notice of the Request for Comments publication. A list of the contaminants with guidance under consideration was included in the email, along with links to MDH HRL Rules webpage and to the Request for Comments in the *State Register*.

- MDH HRL rule amendment public meeting: MDH hosted a public meeting on Thursday, September 15, 2016, at the Orville Freeman Building in St. Paul, MN. MDH sent notification about the public meeting via its GovDelivery account for Water Rules, Guidance and Chemical Review on August 22, 2016 to the 3,049 people subscribed to the email at that time. MDH offered a call-in option remote participation during the meeting. There were nine people who attended the meeting in person and two additional people who participated via the phone conference line. Organizations represented by these interested participants included an analytical lab, a public utility, a trade organization, and MDH.

  At this meeting, MDH staff gave an overview of 1) the chemical selection and review process; 2) the types of guidance MDH develops for groundwater contaminants; 3) and the proposed HRL amendments. MDH encouraged attendees to ask questions, engage in discussion with staff and submit written comments. Questions focused on how other agencies applied MDH guidance. Because MDH is only authorized to derive water-based guidance, not apply the guidance, the way other agencies use the guidance is outside of MDH's control. However, MDH can have discussions with regulators to ensure people understand how the guidance is developed and best practices for their use.

  MDH made all meeting materials, including answers to the questions asked at the meeting, available on MDH's HRL rule amendments webpages after the public meeting.[14]

  As of September 1, 2017, MDH has received questions about how to comment on the rules from three parties, one written comment and one request for a meeting.

[14] Materials and handouts for MDH's meeting on the amendments to the rules are available at Public Input: How to Comment (http://www.health.state.mn.us/divs/eh/risk/rules/water/publicinput.html)

MDH responded to all comments and questions, and asked the party who requested the meeting to suggest meeting dates.

- Notice of Intent to Adopt Rules: MDH plans to publish the *Notice of Intent to Adopt Rules –Dual Notice* in the *State Register*. MDH will mail the proposed rules and the *Notice of Intent to Adopt Rules* to the parties listed on MDH's rulemaking list under Minnesota Statutes, section 14.14, subdivision 1a. MDH will also send the *Notice of Intent to Adopt Rules – Dual Notice* and a copy of the SONAR to the Legislature and the Legislative Reference Library. Further, MDH will send a notice to the 3,326 subscribers of its GovDelivery Water Rules, Guidance and Chemical Review account. MDH will also to send information to the offices of interested stakeholders such as water resource interests groups and industry or commerce organizations to distribute to their members at their discretion. Upon request, copies of the proposed rules and the SONAR will be made available at no charge.

MDH's Notice Plan does not include notifying the Commissioner of Agriculture because the rules do not affect farming operations per Minnesota statutes, section 14.111.

MDH will continue to use the following methods to communicate with stakeholders and to make information available during the rules process:

- MDH HRL rule amendment website: MDH created new web pages for the 2016/2018 HRL rule amendment.[15] MDH periodically updates these web pages which include, or will include, information such as: drafts of the proposed amendments to the rules (made available online before MDH's HRL public meeting—see details below), the SONAR, notices requesting public comments, public meeting announcements and related handouts, the rule amendment schedule, and brief explanations about the rulemaking process.

- MDH email subscription service: MDH maintains a free email subscription list for sending updates on water rules and guidance on the chemicals reviewed. Anyone may subscribe through links on the MDH HRL rules amendment webpages. MDH routinely sends updates on the HRL rule amendment to the email subscribers. The updates include information such as: information on new or updated guidance values for specific chemicals, the publication of notices requesting comments, announcements regarding the public meeting, and the availability of drafts of the proposed rules and the SONAR. As of September 12, 2017, MDH's Groundwater Rules, Guidance and Chemical Review email subscription account had 3,326 subscribers.

[15] MDH's amendments to the rules on Health Risk Limits for Groundwater are available at: Overview and Links (http://www.health.state.mn.us/divs/eh/risk/rules/water/overview.html)

F. IMPACT OF PROPOSED RULES

1. Consultation with MMB on Local Government Impact

As required by Minnesota Statutes, section 14.131, MDH will consult with Minnesota Management and Budget (MMB) about the impact the proposed rules might have on local governments. MDH will do so by sending to the MMB Commissioner copies of the documents sent to the Governor's Office for review and approval before MDH publishes the *Notice of Intent to Adopt Rules*. We will send: the Governor's Office Proposed Rule and SONAR Form; the proposed rules; and the SONAR. MDH plans to send the documents to MMB as soon as these documents have been approved by the MDH Commissioner for distribution.

2. Determination about rules requiring local implementation

As required by Minnesota Statutes, section 14.128, subdivision 1, MDH has considered whether the proposed rules will require a local government to adopt or amend any ordinance or other regulation to comply with these rules. MDH has determined that they *do not* because local governments do not develop or enforce groundwater quality standards through ordinances or regulations. The Commissioner of Health has exclusive authority to establish Health Risk Limits for ground water quality. Local units of government have consulted with MDH on the use of HRL values for interpreting the results of well monitoring.

3. Cost of complying for small business or city

MDH *cannot* determine small business or city costs incurred in complying with the proposed amendments because the rules do not have any implementation, regulation or enforcement requirements. The amendments simply provide health-based guidance for water contaminants; the rules do not address application or use. The guidance is one set of criteria for risk managers to evaluate potential health risks from contaminated groundwater. Risk managers have the flexibility in determining if and when to apply the HRL values and how costs should be considered.

LIST OF WITNESSES

MDH intends to publish a "Notice of Intent to Adopt—Dual Notice" and may cancel the scheduled hearing unless 25 or more persons request a hearing. If the proposed rules require a public hearing, MDH anticipates having the following personnel testify in support of the need and reasonableness of the rules:

- Helen Goeden, Toxicologist/Risk Assessor, Health Risk Assessment Unit, MDH
- James Jacobus, Toxicologist/Risk Assessor, Health Risk Assessment Unit, MDH
- Sarah Johnson, Toxicologist/Risk Assessor, Health Risk Assessment Unit, MDH
- Ashley Suchomel, Toxicologist/Risk Assessor, Health Risk Assessment Unit, MDH

VI. CONCLUSION

As stated in Minnesota statute, “the actual or potential use of the waters of the state for potable water supply is the highest priority use of that water and deserves maximum protection by the state.” (Minnesota Statutes, section 115.063(2)). Roughly 75 percent of Minnesota’s drinking water is from groundwater. The proposed amendments update MDH’s human health-based guidance as requested and needed by risk managers to protect groundwater and public health. This work is part of MDH’s long-term plan to continue to review, develop, update, and add to the HRL rules on groundwater contaminants.

With the proposed amendments, MDH meets its statutory requirements to use methods that are scientific, based on current U.S. EPA risk-assessment guidelines, and provide protections to vulnerable populations (Minnesota Statutes, section 103H.201 and Minnesota Statutes, section 144.0751). MDH used reasonable and well-established methods adopted in 2009 (Minnesota Rules, part 4717.7830, subpart. 2), and peer-reviewed data and scientific research in developing the HRL values for each chemical. The proposed amendments align with MDH’s mission to protect, maintain and improve the health of all Minnesotans.

APPENDIX A: GLOSSARY OF TERMS USED IN RISK ASSSESSMENT

Acute duration: A period of 24 hours or less.

Additional Lifetime cancer Risk (ALR): The probability that daily exposure to a carcinogen over a lifetime may induce cancer. The Department of Health uses an additional cancer risk of 1×10^{-5} (1 in 100,000) to derive cancer HRL values. One common interpretation of this additional cancer risk is that if a population of 100,000 were exposed over an extended period of time to a concentration of a carcinogen at the level of the HRL, at most one case of cancer would be expected to result from this exposure. Because conservative techniques are used to develop these numbers, they are upper bound risks; the true risk may be as low as zero.

Additivity Endpoint: See *Health risk index endpoint(s).*

Adverse Effect: A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge.

$AF_{lifetime}$ or lifetime adjustment factor: An adjustment factor used to adjust the adult-based cancer slope factor for lifetime exposure based on chemical-specific data.

Age-Dependent Adjustment Factor (ADAF): A default adjustment to the cancer slope factor that recognizes the increased susceptibility to cancer from early-life exposures to linear carcinogens in the absence of chemical-specific data. For the default derivation of cancer HRL values the following ADAFs and corresponding age groups are used: $ADAF_{<2} = 10$, for birth until 2 years of age; $ADAF_{2<16} = 3$, for 2 up to 16 years of age; and $ADAF_{16+} = 1$, for 16 years of age and older.

Animal Study: A controlled experiment in which a cohort of test animals, usually mice, rats, or dogs, is exposed to a range of doses of a chemical and assessed for health effects. For the purposes of the MDH HRL rules, only studies of mammalian species were considered; studies relating to fish, amphibians, plants, etc. are not used because of the greater uncertainty involved in extrapolating data for these species to human health effects, as compared to studies involving mammals.

Benchmark Dose (BMD): Dose or concentration that produces a predetermined change in the response rate of an adverse or biologically meaningful effect. The BMD approach uses mathematical models to statistically determine a dose associated with a predefined effect level (e.g., 10 percent).

Benchmark Dose Level (BMDL): A statistical lower confidence limit on the benchmark dose (BMD).

Cancer classification: Most substances are classified under the system put in place in the U.S. EPA Risk Assessment Guidelines of 1986. This system uses the categories:

- A - known human carcinogen;
- B - probable human carcinogen;
- C - possible human carcinogen;
- D - not classifiable as to carcinogenicity; and
- E - evidence of non-carcinogenicity for humans.

In 2005, U.S. EPA finalized revised guidelines calling for a "weight of the evidence" narrative, which is a short summary that explains the potential of a substance to cause cancer in humans and the conditions that characterize its expression. The following general descriptors were suggested:

- carcinogenic to humans;
- likely to be carcinogenic to humans;
- suggestive evidence of carcinogenic potential;
- inadequate information to assess carcinogenic potential; and
- not likely to be carcinogenic to humans.

Cancer Slope Factor: See *Slope Factor*.

Carcinogen: Generically, a carcinogen is a chemical agent that causes cancer. For the purposes of these Rules, a carcinogen is a chemical that is:

A) Classified as a human carcinogen (Group A) or a probable human carcinogen (Group B) according to the U.S. EPA (1986a) classification system. This system has been replaced by a newer classification scheme (EPA 2005), but many chemicals still have classifications under the 1986 system. Possible human carcinogens (Group C) will be considered carcinogens under these Rules if a cancer slope factor has been published by U.S. EPA and that slope factor is supported by the weight of the evidence.

OR

B) Classified pursuant to the Final Guidelines for Carcinogenic Risk Assessment (EPA 2005b) as "Carcinogenic to Humans" or "Likely to be carcinogenic to humans."

See also: *Linear carcinogen, Non-linear carcinogen.*

CAS number: The Chemical Abstract Service (CAS) Registry Number. This number, assigned by the Chemical Abstracts Service, a division of the American Chemical Society, uniquely identifies each chemical.

Chronic duration: A period of more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used mammalian laboratory animal species).

Co-critical effect(s): Generally, effects that are observed at doses up to or similar to the exposure level of the critical study associated with the critical effect(s).

Conversion Factor (CF): A factor (1,000 µg/mg) used to convert milligrams (mg) to micrograms (µg). There are 1,000 micrograms per milligram.

Critical effect(s): The health effect or health effects from which a non-cancer toxicity value is derived; usually the first adverse effect that occurs to the most sensitive population as the dose increases.

Database Factor: see Uncertainty Factor.

Developmental health endpoint: Adverse effects on the developing organism that may result from exposure before conception (either parent), during prenatal development, or post-natally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) function deficiency.

Dose-Response Assessment: The determination of the relationship between the magnitude of administered, applied, or internal dose and a specific biological response. Response can be expressed as measured or observed incidence, percent response in groups of subjects (or populations), or the probability of occurrence of a response in a population.

Dosimetric Adjustment Factor (DAF): A mathematical term that is based on body weight scaling that is used to calculate human equivalent exposure concentrations from laboratory animal exposure concentration..

Duration: Duration refers to the length of the exposure period under consideration. The default durations evaluated for non-cancer health effects are acute, short-term, subchronic, and chronic. See individual definitions for more information. These definitions are from "A Review of the Reference Dose and Reference Concentration Processes," U.S. EPA, Risk Assessment Forum (December 2002, http://www.epa.gov/raf/publications/pdfs/rfd-final).

The default durations evaluated for cancer health effects correspond to the age groups upon which the age dependent adjustment factors (ADAF) are based. These age groups were identified in the "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens," U.S. EPA, Risk Assessment Forum (March 2005, http://www.epa.gov/cancerguidelines/guidelines-carcinogen-supplement.htm). The age groups are: from birth up to 2 years of age; from 2 up to 16 years of age; and 16 years of age and older.

The duration of concern may also be determined by chemical-specific information. For example, the non-cancer health effect may be linked to the time point at which the concentration of the chemical in the blood reaches a level associated with an adverse effect. Another example is if the cancer slope factor is based on a lifetime rather than an adult-only exposure protocol. In this case, a lifetime duration rather than the three age groups identified above would be used.

Endocrine (hormone) system: All the organs, glands, or collections of specialized cells that secrete substances (hormones) that exert regulatory effects on distant tissues and organs through interaction with receptors, as well as the tissues or organs on which these substances exert their effects. The hypothalamus, pituitary, thyroid, parathyroids, adrenal glands, gonads, pancreas, paraganglia, and pineal body are all endocrine organs; the intestines and the lung also secrete hormone-like substances.

Endocrine (E): For the purpose of the HRL revision, "endocrine" or "E" means a change in the circulating hormones or interactions with hormone receptors, regardless of the organ or organ system affected. Because of the many organs and tissues that secrete and/or are affected by hormones, the Department has not considered the endocrine system to be a discrete classification of toxicity. An endpoint is given an "E" designation only if a change in circulating hormones or receptor interactions has been measured. Endpoints with or without the (E) designation are deemed equivalent (e.g., thyroid (E) = thyroid) and shall be included in the same Health Risk Index calculation.

Exposure Assessment: An identification and evaluation of the human population exposed to a toxic agent that describes its composition and size and the type, magnitude, frequency, route, and duration of exposure.

Goundwater: Water contained below the surface of the earth in the saturated zone including, without limitation, all waters whether under confined, unconfined, or perched conditions, in near-surface unconsolidated sediment or regolith, or in rock formations deeper underground (*Minnesota Groundwater Protection Act*, Minnesota Statutes, section 103H.005, subdivision 8).

Hazard Assessment: The process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defect) and whether the adverse health effect is likely to occur in humans.

Health-Based Value (HBV): A health-based value (HBV) is the concentration of a groundwater contaminant that can be consumed daily with little or no risk to health. HBVs are derived using the same algorithm as HRL values but have not yet been as adopted into rule. An HBV is expressed as a concentration in micrograms per liter (µg/L).

Health risk index: A health risk index is a sum of the quotients calculated by identifying all chemicals that share a common health endpoint and dividing the measured or surrogate concentration of each chemical by its HRL. The multiple-chemical health risk index is compared to the cumulative health risk limit of 1 to determine whether an exceedance has occurred.

Health risk index endpoint(s): The general description of critical and co-critical effects used to group chemicals for the purpose of evaluating risks from multiple chemicals. For example, the effect "inhibition of acetyl cholinesterase" is listed as the health risk index endpoint "nervous system," and all chemicals that can affect the nervous system would be considered together.

Health Risk Limit (HRL): A health risk limit (HRL) is the concentration of a groundwater contaminant, or a mixture of contaminants that can be consumed with little or no risk to health, and which has been adopted into rule. An HRL is expressed as a concentration in micrograms per liter (µg/L).

Health Standards Statute: Minnesota Statutes, section 144.0751. This statute requires that drinking water and air quality standards include a reasonable margin of safety to protect infants, children, and adults, taking into consideration the risk of a number of specified health effects, including: "reproductive development and function, respiratory function, immunologic suppression or hypersensitization, development of the brain and nervous system, endocrine (hormonal) function, cancer, and general infant and child development."

Hemosiderosis: An excessive accumulation of iron in tissue that normally does not contain iron.

Human Equivalent Dose (HED): The human dose (for routes other than inhalation) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species dose. This adjustment may incorporate toxicokinetic information on the particular agent, if available, or use a default procedure, such as assuming that daily oral doses experienced for a lifetime are proportional to body weight raised to the 0.75 power ($BW^{3/4}$).

Immunotoxicity: Adverse effects resulting from suppression or stimulation of the body's immune response to a potentially harmful foreign organism or substance. Changes in immune function resulting from immunotoxic agents may include higher rates or more severe cases of disease, increased cancer rates, and auto-immune disease or allergic reactions.

Immune system: A complex system of organs, tissues, cells, and cell products that function to distinguish self from non-self and to defend the body against organisms or substances foreign to the body, including altered cells of the body, and prevent them from harming the body.

Intake Rate (IR): Rate of inhalation, ingestion, and dermal contact, depending on the route of exposure. For ingestion of water, the intake rate is simply the amount of water, on a per body weight basis, ingested on a daily basis (liters per kg body weight per day, L/kg-day) for a specified duration. For the derivation of non-cancer and cancer HRL values, the time-weighted average of the 95th percentile intake rate for the relevant duration was used.

Interspecies Factor: see *Uncertainty Factor.*

Intraspecies Factor: see *Uncertainty Factor.*

Kilogram (kg): One kilogram is equivalent to 2.21 pounds.

Latency Period: The time between exposure to an agent and manifestation or detection of a health effect of interest.

Linear carcinogen: A chemical agent for which the associated cancer risk varies in direct proportion to the extent of exposure, and for which there is no risk-free level of exposure.

Linear Dose Response: A pattern of frequency or severity of biological response that varies directly with the amount of dose of an agent. In other words, more exposure to the substance could produce more of an effect. This linear relationship holds only at low doses in the range of extrapolation.

Liter (L): One liter is equivalent to 1.05671 quarts.

Liters per kilogram per day (L/kg-day): A measure of daily water intake, relative to the individual's body weight.

LOAEL-to-NOAEL: see *Uncertainty Factor.*

Lowest Observed Adverse Effect Level (LOAEL): The lowest exposure level at which a statistically or biologically significant increase in the frequency or severity of adverse effects is observed between the exposed population and its appropriate control group. A LOAEL is expressed as a dose rate in milligrams per kilogram body weight per day (mg/kg-day).

MCL-based HRL: A Health Risk Limit for groundwater adopted by reference to the U.S. EPA's Maximum Contaminant Level (MCL) rather than through the standard MDH chemical evaluation process.

Mechanism of Action: The complete sequence of biological events (i.e., including toxicokinetic and toxicodynamic events) from exposure to the chemical to the ultimate cellular and molecular consequences of chemical exposure that is required to produce the toxic effect. However, events that are coincident but not required to produce the toxic outcome are not included.

Microgram (µg): 10^{-6} grams or 10^{-3} milligrams. 1,000 micrograms = 1 milligram

Micrograms per liter (µg/L): A unit of measure of concentration of a dissolved substance in water.

Milligram (mg): 10^{-3} grams. 1,000 milligrams = 1 gram.

Milligrams per kilogram of body weight per day (mg/kg-day or mg/kg-d): A measure of daily exposure to a contaminant, relative to the individual's body weight.

Mode of Action (MOA): The sequence of key event(s) (i.e., toxicokinetics and toxicodynamics) after chemical exposure upon which the toxic outcomes depend.

Neurotoxicity: Any adverse effect on the structure or function of the central and/or peripheral nervous system related to exposure to a chemical.

Non-linear carcinogen: A chemical agent for which, particularly at low doses, the associated cancer risk does not rise in direct proportion to the extent of exposure, and for which there may be a threshold level of exposure below which there is no cancer risk.

Non-linear Dose Response: A pattern of frequency or severity of biological response that does not vary directly with the amount of dose of an agent. When mode of action information indicates that responses may fall more rapidly than dose below the range of the observed data, non-linear methods for determining risk at low dose may be justified.

No Observed Adverse Effect Level (NOAEL): An exposure level at which there is no statistically or biologically significant increase in the frequency or severity of adverse effects between the exposed population and its appropriate control group.

Physiologically Based Toxicokinetic (PBTK) Model: A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion. (Also referred to as physiologically based pharmacokinetic model.)

Point of Departure (POD): The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD) or a NOAEL or LOAEL for an observed incidence, or change in level of response.

Reference Dose (RfD): An estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects for a given exposure duration. It is derived from a suitable exposure level at which there are few or no statistically or biologically significant increases in the frequency or severity of an adverse effect between an exposed population and its appropriate control group. The RfD is expressed in units of milligrams of the chemical per kilogram of body weight per day (mg/kg-day).

Relative Source Contribution (RSC): The portion of the RfD that is "allocated" to ingestion of water. Applying this factor acknowledges that non-ingestion exposure pathways (e.g., dermal contact with water, inhalation of volatilized chemicals in water) as well as exposure to other media, such as air, food, and soil may occur. The *Minnesota Groundwater Protection Act*, in Minnesota Statutes, section 103H.201, subdivision 1(d), requires that MDH use a relative source contribution in deriving health risk limits for systemic toxicants. MDH relied upon U.S. EPA's Exposure Decision Tree approach contained in Chapter 4 of the Ambient Water Quality Criteria document to determine appropriate RSC values.

HRL values are often applied at contaminated sites where media other than groundwater may also be contaminated. The level of media contamination and the populations potentially exposed will vary from site to site and from chemical to chemical. Using a qualitative evaluation and the Exposure Decision Tree, MDH determined the following default RSC values: 0.2 for highly volatile contaminants (chemicals with a Henry's Law Constant greater than 1×10^{-3} atm-m^3/mole) and 0.5 for young infants or 0.2 for older infants, children and adults for chemicals that are not highly volatile. There may be chemical-specific or site-specific exposure information where the Exposure Decision Tree could be used to derive a chemical- or site-specific RSC that is different than the default value.

Reproductive toxicity: Effects on the ability of males or females to reproduce, including effects on endocrine systems involved in reproduction and effects on parents that may affect pregnancy outcomes. Reproductive toxicity may be expressed as alterations in sexual behavior, decreases in fertility, changes in sexual function that do not affect fertility, or fetal loss during pregnancy.

Risk: In the context of human health, the probability of adverse effects resulting from exposure to an environmental agent or mixture of agents.

Risk Assessment: The evaluation of scientific information on the hazardous properties of environmental agents (hazard characterization), the dose-response relationship (dose-response assessment), and the extent of human exposure to those agents (exposure assessment). The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree (risk characterization).

Risk Assessment Advice (RAA): A type of MDH health-based guidance that evaluates potential health risks to humans from exposures to a chemical. Generally, RAA may contain greater uncertainty than HRL values and HBVs due to limited availability of information, or may use novel methods to derive health-based guidance. Based on the information available, RAA may be quantitative (e.g., a concentration of a chemical that is likely to pose little or no health risk to humans expressed in µg/L) or qualitative (e.g., a written description of how toxic a chemical is in comparison to a similar chemical).

Risk Characterization: The integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.

Risk Management: A decision-making process that accounts for political, social, economic, and engineering implications together with risk-related information to develop, analyze, and compare management options and select the appropriate managerial response to a potential health hazard.

Secondary Observation: Notation indicating that although endpoint-specific testing was not conducted, observations regarding effects on the endpoint were reported in a toxicity study.

Short-Term Duration: A period of more than 24 hours, up to 30 days.

Slope Factor (SF): An upper-bound estimate of cancer risk per increment of dose that can be used to estimate risk probabilities for different exposure levels. This estimate is generally used only in the low-dose region of the dose-response relationship; that is, for exposures corresponding to risks less than 1 in 100. A slope factor is usually expressed in units of cancer incidence per milligram of chemical per kilogram of body weight per day (per [mg/kg-day] or $[mg/kg\text{-}day]^{-1}$).

Statistical Significance: This describes the probability that a result is not likely to be due to chance alone. By convention, a difference between two groups is usually considered statistically significant if chance could explain it only 5% of the time or less. Study design considerations may influence the *a priori* choice of a different level of statistical significance.

Subchronic Duration: A period of more than 30 days, up to approximately 10% of the life span in humans (more than 30 days up to approximately 90 days in typically used mammalian laboratory animal species).

Subchronic-to-Chronic Factor: See *Uncertainty Factor*.

Target Organ: The biological organ(s) most adversely affected by exposure to a chemical or physical agent.

Time-Weighted Average (TWA): In quantifying a measurement that varies over time, such as water intake, a time-weighted average takes measured intakes, which may occur at unevenly-spaced intervals, and multiplies each measurement by the length of its interval. These individual weighted values are then summed and divided by the total length of *all* of the individual intervals. The result is an average of all of the measurements, with each measurement carrying more or less weight in proportion to its size.

Threshold: The dose or exposure below which no toxic effect is expected to occur.

Toxicity: Deleterious or adverse biological effects elicited by a chemical, physical, or biological agent.

Toxicodynamics (TD): The determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent (sometimes referred to as pharmacodynamics and also MOA).

Toxicokinetics (TK): The determination and quantification of the time course of absorption, distribution, metabolism, and excretion of chemicals (sometimes referred to as pharmacokinetics).

Uncertainty Factor (UF): One of several factors used in deriving a reference dose from experimental data. UFs are intended to account for:

- **Interspecies UF** - the uncertainty in extrapolating from mammalian laboratory animal data to humans. This uncertainty factor is composed of two subfactors: one for toxicokinetics and one for toxicodynamics.
- **Intraspecies Variability Factor** - the variation in sensitivity among the members of the human population;
- **Subchronic-to-Chronic Factor** (Use of a less-than-chronic study for a chronic duration) - the uncertainty in extrapolating from effects observed in a shorter duration study to potential effects from a longer exposure;
- **LOAEL-to-NOAEL** (Use of a LOAEL rather than a NOAEL) - the uncertainty associated with using a study in which health effects were found at all doses tested; and
- **Database Uncertainty** - the uncertainty associated with deficiencies in available data.

Uncertainty factors are normally expressed as full or half powers of ten, such as 10^0 (=1), $10^{0.5}$ (≈3), and 10^1 (=10). All applicable uncertainty factors are multiplied together to yield a composite uncertainty factor for the RfD. Half-power values such as $10^{0.5}$ are

factored as whole numbers when they occur singly but as powers or logs when they occur in tandem (EPA 2002c). Therefore, a composite UF using values of 3 and 10 would be expressed as 30 (3×10^{1}), whereas a composite UF using values of 3 and 3 would be expressed as 10 ($10^{0.5} \times 10^{0.5} = 10^{1}$).

In keeping with the U.S. EPA RfC/RfD Technical Panel (EPA, 2002c) recommendation and the rationale supporting it, MDH has not derived an HRL for any chemical if the product of all applicable uncertainty factors exceeds 3,000 (Minnesota Rules, part 4717.7820, subpart. 21).

Volatile: Volatility is the tendency of a substance to evaporate. Inhalation exposure to volatile chemicals in groundwater may be a health concern. Chemical characteristics that affect volatility include molecular weight, polarity, and water solubility. Typically, a chemical is considered volatile if it has a Henry's law constant greater than 3×10^{-7} atm-m^3/mol. Chemicals are characterized as being nonvolatile, or being of low, medium, or high volatility as follows:

- Henry's Law constant < 3×10^{-7} atm-m^3/mol = nonvolatile
- Henry's Law constant > 3×10^{-7} to 1×10^{-5} atm-m^3/mol = low volatility
- Henry's Law constant >1×10^{-5} to 1×10^{-3} atm-m^3/mol = moderate volatility
- Henry's Law constant >1×10^{-3} atm-m^3/mol = high volatility

Weight of Evidence (WOE): An approach requiring a critical evaluation of the entire body of available data for consistency and biological plausibility. Potentially relevant studies should be judged for quality and studies of high quality given much more weight than those of lower quality.

APPENDIX B: REFERENCES

Note: The following references were used to develop an updated methodology and Health Risk Limit values in MDH's effort on revising and updating the rules on Health Risk Limits for Groundwater. These materials are available for review online, or at the Minnesota Department of Health, or through the Minitex Interlibrary Loan System.

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APPENDIX C: CONCEPTS USED IN MDH-DERIVED HRLs

Described below are the basic principles that underlie MDH's risk algorithm adopted in 2009 (Minnesota Rules, part 4717.7830, subpart 2) as stated in Section II.D. MDH used these methods to derive the HRL values that are included in the 2016/2018 proposed amendments. Detailed descriptions of these concepts are also available in MDH's 2008/2009 SONAR (MDH, 2008. See Part IV).

HRL rules employ two types of assessments. One assessment is for chemicals for which it is assumed that any dose of that chemical above zero carries some potential increased risk of cancer. These chemicals are identified as "linear" or "non-threshold" carcinogens. The second type of assessment is for evaluating non-cancer effects. This method can also be applied to address chemicals that have the potential to cause cancer through a "non-linear" mechanism. The assessment of a non-carcinogen or a non-linear carcinogen assumes that there is a threshold dose that must be exceeded before adverse health effects (including cancer) will develop.

Toxicity

Toxicity is one of the factors in determining HRL values. In evaluating the dose and response, researchers seek to determine the lowest dose at which adverse effects are observed (the "lowest observed adverse effect level," or LOAEL) and the highest dose at which no adverse effects are observed (the "no observed adverse effect level," or NOAEL). Alternatively, researchers may statistically model the data to determine the dose expected to result in a response in a small percentage of the dosed animals (e.g., the benchmark dose, or BMD). The dose resulting from the dose-response evaluation, also referred to as a point-of-departure (POD) dose, serves as the starting point for deriving health-protective concentrations for air, water and soil, collectively referred to as the "environmental media."

For effects other than cancer, the dose selected from the dose-response evaluation is divided by variability and uncertainty factors (UFs) to account for what is not known about a chemical's toxicity to a human population. The result, called a reference dose (RfD), is an estimate of a dose level that is likely to be without an appreciable risk of adverse effects. An RfD is expressed in milligrams of chemical per kilogram of body weight per day (mg/kg-day).

Understanding the relationship between the timing and duration of exposure and the subsequent adverse effect is essential in deriving criteria that are protective of sensitive life stages (e.g., development early in life) and short periods of high exposure (e.g., infancy). In *A Review of the Reference Dose (RfD) and Reference Concentration (RfC) Processes*, U.S. EPA recommends the derivation of acute, short-term, subchronic, and chronic RfDs (EPA, 2002c). In cases where sufficient toxicological information is available, MDH derives RfDs for the various time periods as defined by EPA.

In evaluating the proposed nHRL values, MDH staff compiled and assessed the available toxicity information for the following durations of exposure:

- Acute: up to 24 hours
- Short-term: greater than 24 hours and up to 30 days
- Subchronic: greater than 30 days and up to 10% of a lifetime
- Chronic: greater than 10% of a lifetime.

The current HRL methods not only list the specific effects occurring at the lowest effect dose, but also effects that occur at doses similar to the Lowest-Observed-Adverse Effect Level (LOAEL), from other available toxicity studies. This provides more information to risk managers and can affect the results of an assessment when multiple chemicals are present (also see Minnesota Rules, part 4717.7880). Within each chemical's toxicology summary (see Appendix E), MDH has also indicated which chemicals are associated with endocrine effects and which chemicals have their greatest effects as a result of exposure *in utero* or during child development. Further, MDH notes whether the information reviewed for each chemical includes assessments of developmental, reproductive, immunological, endocrine, or neurological effects. This information is provided for each chemical in part to meet the stipulations of the *2001 Health Standards Statute*.

For cancer HRLs, as stated in MDH 2008/2009 SONAR, "it is usually assumed that any amount of exposure, no matter how small, potentially carries some risk. Derivations of HRLs based on the endpoint of cancer for chemicals considered to be linear carcinogens do not, therefore, employ an RfD. Instead, Minnesota's long-standing public health policy is to derive values that limit the excess cancer risk to 1 in 100,000. Cancer potency is expressed as an upper bound estimate of cases of cancer expected from a dose of one milligram of substance per kilogram of body weight per day (i.e., cancer incidence per 1 mg/kg-day). From these estimates, a cancer potency slope, or "slope factor" (SF), can be calculated." (MDH, 2008).

To derive a cancer HRL, MDH is required by the Groundwater Protection Act to use a cancer potency slope published by EPA. To account for the potential for increased cancer potency when exposure occurs early in life, MDH used methodology contained in the EPA *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA, 2005a). This approach involves applying age-dependent cancer potency adjustment factors to three life stages. The adjustment factors and corresponding life stages are: a 10-fold adjustment for individuals from birth to 2 years of age; a 3-fold adjustment for individuals from 2 to 16 years of age and no adjustment for individuals 16 years of age and older (MDH, 2008). For additional information about methodology for derivation of cancer HRLs, please see the 2008/2009 SONAR (MDH, 2008).

Examples of sources of toxicity information that MDH considers in deriving HRL values include the following:

- U.S. Environmental Protection Agency (EPA)
    - Reregistration Eligibility Decisions (REDs) from the Office of Pesticide Programs. Updates are provided on EPA's Pesticide Chemical Search page at https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1
    - Health Effects Supporting Documents in the The Drinking Water Contaminant Candidate List (CCL) and Regulatory Determination (https://www.epa.gov/ccl#supportdocs) from the Office of Ground Water and Drinking Water
    - The Integrated Risk Information System (IRIS) (https://www.epa.gov/iris)
    - The National Center for Environmental Assessment (NCEA) (https://www.epa.gov/aboutepa/about-national-center-environmental-assessment-ncea) risk assessments
- California EPA
    - The Public Health Goal (http://oehha.ca.gov/water/public-health-goals-phgs) technical supporting documents from the Office of Environmental Health Hazard Assessment (OEHHA)
- Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles (https://www.atsdr.cdc.gov/toxprofiles/index.asp);
- National Toxicology Program (https://ntp.niehs.nih.gov/) (NTP) study report and toxicity studies;
- Health Canada's Priority Substances Assessment Program and Screening Assessment Reports (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/index-eng.php#psl)
- European Commission chemical reviews
    - European Chemical Agency Information on Chemicals (https://echa.europa.eu/information-on-chemicals)
    - European Food Safety Authority Scientific Publications (https://www.efsa.europa.eu/en/publications)

    - European Union Pesticides Database (http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=homepage&language=EN)

- The World Health Organization's (WHO) Concise International Chemical Assessment Documents (http://www.who.int/ipcs/publications/cicad/en/); and

- Other published scientific literature.

Intake Rates

An intake rate (IR) is defined as the rate of ingestion of water (Minnesota Rules, part 4717. 7820, subpart 14). In deriving HRL values, the RfD for non-cancer health effects is converted from milligrams per kilogram body weight per day (mg/kg-day) to a water concentration in micrograms per liter of water (µg/L) by dividing by a water intake rate. IR is expressed as the quantity of water consumed in liters per kilogram of body weight per day (L/kg-day).

The initial default values were time-weighted averages based on the data reported in U.S. EPA's Per Capita Report (EPA, 2004c) and a revised assessment for the Child-Specific Exposure Factors Handbook (EPA, 2007b). In 2016, MDH began using the finalized water intake rates from the EPA 2011 Exposure Factors Handbook, shown below.

MDH staff calculated and used the following default time-weighted-average intake rates for non-cancer health-based guidance from the finalized EPA values:

- Acute: 0.285 L/kg-day

- Short-term: 0.285 L/kg-day

- Subchronic: 0.070 L/kg-day

- Chronic: 0.044 L/kg-day

- Pregnant Women: 0.043 L/kg-day

For linear carcinogens HRLs, as noted in the 2008/2009 SONAR, "MDH has adopted EPA's approach for integrating age-dependent sensitivity adjustment factors and exposure information. The default intake rates corresponding to the age-dependent adjustment factor (ADAF) age groups used in deriving cancer HRLs are based on the TWA of the 95th percentile intake rate for each age range. The finalized EPA values are 0.125 L/kg-day (up to 2 years of age), 0.045 L/kg-day (2 to up to 16 years of age), and 0.041 L/kg-day (16 years of age and older)." The duration used to characterize lifetime cancer risk is 70 years, per EPA's practices (MDH, 2008).

The relative source contribution (RSC) was used to allocate a portion of the total daily RfD to exposure from ingestion of water. The balance of the RfD is reserved for other exposures, such as exposures from non-ingestion routes of exposure to water (e.g., inhalation of volatilized chemicals, dermal absorption) as well as exposures via other contaminated media such as food, air, and soil. Minnesota Statutes, section 103H.201, subdivision (1)(c), which establishes methods for deriving HRL values for chemicals other than linear (non-threshold) carcinogens, requires that an RSC be used. The RSC values used are based on the U.S. EPA Ambient Water Quality Criteria document (EPA, 2000c) and the consideration of chemical and physical properties of each chemical (e.g., volatility) as well as other potential sources of exposure.

Based on qualitative evaluation and the U.S. EPA's Exposure Decision Tree (EPA, 2000c), MDH used the following default RSC values: for nonvolatile, low and moderately volatile chemicals, an RSC of 50 percent (0.5) is used for the acute and short-term durations that use the intake rate for young infants; for subchronic and chronic durations, 20 percent (0.2) is used. In contrast, for all durations for highly volatile chemicals, an RSC of 20 percent (0.2) is used for all durations because inhalation exposure is a concern for any duration or age of exposure, including infancy. The volatility classification for each chemical is determined by the following definition (Minnesota Rules, part 4717.7820, subpart 25):

Nonvolatile – Henry's Law constant $<3 \times 10^{-7}$ atm-m^3/mol

- Low volatility – Henry's Law constant $>3 \times 10^{-7}$ to 1×10^{-5} atm-m^3/mol
- Moderate volatility – Henry's Law constant $>1 \times 10^{-5}$ to 1×10^{-3} atm-m^3/mol
- High volatility – Henry's Law constant $> 1 \times 10^{-3}$ atm-m^3/mol

Uncertainty Factors (UFs)

To account for what is not known about a chemical's toxicity to a human population, uncertainty and variability factors are applied to threshold (non-linear) toxicants when deriving HRL values for non-cancer and non-linear carcinogens. Once the dose level (e.g., NOAEL, LOAEL or BMD) has been selected as the point of departure (POD), it is then divided by uncertainty and/or variability factors to derive the RfD:

$$\frac{\text{Point of Departure (POD)}}{\text{Uncertainty and Variability Factors (UFs)}} = \text{Reference Dose (RfD)}$$

As risk-assessment methods have evolved, risk assessors consider the applying five uncertainty and variability factors. Each of these factors and guidelines for application are explained below:

- Interspecies Extrapolation Factor – This factor accounts for the uncertainty or the difference between animals and humans when laboratory animal data are used as the source of the point of departure (POD). It is composed of two subfactors: 1) toxicokinetics (absorption, distribution, metabolism and elimination of the chemical) and 2) toxicodynamics (the body's response to the chemical). The current practice is to use either chemical-specific toxicokinetic data or a data-based adjustment for toxicokinetics rather than an uncertainty factor for toxicokinetics. If there is no chemical-specific information regarding quantitative differences between laboratory animals and humans, a body-weight scaling adjustment based on EPA guidance (EPA, 2011c) is used to calculate the Human Equivalent Dose or HED. Less information is typically available concerning the toxicodynamic portion of this factor. If no chemical-specific toxicodynamic information is available, a default uncertainty factor of 3 is applied for the toxicodynamics. Chemical-specific information for either or both subparts may lead to a combined factor of greater than 10. If human data is the source of the POD then a factor of 1 may be used.

- Intraspecies Variability Factor – This factor accounts for the variation in sensitivity between individuals in the human populations (including life stages) and for the fact that some subpopulations might be more sensitive to the toxicological effects than the average population. As with the interspecies extrapolation factor, this factor is also composed of two subfactors: toxicokinetics and toxicodynamics. If no information on human variability is available then a default value of 10 is used. If adequate information is available for either subfactor then this information is used along with a default factor of 3 for the remaining subfactor. If the POD is based on human data gathered in the known sensitive subpopulations, a value of less than 10 (including 1) may be chosen.

- Subchronic-to-Chronic Extrapolation Factor – This factor accounts for the uncertainty in extrapolating from the effects observed in a shorter-duration study to potential effects of longer-duration exposure due to lack of adequate information in the dataset. In determining whether to apply this factor, MDH considers: 1) data indicating other, more sensitive, health effects as the duration of exposure increases, 2) data indicating that the critical effect(s) progress in severity as exposure duration increases, or 3) data indicating that the POD decreases in value as exposure duration increases. A default value of 10 is often applied to shorter-duration PODs to derive chronic values unless data suggest a lack of progression with increasing exposure duration. If data addresses only some of the considerations, a value of less than 10 (e.g., 3) may be used.

- LOAEL-to-NOAEL Extrapolation Factor – This factor accounts for the uncertainty in using a study in which even the lowest dose tested causes some adverse effect(s), and is in contrast to the preferred case where at least one of the administered doses caused no adverse effects. Since the RfD is considered to be a

threshold value that protects against any adverse health effects, the LOAEL-to-NOAEL factor is applied when the critical study(s) lacks information or the threshold/NOAEL cannot be determined with confidence (e.g., when LOAEL is used as a POD). The default value is 10, however, if the adverse effect observed is considered to be of minimal severity a default value of 3 may be appropriate.

- Database Uncertainty Factor – This factor accounts for uncertainty based on existing data or deficiencies in the available dataset, resulting in the potential for additional data to yield a lower reference value (EPA, 2004a) (i.e., additional studies may show the chemical to be more harmful). A high-confidence database would contain a minimum of two chronic bioassays testing system toxicity by the appropriate route of exposure in different species, one 2-generation reproductive toxicity study, and two developmental toxicity studies in different species. A database UF is used when a potentially more sensitive health effect cannot be identified because the database is missing a particular type of study or the existing data suggest the potential for a health effect but the effect has not been adequately assessed. In general, a default factor of 10 is used if more than one particular type of study is missing. A value of 3 has been used if one particular type of study is missing (e.g., no 2-generation reproductive or developmental study).

In the absence of chemical-specific information, each of the five factors is typically assigned a value between 1 and 10. Uncertainty factors are normally expressed as full or half powers of ten, such as 10^0 (=1), $10^{0.5}$ (≈3), and 10^1 (=10). All applicable uncertainty factors are multiplied together to yield a composite uncertainty factor for the RfD. Half-power values such as $10^{0.5}$ are factored as whole numbers when they occur singly but as powers or logs when they occur in tandem (EPA, 2002c). Therefore, a composite UF using values of 3 and 10 would be expressed as 30 (3×10^1), whereas a composite UF using values of 3 and 3 would be expressed as 10 ($10^{0.5} \times 10^{0.5} = 10^1$).

In keeping with the U.S. EPA RfC/RfD Technical Panel (EPA, 2002c) recommendation and the rationale supporting it, MDH has not derived an HRL for any chemical if the product of all applicable uncertainty factors exceeds 3,000 (Minnesota Rules, part 4717.7820, subpart 21). Chemicals with higher total uncertainty factors are not necessarily more toxic than chemicals with lower total uncertainty factors. The use of a larger total uncertainty factor only means that there is less information available about the toxicity of the chemical.

MDH Health Risk Limit Algorithms

As noted in Section II.D., MDH uses formulas called “algorithms,” to derive HRL values. The formulae and explanation of components are described below:

Non Cancer HRLs (nHRLs)

The algorithm for nHRLs is:

$$nHRL_{duration} = \frac{RfD_{duration} \times RSC \times 1{,}000}{IR_{duration}}$$

Where:

$nHRL_{duration}$ = the non-cancer health risk limit (nHRL), for a given duration, expressed in units of micrograms of a chemical per liter of water (µg/L) (Minnesota Rules, part 4717.7820, subpart 13).

$RfD_{duration}$ = the reference dose (RfD) for a given duration, expressed in units of milligrams per kilogram per day (mg/kg-day). The following default durations are used: (i) acute – a period of 24 hours or less; (ii) short-term – a period of more than 24 hours, up to 30 days; (iii) subchronic – a period of more than 30 days, up to approximately 10% of the life span in humans; or (iv) chronic – a period of more than approximately 10% of the life span in humans (Minnesota Rules, part 4717.7820, subpart 9 and 21).

RSC = the relative source contribution (RSC) factor which represents the percentage of total exposure to a substance or chemical that is allocated to ingestion of water. MDH uses the U.S. EPA Exposure Decision Tree (U.S. EPA, 2000) to select appropriate RSCs, ranging from 0.2 to 0.8. The default RSC is 20 percent (0.2) for highly volatile chemicals. For other chemicals, the default RSC is 50 percent (0.5) for acute and short-term HRL values and 20 percent (0.2) for subchronic or chronic HRL values (Minnesota Rules, part 4717.7820, subpart 22). In some cases, a chemical-specific RSC is applied. For example a value of 0.8 has been used for pharmaceuticals when, for persons not using the pharmaceutical, no other route of exposure other than drinking water is likely.

1,000 = a factor used to convert milligrams (mg) to micrograms (µg) (Minnesota Rules, part 4717.7830, subpart 2, item D).

$IR_{duration}$ = the intake rate (IR) of ingestion of water, or simply the amount of water, on a per body weight basis, ingested on a daily basis (liters per kg body weight per day or L/kg-day). The default IR corresponds to the time-weighted average (TWA) of the 95th percentile intake rate during the relevant duration: acute and short-

term - 0.285 L/kg-day, based on intake for 1 up to 3 months of age; subchronic - 0.070 L/kg-day, based on a TWA up to 8 years of age; and chronic - 0.044 L/kg-day, based on a TWA over a lifetime of approximately 70 years (Minnesota Rules, part 4717.7820, subpart 14).

MDH departed from the above default HRL algorithm and parameter values if sufficient chemical-specific information indicated that a different duration or intake rate was more appropriate. In these cases, a time-weighted intake rate was calculated over the duration specified by the chemical-specific information. The RfD, RSC and IR values used in deriving each nHRL for chemicals included in the 2012 proposed rules are presented in Section IV.B.

As indicated in the risk algorithm, the magnitude of the HRL value is a function of the RfD and the IR. In general, for a given chemical, the shorter-duration RfD values will be higher than the longer-duration RfD values because the human body can usually tolerate a higher dose when the duration of the dose is short, even if that same dose would be harmful when it occurs over a longer duration. It is possible, however, that the RfD for a shorter duration is similar to, or in rare cases lower, than the RfD for a longer duration. This could occur for various reasons such as if a short duration was sufficient to elicit the same adverse effect found in longer-duration study; or if the health effect assessed only in the shorter-duration study occurred at a lower dose than the effect assessed in the longer-duration study; or if the life stage or species assessed only in the shorter-duration study was more sensitive to the toxicant than the life stage or species assessed in the longer-duration study.

The intake rate also affects the magnitude of the HRL value. As described above, the shorter-duration intake rates are higher than the longer-term intake rates. These higher intake rates combined with the RfD may produce a shorter-duration HRL that is less than the calculated longer-duration HRL. When this occurs, the longer-duration HRL is set equal to the lower, shorter-duration HRL. This ensures that the HRL for a longer duration is protective of higher shorter-term intakes that occur within the longer duration. In instances where the calculated longer-duration HRL value is set at the shorter-duration HRL value, the health endpoints identified will include the health endpoints specified for the shorter-duration, and may include additional health endpoints. These additional health endpoints are included if they are associated with longer-duration exposure to drinking water concentrations similar in magnitude to the shorter-duration HRL.

In accordance with the general rule for calculations involving multiplication or division, HRL values are rounded to the same number of significant figures as the least precise parameter used in their calculation (EPA, 2000c). As a result, the HRL values are rounded to one significant figure. MDH rounded the values as the final step in the calculation (see chemical-specific summary sheets in Appendix E).

The example below shows the derivation of the short-term nHRL value for carbon tetrachloride, using the algorithm for nHRLs:

$$nHRL_{duration} = \frac{(RfD) \times (RSC) \times (Conversion\ Factor)}{(IR_{duration}, L/kg/d)}$$

$$nHRL_{short\ term} = \frac{(0.0037\ mg/kg/d) \times (0.2) \times (1000\ \mu g/mg)}{(0.285\ L/kg\text{-}d)}$$

$$= 2.6 \text{ rounded to } 3\ \mu g/L$$

The next example below shows the derivation of the subchronic nHRL for carbon tetrachloride:

$$nHRL_{subchronic} = \frac{(0.0098\ mg/kg/d) \times (0.2) \times (1000\ \mu g/mg)}{(0.070\ L/kg\text{-}d)}$$

$$= 28 \text{ rounded to } 30\ \mu g/L$$

The calculated subchronic nHRL (30 µg/L) is greater than carbon tetrachloride's short-term HRL value of 3 µg/L. Since the subchronic HRL must be protective of the short-term exposures that occur within the subchronic period, the subchronic nHRL is set equal to the short-term nHRL value. Hence, the subchronic nHRL value for carbon tetrachloride is set equal to 3 µg/L. The health endpoints include the hepatic (liver) system and the immune system. In this case:

$$nHRL_{subchronic} = nHRL_{short\text{-}term} = 3\ \mu g/L$$

Notes

- RfDs and uncertainty adjustments are derived by MDH, unless otherwise noted. The RfDs and the endpoints are usually based on animal studies but may be based on human studies.

- RfDs are based on human equivalent dose (HED) calculated from the point of departure in the selected animal studies. HED is the human dose (for routes other than inhalation) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species dose (MDH, 2011).

- A health endpoint designation of "none" is used when a general adverse effect (e.g., decreased adult body weight) cannot be attributed to a specific organ system.

- The duration-specific nHRL value is derived using the following equation as previously stated in Section II.D. and specified in Minnesota Rules, part 4717.7830, subp 2:

- The terms used in this section are explained in the Glossary (see Appendix A).

Cancer HRLs:

For the derivation of cancer HRLs for linear carcinogens, MDH applied the age-dependent cancer potency adjustment factors and corresponding intake rates to the default HRL algorithm for cancer:

$$cHRL = \frac{(1\times10^{-5})\times1{,}000\,\frac{\mu g}{mg}}{\left[(SF\times ADAF_{<2}\times IR_{<2}\times D_{<2}) + (SF\times ADAF_{2\,to\,<16}\times IR_{2\,to\,<16}\times D_{2\,to\,<16}) + (SF\times ADAF_{16+}\times IR_{16+}\times D_{16+})\right]\div 70\ years}$$

Where:

cHRL = the cancer health risk limit expressed in units of micrograms of chemical per liter of water (µg/L).

(1×10^{-5}) = the additional cancer risk level.

1,000 = a factor used to convert milligrams (mg) to micrograms (µg).

SF = the cancer slope factor for adult exposure, expressed in units of the inverse of milligrams per kilogram of body weight per day ([cancer incidence per mg/kg-day] or $[mg/kg\text{-}day]^{-1}$).

ADAF = the age-dependent adjustment factor for each age group: 10, for up to 2 years of age ($ADAF_{<2}$); 3, for 2 up to 16 years of age ($ADAF_{2<16}$); and 1, for 16 years of age and older ($ADAF_{16+}$). ADAFs are default adjustments to the cancer slope factor that recognize the increased susceptibility to cancer from early life exposures to linear carcinogens. They are incorporated into the denominator of the cancer HRL equation.

IR = the intake rate for each age group: 0.125 L/kg-day, for up to 2 years of age ($IR_{<2}$); 0.045 L/kg-day, for 2 up to 16 years of age ($IR_{2<16}$); and 0.041 L/kg-day, for 16 years of age and older (IR_{16+}).

D = the duration for each age group: 2 years, for up to 2 years of age ($D_{<2}$); 14 years, for 2 up to 16 years of age ($D_{2<16}$); and 54, for 16 years of age and older (D_{16+}).

70 years = the standard lifetime duration used by U.S. EPA in the characterization of lifetime cancer risk.

MDH departs from the above default HRL algorithm if sufficient information is available to derive a chemical-specific lifetime adjustment factor ($AF_{lifetime}$). In these cases a time-weighted intake rate over a lifetime is applied, resulting in the following equation:

$$cHRL = \frac{(1 \times 10^{-5}) \times 1{,}000 \frac{\mu g}{mg}}{SF \times AF_{lifetime} \times 0.044 \frac{L}{kg-day}}$$

Where

(1×10^{-5}) = the additional cancer risk level.

1,000 = a factor used to convert milligrams (mg) to micrograms (µg).

SF = adult-exposure based cancer slope factor.

$AF_{lifetime}$ = the lifetime adjustment factor based on chemical-specific data.

0.044 L/kg-day = 95th percentile water intake rate representative of a lifetime period.

Additional explanations of the concepts used in deriving the HRL values are available in MDH's 2008 SONAR, Part IV (MDH, 2008).

APPENDIX D: SELECTION OF 2016/2018 CONTAMINANTS

MDH selected the contaminants for the 2016/2018 amendments based on input from programs within MDH, such as the Site Assessment and Consultation Unit, Drinking Water Protection Section, and Contaminants of Emerging Concern (CEC) programs. It also relied on advice from partner state agencies, such as the Minnesota Pollution Control Agency (MPCA) and the Minnesota Department of Agriculture (MDA). At periodic interagency meetings, representatives from these agencies nominated chemicals for review and discussed their concerns and priorities. Further, MDH initiated a system to re-evaluate previously adopted HRLs to ensure that values remain up-to-date. In 2016-2018 HRLs adopted in 2009 were re-evaluated. Listed below are the 2016/2018 chemicals with proposed HRLs and the origin of the guidance requests.

Request for Guidance on Groundwater Contaminants

Origin of Guidance Request	**Chemical**	**Origin of Guidance Request**	**Chemical**
Interagency priority	Acenapthene	2009 HRL re-evaluation	Acetochlor
2011 HRL re-evaluation	Acetochlor ESA	2011 HRL re-evaluation	Acetochlor OXA
2009 HRL re-evaluation	Alachlor	2009 HRL re-evaluation	Benzene
2009 HRL re-evaluation	Chloroform	Interagency priority	Clothianidin
2009 HRL re-evaluation	Cyanazine	Interagency priority	*cis*-1,2-Dichloroethane
CEC nomination	2,4-Dichlorophenoxyacetic acid (2,4-D)	2009 HRL re-evaluation	Dieldrin
Interagency priority	Dinoseb	Interagency Priority	S-Ethyl-N,N-dipropylthiocarbamate (EPTC)
Interagency priority	Fluroanthene	Interagency priority	Perfluorobutyrate (PFBA)

Origin of Guidance Request	Chemical	Origin of Guidance Request	Chemical
Interagency priority	Perfluorooctanoic Acid (PFOA) and Salts	Interagency priority	Perfluorooctane Sulfonate (PFOS) and Salts
Interagency priority	Pyrene	CEC nomination	Tetrahydrofuran
Interagency priority	Thiamethoxam	2009 HRL re-evaluation	1,1,1-Trichloroethane
2009 HRL re-evaluation	Vinyl Chloride		

APPENDIX E: CHEMICAL SUMMARY SHEETS

Note: The following documents represent the Health Based Values (HBVs) for chemicals included in the 2016/2018 proposed amendments. These chemical summary sheets are also available on MDH's Human Health-Based Water Guidance Table[16] and the HRL rule amendment webpages [17]. Upon adoption of the 2016/2018 amendments, these HBV summary sheets will be updated as HRL summary sheets, and posted online.

[16] Found at http://www.health.state.mn.us/divs/eh/risk/guidance/gw/table.html

[17] Found at http://www.health.state.mn.us/divs/eh/risk/rules/water/chemicals.html

Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
Web Publication Date: July 2016

Toxicological Summary for: Acenaphthene

CAS**: 83-32-9**

Synonyms: 1,2-Dihydroacenaphthylene (IUPAC), 1,8-Ethylenenaphthalene, *peri*-Ethylenenaphthalene, Naphthyleneethylene

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 200 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.07 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.070** L/kg-d)}}$$

= **200 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.07 mg/kg-d (CD-1 mice)
Source of toxicity value:	MDH, 2015
Point of Departure (POD):	162 mg/kg-d $BMDL_{10}$ (MDH derived, based on U.S. Environmental Protection Agency, 1989)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 162 x 0.13 = 21 mg/kg-d
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty due to a lack of reproductive/developmental studies and a lack of testing in a second species
Critical effect(s):	Increased relative liver weight in female mice
Co-critical effect(s):	Decreased relative adrenal weight
Additivity endpoint(s):	Adrenal, Hepatic (liver) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.021 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.044** L/kg-d)}}$$

= 95.5 rounded to **100 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.021 mg/kg-d (CD-1 mice)
Source of toxicity value:	MDH, 2015
Point of Departure (POD):	162 mg/kg-d $BMDL_{10}$ (MDH derived, based on U.S. Environmental Protection Agency, 1989, subchronic study)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 162 x 0.13 = 21 mg/kg-d
Total uncertainty factor:	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for extrapolation from a subchronic to a chronic study, and 10 for database uncertainty due to a lack of reproductive/developmental studies and a lack of testing in a second species
Critical effect(s):	Increased relative liver weight in female mice
Co-critical effect(s):	Decreased relative adrenal weight
Additivity endpoint(s):	Adrenal, Hepatic (liver) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Applicable
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (moderate)

Summary of Guidance Value History:

Acenaphthene has a 1993 chronic HRL of 400 µg/L. In addition, a Pesticide Rapid Assessment Result of 40 µg/L was derived in 2014 and was lower than the HRL due to the conservative rapid assessment method (MDH 2014). Subchronic and Chronic HBVs of 200 µg/L and 100 µg/L were derived in 2015. The 2015 Chronic HBV is 4 times lower than the 1993 HRL as the result of: 1) using updated risk assessment methodology, including use of body weight scaling and updated water intake rates, and 2) rounding to one significant digit. In 2016 MDH updated the intake rate values used to derive guidance values. The updated intake rates did not result in

changes to the values derived in 2015. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process acenaphthene would undergo re-evaluation in 2020.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	No	No	No
Effects observed?	Yes[1]	No	No	No	No

Comments on extent of testing or effects:

[1] A study in mice reported that the adrenal gland weight was decreased at dose levels more than 325 times the subchronic reference dose. Hormone levels were not assessed.

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Minnesota Department of Health

Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: February 2017

Toxicological Summary for: Acetochlor

CAS**: 34256-82-1**
Synonyms: 2-Chloro-2'-methyl-6'-ethyl-N-ethoxymethyl-acetanilide; 2-Chloro-N-(ethoxymethyl)-6'-ethyl-o-acetotoluidide; 2-Chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl)acetamide; 2'-Ethyl-6'-methyl-N-(ethoxymethyl)-2-chloroacetanilide

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 30 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.016 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 28.1 rounded to **30 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.016 mg/kg-d (Rat)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	22.4 mg/kg-d (NOAEL, Milburn 2001 (MRID 45357503) aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.22 (Body weight scaling, subchronic average female rat) (US EPA 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 22.4 mg/kg-d x 0.22 = 4.93 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of developmental neurotoxicity studies and lack of short-term study in sensitive species (dog))
Critical effect(s):	Decreased pup body weight, decreased number of pups per litter, decreased pup spleen and brain weight

Co-critical effect(s):	Decreased mean pup body weight, increased UDGPT activity, increased T4, and decreased T3
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Thyroid (E)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 30 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.012 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}}$$

= 34.3 rounded to **30 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.012 mg/kg-d (Beagle Dog)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	2 mg/kg-d (NOAEL, Broadmeadow 1988 (MRID 41565118), aci USEPA, 2006))
Dose Adjustment Factor (DAF):	0.59 (Body weight scaling, 1 year female dog) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 2 mg/kg-d x 0.59 = 1.18 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for database uncertainty (for lack of developmental neurotoxicity studies
Critical effect(s):	increased salivation, increased incidence of renal interstitial nephritis, testicular histopathology (testicular degeneration and hypospermia), liver glycogen depletion
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Male Reproductive system, Nervous system, Renal (kidney) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 20 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0039 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044L/kg-d)}^{**}}$$

= 18.2 rounded to **20 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.0039 mg/kg-d (Beagle Dog)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	2 mg/kg-d (NOAEL, Broadmeadow 1988 (MRID 41565118) (subchronic exposure), aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.59 (Body weight scaling, 1 year female dog) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 2 mg/kg-d x 0.59 = 1.18 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for extrapolation from subchronic to chronic
Critical effect(s):	Increased salivation, increased incidence of renal interstitial nephritis and chronic vasculitis, testicular histopathology (testicular degeneration and hypospermia), liver glycogen depletion
Co-critical effect(s):	Increased incidence of bronchiolar hyperplasia and renal tubular hyperplasia, decreased body weight gain
Additivity endpoint(s):	Hepatic (liver) system, Male Reproductive system, Nervous system, Renal (kidney) system, Respiratory system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Suggestive Evidence of Carcinogenic Potential by all routes (USEPA, 2013)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Nasal, lung, thyroid, and histiocytic sarcoma

Statement for non-linear carcinogens:

> Acetochlor is a nonlinear carcinogen and the chronic RfD is considered to be protective against cancer.

Volatile: No

Summary of Guidance Value History:

A noncancer chronic Health Based Value (HBV) of 10 µg/L was derived in 1995. In 2009, acute, short-term, subchronic HRLs of 40 µg/L and a chronic HRL of 9 µg/L were derived. In 2016, MDH re-evaluated the non-cancer HRLs, resulting in new noncancer short-term, and subchronic HBVs of 30 µg/L and a chronic HBV of 20 µg/L. The acute guidance was removed, the short-term and subchronic values are lower, and the chronic value is higher as a result of 1) using MDH's most recent risk assessment methodology, including the application of Human Equivalence Doses and 2) rounding to one significant digit. MDH intends to re-evaluate

guidance values on an approximately five year cycle in order to keep guidance values current with scientific knowledge. Under this process, Acetochlor will undergo re-evaluation in 2022.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	No	Yes	Yes	No
Effects observed?	Yes[1]	-	Yes[2]	Yes[3]	-[4]

Comments on extent of testing or effects:

[1] Increased adrenal and thyroid organ weights have been reported following exposure to doses up to 2 to 4 fold higher than the administered subchronic/chronic critical study LOAEL. Thyroid mechanism of action studies at high doses suggest that acetochlor disrupts the thyroid-pituitary homeostasis via increased hepatic UDPGH-mediated increased clearance of thyroxin (T4). Changes in circulating thyroid hormone levels were observed at these higher doses. These effects have been identified as co-critical effects for the short-term exposure duration.

[2] Developmental effects have been listed as an endpoint in several studies. Decreased pup weight, decreased litter size (suggestive of fetal loss) and changes in spleen and brain weights were observed at the administered acute/short-term critical study LOAEL. These effects have been identified as acute/short-term critical effects.

[3] Histological changes in the epidiymides and testes, hypospermia, degeneration of seminiferous tubules, decreased relative testes weight, and testicular atrophy were observed at the administered subchronic/chronic critical study LOAEL. Male reproductive effects are listed as a subchronic/chronic critical effect.

[4] Neurological symptoms (e.g., salivation) were reported at the subchronic/chronic critical study LOAEL. These effects are listed as a subchronic/chronic critical effect. Severe neurological effects (e.g., ataxia) were observed at administered dose levels 5-fold higher. Developmental and short-term studies did not include adequate assessments of neurotoxicity. As a result a database uncertainty factor of 10 was incorporated into the derivation of the short-term RfD and subchronic RfD.

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Web Publication Date: August 2017

Toxicological Summary for: Acetochlor ESA

CAS**: 187022-11-3**
Synonyms: Acetochlor Ethane Sulfonic Acid

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 500 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.29 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 509 rounded to **500 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 86.2/300 = 0.29 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	374.6 mg/kg-d (LOAEL, MRID 45300503, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.23 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 374.6 mg/kg-d x 0.23 = 86.2 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for extrapolation from a LOAEL to a NOAEL, and 3 for database uncertainty (lack of developmental or multigenerational reproductive studies)
Critical effect(s):	Increased free thyroxine (T4)
Co-critical effect(s):	Increased thyroid stimulating hormone (TSH)
Additivity endpoint(s):	Thyroid (E)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 500 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.19 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 543 rounded to **500 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 56.4/300 = 0.19 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	225.4 mg/kg-d (NOAEL, MRID 45313801, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.25 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 225.4 mg/kg-d x 0.25 = 56.4 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of 2 generation study, lack of sensitive endpoint testing (thyroid), lack of second species (based on parent compound, dog appears to be more sensitive)
Critical effect(s):	Decreased body weight and body weight gain, decreased food utilization
Co-critical effect(s):	Increased thyroid stimulating hormone (TSH), increased free thyroxine (T4), increased free triiodothyronine (T3), increased relative testes weight
Additivity endpoint(s):	Male Reproductive system, Thyroid (E)

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 300 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.056 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 255 rounded to **300 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 56.4/1000 = 0.056 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	225.4 mg/kg-d (NOAEL, MRID 45313801, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.25 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 225.4 mg/kg-d x 0.25 = 56.4 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for subchronic to chronic extrapolation, and 10 for database uncertainty (lack of 2 generation study, lack of sensitive endpoint testing (thyroid), lack of second species (based on parent compound, dog appears to be more sensitive)
Critical effect(s):	Decreased body weight and body weight gain, decreased food utilization
Co-critical effect(s):	Increased thyroid stimulating hormone (TSH), increased free thyroxine (T4), increased free triiodothyronine (T3), increased relative testes weight
Additivity endpoint(s):	Male Reproductive system, Thyroid (E)

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History:

In 2005, MDH derived a chronic noncancer Health-Based Value (HBV) of 50 µg/L. In 2009, MDH derived short-term, subchronic, and chronic noncancer HBVs of 600, 600, and 300 µg/L, respectively. These HBVs were adopted as Health Risk Limits (HRLs) in 2011. In 2017, MDH re-evaluated the noncancer HRLs, resulting in new noncancer short-term, subchronic, and chronic HBVs of 500, 500, and 300 µg/L, respectively. The short-term and subchronic values are lower and the chronic value is unchanged as a result of 1) using MDH's most recent risk assessment methodology including the application of Human Equivalence Doses (HED) and 2) rounding to one significant digit. MDH intends to re-evaluate guidance values in order to keep guidance values current with scientific knowledge.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	No	No[2]	No[3]	Yes
Effects observed?	Yes[1]	-	-	-	Yes[4]

Comments on extent of testing or effects:

[1] Alterations in thyroid hormone levels were reported at the lowest dose tested in a 28-day range-finding study and form the basis of the Short-term HBV. Alterations in thyroid hormone levels have also been reported for acetochlor OXA and the parent, acetochlor. Thyroid mechanism of action studies conducted on the parent, acetochlor, indicate that acetochlor disrupts thyroid-pituitary homeostasis via increased clearance of serum thyroxin (T4). The subchronic study did not include an evaluation of thyroid hormone levels. The subchronic HBV is based on the no adverse effect level (NOAEL) identified in the subchronic study and includes an uncertainty factor for database deficiency to address the need for additional testing on acetochlor ESA regarding altered thyroid hormone levels.

[2] No developmental study has been conducted. Registrant recommended that the OPP consider the alachlor ESA developmental study in rats as evidence that development is not a sensitive endpoint. The developmental study on the parent, acetochlor, identified HED LOAELs of 88-132 mg/kg-d and HED NOAELs of 33-44 mg/kg-d, based on signs of clinical toxicity and decreased weight gain in pregnant animals, increased resorptions and decreased fetal weights. However, the multiple generation study on the parent identified significantly lower HED NOAEL/LOAEL values (4.9/15.6 mg/kg-d), indicating that the standard developmental study protocol is not a sensitive test. A database uncertainty factor was incorporated into the derivation of the RfD, in part, due to the lack of a multigenerational reproductive study.

[3] Male reproductive toxicity (testicular degeneration and decreased testes weight) was a critical effect for the parent, acetochlor. Alterations in testes weights were reported in the short-term range finding study but not in the 90-day study. A database uncertainty factor was incorporated into the derivation of the RfD, in part, due to concerns that additional testing should be conducted.

[4] A functional observation battery for neurotoxicity was conducted and histopathology of the sciatic nerve was assessed in a 90-day study for general toxicity. There were possible signs of neurotoxicity, but none showed dose dependency. Neurological effects were a sensitive endpoint for the parent, acetochlor. A database uncertainty factor was incorporated into the derivation of the subchronic and chronic RfDs, in part, due to concerns that additional testing should be conducted.

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Web Publication Date: August 2017

Toxicological Summary for: Acetochlor OXA

CAS: 184992-44-4
Synonyms: Acetochlor Oxanilate Metabolite

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.081 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 142 rounded to **100 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:HED/Total UF = 80.8/1000 = 0.081 mg/kg-d (laboratory rat)

Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	367.2 mg/kg-d (LOAEL, MRID 45300506, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.22 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 367.2 mg/kg-d x 0.22 = 80.8 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for extrapolation from a LOAEL to NOAEL, and 3 for database uncertainty (lack of multigenerational reproductive study)
Critical effect(s):	Decreased thyroid stimulating hormone (TSH)
Co-critical effect(s):	Decreased body weight gain, decreased total triiodothyronine (tT3), increased relative thyroid weight
Additivity endpoint(s):	Thyroid (E)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.062 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 177 rounded to 200 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 18.5/300 = 0.062 mg/kg-d (rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	77.2 mg/kg-d (NOAEL, MRID 45313805 and 45300506, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.24 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 77.2 mg/kg-d x 0.24 = 18.5 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of multigenerational reproductive study, lack of studies in a second species (based on parent compound, dog appears to be more sensitive), lack of thyroid and motor activity effects studies [sensitive endpoints for parent compound, acetochlor])
Critical effect(s):	Decreased body weight and body weight gain, decreased food utilization
Co-critical effect(s):	Decreased thyroid stimulating hormone (TSH)
Additivity endpoint(s):	Thyroid (E)

The Subchronic nHBV must be protective of the acute, and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 100 µg/L. Additivity endpoints: Thyroid (E)

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 90 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.019 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 86.4 rounded to **90 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 18.5/1000 = 0.019 mg/kg-d (lab rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	77.2 mg/kg-d (NOAEL, MRIDs 45313805 & 45300506, aci USEPA, 2006)
Dose Adjustment Factor (DAF):	0.24 (body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 77.2 mg/kg-d x 0.24 = 18.5 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for subchronic to chronic extrapolation, and 10 for database uncertainty (lack of multigenerational reproductive study, lack of studies in a second species (based on parent compound, dog appears to be more sensitive), lack of studies showing thyroid and motor activity effects [sensitive endpoints for parent compound, acetochlor])
Critical effect(s):	Decreased body weight and body weight gain, decreased food utilization
Co-critical effect(s):	Decreased thyroid stimulating hormone (TSH)
Additivity endpoint(s):	Thyroid (E)

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History:

In 2005, MDH derived a noncancer Health-Based Value (HBV) of 50 µg/L. In 2009, MDH derived short-term, subchronic, and chronic noncancer HBVs of 200, 200, and 100 µg/L, respectively. These HBVs were adopted as Health Risk Limits (HRLs) in 2011. In 2017, MDH re-evaluated the noncancer HRLs, resulting in new noncancer short-term, subchronic, and chronic HBVs of 100, 100, and 90 µg/L, respectively. The short-term, subchronic, and chronic values are lower as a result of 1) using MDH's most recent risk assessment methodology including the application of Human Equivalence Doses (HED) and 2) rounding to one significant digit. MDH intends to re-evaluate guidance values in order to keep guidance values current with scientific knowledge.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	No	Yes	No	No
Effects observed?	Yes[1]	-	No[2]	-[3]	-[4]

Comments on extent of testing or effects:

[1] Alterations in thyroid hormone levels were reported at the lowest dose tested in a 28-day range-finding study and form the basis of the Short-term HBV. Alterations in thyroid hormone levels have also been reported for acetochlor ESA and the parent, acetochlor. Thyroid mechanism of action studies conducted on the parent, acetochlor, indicate that acetochlor disrupts thyroid-pituitary homeostasis via increased clearance of serum thyroxin (T4). The Subchronic study did not include an evaluation of thyroid hormone levels. The Subchronic HBV is based on the no adverse effect level (NOAEL) identified in the subchronic study and includes an uncertainty factor for database deficiency to address the need for additional testing on acetochlor OXA regarding altered thyroid hormone levels.

[2] A single developmental study has been conducted. No adverse developmental effects were reported at the highest dose tested. An increase in maternal mortality was observed in this study. Based on data for the parent, acetochlor, the 2-generation study reported significantly lower NOAEL/LOAEL value than the developmental study indicating that the standard developmental study protocol is not a sensitive test.

[3] Male reproductive toxicity was a critical effect for the parent, acetochlor. The database uncertainty factor was, in part, applied to address the absence of a 2-generational reproductive study.

[4] A dose-dependent increase in motor activity in males was observed in a 90 day study, however, this parameter was highly variable and only reached statistical significance ($p<0.01$) at the highest dose level. Researchers reported, but did not substantiate, that observations were within the range of historical controls. The nervous system has been identified as a chronic critical effect for the parent, acetochlor. The uncertainty factor for database deficiency is applied to the subchronic and chronic RfDs, in part, due to concerns that additional testing should be conducted.

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Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: February 2017

Toxicological Summary for: Alachlor

CAS**: 15972-60-8**
Synonyms: 2-Chloro-N-(2,6-diethylphenyl)-N-(methoxymethyl)acetamide;
Methoxymethyl-2',6'-diethylanilide chloroacetate;

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.077 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 135 rounded to **100 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.077 mg/kg-d (Sprague Dawley Rat)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	10 mg/kg-d (NOAEL, Schroeder et al., 1981 (MRID 00075062) aci USEPA, 1998)
Dose Adjustment Factor (DAF):	0.23 (Body weight scaling, subchronic Female Sprague Dawley Rat) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 10 mg/kg-d x 0.23 = 2.3 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased kidney weight in pups and adult animals, nephritis, kidney damage
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental, Renal (kidney) system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 60 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.020 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 57.1 rounded to **60 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.020 mg/kg-d (Beagle Dog)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	1 mg/kg-d (NOAEL, Naylor et al., 1984 (MRID 00148923) aci USEPA, 1998)
Dose Adjustment Factor (DAF):	0.61 (Body weight scaling, 1 year male dog) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 1 mg/kg-d x 0.61 = 0.61 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Hemosiderosis of the kidney and spleen
Co-critical effect(s):	Increased liver weight
Additivity endpoint(s):	Hematological (blood) system, Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 9 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0020 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044L/kg-d)}^{**}}$$

= 9.1 rounded to **9 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.0020 mg/kg-d (Beagle Dog)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	1 mg/kg-d (NOAEL, Naylor et al., 1984 (MRID 00148923) aci (USEPA, 1988) subchronic study)
Dose Adjustment Factor (DAF):	0.61 (Body weight scaling, 1 year male dog) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 1 mg/kg-d x 0.61 = 0.61 mg/kg-d
Total uncertainty factor (UF):	300

Uncertainty factor allocation:	3 for interspecies differences (toxicodynamics), 10 for intraspecies variability, and 10 for extrapolation from subchronic to chronic duration
Critical effect(s):	Hemosiderosis of the kidney and spleen,
Co-critical effect(s):	Increased liver weight
Additivity endpoint(s):	Hematological (blood) system, Hepatic (liver) system, Renal (kidney) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Likely to be carcinogenic at high doses, but not likely at low doses, by all exposure routes (USEPA, 1988, 2007)
Slope factor (SF):	0.08 per $(mg/kg\text{-}d)^{-1}$, however a nonlinear approach is recommended (USEPA, 1988)
Source of cancer slope factor (SF):	USEPA, 1998
Tumor site(s):	Nasal, stomach, and thyroid tumors

Statement for non-linear carcinogens:

Alachlor is a nonlinear carcinogen and the chronic RfD is considered to be protective against cancer.

Volatile: No

Summary of Guidance Value History:

A noncancer chronic Health Risk Limit (HRL) of 4 µg/L was promulgated in 1993/1994. In 2007, as required by a Legislative Session Law (Chapter 147, Article 17, section 2), the HRL was set equal to the MCL of 2 µg/L until MDH conducted a full review. Later in 2007 MDH derived short-term, subchronic, and chronic noncancer Health Based Values (HBVs) of 200, 30, and 5 µg/L, respectively. These HBVs were adopted as HRLs in 2009.In 2016, MDH re-evaluated the non-cancer HRLs, resulting in new noncancer short-term, subchronic, and chronic noncancer HBVs of 100, 60, and 9 µg/L, respectively. The short-term value is lower and the subchronic and chronic values are higher than previous guidance as a result of 1) using MDH's most recent risk assessment methodology including the application of Human Equivalence Doses and 2) rounding to one significant digit. MDH intends to re-evaluation guidance values on an approximately five year cycle in order to keep guidance values current with scientific knowledge. Under this process, Alachlor will undergo re-evaluation in 2022.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	Yes	Yes	No

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Effects observed?	-[1]	No	No[2]	No[3]	-[4]

Comments on extent of testing or effects:

[1] Alachlor was not specifically tested for endocrine effects. Alachlor has been shown to cause an increase in thyroid weights at doses 2-fold higher than the subchronic and chronic critical study LOAEL. Thyroid tumors were also observed in rats exposed to doses ~6-fold higher than the subchronic and chronic critical study LOAEL.

[2] Developmental studies have reported increased resorptions and decreased litter size at dose levels ~13-fold higher than the short-term critical study LOAEL and ~50-fold higher than the subchronic and chronic critical study LOAEL. The 3-generation study reported renal effects in rat pups at levels ~4-fold higher than the subchronic and chronic critical study LOAEL.

[3] A single multigenerational study has been conducted. No effect on reproductive parameters was reported, however, significant decreases in ovarian weight were observed in the F0, parental generation. No microscopic changes were reported.

[4] Based on toxicity profile for alachlor, OPP concluded that a developmental neurotoxicity study was not needed.

Resources Consulted During Review:

Australian Environment Protection and Heritage Council. (2008). "Australian Guidelines for Water Recycling: Managing Health and Environmental Risks - Augmentation of Drinking Water Supplies." from Australian Guidelines for Water Recycling: Managing Health and Environmental Risks - Augmentation of Drinking Water Supplies. https://www.nhmrc.gov.au/guidelines-publications/eh56.

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World Health Organization (WHO). (2011). "Guidelines for Drinking Water Fourth Edition." from http://apps.who.int/iris/bitstream/10665/44584/1/9789241548151_eng.pdf.

Minnesota Department of Health

Web Publication Date: February 2017

Toxicological Summary for: Chloroform

CAS**: 67-66-3**
Synonyms: Trichloroform, Trichloromethane

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)[1]

[1] Note: the developmental/reproductive endpoints listed for subsequent durations are co-critical effects taken from supportive studies that do not constitute sufficient information to provide the basis for an acute nHBV value.

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 20 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.022 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 15.4 rounded to **20 µg/L**

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.022 mg/kg-d (CD-1 Mouse)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	50 mg/kg-d (LOAEL, Munson et al. 1982)
Dose Adjustment Factor (DAF):	0.13 (Body weight scaling, subchronic average female mouse) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 50 mg/kg-d x 0.13 = 6.5 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for extrapolation from a LOAEL to a NOAEL
Critical effect(s):	Suppression of the humoral immune system (antigen forming cells)
Co-critical effect(s):	Increased liver weight, liver lesions, decreased body weight gain in pups, increased frequency of incomplete skull ossification in fetuses
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Immune system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short-term}$ = 20 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.022 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 62.9 rounded to 60 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.022 mg/kg-d (CD-1 Mouse)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	50 mg/kg-d (LOAEL, Munson et al. 1982)
Dose Adjustment Factor (DAF):	0.13 (Body weight scaling, subchronic average female mouse) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 50 mg/kg-d x 0.13 = 6.5 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for extrapolation from a LOAEL to a NOAEL
Critical effect(s):	Suppression of the humoral immune system (antigen forming cells)
Co-critical effect(s):	Increased liver weight and liver lesions, increased epididymal weights and degeneration of epididymal ductal epithelium, decreased body weight gain in pups, increased frequency of incomplete skull ossification in fetuses
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Immune system, Male Reproductive system

The Subchronic nHBV must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 20 µg/L. Additivity endpoints: Developmental, Hepatic (liver) system, Immune system.

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short-term}$ = 20 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.020 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044L/kg-d)}^{**}}$$

= 90.9 rounded to 90 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.020 mg/kg-d (Beagle Dogs)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	1 mg/kg-d (time adjusted BMDL, Heywood et al. 1979)
Dose Adjustment Factor (DAF):	0.61 (Body weight scaling, 2+ year female dog) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 1 mg/kg-d x 0.61 = 0.61 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Fatty cysts in the liver
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 20 µg/L. Additivity endpoints: Developmental, Hepatic (liver) system, Immune system.

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not likely to be carcinogenic to humans at doses that do not cause cytotoxicity and cell regeneration (USEPA, 2001)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Hepatic (liver) and Renal (kidney)

Statement for non-linear carcinogens:

Chloroform is a nonlinear carcinogen and the water guidance of 20 µg/L is considered to be protective against cancer. Per USEPA 2001, cancer classification is described as “Likely to be carcinogenic to humans by all routes of exposure under dose conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues [and] not likely to be carcinogenic to humans by all routes of exposure at dose levels that do not cause cytotoxicity and cell regeneration”. (USEPA, 2001)

Volatile: Yes (high)

Summary of Guidance Value History:

A cancer Health Risk Limit (HRL) of 60 µg/L, based on an EPA cancer slope factor derived in 1992, was promulgated in 1993/1994. In 2001, EPA updated its IRIS review, stating that EPA now considers chloroform to be a carcinogen with a nonlinear threshold mode of action, therefore, a cancer slope factor was no longer applicable, and the RfD approach was sufficiently protective. Short-term, subchronic, and chronic noncancer HRLs all equal to 30 µg/L were promulgated in 2009. In 2016, MDH re-evaluated the noncancer HRLs, resulting in new noncancer short-term, subchronic, and chronic values of 20 µg/L. The 2016 noncancer HBVs are lower than the previous HRLs as a result of 1) using MDH’s most recent risk assessment

methodology including the application of Human Equivalence Doses and 2) rounding to one significant digit. MDH intends to re-evaluate guidance values on an approximately five year cycle in order to keep guidance values current with scientific knowledge. Under this process, Chloroform will undergo re-evaluation in 2022.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	Yes	Yes	Yes	Yes
Effects observed?	-	Yes[1]	Yes[2]	No[3]	Yes[4]

Comments on extent of testing or effects:

[1] General toxicity studies with immunological endpoints (Munson et al, 1982) are the critical studies for the short term and subchronic durations with a significant decrease in humoral immunity reported at 50 mg/kg-d (administered dose) in male and female mice following 14 and 90 day exposures. Decreased humoral immunity is identified as a critical effect. Higher doses (250 mg/kg-d (administered dose)) caused changes in cell-mediated immunity in female mice at 90 days.

[2] Developmental studies show that doses that are maternally toxic may also be toxic to the fetus and cause the same types of liver damage as observed in adult animals. In one reproductive study in which the animals were exposed throughout their entire lifespan, damage to the liver was observed in adult offspring at a dose that was lower than the dose that was toxic after exposure to mature animals. In addition, changes in the epididymis of the male rats were noted at levels similar to the administered subchronic critical study LOAEL. The liver and epididymal effects have been identified as subchronic co-critical effects. In one study, administered doses about 3-fold higher than the short-term and subchronic critical study administered LOAEL caused changes in rib development. These studies were conducted in rats and the effects were observed at doses higher than the chronic critical study LOAEL observed in dogs (the more sensitive species).

[3] A single 2 generation study has been conducted. Changes in the epididymis were noted at levels similar to the administered levels in the short-term and subchronic critical study LOAEL, however, reproductive capacity was not affected. The epididymal effects have been identified as subchronic co-critical effects. Reproductive studies have shown changes in development and liver toxicity in offspring without affecting reproduction of the animals.

[4] Neurotoxic effects of changes in operant behavior occur at administered doses at least 2-fold higher than the subchronic and 8-fold higher than the chronic critical chronic study LOAEL. Very high administered acute doses (> 10-fold and higher than the short-term, subchronic and chronic critical study LOAELs) can cause changes in motor coordination (such as ataxia) and other acute affects expected from anesthetics.

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Minnesota Department of Health

Web Publication Date: July 2016

Toxicological Summary for: Clothianidin

CAS: **210880-92-5 (Former CAS # 205510-53-8)**
Synonyms: CGA-322704, *(E)-N*-[(2-chloro-5-thiazolyl)methyl]-*N'*-methyl-*N''*-nitroguanidine, (*E*)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 200 µg/L

$$\frac{\text{(Reference Dose mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.093 mg/kg-d) x (0.5*) x (1000 µg/mg)}}{\text{(0.285** L/kg-d)}}$$

= 163 rounded to **200 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.093 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Derived by MDH, 2016
Point of Departure (POD):	12 mg/kg-d (NOAEL, Freshwater 2000)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 12 mg/kg/d x 0.23 = 2.8 mg/kg-d
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight gain
Co-critical effect(s):	Decreased body weight gain in pregnant adult rats
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 200 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \text{(0.093}^{\#}\text{ mg/kg-d) x (0.2) x (1000 µg/mg)}$$

(0.070** L/kg-d)

= 266 rounded to 300 µg/L

#The calculated Subchronic RfD (0.28 mg/kg-d) is higher than the Short-term RfD (0.093 mg/kg-d), which is based on developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Subchronic RfD.

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

The Subchronic nHBV must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 200 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = ($nHBV_{Subchronic}$) = 200 µg/L

(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)
(Chronic Intake Rate, L/kg-d)

= $\frac{(0.077\ mg/kg\text{-}d) \times (0.2^*) \times (1000\ \mu g/mg)}{(0.044^{**} L/kg\text{-}d)}$

= 350 rounded to 400 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	0.077 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Derived by MDH, 2016
Point of Departure (POD):	8.9 mg/kg-d (BMDL, Biegel 2000b)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 8.9 x 0.26 = 2.3 mg/kg-d
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Ovarian interstitial gland hyperplasia
Co-critical effect(s):	Decreased pup body weight gain, decreased body weight gain in pregnant adult rats
Additivity endpoint(s):	Developmental, Female reproductive system

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period, and therefore, the Chronic nHBV is set equal to the Short-term and Subchronic nHBV of 200 µg/L. Additivity endpoints: Developmental

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not likely to be carcinogenic (US EPA 2009)
Slope factor:	Not Applicable

Source of slope factor: Not Applicable
Tumor site(s): Not Applicable

Volatile: No

Summary of Guidance Value History:
A pesticide rapid risk assessment was derived in 2014 and resulted in a value of 200 µg/L. This 2016 toxicological summary of Clothianidin contains the first HBVs calculated for Clothianidin by MDH. In 2016 MDH updated the intake rate values used to derive guidance values. Due to rounding to one significant digit the updated intake rates resulted in a revised calculated Subchronic nHBV of 300 µg/L, therefore it was set to the Short-term nHBV of 200 µg/L. Incorporation of updated intake rates did not result in any change to the Chronic nHBV value derived in 2015. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process clothianidin would undergo re-evaluation in 2021

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Endocrine effects such as increased relative testes weights occurred in male rats at 600 times the short-term reference dose. Reduced relative uterine and ovarian weights in female rats occurred at doses 500 times higher than the short-term reference dose. Thyroid follicular cysts occurred in female rats at doses 600 times higher than the chronic reference dose. Male mice had seminiferous tubule atrophy at levels 1000 times higher than the short-term reference dose. In a toxicity study designed to study thyroid changes, after clothianidin exposure in rats, there were no changes in triiodothyronine, thyroxine, and TSH levels.

[2] Although two toxicity studies specifically focused on immunotoxicity did not detect any changes in spleen activity up to 700 times the short-term reference dose, and no adverse effects on humoral or T-cell mediated immunity at levels up to 5,000 times the short-term reference dose, immunological effects were observed in other toxicity studies. These included thymus atrophy and reduced relative thymus weights in mice and rats at levels between 500-1,300 times higher than the short-term reference dose. Changes in spleen weight and spleen atrophy were observed in various toxicity studies in rats and mice at dosing levels 300 to 1,300 times higher than the short-term reference dose. Beagles were most sensitive to clothianidin in relation to changes in white blood cell, lymphocyte, eosinophil, neutrophil,

monocyte, and platelet counts, often occurring at 200 times higher than the short-term reference dose.

[3] The short-term reference dose is based on decreased pup body weights. At doses 600 times higher than the short-term reference dose, a delay in vaginal patency was observed, and at doses 100 times higher than the short-term reference dose, a delay in preputial separation was noted. Both of these observations could be related to the decrease in pup body weight. Fetal abnormalities occurred at levels 400 to 1,300 times higher than the short-term reference dose.

[4] The chronic reference dose is based on increased ovarian interstitial gland hyperplasia. Changes in uterine and ovary weights were noted at levels beginning at 300 times higher than the short-term reference dose. Changes in testes weight and sperm motility were observed at doses beginning at 500 times higher the short-term reference dose. Changes in metabolism in the testes was seen in rats beginning at 5 times higher than the short-term reference dose. In rabbits, there was an increased incidence of abortion and premature deliveries at levels 400 times higher than the short-term reference dose. Conversely, other studies noted no changes in the estrus cycle up to 600 times the short-term reference dose and no changes in reproductive effects up to 400 times the short-term reference dose.

[5] Neurotoxic effects were most prominent in mice, occurring at levels 40 to 500 times higher than the short-term reference dose. Tremors, convulsions, and reduced motor and locomotor activity in rats were noticed at levels 300 times the short-term reference dose. Increased secretion of tears was observed in rats at 1,300 times higher than the short-term reference dose. In a developmental neurotoxicity study designed specifically to assess neurotoxic parameters in rat pups, reduced response to loud noise, motor activity, time spent in movement, and increased brain thickness occurred at doses 800 times higher than the short-term reference dose.

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Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

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Toxicological Summary for: Cyanazine

CAS: **21725-46-2**
Synonyms: Bladex, 2-chloro-4-(1-cyano-1-methylethylamino)-6-ethylamino-s-triazine

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = 3 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Acute Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0015 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 2.6 rounded to **3 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	HED/Total UF = 0.46/300 = 0.0015 mg/kg-d (New Zealand White Rabbit)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	1.0 mg/kg-d (NOAEL, Shell Toxicology Lab [Turnstall] 1982 aci WHO, 2003 and USEPA 1988)
Dose Adjustment Factor (DAF):	0.46 (Body weight scaling, subchronic female New Zealand White Rabbit) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.0 mg/kg-d x 0.46 = 0.46 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed)
Critical effect(s):	Increased post-implantation loss
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental, Female Reproductive System

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 3 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{}$$

(Short-term Intake Rate, L/kg-d)

$$= \frac{(0.0015 \text{ mg/kg-d}) \times (0.5)^{*} \times (1000 \text{ µg/mg})}{(0.285 \text{ L/kg-d})^{**}}$$

= 2.6 rounded to **3 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.46/300 = 0.0015 mg/kg-d (New Zealand White Rabbit)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	1.0 mg/kg-d (NOAEL; Shell Toxicology Lab [Turnstall] 1982 aci WHO, 2003 and USEPA 1988)
Dose Adjustment Factor (DAF):	0.46 (Body weight scaling, subchronic female New Zealand White Rabbit) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.0 mg/kg-d x 0.46 = 0.46 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed)
Critical effect(s):	Alterations in fetal skeletal ossification sites and decreased litter size
Co-critical effect(s):	Increased post implantation loss, altered fetal skeletal ossification, increased relative brain weight and decreased relative kidney weight in weanlings, decreased adult body weight gain and food intake
Additivity endpoint(s):	Developmental, Female Reproductive System

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 3 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d)} \times \text{(Relative Source Contribution)} \times \text{(Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{(0.0011 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.070 \text{ L/kg-d})^{**}}$$

= 3.1 rounded to **3 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.33/300 = 0.0011 mg/kg-d (Beagle Dog)
Source of toxicity value:	Determined by MDH in 2017

Point of Departure (POD):	0.625 mg/kg-d (NOAEL; Dickie 1986 aci WHO, 2003)
Dose Adjustment Factor (DAF):	0.53 (Body weigh scaling, 3 month female dog) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.625 mg/kg-d x 0.53 = 0.33 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed)
Critical effect(s):	Decreased adult body weight and body weight gain, increased relative liver and kidney weights in adults
Co-critical effect(s):	Increased post implantation loss, altered fetal skeletal ossification, increased relative brain weight and decreased relative kidney weight in weanlings, decreased adult body weight gain and food intake
Additivity endpoint(s):	Developmental, Female Reproductive System, Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 1 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.00022 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044L/kg-d)}^{**}}$$

= 1.0 rounded to **1 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.067/300 = 0.00022 mg/kg-d (Sprague Dawley Rat)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	0.259 mg/kg-d (NOAEL; Bogdanffy, 2000)
Dose Adjustment Factor (DAF):	0.26 (Body weight scaling, Chronic Sprague Dawley female rat) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.259 mg/kg-d x 0.26 = 0.067 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (neuroendocrine effects, shown to be sensitive effects for triazines, have not been adequately assessed)
Critical effect(s):	Significant decrease in adult mean body weight and body weight gain, decreased food consumption and food efficiency

Co-critical effect(s):	Decreased body weight gain in adults, reduced growth and food consumption
Additivity endpoint(s):	None

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Group C (possible human carcinogen) (USEPA, 1994b)
Slope factor (SF):	1.0 $(mg/kg\text{-}d)^{-1}$ (Sprague-Dawley Rat)
Source of cancer slope factor (SF):	(USEPA, 1994b)
Tumor site(s):	Mammary gland tumors in female Sprague Dawley rats are induced via a neuroendocrine-mediated mechanism of action. The tumors produced via this mechanism of action are not relevant in humans, however, the neuroendocrine disruption is a noncancer endpoint of concern.[1]

[1] As part of the 2008 HRL revision, the MDH Group C review committee evaluated the weight of evidence regarding the carcinogenicity of cyanazine per the 2005 EPA Final Guidelines for Carcinogenic Potential and concurred with EPA (USEPA 2002a) that based on the scientific evidence specific for cyanazine, and cholo-s-triazines in general (including atrazine), tumor production is not relevant to humans. The chronic nHBV is considered to be protective and no additional Group C uncertainty factor should be applied.

Volatile: No

Summary of Guidance Value History:

A cancer health based value (HBV) of 0.4 µg/L was derived in 1995. In 2005, a noncancer chronic HBV of 1 µg/L was derived. In 2009, acute, short-term, and subchronic health risk limits (HRL) of 2 µg/L, and a chronic HRL of 1 µg/L were derived. In 2016, MDH re-evaluated the HRLs, resulting in no changes to any value. The 2016 values are the same as the 2009 values, but the basis of the values has changes as the result: 1) use of MDH's most recent risk assessment methodology, and 2) rounding to one significant digit. MDH intends to re-evaluate guidance values on an approximately five year cycle in order to keep guidance values current with scientific knowledge. Under this process, Cyanazine would undergo re-evaluation in 2022.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No[1]	No[2]	Yes	Yes	No
Effects observed?	-	-	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] No studies on cyanazine. Studies on several chloro-s-triazines (e.g., atrazine, propazine, simazine) have shown endocrine effects. Suppression of the luteinizing hormone (LH) surge is thought to be the most sensitive effect of chloro-s-triazines. It is believed that cyanazine is similar to other triazines. Therefore, neuroendocrine effects could be a more sensitive endpoint than fetotoxity, which is the basis of the acute & short-term HBV. Because of the lack of testing regarding this endpoint a database UF of 10 has been included in the derivation of the RfDs and HBVs for all durations.

[2] No studies on cyanazine. Immunological studies have been conducted for atrazine. These studies found that the immune system was not more sensitive than the neuroendocrine endpoints.

[3] Alterations in skeletal ossification sites and decreased litter size are the basis of the short-term critical study LOAEL. Post implantation loss was observed in a teratology study and is the basis of the acute HBV. Additional developmental effects (malformations of eye, brain, and chest wall as well as altered relative organ weights, higher incidence of a 13th rib, and complete loss of the litter) were reported at doses at least 2 times above the short-term critical study LOAEL.

[4] Limited reproductive testing for cyanazine. Post implantation loss was observed in a teratology study and is the basis of the acute HBV. Neuroendocrine effects, i.e., suppression of LH and disruption of the estrous cycle (disrupted and lengthened cycles) are thought to be the most sensitive effect of chloros-triazines. It is believed that cyanazine is similar to other triazines. Therefore, neuroendocrine effects could be a more sensitive endpoint than fetotoxity, which is the basis of the short-term HBV. Because of the lack of testing regarding this endpoint a database UF of 10 has been included in the derivation of the RfDs and HBVs for all durations.

[5] Increased relative brain weight was observed in offspring in a three-generation study at doses similar to the acute & short-term critical study LOAEL. This developmental effect is a co-critical effect for the short-term and subchronic durations. Neurotoxicity of cyanazine has not been studied. However, triazines disrupt the hypothalamic control of pituitaryovarian function providing evidence of associated central nervous system toxicity. Because of the lack of testing regarding this endpoint a database UF of 10 has been included in the derivation of the RfDs and HBVs for all durations.

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Minnesota Department of Health

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Toxicological Summary for: *cis*-1,2-Dichloroethene

CAS**: 156-59-2**
Synonyms: Cis-1,2-Dichloroethene, 1,2-DCE

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 20 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term intake rate, L/kg-d)}}$$

$$= \frac{\text{(0.033 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.285** L/kg-d)}}$$

= 23.2 rounded to **20 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	HED/Total UF = 9.9/300 = 0.033 mg/kg-d (Sprague Dawley rats))
Source of toxicity value:	MDH 2014
Point of Departure (POD):	43.3 mg/kg-d ($BMDL_{10}$; McCauley et al. 1995; short term study)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 43.3 x 0.23 = 9.9 mg/kg-day
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainties related to a lack of reproductive, developmental, neurological, or immune testing, as well as a lack of testing in species other than the rat.
Critical effect(s):	Increased liver weights in females
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 10 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic intake rate, L/kg-d)}}$$

$$= \frac{(0.0043^{*}\ \text{mg/kg-d}) \times (0.2) \times (1000\ \mu\text{g/mg})}{(0.070^{**}\ \text{L/kg-d})}$$

= 12.3 rounded to **10 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.0043 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	MDH 2014
Point of Departure (POD):	5.1 mg/kg-d ($BMDL_{10}$; EPA, 2010,McCauley et al. 1995; subchronic study)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 5.1 x 0.25 = 1.28 mg/kg-day
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainties related to a lack of reproductive, developmental, neurological, or immune testing, as well as a lack of testing in species other than the rat.
Critical effect(s):	Increased kidney weights in males
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 6 µg/L

$$\frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Chronic intake rate, L/kg-d})}$$

$$= \frac{(0.0013\ \text{mg/kg-d}) \times (0.2^{*}) \times (1000\ \mu\text{g/mg})}{(0.044^{**}\ \text{L/kg-d})}$$

= 5.9 rounded to **6 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.0013 mg/kg-d (Sprague Dawley rats
Source of toxicity value:	MDH 2014
Point of Departure (POD):	5.1 mg/kg-d ($BMDL_{10}$; EPA 2010, McCauley et al. 1995; subchronic study)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 5.1 x 0.25 = 1.28 mg/kg-d
Total uncertainty factor:	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for extrapolation from a subchronic study to a chronic study, and 10 for database uncertainties related to a lack of reproductive, developmental, neurological, or

	immune testing, as well as a lack of testing in species other than the rat.
Critical effect(s):	Increased kidney weights in males
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Inadequate information to assess the carcinogenic potential (U.S. Environmental Protection Agency, 2010a)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (high)

Summary of Guidance Value History:

In 1993/94 MDH promulgated an HRL value of 70 µg/L. In 2009 this value was repealed and replaced with revised HRL values. The 2009 HRL values were 70 µg/L for short term and subchronic durations, and 50 µg/L for the chronic duration. The 2014 values are lower than the 2009 values as a result of 1) selection of different, more sensitive critical effects; and 2) rounding to one significant digit. In 2016 MDH updated the intake rate values used to derive guidance values. This did not result in any change to the nHBV values derived in 2014. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process cis 1,2-dichloroethylene would undergo re-evaluation in 2019.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	No	No	No	No
Effects?	No	Secondary Observations[1]	No	No	Secondary Observations [2]

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:

[1] Immune effects were not directly tested. An increase in absolute and relative thymus weights was observed in female rats exposed to a dose more than 650,000 times the chronic RfD for 90 days.

[2] Neurotoxicity was not directed tested. At lethal doses, symptoms such as decreased activity, ataxia, suppressed or total loss of righting reflex, and depressed respiration were observed. The short term, subchronic, and chronic RfDs are protective of these effects.

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Toxicological Summary for: 2,4-Dichlorophenoxyacetic acid

CAS**: 94-75-7**
Synonyms: 2,4-D, ACETIC ACID-(2,4-DICHLOROPHENOXY)-, Dichlorophenoxyacetic acid, *IUPAC* name (2,4-Dichlorophenoxy)acetic acid

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 30 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.048 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 33.7 rounded to **30 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-water sources of exposure an RSC of 0.2 rather than the default of 0.5 has been selected.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	(POD x DAF)/Total UF = 0.048 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	21 mg/kg-d (NOAEL, MRID 47972101/Marty et al., 2013)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 21 mg/kg-d x 0.23 = 4.8 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for interspecies differences (toxicokinetic portion retained after DAF application due to remaining uncertainty) and 10 for intraspecies variability
Critical effect(s):	Increased thyroid stimulating hormone in pregnant rats, and decreased adrenal weight and thyroxine in offspring
Co-critical effect(s):	Increased skeletal abnormalities in offspring and decreased offspring body weight
Additivity endpoint(s):	Adrenal, Developmental, Thyroid (E)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short-term}$ = 30 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.017 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 48.6 rounded to 50 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	(POD x DAF)/Total UF = 0.017 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	6.8 mg/kg-d (NOAEL, MRID 47972101/Marty et al., 2013)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 6.8 mg/kg-d x 0.25 = 1.7 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for interspecies differences (toxicokinetic portion retained after DAF application due to remaining uncertainty) and 10 for intraspecies variability
Critical effect(s):	Proximal tubule degeneration in kidney
Co-critical effect(s):	Decreased pup body weight and body weight gain
Additivity endpoint(s):	Developmental, Renal (kidney) system

The Subchronic nHBV must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 30 µg/L. Additivity endpoints: Adrenal, Developmental, Thyroid (E)

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short-term}$ = 30 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.017 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 77.3 rounded to 80 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	(POD x DAF)/Total UF = 0.017 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	6.8 mg/kg-d (NOAEL, MRID 47972101/Marty et al., 2013)

Human Equivalent Dose (MDH, 2011):	POD x DAF = 6.8 mg/kg-d x 0.25 = 1.7 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for interspecies differences (toxicokinetic portion retained after DAF application due to remaining uncertainty) and 10 for intraspecies variability
Critical effect(s):	Proximal tubule degeneration in kidney
Co-critical effect(s):	Increased thyroid weight and histopathological changes of the proximal tubule in kidney, decreased pup body weight and body weight gain
Additivity endpoint(s):	Developmental, Renal (kidney) system, Thyroid

The Chronic nHBV must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 30 µg/L. Additivity endpoints: Adrenal, Developmental, Thyroid (E)

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	EPA Group D, Not Classifiable as to Human Carcinogenicity (EPA, 1997, EPA, 2013) IARC Group 2B, Possibly Carcinogenic to Humans (IARC, 2016)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Statement regarding carcinogenicity of 2,4-D:

The International Agency for Research on Cancer (IARC, 2016) concluded that 2,4-D is a possible human carcinogen based on strong mechanistic evidence for oxidative stress, moderate evidence for immunosuppression, limited evidence in animals, and inadequate evidence of cancer in humans. In addition, IARC determined that evidence was weak for genotoxicity, receptor activity, and altered cell proliferation following 2,4-D exposure. IARC evaluates cancer hazards without considering exposure levels or route of exposure and does not conduct quantitative cancer risk assessments. Agencies that develop quantitative cancer risk assessments, including the US EPA and the European Food Safety Authority (EFSA), currently conclude that 2,4-D is either not classifiable as a carcinogen or that it is unlikely to pose a cancer risk to humans ingesting foods treated with 2,4-D. Additionally, the mechanisms for carcinogenicity, suggested by IARC, were threshold or nonlinear in nature, and no tumors were consistently reported in rats or mice at the highest doses tested, which were over 1,000 times higher than the Chronic RfD. MDH will continue to monitor 2,4-D and its associated cancer risks, but at this time the noncancer health-based guidance values are considered protective for possible cancer risks associated with 2,4-D in drinking water.

Volatility: Non-volatile

Summary of Guidance Value History:

A chronic noncancer HRL for 2,4-D was set at 70 µg/L in 1993. A pesticide rapid assessment value was calculated for 2,4-D in 2014 at 2 µg/L. Short-term, Subchronic, and Chronic nHBVs of 30 µg/L were derived for 2,4-D in 2016. The 2016 nHBVs of 30 µg/L are lower than the 1993 HRL as a result of: 1) the use of more recent toxicological data, 2) the use of MDH's most recent risk assessment methodology, and 3) rounding to one significant digit. The 2016 nHBVs of 30 µg/L are higher than the pesticide rapid assessment due to the methodological differences between rapid assessment values and nHBVs. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process 2,4-D would undergo re-evaluation in 2021.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Endocrine effects have been thoroughly studied. Estrogenicity and androgenicity have been carefully examined in the critical study, with no treatment-related effects shown at doses nearly 200-fold higher than the short-term reference dose. Multiple studies show effects on thyroid and thyroid hormones, including the critical study, where these effects are important for deriving the short-term reference dose. Overall, thyroid effects occur at relatively high doses, with studies reporting thyroid hormone alterations and thyroid weight decreases at doses 200 -1,000 times higher than the short-term reference dose. Adrenal effects are also identified as a critical effect for short-term guidance. Additionally, hormones involved in milk production for offspring have been reported to be altered at doses nearly 70 times higher than the short-term reference dose.

[2] In humans, contradictory immunotoxicity results based on lymphocyte proliferation have been reported in studies of agricultural pesticide applicators. Several animal studies have examined immunotoxicity following 2,4-D exposure. Effects such as immune system organ weight changes were noted in the absence of other significant toxicity at doses greater than 100 times higher than the short-term reference dose following dietary exposure, while other studies in animals reported both stimulatory and suppressive effects at doses 10 to more than 100 times higher than the short-term reference dose. IARC (2016) recently determined there was moderate evidence for immune suppression, but the results are mixed and potentially contradictory across species and study types.

[3] The short-term reference dose is partially based on developmental effects. Offspring body weight decreases have been observed in studies at doses 300-750 times higher than the short-term reference dose. One study reported offspring body weight decreases beginning at doses roughly 11 times higher than the short-term reference dose. Other developmental effects

include decreased offspring viability, skeletal malformations in developing rats, and litter loss, at doses 300 – 600 times higher than the short-term reference dose.

[4] Reproductive effects have been extensively studied for 2,4-D. In adult animals, male reproductive glands have been altered at doses over 250 times higher than the subchronic reference dose. Milk production and lipid content were reported to be decreased in animals exposed to doses over 10 – 100 times higher than the short-term reference dose. Maternal behavior changes and decreased maternal body weight was altered at doses over 200 times higher than the short-term reference dose. Even in dogs, an organism overtly sensitive to 2,4-D toxicity, reproductive harm in males did not occur until doses exceeded nearly 100 times the subchronic reference dose.

[5] Neurotoxicity has been evaluated in multiple studies, and effects only occur at extremely high doses, especially if given as a single dose all at once (gavage). Animals were noted to have altered coordination and balance issues following doses over 1,000 times higher than the short-term reference dose. In a study with only a single exposure group, it was noted that myelin in the brain is affected at a dose approximately 450 times higher than the short-term reference dose. In pregnant animals, decreased control of movements and lowered overall activity were noted at a dose over 800 times higher than the short-term reference dose. Neurotransmitter levels in the brain have also been shown to be altered following 2,4-D exposure at doses 70 – 100 times higher than the short-term reference dose. Finally, lactating animals exposed to 2,4-D demonstrated altered activity, decreased myelin in their brains, and decreased brain weight at doses 300-450 times higher than the short-term reference dose.

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Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

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Toxicological Summary for: Dieldrin

CAS**: 60-57-1**

Synonyms: 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-exo-5,8-dimethanonaphthalene

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 0.2 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.00011 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 0.19 rounded to **0.2 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.00011 mg/kg-d (Squirrel Monkey)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	0.01 mg/kg-d (NOAEL, Smith et al. 1976)
Dose Adjustment Factor (DAF):	0.32 (Body weight scaling, subchronic Squirrel Monkey (USEPA, 2011) (Wisconsin, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.01 mg/kg-d x 0.32 = 0.0032 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Impaired learning
Co-critical effect(s):	Decrease in pup viability, increased preweaning pup mortality decreased antigen processing by

	alveolar macrophages, decreased tumor cell-killing ability
Additivity endpoint(s):	Developmental, Immune system, Nervous system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short-term}$ = 0.2 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.00009 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 0.26 rounded to 0.3 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.00009 mg/kg-d (Beagle Dog)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	0.005 mg/kg-d (NOAEL, Walker et al. 1969 aci USEPA, 2003)
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, 3 month female dog DAF) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.005 mg/kg-d x 0.53 = 0.0027 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased plasma alkaline phosphatase (AP) activity,
Co-critical effect(s):	Decrease in pup viability, decreased litter size, decreased survival as a result of hyperesthetia in both dams and pups, decreased antigen processing by alveolar macrophages, decreased tumor cell-killing ability, impaired learning
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Immune system, Nervous system

The Subchronic nHBV must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 0.2 µg/L. Additivity endpoints: Developmental, Immune system, Nervous system.

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 0.2 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{}$$

(Chronic Intake Rate, L/kg-d)

$$= \frac{(0.000043 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.044\text{L/kg-d})^{**}}$$

= 0.19 rounded to **0.2 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.000043 mg/kg-d (Carworth Farm E Rats))
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	0.005 mg/kg-d (NOAEL, Walker et al. 1969 aci USEPA, 2003)
Dose Adjustment Factor (DAF):	0.26 (Body weight scaling, average chronic female rat (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.005 mg/kg-d x 0.26 = 0.0013 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased relative liver weight
Co-critical effect(s):	Cerebral edema and small foci degeneration, decreased litter size, increased relative liver weight, decreased antigen processing by alveolar macrophages, decreased tumor cell-killing ability
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Immune system, Nervous system

Cancer Health Based Value (cHBV) = 0.006 µg/L

$$\frac{(\text{Additional Lifetime Cancer Risk, } 1 \times 10^{-5}) \times (\text{Conversion Factor, 1000 µg/mg})}{(\text{Slope Factor, per mg/kg-d}) \times (\text{Lifetime Adjustment Factor}) \times (\text{Lifetime Intake Rate, L/kg-d})}$$

$$= \frac{(1\text{x}10^{-5}) \times 1{,}000}{[(16 \times 2.5) \times 0.044 \text{ L/kg-day}]^{*}}$$

= 0.0057 rounded to **0.006 µg/L**

*Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Cancer classification:	B2, probable human carcinogen (USEPA, 1993) 2A probably carcinogenic to humans (IARC, 2016)
Slope factor (SF):	16 $(\text{mg/kg-d})^{-1}$ (geometric mean of 13 slope factors from several mouse strains) (USEPA, 1993)
Source of cancer slope factor (SF):	USEPA, 1993
Tumor site(s):	Liver

Volatile: No

Summary of Guidance Value History:

A cancer health based value (HBV) of 0.02 µg/L was first derived in 1997. In 2009, acute, short-term, subchronic, chronic health risk limits (HRL) of 0.2 µg/L and a cancer HRL of 0.006 µg/L were derived. In 2016, MDH re-evaluated the HRLs, resulting in no changes to the short-term, subchronic, chronic, and cancer HRLs. The acute guidance was removed. The 2016 values are the same as the 2009 values with the exception of the acute guidance being removed. However, the basis of the values has changed as the result of: 1) use of MDH's most recent risk assessment methodology, and 2) rounding to one significant digit. MDH intends to re-evaluate guidance values on an approximately five year cycle in order to keep guidance values current with scientific knowledge. Under this process, Dieldrin would undergo re-evaluation in 2022.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes
Effects observed?	No[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] No effect was found on levels of a limited number of circulating hormones (thyroxin, FSH, LH, TSH, prolactin, or growth hormone). There are some *in vivo* and *in vitro* data to suggest that dieldrin has weak estrogenic properties.

[2] Several studies in mice suggest that exposure may induce immunosuppression at dose levels similar to the short-term, subchronic, and chronic critical study HED LOAELs. Immune system has been listed as a short-term, subchronic, and chronic health endpoint.

[3] Several studies have demonstrated that dose levels similar to the short-term and subchronic critical study HED LOAELs can result in reduced pup survival, increase dopamine transporter levels and increase the incidence of hepatic lesions. Developmental effects has been listed as a short-term, subchronic, and chronic health endpoint.

[4] Several reproductive and multigenerational studies have been conducted. At levels within 3-6 fold slightly of the short-term and subchronic critical study HED LOAELs mothers were not able to adequately nurse their young because both the mother and offspring were too hyperesthetic. Rats appear to be more sensitive than mice. Nervous system is listed as a short-term, subchronic and chronic health endpoint.

[5] Impaired learning, increases in dopamine transporters, and hyperesthetia were observed at the short-term, subchronic and chronic critical study HED LOAELs. Nervous system is listed as a short-term, subchronic and chronic critical health endpoint. As dose levels increase irritability, salivation, hyperexcitability, tremors followed by convulsions, loss of body weight, depression, prostrations, and death are observed.

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Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

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Toxicological Summary for: Dinoseb

CAS**: 88-85-7**

Synonyms: 2-sec-Butyl-4,6-dinitrophenol, dinitrobutylphenol, Dinitro-ortho-sec-butyl phenol, 4,6-Dinitro-o-sec-butylphenol, 2,4-dinitro-6-sec-butylphenol, 4,6-dinitro-2-sec-butylphenol, 2,4-dinitro-6-(1-methylpropyl)phenol, 4,6-dinitro-2-(1-methyl-propyl)phenol, 2,4-dinitro-6-(1-methyl-propyl)phenol

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 8 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0048 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 8.4 rounded to **8 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 1.43/300 = 0.0048 mg/kg-d (SPF Crl;cd rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	6.52 mg/kg-d (LOAEL, Matsumoto et al., 2010)
Dose Adjustment Factor (DAF):	0.22 (Body weight scaling, MDH 2001, USEPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 6.52 mg/kg-d x 0.22 = 1.43 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for use of a LOAEL instead of a NOAEL, and 3 for database uncertainty for lack of an adequate multigenerational study and because the current studies were unable to identify a NOAEL.
Critical effect(s):	Increased number of fetuses with skeletal variations and short supernumerary ribs

Co-critical effect(s):	Decreased pup survival at birth, decreased maternal body weight, decreased fetal body weight, decreased body weight gain during pregnancy, decreased body weight of live fetuses, increased number of fetuses with external malformations, increased incidence of micropthalmia, increased number of skeletal malformations, decreased placenta weight
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 8 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0048*** mg/kg-d) x (0.2)* x (1000 µg/mg)}}{\text{(0.070 L/kg-d)**}}$$

= 13.7 rounded to 10 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-8
***The calculated subchronic RfD (0.0091 mg/kg-d) is higher than the short term RfD (0.0048 mg/kg-d), which is based on developmental effects. The subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008). Therefore, the subchronic RfD is set to the short-term RfD. See the short-term information above for details about the reference dose.

The Subchronic nHBV must be protective of the acute, and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 8 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 8 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0030 mg/kg-d) x (0.2)* x (1000 µg/mg)}}{\text{(0.044 L/kg-d)**}}$$

= 13.6 rounded to 10 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.912/300 = 0.0030 mg/kg-d (Sherman rats)
Source of toxicity value:	Determined by MDH in 2016 NOAEL= 0.912 mg/kg-d (Linder et al., 1982, subchronic duration)

Dose Adjustment Factor (DAF):	0.24 (Body weight scaling, MDH 2011, USEPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 3.8 mg/kg-d x 0.24 = 0.912 mg/kg-day
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for subchronic-to-chronic extrapolation, and 3 for database uncertainty for lack of an adequate multigenerational study
Critical effect(s):	Decreased sperm counts, and decreased sperm content of the caudae and vasa deferentia
Co-critical effect(s):	Decreased fetal body weight, decreased pup survival, increased incidence of supernumerary ribs, decreased sperm motility and velocity, increased sperm abnormalities
Additivity endpoint(s):	Developmental, Male reproductive system

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 8 µg/L. Additivity endpoints: Developmental

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	D (Not classifiable as to human carcinogenicity, USEPA, 1987b)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (moderate)

Summary of Guidance Value History:

Health-Based Values (HBVs) were first derived for Dinoseb in 2017. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process, Dinoseb will undergo re-evaluation in 2022.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	Yes	Yes	Yes	Yes
Effects observed?	-[1]	Yes[2]	Yes[3]	Yes[4]	-[5]

Comments on extent of testing or effects:

[1] Endocrine effects have not been specifically evaluated. However, a single study reported decreased thyroid gland weights in male rats at a 73 fold higher dose than the chronic reference dose (RfD).

[2] Immunotoxicity has not been adequately evaluated. In a single-dose immunology study where antigen was injected in the footpad, a dinoseb dose more than 700 fold higher than the short-term RfD markedly depressed the cellular immune response and the humoral immune response in hamsters.

[3] An increased number of fetuses with skeletal variations and short supernumerary ribs, developmental effects, are the basis for the short term RfD. Many studies reported decreased weight gain during pregnancy, and decreased weight in dams before and during gestation, and in pups and live embryos, indicating that treatment with dinoseb, is generally toxic to pregnant rats and mice and their offspring. Increases in internal/external malformations and anomalies, such as supernumerary ribs and loss of ossification, were seen at doses ranging from 50 - >1,000 fold higher than the short-term RfD. One study, at nearly 1,000 fold higher dose than the short-term RfD reported neural tube defects as the major common toxicological endpoint. Decreased gravid uterine weight was observed at a dose 400 fold higher than the short-term RfD.

[4] The chronic RfD is based on male reproductive effects. A number of studies reported many abnormal sperm parameters at doses ranging from more than 550-800 fold higher than the chronic RfD. Examples of sperm parameters affected include decreased number of sperm, decreased epididymal motility, decrease weight of seminal vesicle and prostate, abnormal sperm, decreased sperm counts, and decreased motile sperm rate. Two studies reported complete reproductive failure in males treated with more than 450 fold higher doses than the subchronic RfD. All mice dosed with more than 50 fold higher dose than the subchronic RfD were observed with endometrial hyperplasia and atrophy, and testicular atrophy and degeneration with hyperspermatogenesis.

[5] At doses over 450-fold higher than the subchronic RfD, there were no effects reported on discrimination/learning tests in adult rats, yet some increase in locomotor activity was noted. In a separate study, no effects were reported in rats given a series of Functional Observational Battery (FOB) neurotoxicity tests at doses over 300 fold higher than the subchronic RfD. Another multigeneration study using neurobehavioral assessments that tested offspring periodically over 14 weeks did not report any effects from doses up 500 fold higher than the subchronic RfD.

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Minnesota Department of Health

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Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for: *S*-Ethyl-*N*,*N*-dipropylthiocarbamate

CAS**: 759-94-4**

Synonyms: EPTC, Torbin, EPTAM, Eptam 6E, Eradicane, Stauffer R 1608, Alirox

Acute Non-Cancer Health Based Value ($nHBV_{acute}$) = 300 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Acute intake rate, L/kg-d)}}$$

$$= \frac{\text{(0.16 mg/kg-d) x (0.5*) x (1000 µg/mg)}}{\text{(0.285** L/kg-d)}}$$

= 281 rounded to **300 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.16 mg/kg-d (lpk:APfSD rats
Source of toxicity value:	MDH 2015
Point of Departure (POD):	200 mg/kg-d (LOAEL, Brammer 1993 aci (U.S. Environmental Protection Agency 2011), MRIDs 43039701 and 43297401)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 200 mg/kg-d x 0.24 = 48 mg/kg-day
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability; 10 for extrapolation from a LOAEL to a NOAEL due to the severity of the effect (brain necrosis).
Critical effect(s):	Necrosis of the pyriform/entorhinal cortex and/or dentate gyrus of the brain
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 300 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term intake rate, L/kg-d)}}$$

$$= \frac{(0.16 \text{ mg/kg-d}) \times (0.5^{*}) \times (1000 \text{ µg/mg})}{(0.285^{**} \text{ L/kg-d})}$$

= 281 rounded to **300 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.16 mg/kg-d (Wistar rats)
Source of toxicity value:	MDH 2015
Point of Departure (POD):	21.9 mg/kg-d (NOAEL, Lees 2004 aci (U.S. Environmental Protection Agency 2011), MRID 46319101)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 21.9 mg/kg-d x 0.22 = 4.8 mg/kg-day
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability
Critical effect(s):	Decreased pup weight at postnatal day 1, clinical signs of neurotoxicity in dams at parturition, increased whole litter losses
Co-critical effect(s):	Decreased pup body weight, decreased pup body weight gain
Additivity endpoint(s):	Developmental, Female Reproductive system, Nervous system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 90 µg/L

$$\frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Subchronic intake rate, L/kg-d})}$$

$$= \frac{(0.033 \text{ mg/kg-d}) \times (0.2^{*}) \times (1000 \text{ µg/mg})}{(0.070^{**} \text{ L/kg-d})}$$

= 94.3 rounded to **90 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.033 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	MDH 2015
Point of Departure (POD):	5 mg/kg-d in females, 4 mg/kg-d in males (NOAEL, Minor et al., 1982 aci (U.S. Environmental Protection Agency 2011), MRIDs 0012128 and 40420408, and Tisdel et al., 1986c aci (U.S. Environmental Protection Agency 2011), MRID 00161597)
Human Equivalent Dose (MDH, 2011):	[((POD x DAF (females)) + (POD x DAF (males)))/2]

	[((5 mg/kg-d x 0.22)+(4 mg/kg-day x 0.24))/2] = 1.0 mg/kg-day
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability
Critical effect(s):	Myocardial degeneration
Co-critical effect(s):	None
Additivity endpoint(s):	Cardiovascular system

Chronic Non-Cancer Health Based Value (nHBV$_{Chronic}$) = 40 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic intake rate, L/kg-d)}}$$

$$= \frac{\text{(0.0083 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.044** L/kg-d)}}$$

= 37.7 rounded to **40 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.0083 mg/kg-d (Crl;CD(SD)BR rats)
Source of toxicity value:	MDH 2015
Point of Departure (POD):	9 mg/kg-d (LOAEL, Dickie 1987 aci (U.S. Environmental Protection Agency 2011), MRID 40215001))
Human Equivalent Dose (MDH, 2011):	POD x DAF = 9 mg/kg-d x 0.28 = 2.5 mg/kg-day
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability; 10 for extrapolation from LOAEL to NOAEL because the effects were severe
Critical effect(s):	Cardiomyopathy
Co-critical effect(s):	Myocardial degeneration
Additivity endpoint(s):	Cardiovascular system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Applicable
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (Moderate)

Summary of Guidance Value History:

The previous 93/94 nHRL for EPTC is 200 µg/L. It represents the chronic duration and is derived from an EPA IRIS reference dose (RfD). There is also an MDH rapid assessment derived in 2014 of 80 µg/L. The current values for EPTC are 300 µg/L for the acute and short term duration, 90 µg/L for the subchronic duration and 40 µg/L for the chronic duration. There were no previous acute, short term or subchronic values. The reasons that the 2015 HBV for the chronic duration is 5x lower than the 1993 HRL are: 1) use of additional, more recent toxicity information; 2) use of enhanced duration-specific intake rates; and 3) rounding to one significant digit. In 2016 MDH updated the intake rate values used to derive guidance values. The updated intake rates did not result in any change to the nHBV values derived in 2015. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process EPTC would undergo re-evaluation in 2020

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	No	Yes	Yes	Yes
Effects?	No	No	Yes[1]	Yes[2]	Yes[3]

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:

[1] Decreased pup body weight is the basis for the short-term RfD. Increased embryotoxicity was observed at doses 130-fold higher than the acute RfD, along with fetal malformation at over 800-fold higher than the short-term RfD.

[2] Total litter loss is part of the basis of the short-term RfD.

[3] Neurotoxicity is the basis for the acute RfD. Effects seen included necrosis of the brain in adults exposed to EPTC, while neurobehavioral testing such as learning and memory tests did not show a difference in EPTC treated animals over control animals. Clinical signs such as hunched posture, pinched in sides, and hair standing on end in pregnant animals near the time of birth is the basis of the short-term RfD. Several studies reported reduced brain weights in adult animals at doses more than 750-fold higher than the subchronic RfD. Another study reported significant decreases in brain weights and neuronal necrosis at doses more than 250-fold higher than the subchronic RfD.

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Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for: Fluoranthene

CAS**: 206-44-0**

Synonyms: Benzo(j,k)fluorine, 1,2-Benzacenaphthene **Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)**

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 200 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.053 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.070** L/kg-d)}}$$

= 151 rounded to **200 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.053 mg/kg-d (CD-1 mice)
Source of toxicity value:	MDH 2015
Point of Departure (POD):	124 mg/kg-d ($BMDL_{10}$, derived by MDH, based on U.S. Environmental Protection Agency, 2012)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 124 x 0.13 = 16 mg/kg-d
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics); 10 for intraspecies variability; 10 for database uncertainty due to lack of reproductive and developmental studies
Critical effect(s):	Nephropathy
Co-critical effect(s):	Increased relative liver weight, increased SGPT
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 70 µg/L

(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)

(Chronic Intake Rate, L/kg-d)

= (0.016 mg/kg-d) x (0.2*) x (1000 µg/mg)

(0.044** L/kg-d)

= 74.4 rounded to **70 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.016 mg/kg-d (CD-1 mice)
Source of toxicity value:	MDH 2015
Point of Departure (POD):	124 mg/kg-d ($BMDL_{10}$, derived by MDH, based on U.S. Environmental Protection Agency, 2012, subchronic study)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 124 x 0.13 = 16 mg/kg-d
Total uncertainty factor:	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics); 10 for intraspecies variability; 3 for extrapolation from a subchronic to chronic study; and 10 for database uncertainty due to lack of reproductive and developmental studies
Critical effect(s):	Nephropathy
Co-critical effect(s):	Increased relative liver weight, increased SGPT
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Class D, not classifiable as to human carcinogenicity (EPA, 1990)
Slope factor:	N/A
Source of slope factor:	N/A
Tumor site(s):	N/A

EPA's finding (EPA, 1990) that fluoranthene cannot be classified (class D) for oral carcinogenicity is due to a lack of suitable data. No oral cancer study or EPA slope factor for fluoranthene is available and MDH has determined that a cancer health based guidance value cannot be developed.

Fluoranthene often occurs in environmental mixtures that are evaluated for carcinogenicity. To evaluate the cancer potency of mixtures, including fluoranthene, please consult the MDH RPF guidance document. http://www.health.state.mn.us/divs/eh/risk/guidance/pahguidance.pdf

Volatile: Yes (low)

Summary of Guidance Value History:
Fluoranthene has a chronic HRL of 300 µg/L from 1993. In addition, a Pesticide Rapid Assessment of 10 µg/L was derived in 2014 and was lower than the HRL due to the conservative rapid assessment method (MDH 2014). Subchronic and Chronic HBVs of 100 µg/L and 70 µg/L were derived in 2015. The 2015 chronic HBV is 4 times lower than the 1993 HRL as a result of: 1) the use of new methodology, including benchmark dose analysis, body weight scaling, and updated water intake rates, and 2) the rounding of values to one significant digit. In 2016 MDH updated the intake rate values used to derive guidance values. Due to rounding to one significant digit the updated intake rates resulted in a revised Subchronic nHBV of 200 µg/L but did not result in any change to the Chronic nHBV value derived in 2015. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process fluoranthene would undergo re-evaluation in 2020.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	No	No	Yes
Effects observed?	No	Yes[1]	No	No	Yes[2]

Comments on extent of testing or effects:

[1] Although the immunotoxicity of fluoranthene has not been studied, effects have been reported in a number of studies. In a single dose study, significantly decreased white blood cell counts were observed in rats at a dose nearly 8000 times the subchronic RfD. White blood cell counts were also decreased in longer studies in rats at a dose 5900 times the subchronic RfD. In addition, white blood cell numbers were decreased in female mice at a dose more than 1200 times the subchronic RfD.

[2] In one study, the following parameters were reported as significantly changed at doses more than 800 times the subchronic RfD: motor activity, neuromuscular, sensorimotor, autonomic, physiological, and excitability. However, none of these effects were replicated in any other study.

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Toxicological Summary for: Perfluorobutyrate

CAS**: 375-22-4**
Synonyms: Perfluorobutanoic Acid (PFBA), Perfluorobutyric acid, Heptafluorobutyric acid

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)*

* While a developmental study is available for PFBA, a human equivalent dose (HED) forms the basis of the reference dose and assumes steady state conditions that cannot be achieved from a one-day exposure. Based on a mean human half-life of 3 days steady-state conditions would be established within ~ 9-15 days. At the present time the information necessary to estimate less than steady-state doses is not available. The short-term HRL assessment incorporated information regarding developmental effects.

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 7 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0038 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 6.67 rounded to **7 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.38/100 = 0.0038 mg/kg-d (rat)
Source of toxicity value:	Determined by MDH in 2008
Point of Departure (POD):	3.01 mg/kg-d ($BMDL_{10}$, calculated by Butenhoff, 2007; based on NOTOX 2007a)
Dose Adjustment Factor (DAF):	Chemical-Specific Toxicokinetic Adjustment ($t½_{Human}$ / $t½_{MaleRat}$ = 72 hours / 9.22 hours = 8) ($t½$ based on Chang et al. 2008, Olsen et al. 2007b)
Human Equivalent Dose (HED):	POD/DAF = 3.01 mg/kg-d / 8 = 0.38 mg/kg-d (chemical specific basis)
Total uncertainty factor (UF):	100

Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (study did not identify a NOAEL or acceptable $BMDL_{10}$ for thyroid effects. A multigeneration reproductive study has not been conducted, however the database does include an extended one generation developmental study)
Critical effect(s):	Decreased cholesterol
Co-critical effect(s):	Increased relative thyroid weight, decreased serum total thyroxine (TT4), decreased dialysis free thyroxine (dFT4)
Additivity endpoint(s):	Hepatic (liver) system, Thyroid (E)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 7 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0029 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 8.29 rounded to 8 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.86/300 = 0.0029 mg/kg-d (rat)
Source of toxicity value:	Determined by MDH in 2008
Point of Departure (POD):	6.9 mg/kg-d (NOAEL, NOTOX 2007b)
Dose Adjustment Factor (DAF):	Chemical-Specific Toxicokinetic Adjustment ($t½_{Human}$ / $t½_{MaleRat}$ = 72 hours /9.22 hours = 8) (t½ based on Chang et al. 2008, Olsen et al. 2007b)
Human Equivalent Dose (HED):	POD/DAF = 6.9 mg/kg-d / 8 = 0.86 mg/kg-d (chemical specific basis)
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (assessment of thyroid effects was compromised by missing serum hormone data. A multigeneration reproductive study has not been conducted, however the database does include an extended one generation developmental study)
Critical effect(s):	Liver weight changes, morphological changes in liver and thyroid gland, decrease TT4, decreased

	red blood cells, decreased hematocrit and hemoglobin
Co-critical effect(s):	Increased relative thyroid weight, decreased serum TT4 and dFT4, decreased cholesterol, delayed eye opening
Additivity endpoint(s):	Developmental, Hematological (blood) system, Hepatic (liver) system, Thyroid (E)

The Subchronic nHBV must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 7 µg/L. Additivity endpoints: Hepatic (liver) system, Thyroid (E)

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 7 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0029 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

$$= 13.2 \text{ rounded to } 10 \text{ µg/L}$$

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.86/300 = 0.0029 mg/kg-d (rat)
Source of toxicity value:	Determined by MDH in 2008
Point of Departure (POD):	6.9 mg/kg-d (NOAEL, NOTOX 2007b)
Dose Adjustment Factor (DAF):	Chemical-Specific Toxicokinetic Adjustment ($t½_{Human}$ / $t½_{MaleRat}$ = 72 hours /9.22 hours = 8) (t½ based on Chang et al. 2008, Olsen et al. 2007b)
Human Equivalent Dose (HED):	POD/DAF = 6.9 mg/kg-d / 8 = 0.86 mg/kg-d (chemical specific basis)
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (assessment of thyroid effects was compromised by missing serum hormone data. A multigeneration reproductive study has not been conducted, however the database does include an extended one generation developmental study)
Critical effect(s):	Liver weight changes, morphological changes in liver and thyroid gland, decrease TT4, decreased red blood cells, decreased hematocrit and hemoglobin

Co-critical effect(s):	Increased relative thyroid weight, decreased serum TT4 and dFT4, decreased cholesterol, delayed eye opening
Additivity endpoint(s):	Developmental, Hematological (blood) system, Hepatic (liver) system, Thyroid (E)

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 7 µg/L. Additivity endpoints: Hepatic (liver) system, Thyroid (E)

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not Classified
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History:

MDH promulgated short-term, subchronic and chronic Health Risk Limits (nHRL) of 7 µg/L in 2011. In 2017, MDH re-evaluated the noncancer HRLs. The values did not change as a result of the evaluation and incorporation of MDH's most recent risk assessment methodology.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	No	Yes	No	Yes
Effects observed?	Yes[1]	-	Yes[2]	-	No[3]

Comments on extent of testing or effects:

[1] Secondary observations, including decreased T4 levels, altered hyperplasia/hypertrophy of the follicular epithelium of the thyroid, and increased thyroid weight were noted in the 28 and 90 day studies. These effects are identified as critical or co-critical effects for the short-term, subchronic, and chronic duration HBVs.

[2] Developmental delays were observed in offspring of mice exposed during pregnancy. This effect was observed at 2-fold higher than the human equivalent dose, upon which the short-term RfD is based. Developmental effects are identified as secondary effects.

[3] No available neurotoxicity studies. Secondary observations reported in the 28 and 90-day studies include delayed bilateral pupillary reflex for males exposed to a dose > 10-fold higher than the BMDL used as the basis of the short-term, subchronic, and chronic HBVs. Histopathological assessment of neuronal tissues (including the optic nerve) and motor activity evaluations did not reveal any treatment-related abnormalities.

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Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: May 2017

Toxicological Summary for: Perfluorooctane Sulfonate

CAS: **1763-23-1 (acid)**
29081-56-9 (ammonium salt)
70225-14-8 (diethanolamine salt)
2795-39-3 (potassium salt)
29457-72-5 (lithium salt)
[Note: perfluorooctanoate anion does not have a specific CAS number.]
Synonyms: PFOS, Perfluorooctane sulfonic acid

MDH conducted a focused re-evaluation, which relied heavily upon EPA's hazard assessment and key study identification contained within the EPA Health Effects Support Document for Perfluorooctane Sulfonate (PFOS) released in May 2016 (EPA 2016a). A complete evaluation of the toxicological literature was not conducted.

Short-term, Subchronic and Chronic* – Non-Cancer Health Based Value (nHBV) = 0.027 µg/L**

*Due to the highly bioaccumulative nature of PFOS and human half-life of nearly 5.4 years, serum concentrations are the most appropriate dose metric and the standard equation to derive the HBV was not appropriate. Short-term exposures have the potential to stay in the body for an extended period of time. Therefore a single HBV has been recommended for short-term, subchronic, and chronic durations. The 2017 HBV was derived using a toxicokinetic (TK) model developed by MDH with input from an external peer review panel. Model details are presented below.

**Relative Source Contribution (RSC): based on current biomonitoring serum concentrations from local and national general populations to represent non-water exposures, an RSC of 0.5 (50%) was selected for water ingestion.

Intake Rate: In keeping with MDH's practice, 95th percentile water intake rates (Table 3-1 and 3-3, USEPA 2011) or upper percentile breastmilk intake rates (Table 15-1, USEPA 2011) were used. Breastmilk concentrations were calculated by multiplying the maternal serum concentration by a PFOS breastmilk transfer factor of 1.3%. For the breast-fed infant exposure scenario, a period of exclusive breastfeeding for one year was used as representative of a reasonable maximum exposure scenario.

A simple equation is typically used to calculate HBVs at the part per billion level with results rounded to one significant digit. However, the toxicokinetic model used to derive the HBV for

PFOS showed that serum concentrations were impacted by changes in water concentrations at the part per trillion level. As a result, the 2017 HBV contains two digits.

Reference Dose/Concentration:	HED/Total UF = 0.00051/100 = 0.0000051 mg/kg-d (Crl:CD(SD)IGS VAF Rats). *[The corresponding serum concentration is 6.26/100 = 0.063 mg/L. Note: this serum concentration is inappropriate to use for individual assessment.***]*
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	6.26 mg/L serum concentration (EPA 2016a predicted average serum concentration for F2 generation. NOAEL from Luebker et al 2005b)
Dose Adjustment Factor (DAF):	0.000081; Toxicokinetic Adjustment based on Chemical-Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half-life, days) = 0.23 L/kg x (0.693/1971 days) = 0.000081 L/kg-day (US EPA 2016a)
Human Equivalent Dose (MDH, 2017):	POD x DAF = 6.26 mg/L x 0.000081 L/kg/day = 0.00051 mg/kg-day
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability and 3 for database uncertainty (additional studies regarding immunotoxicity are warranted)
Critical effect(s):	Decreased pup body weight
Co-critical effect(s):	In offspring exposed during development: delayed eye opening, increased sternal defects, changes in lung development, decreased glucose tolerance, increased motor activity and decreased habituation, decreased levels of thyroxine (T4), and decreased survival. In adult animals: liver weight changes accompanied by changes in cholesterol levels and histology; decreased levels of thyroxine (T4); decreased SRBC response, increased NK cell activity, decreased spleen and thymus weight and cellularity
Additivity endpoint(s):	Developmental, Hepatic (Liver) system, Immune system, Thyroid (E)

*** Serum concentration is useful for informing public health policy and interpreting population-based exposures. This value is based on population-based parameters and should not be used for clinical assessment or for interpreting serum levels in individuals.

Toxicokinetic Model Description:

Serum concentrations can be calculated from the dose and clearance rate using the following equation. This equation was used by EPA, to calculate the HEDs from the POD serum concentrations.

$$Serum\ Concentration\ \left(\frac{mg}{L}\right) = \frac{Dose\left(\frac{mg}{kg \cdot day}\right)}{Clearance\ Rate\left(\frac{L}{kg \cdot day}\right)}$$

Where:

Dose (mg/kg-day) = Water or Breastmilk Intake (L/kg-day) x Level in Water or Breastmilk (mg/L)

and

Clearance (L/kg-d) = Volume of distribution (L/kg) x (Ln 2/half-life (days))

Two exposure scenarios were examined: 1) an infant fed with formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water. In both scenarios the simulated individuals began life with a pre-existing body burden through placental transfer of PFOS (maternal serum concentration x 46%) based on average cord to maternal serum concentration ratios reported in the literature. The serum concentration of the mother at delivery was assumed to be at steady-state.

Consistent with MDH methodology, 95th percentile water intake and upper percentile breastmilk intake rates were used to simulate a reasonable maximum exposed individual. A PFOS breastmilk transfer factor of 1.3%, based on average breastmilk to maternal serum concentration ratios reported in the literature, was used to calculate breastmilk concentration. According to the 2016 Breastfeeding Report Card (CDC, 2016), nearly 66 percent of mothers in Minnesota report breastfeeding at six months, with 31.4 percent exclusively breastfeeding. The percent breastfeeding dropped to 41% at twelve months. MDH selected an exclusive breastfeeding duration of one year for the breast-fed infant scenario.

Daily post-elimination serum concentration was calculated as:

$$Serum\ Conc.\left(\frac{mg}{L}\right) = \left[Prev.\ day\ Serum\ Conc.\left(\frac{mg}{L}\right) + \frac{Today's\ Intake(mg)}{V_d\left(\frac{L}{kg}\right) \times BW(kg)}\right] \times e^{-k}$$

To maintain mass balance, daily maternal serum concentrations and loss-of-chemical via transfer to the infant as well as excretion represented by the clearance rate, were calculated.

Summary of Model Parameters

Model Parameter	Value Used
Half-life	1971 days (US EPA 2016c)
Volume of distribution (Vd)	0.23 L/kg (US EPA 2016c)
Vd Age Adjustment Factor	2.1 age 1-30 days decreasing to 1.2 age 5-10 years and 1.0 after age 10 years (Friis-Hansen 1961)

Model Parameter	Value Used
Clearance Rate (CR)	0.000081 L/kg-d, calculated from Vd x (Ln 2/half-life)
Placental transfer factor ***(% of maternal serum level)***	46% (MDH 2017b)
Breastmilk transfer factor ***(% of maternal serum level)***	1.3% (MDH 2017b)
Water Intake Rate (L/kg-d)	95th percentile consumers only (default values, MDH 2008) (Table 3-1 & 3-3, USEPA 2011)
Breastmilk Intake Rate (L-kg-d)	Upper percentile exclusively breast-fed infants (Table 15-1, US EPA 2011)
Body weight (kg)	Calculated from water intake and breastmilk intake rate tables

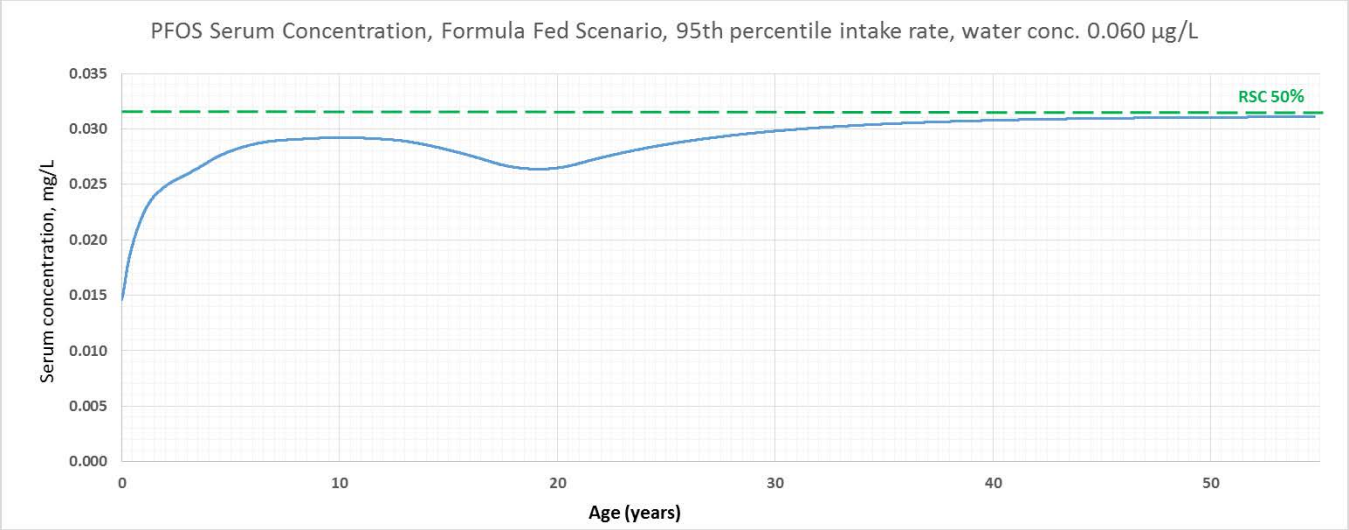
A relative source contribution factor (RSC) is incorporated into the derivation of a health-based water guidance value to account for non-water exposures. MDH utilizes the Exposure Decision Tree process presented in US EPA 2000 to derive appropriate RSCs. MDH relied upon the percentage method to reflect relative portions of water and non-water routes of exposure. The values of the duration specific default RSCs (0.5, 0.2, and 0.2 for short-term, subchronic, and chronic, respectively) are based on the magnitude of contribution of these other exposures that occur during the relevant exposure duration (MDH 2008). However, in the case of PFOS, application of an RSC needs to account for the long elimination half-life, such that a person's serum concentration at any given age is not only the result of his or her current or recent exposures within the duration of concern, but also from exposure from years past.

Serum concentrations are the best measure of cumulative exposure and can be used in place of the RfD in the Decision Tree process. Biomonitoring results from new residents who were not historically exposed to contaminated water in the East Metro can be used to represent non-water exposures (Nelson, 2016). The serum concentrations in these residents were similar in magnitude to those for the general public reported in the most recent National Report on Human Exposure to Environmental Chemicals (CDC 2017). MDH selected an RSC of 50% for exposure from water ingestion based on:

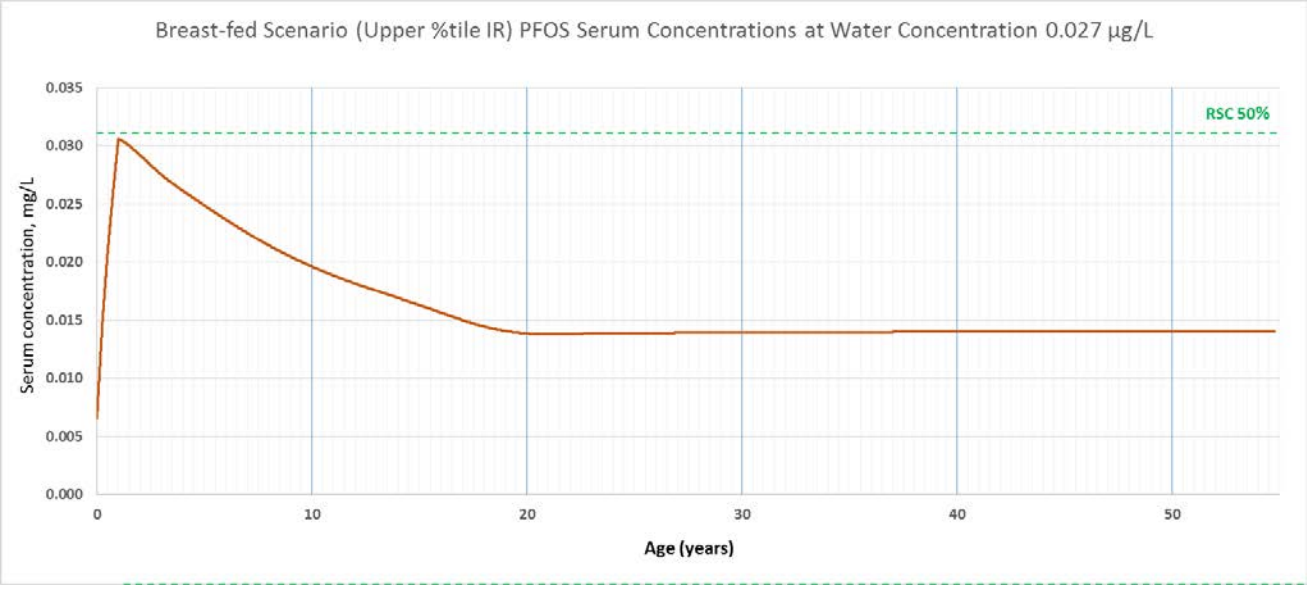
- A high-end, conservative estimate of background, non-water exposures represented by the 95th percentile serum concentration for new East Metro residents (0.021 mg/L serum), and
- The USEPA Decision Tree RSC ceiling of 80% to ensure a margin of safety to account for possible unknown sources of exposure

As mentioned above, two exposure scenarios were examined: 1) an infant fed formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water through life.

For the first scenario, the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water below an RSC of 50% throughout life is 0.060 µg/L. Because of the long half-life, the serum concentration curve is very flat and even a small increment increase in the water concentration (0.061 µg/L) raises the serum concentration above the 50 percent threshold for nearly 9 years.



Applying this water concentration of 0.060 µg/L in the context of a breast-fed infant resulted in not only an exceedance of the 50% RSC threshold, but of the entire reference serum concentration for more than one year. In order to maintain a serum concentration at or below an RSC of 50% for breast-fed infants, the water concentration should not exceed 0.027 µg/L.



Due to chronic bioaccumulation in the mother and subsequent transfer to breastmilk, the breast-fed infant exposure scenario is the most limiting scenario in terms of water concentrations. To ensure protection of all segments of the population, the final health-based value for PFOS is set at 0.027 µg/L.

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Suggestive Evidence of Carcinogenic Potential (EPA 2016b)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Liver and thyroid tumors were identified in both control and exposed animals at levels that did not show a direct relationship to dose.

Volatile: **No**

Summary of Guidance Value History:
A chronic nHBV of 1 µg/L was first derived in 2002. A revised chronic nHBV of 0.3 µg/L was derived in 2007 and promulgated as an nHRL in 2009. In 2016, EPA released a Health Advisory of 0.07 µg/L for PFOS. MDH conducted a re-evaluation and derived a revised nHBV (applicable to all durations) of 0.027 µg/L in 2017. The 2017 nHBV is lower than the previous value as the result of: 1) incorporating the most recent toxicological information and 2) chemical-specific exposure concerns from breastmilk.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[Note: MDH conducted a focused re-evaluation which relied upon EPA's hazard assessment and key study identification (EPA 2016a). A complete evaluation of the toxicological literature was not conducted.]

[1] Numerous human epidemiological studies have evaluated thyroid hormone levels and/or thyroid disease in association with serum PFOS. Results from these studies have provided limited support for an association. Stronger associations were found in populations at risk for iodine deficiency or positive anti-TPO antibodies (a marker for autoimmune thyroid disease).

Studies in laboratory animals have reported decreased serum thyroid levels, in particular, thyroxin (T4) in offspring and adult animals at exposure levels similar in magnitude to the critical

effect. Decreased T4 has been identified as a co-critical effect and Thyroid has been identified as an Additivity Endpoint.

[2] A few human epidemiology studies have evaluated associations between immunosuppression measures and serum PFOS. However, no clear associations were reported between serum PFOS and rates of infectious disease.

Studies in laboratory animals have shown that PFOS exposure alters several immunologic measures (e.g., suppression of SRBC response, and/or increased natural killer cell activity). Some of these effects occur at exposure levels similar to the POD. As a result the immune system has been identified as an Additivity Endpoint and a database uncertainty factor has been incorporated into the derivation of the RfD.

[3] Human epidemiology studies have suggested an association between prenatal PFOS serum levels and lower birth weight, however, this association has not been consistent.

Studies conducted in laboratory animals have identified several sensitive developmental effects. Decreased pup body weight appears to be among the most sensitive effects and, in part, forms the basis of the Reference Dose and corresponding serum concentration of concern. A limited number of studies have also reported changes in male reproductive development and changes in energy metabolism (e.g., glucose levels, lipid metabolism) following exposure during development. Additional effects, including increased pup death, were observed at higher exposure levels.

[4] A small number of human epidemiology studies have reported an association between preconception serum PFOS and gestational diabetes and pregnancy-induced hypertension. There has also been some evidence of associations between serum PFOS and decreased fertility, however, concerns have been raised over the possibility that this is due to reverse causation.

Studies in laboratory animals do not indicate that fertility is a sensitive endpoint, with decreases in male reproductive organs weights, decreased epididymal sperm count, and evidence of disruption of the blood-testes-barrier occurring at exposure levels higher than those causing developmental toxicity (see above). Therefore, the RfD would be protective of these effects.

[5] Developmental neurotoxicity and adult neurotoxicity studies have been conducted in laboratory animals. Increased motor activity and decreased habituation of male offspring was reported following gestational and lactational exposure at levels similar to the critical effect and have been included as co-critical effects. These effects are encompassed by the developmental additivity endpoint. Results from studies using water maze tests for learning and memory in animals exposed during development or as adults have yielded inconsistent results or effects at higher dose levels.

Resources Consulted During Review:

[Note: MDH conducted a focused re-evaluation which relied upon EPA's hazard assessment and key study identification (EPA 2016a). A complete evaluation of the toxicological literature was not conducted.]

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Web Publication Date: May 2017

Toxicological Summary for: Perfluorooctanoic Acid

CAS: **335-67-1(free acid)**
335-66-0 (acid fluoride)
3825-26-1 (ammonium salt, APFO)
2395-00-8 (potassium salt)
335-93-3 (silver salt)
335-95-5 (sodium salt)
[Note: perfluorooctanoate anion does not have a specific CAS number.]
Synonym: PFOA

MDH conducted a focused re-evaluation which relied heavily upon EPA's hazard assessment and key study identification contained within the EPA Health Effects Support Document for Perfluorooctanoic Acid (PFOA) released in May 2016 (EPA 2016a). A complete evaluation of the toxicological literature was not conducted.

Short-term, Subchronic and Chronic* - Non-Cancer Health Based Value (nHBV) = 0.035 µg/L**

*Due to the highly bioaccumulative nature of PFOA and human half-life of approximately 2- 3 years, serum concentrations are the most appropriate dose metric and the standard equation to derive the HBV was not appropriate. Short-term exposures have the potential to stay in the body for an extended period of time. Therefore a single HBV has been recommended for short-term, subchronic, and chronic durations. The 2017 HBV was derived using a toxicokinetic (TK) model developed by MDH with input from an external peer review panel. See details about the model presented below.

**Relative Source Contribution (RSC): based on current biomonitoring serum concentrations from local and national general populations to represent non-water exposures, an RSC of 0.5 (50%) was selected for water ingestion.

Intake Rate: In keeping with MDH's practice, 95th percentile water intake rates (Table 3-1 and 3-3, USEPA 2011) or upper percentile breastmilk intake rates (Table 15-1, USEPA 2011) were used. Breastmilk concentrations were calculated by multiplying the maternal serum concentration by a PFOA breastmilk transfer factor of 5.2%. The intake rates and breastfeeding period of one year were used as representative of a reasonable maximum exposure scenario.

MDH typically uses a simple equation to calculate HBVs at the part per billion level with results rounded to one significant digit. However, the toxicokinetic model used to derive the HBV for

PFOA showed that serum concentrations were impacted by changes in water concentrations at the part per trillion level. As a result, the HBV contains two digits.

Reference Dose/Concentration:	HED/Total UF = 0.0053/300=0.000018 mg/kg-d (CD-1 Mice). *[The corresponding serum concentration is 38/300 = 0.13 mg/L (or µg/mL). NOTE: this serum concentration is inappropriate to use for individual assessment.***]*
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	38 mg/L serum concentration (EPA 2016a predicted average serum concentration for maternal animals from Lau et al 2006)
Dose Adjustment Factor (DAF):	0.00014; Toxicokinetic Adjustment based on Chemical-Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half-life, days) = 0.17 L/kg x (0.693/840 days) = 0.00014 L/kg-day (US EPA 2016a)
Human Equivalent Dose (HED):	POD x DAF = 38 mg/L x 0.00014 L/kg/day = 0.0053 mg/kg-day
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics); 10 for intraspecies variability. With the exception of accelerated preputial separation (PPS), the effects observed at the LOAEL were mild. A LOAEL-to-NOAEL uncertainty factor of 3 was used, along with a database uncertainty factor of 3 for the lack of an acceptable 2-generation study.
Critical effect(s):	Delayed ossification, accelerated PPS in male offspring, trend for decreased pup body weight, and increased maternal liver weight
Co-critical effect(s):	In offspring exposed during development: changes in liver weight, histology, and triglycerides, and delayed mammary gland development. In adult animals: liver weight changes accompanied by changes in liver enzyme levels, changes in triglyceride and cholesterol levels, and microscopic evidence of cellular damage, decreased spleen weight, decreased spleen lymphocytes, and decreased IgM response, and kidney weight changes.
Additivity endpoint(s):	Developmental, Hepatic (Liver) system, Immune system, and Renal (Kidney) system.

*** Serum concentration is useful for informing public health policy and interpreting population-based exposures. This value is based on population-based parameters and should not be used for clinical assessment or for interpreting serum levels in individuals.

Toxicokinetic Model Description:

Serum concentrations can be calculated from the dose and clearance rate using the following equation. This equation was used by EPA, to calculate the HEDs from the POD serum concentrations.

$$Serum\ Concentration\ \left(\frac{mg}{L}\right) = \frac{Dose\left(\frac{mg}{kg \cdot day}\right)}{Clearance\ Rate\left(\frac{L}{kg \cdot day}\right)}$$

Where:

Dose (mg/kg-day) = Water or Breastmilk Intake (L/kg-day) x Level in Water or Breastmilk (mg/L)

and

*Clearance (L/kg-d) = Volume of distribution (L/kg) x (Ln 2/half-life (days))*Two exposure scenarios were examined: 1) an infant fed with formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water. In both scenarios the simulated individuals began life with a pre-existing body burden through placental transfer (maternal serum concentration x 87%) based on average cord to maternal serum concentration ratios reported in the literature. The serum concentration of the mother at delivery was assumed to be at steady-state.

Consistent with MDH methodology, 95th percentile water intake and upper percentile breastmilk intake rates were used to simulate a reasonable maximum exposed individual. A breastmilk transfer factor of 5.2%, based on average breastmilk to maternal serum concentration ratios reported in the literature, was used to calculate breastmilk concentration. According to the 2016 Breastfeeding Report Card (CDC 2016) nearly 66 percent of mothers in Minnesota report breastfeeding at six months, with 31.4 percent exclusively breastfeeding. The percent breastfeeding dropped to 41% at twelve months. MDH selected an exclusive breastfeeding duration of one year for the breast-fed infant scenario.

Daily post-elimination serum concentration was calculated as:

$$Serum\ Conc.\left(\frac{mg}{L}\right) = \left[Prev.\ day\ Serum\ Conc.\left(\frac{mg}{L}\right) + \frac{Today's\ Intake(mg)}{V_d\left(\frac{L}{kg}\right) \times BW(kg)}\right] \times e^{-k}$$

To maintain mass balance, daily maternal serum concentrations and loss-of-chemical via transfer to the infant as well as excretion represented by the clearance rate, were calculated.

Summary of Model Parameters

Model Parameter	Value Used
Half-life	840 days (US EPA 2016a)
Volume of distribution (Vd)	0.17 L/kg (US EPA 2016a)
Vd Age Adjustment Factor	2.1 age 1-30 days decreasing to 1.2 age 5-10 years and 1.0 after age 10 years (Friis-Hansen 1961)
Clearance Rate (CR)	0.00014 L/kg-d, calculated from Vd x (Ln 2/half-life)
Placental transfer factor ***(% of maternal serum level)***	87% (MDH 2017b)
Breastmilk transfer factor ***(% of maternal serum level)***	5.2% (MDH 2017b)
Water Intake Rate (L/kg-d)	95th percentile consumers only (default values, MDH 2008) (Table 3-1 & 3-3, USEPA 2011)
Breastmilk Intake Rate (L-kg-d)	Upper percentile exclusively breast-fed infants (Table 15-1, US EPA 2011)
Body weight (kg)	Calculated from water intake and breastmilk intake rate tables

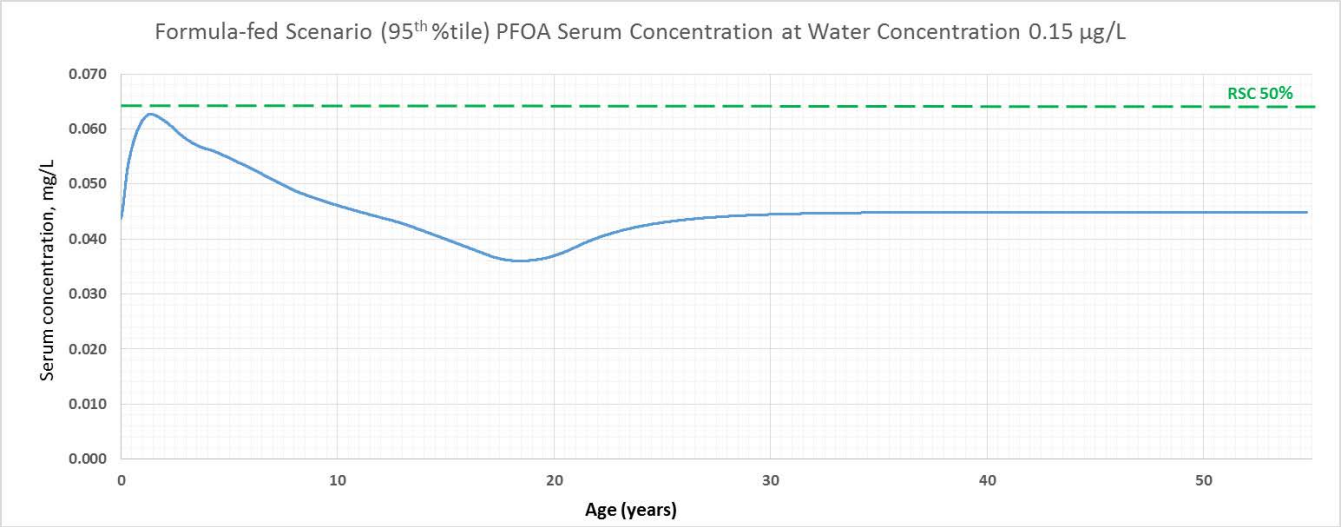
A relative source contribution factor (RSC) is incorporated into the derivation of a health-based water guidance value to account for non-water exposures. MDH utilizes the Exposure Decision Tree process presented in US EPA 2000 to derive appropriate RSCs. MDH relied upon the percentage method to reflect relative portions of water and non-water routes of exposure. The values of the duration-specific default RSCs (0.5, 0.2, and 0.2 for short-term, subchronic, and chronic, respectively) are based on the magnitude of contribution of these other exposures that occur during the relevant exposure duration (MDH 2008). However, in the case of PFOA, application of an RSC needs to account for the long elimination half-life, such that a person's serum concentration at any given age is not only the result of his or her current or recent exposures within the duration of concern, but also from exposure from years past.

Serum concentrations are the best measure of cumulative exposure and can be used in place of the RfD in the Decision Tree process. Biomonitoring results for the general public reported in the most recent National Report on Human Exposure to Environmental Chemicals (CDC 2017) can be used to represent non-water exposures. MDH selected an RSC of 50% for exposure from water ingestion based on:

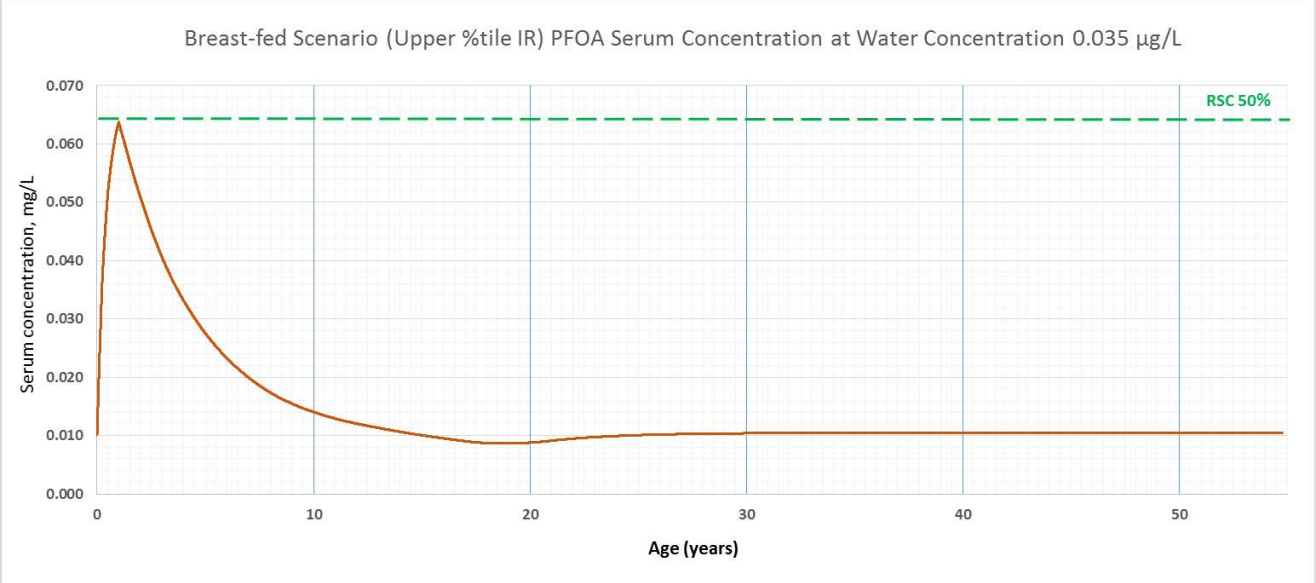
- A high-end, conservative estimate of background, non-water exposures represented by the 95th percentile serum concentration from 2013-14 NHANES (0.00557 mg/L serum), and
- The USEPA Decision Tree RSC ceiling of 80% to ensure a margin of safety to account for possible unknown sources of exposure

As mentioned above, two exposure scenarios were examined: 1) an infant fed formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water through life.

For the first scenario, the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water below an RSC of 50% throughout life is 0.15 µg/L. Because of the long half-life, the serum concentration curve is very flat and even a small increment increase in the water concentration (0.16 µg/L) raises the serum concentration above the 50 percent threshold for over a year.



Applying this water concentration of 0.15 µg/L in the context of a breast-fed infant resulted in not only an exceedance of the 50% RSC threshold, but of the entire reference serum concentration for more than four years. In order to maintain a serum concentration at or below an RSC of 50% for breast-fed infants, the water concentration should not exceed 0.035 µg/L.



Due to chronic bioaccumulation in the mother and subsequent transfer to breastmilk, the breast-fed infant exposure scenario is the most limiting scenario in terms of water concentrations. To

ensure protection of all segments of the population, the final health-based value for PFOA is set at 0.035 µg/L.

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Suggestive Evidence of Carcinogenic Potential (EPA 2016b)
Slope factor (SF):	Not Applicable. [EPA derived a slope factor of 0.07 $(mg/kg\text{-}d)^{-1}$. However, this slope factor cannot be used to derive quantitative guidance for PFOA because it was based on body weight scaling rather than established chemical-specific toxicokinetic differences.]
Source of cancer slope factor (SF):	Not Applicable (see above)
Tumor site(s):	Leydig Cell Tumors*

*An increased incidence of Leydig Cell Tumors (LCT) was observed in male rats. MDH considers the existing database to be inadequate for assessing carcinogenic potential of PFOA. No mode of action(s) (MOAs) has been identified, however, PFOA is not genotoxic and a hormonal cancer mechanism has been suggested. It is likely that the MOA(s) would have a threshold. Leydig cell turmors are common in rats but rare in humans. In addition, the MOA for LCTs in rats has questionable relevance to humans (Cook 1999) (Steinbach 2015). Some epidemiology studies reported a possible link between PFOA and testicular cancer in humans. Most human testicular cancers are not Leydig cell tumors and the type of testicular tumor associated with PFOA in humans was not characterized in the published literature. MDH considers the noncancer-based water guidance value of 0.035 µg/L to be protective for potential cancer effects, based on currently available data.

Volatile: No

Summary of Guidance Value History:

A chronic nHBV of 7 µg/L was first derived in 2002. A revised chronic nHBV of 0.3 µg/L was derived in 2007 and promulgated as an nHRL in 2009. In 2016, EPA released a Health Advisory of 0.07 µg/L for PFOA. MDH conducted a re-evaluation and derived a revised nHBV (applicable to all durations) of 0.035 µg/L in 2017. The 2017 nHBV is lower than the previous value as the result of: 1) incorporating the most recent toxicological information and 2) addressing chemical-specific exposure concerns from breastmilk.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[Note: MDH conducted a focused re-evaluation which relied upon EPA's hazard assessment and key study identification (EPA 2016a). A complete evaluation of the toxicological literature was not conducted.]

[1] Three large epidemiological studies provide support for an association between PFOA exposure and incidence or prevalence of thyroid disease in female adults or children, but not in males. In addition, associations between PFOA and Thyroid Stimulating Hormone (TSH) have also been reported in some populations of pregnant females. However, no significant associations were found between PFOA and TSH or thyroid hormones (T4 or T3) in people who have not been diagnosed with thyroid disease.

Effects of PFOA on thyroid hormones in animals are generally not as well characterized as those of PFOS. Reduced total and free T4 were reported in adult male rats and monkeys at serum levels > 500-fold higher than the serum level corresponding to the RfD. However, these doses were the lowest doses tested within the study and the dose-response relationship of serum total T4 with PFOA exposure has yet to be fully evaluated. As a result, the lowest effective dose remains unknown.

Other endocrine effects beyond thyroid have not been well-studied, and study results are not entirely consistent. A few studies reported sperm abnormalities, decreased testosterone and increased estradiol in male rats and mice at PFOA levels similar to those which form the basis of the RfD, whereas other studies only reported these effects at higher doses.

[2] Associations between prenatal, childhood, or adult PFOA exposure and risk of infectious diseases (as a marker of immune suppression) have not been consistently seen in epidemiological studies, although there was some indication of effect modification by gender (i.e., associations seen in female children but not in male children). Three studies examined associations between maternal and/or child serum PFOA levels and vaccine response (measured by antibody levels) in children and adults. The study in adults reported that a reduction in antibody response to one of the three influenza strains tested after receiving the flu vaccine was associated with increasing levels of serum PFOA. While decreased vaccine response was associated with PFOA levels in these studies, similar results were also observed with other perfluorinated chemicals and, therefore, could not be attributed specifically to PFOA.

Several animal studies demonstrate effects on the spleen and on thymus weights as well as decreased immune response. These effects were observed at serum concentrations similar to the critical study LOAEL. The immune system is listed as one of the co-critical effects and Additivity Endpoints.

[3] There have been numerous human epidemiological studies examining PFOA exposure and developmental effects. Some studies reported an association between PFOA and birth weight, while others have not. Two epidemiological studies examined development of puberty in females in relation to prenatal exposure to PFOA, however, the results of these two studies are conflicting.

Among the animal studies, decreased postnatal growth leading to developmental effects (e.g., lower body weight, delayed eye opening, delayed vaginal opening, and accelerated preputial separation) have been observed. These effects form the basis of the RfD and were observed at serum concentrations ~300-fold higher than the serum concentration corresponding to the RfD.

Delayed mammary gland development in female mice exposed *in utero* has been reported. Qualitative and quantitative scoring assessments have identified different thresholds for this effect. MDH had more confidence in using quantitative measurements of mammary gland development and these measures were used in identifying mammary gland development as a co-critical effect. An additional study evaluated the correlation between mammary duct branching patterns and the ability to support pup growth through lactation. No significant impacts were found.

Doses resulting in serum concentrations >700-fold higher than the serum concentration corresponding to the RfD resulted in decreased neonatal survival.

[4] A series of studies in a high-exposure study population reported associations between PFOA exposure and pregnancy-induced hypertension or preeclampsia. Limited data suggest a correlation between higher PFOA levels in females and decreases in fecundity and fertility, however, loss of body burden via birth and lactation could impact this correlation. No clear effects of PFOA on male fertility endpoints have been identified.

Among the animal studies, there was no effect of PFOA on reproductive or fertility parameters in female rats. However, it should be noted that female rats have a very high elimination rate compared to male rats or other species. Increased full litter resorptions and increased stillbirths were observed in pregnant mice exposed at serum concentrations >700-fold higher than the serum concentration corresponding to the RfD.

No evidence of altered testicular and sperm structure or function was reported in adult male rats exposed to doses producing serum concentrations >350-fold higher than the serum concentration corresponding to the RfD. Increased sperm abnormalities and decreased testosterone have been reported, but typically at serum concentrations 100-fold higher than the serum concentration corresponding to the RfD.

[5] The human data pertaining to neurotoxicity (including neurodevelopmental effects) of PFOA are limited, but do not indicate the presence of associations between PFOA and a variety of outcomes. Epidemiology studies of children found a weak statistical association between serum PFOA and parental reports of ADHD.

Information from animal studies is also quite limited. The offspring of mice fed PFOA throughout gestation had detectable levels of PFOA in their brains at birth. Locomotor activity, anxiety-related or depression-like behavior, or muscle strength were not altered. Circadian activity tests revealed gender-related differences in exploratory behavior patterns. These data suggest a need for additional studies to fully understand the neurological effects of PFOA.

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[Note: MDH conducted a focused re-evaluation which relied upon EPA's hazard assessment and key study identification (EPA 2016a). A complete evaluation of the toxicological literature was not conducted.]

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Minnesota Department of Health

Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: July 2016

Toxicological Summary for: Pyrene

CAS**: 129-00-0**

Synonyms: Benzo[d,e,f]phenanthrene**Acute Non-Cancer Health Based Value (nHBV$_{Acute}$) = Not Derived (Insufficient Data)**

Short-term Non-Cancer Health Based Value (nHBV$_{Short-term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value (nHBV$_{Subchronic}$) = 90 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.033 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.070** L/kg-d)}}$$

= 94.3 rounded to **90 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.033 mg/kg-d (CD-1 mice)
Source of toxicity value:	MDH 2015
Point of Departure (POD):	75 mg/kg-d NOAEL (U. S. Environmental Protection Agency, 1989)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 75 x 0.13 = 10 mg/kg-d
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics); 10 for intraspecies variability; 10 for database uncertainty due to lack of reproductive/developmental studies and a lack of studies in a second species
Critical effect(s):	Nephropathy in female mice, decreased kidney weight

Co-critical effect(s):	N/A
Additivity endpoint(s):	Renal (kidney) system

Chronic Non-Cancer Health Based Value (nHBV) = 50 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.010 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.044** L/kg-d)}}$$

= 45.5 rounded to **50 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration:	0.010 mg/kg-d (CD-1 mice)
Source of toxicity value:	MDH 2015
Point of Departure (POD):	75 mg/kg-d NOAEL (U.S. Environmental Protection Agency, 1989, subchronic study)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 75 x 0.13 = 10 mg/kg-d
Total uncertainty factor:	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics); 10 for intraspecies variability; 3 for extrapolation from a subchronic study to a chronic study due to the lack of severity of the critical effect; 10 for database uncertainty due to lack of reproductive and developmental studies and a lack of studies in a second species
Critical effect(s):	Nephropathy in female mice, decreased kidney weight
Co-critical effect(s):	N/A
Additivity endpoint(s):	Renal (kidney) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Group D, Not classifiable as to carcinogenicity
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (Moderate)

Summary of Guidance Value History:
Pyrene has a 1993 chronic HRL of 200 µg/L. In addition, a Pesticide Rapid Assessment Value of 20 µg/L was derived in 2014 and was lower than the HRL due to the conservative rapid

assessment method (MDH 2014). Subchronic and Chronic HBVs of 90 µg/L and 50 µg/L were derived in 2015. The 2015 Chronic HBV is 4 times lower than the 1993 HRL as a result of: 1) the use of new methodology including use of body weight scaling and updated water intake rates; and 2) rounding to one significant digit. In 2016 MDH updated the intake rate values used to derive guidance values. Use of updated intake rates did not result in any changes to the Subchronic or Chronic nHBV values derived in 2015. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process pyrene would undergo re-evaluation in 2020.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	No	No	No
Effects observed?	No	No	No	No	No

Comments on extent of testing or effects: N/A

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Minnesota Department of Health

Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

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Toxicological Summary for: Tetrahydrofuran

CAS: **109-99-9**
Synonyms: Oxolane; 1,4-Epoxybutane; THF

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 600 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.82 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 575 rounded to **600 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-water sources of exposure an RSC of 0.2 rather than the default of 0.5 has been selected.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1.

Reference Dose/Concentration:	(POD x DAF)/Total UF = 0.82 mg/kg-d (Wistar rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	371 mg/kg-d (NOAEL, Hellwig et al. 2002)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 371 mg/kg-d x 0.22 = 82 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (oral data gaps include assessment of neurological effects and evaluation in a second species as limited oral data suggest rat may not be the most sensitive species)
Critical effect(s):	Decreased pup body weight gain, delayed eye opening
Co-critical effect(s):	Decreased pup body weight gain, decreased maternal body weight gain during gestation
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 600 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.82 mg/kg-d)}^{\#} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 2343 rounded to 2,000 µg/L

[#]The calculated Subchronic RfD (1.7 mg/kg-d) is higher than the Short-term RfD (0.82 mg/kg-d), which is based on developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Subchronic RfD.

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011b, Exposure Factors Handbook, Tables 3-1

The Subchronic nHBV must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 600 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 600 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.57 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 2591 rounded to 3,000 µg/L

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011b, Exposure Factors Handbook, Tables 3-1.

Reference Dose/Concentration:	(POD x DAF)/Total UF = 0.57 mg/kg-d (Wistar rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	714 mg/kg-d (NOAEL, Hellwig et al 2002, subchronic exposure in a 2 generation study)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 714 mg/kg-d x 0.24 = 170 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for subchronic-to-chronic extrapolation, and 3 for database uncertainty (oral data gaps include assessment of neurological effects and evaluation in a second species as limited oral data suggest rat may not be the most sensitive species)
Critical effect(s):	None (slight increase in relative kidney weight at

	NOAEL)
Co-critical effect(s):	None
Additivity endpoint(s):	None

The Chronic nHBV must be protective of the short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 600 µg/L. Additivity endpoints: Developmental

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	"Suggestive evidence of carcinogenic potential" by all routes of exposure (EPA 2012)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Liver and kidney tumors in female mice and male rats, respectively, following inhalation exposure Oral cancer bioassays have not been conducted.

The modes of action for tumor induction by tetrahydrofuran are not well understood. The EPA Science Advisory Panel recommended that tetrahydrofuran is a weak, nongenotoxic carcinogen that would have a threshold. The chronic RfD (0.57 mg/kg-d) and the Short-term, Subchronic, and Chronic nHBV of 600 µg/L are adequately protective for cancer risk.

Volatile: Moderate

Summary of Guidance Value History:

A noncancer chronic HBV of 100 µg/L was derived by MDH in 1995. Short-term, Subchronic, and Chronic nHBVs of 600 µg/L were derived in 2016. The 2016 Chronic nHBV is higher than the 1995 chronic HBV as a result of: 1) using more recent toxicological data, 2) use of MDH's most recent risk assessment methodology, and 3) rounding to one significant digit. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process tetrahydrofuran would be scheduled for re-evaluation in 2021.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

17	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	Yes	Yes	No
Effects observed?	-	-[1]	Yes[2]	No[3]	-[4]

Comments on extent of testing or effects:

[1] No oral studies assessing immunotoxicity have been conducted. Results from inhalation exposure studies do not provide consistent results, with some studies suggesting effects and others showing no effect. Decreased thymus weight and white blood cell counts have been reported in animals exposed to concentrations of ≥1770 mg/m^3. It is unclear whether these effects represent a functional effect on the immune system or represent a general stress response.

[2] Decreases in pup body weight gain and delayed eye opening was reported in both the one- and two-generation drinking water studies in rats. These effects form the basis of the Short-term RfD. Inhalation exposure of pregnant rats to concentrations of >5000 mg/m3 resulted in decreased number of implants, decreased pup body weight, and delayed development.

[3] No effects on reproductive endpoints were reported in the one- or two-generation drinking water studies in rats at doses up to 200-fold greater than the Short-term RfD and ~300-fold greater than the Chronic RfD.

[4] Oral studies evaluating neurotoxicity have not been conducted. Signs of CNS (central nervous system) effects such as ataxia have been reported after bolus gavage dosing at doses ≥200-fold greater than the Short-term RfD and ≥300-fold greater than the Chronic RfD. An older study reported paralysis of hind limbs in animals following exposure to THF, but this study was poorly reported and the results are inconsistent with other better designed and reported studies.

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Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: October 2016

Toxicological Summary for: Thiamethoxam

CAS: **153719-23-4**

Synonyms: CGA 293343, 4H-1,3,5-Oxadiazin-4-imine, 3-[(2-chloro-5-thiazolyl)methyl] tetrahydro-5-methyl-N-nitro-, 3-((2-Chloro-5-thiazolyl)methyl)tetrahydro-5-methyl- N-nitro-4H-1,3,5-oxadiazin-4-imine
IUPAC name: 3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 400 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.25 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 439 rounded to **400 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	(POD x DAF)/Total UF = 0.25 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	34.5 mg/kg-d (NOAEL, Brammer 2007)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 34.5 mg/kg-d x 0.22 = 7.6 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Reduced pup body weight

Co-critical effect(s):	Hepatocyte hypertrophy, maternal death during pregnancy accompanied by hemorrhage of the uterus, bloody discharge in the perineal area, decreased number of animals with live fetuses, decreased fetal body weight, and increased fetal skeletal anomalies (fused sternebrae)
Additivity endpoint(s):	Developmental, Female Reproductive system, Hepatic (liver) system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 200 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.057 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 163 rounded to **200 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011b, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	(POD x DAF)/Total UF = 0.057 mg/kg-d (Beagles)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	4.05 mg/kg-d (NOAEL, Altmann 1998)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 4.05 mg/kg-d x 0.43 = 1.7 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Seminiferous tubule atrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Male Reproductive system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Subchronic}$ = 200 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.057 mg/kg-d***) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 259 rounded to 300 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011b, Exposure Factors Handbook, Tables 3-1 and 3-81

***The calculated chronic RfD (0.43 mg/kg-d) is higher than the subchronic RfD (0.057 mg/kg-d), which is based on male reproductive effects. The chronic RfD must be protective of all types of adverse effects that could occur as a

result of chronic exposure, including subchronic effects (MDH 2008). Therefore, the chronic RfD is set to the subchronic RfD. See the subchronic information above for details about the reference dose.

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the chronic duration; and therefore, the Chronic nHBV is set equal to the Subchronic nHBV of 200 µg/L. Additivity endpoints: Male Reproductive system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Not likely to be carcinogenic to humans
Slope factor (SF):	Not Applicable
Source of cancer SF:	Not Applicable
Tumor site(s):	Not Applicable

Volatile: No

Summary of Guidance Value History:

A pesticide rapid assessment of 20 µg/L was completed for thiamethoxam in 2014 by MDH. The 2016 nHBVs of 200 µg/L are higher than the pesticide rapid assessment due to the conservative method used for rapid assessments (MDH 2014). MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process, thiamethoxam will undergo re-evaluation in 2021.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

[1] A comprehensive toxicity study, specific for endocrine effects after thiamethoxam exposure, has not been completed; however, endocrine effects were observed in other studies. Endocrine effects included changes to the adrenal cortex and thyroid. In short-term and subchronic durations, adrenal gland changes occurred in male and female rats at thiamethoxam levels 400 to 700 times higher than the corresponding duration's reference dose. Thyroid gland changes occurred in rats between 200 - 700 times higher than the short-term reference dose.

[2] Immunological effects observed in thiamethoxam studies include changes in the thymus, spleen, and white blood cells. Changes to the thymus in rats were varied, with a range of changes between 250 to 1,400 times higher than the reference dose in short-term and subchronic durations. Conversely, one report observed no changes to the thymus at levels up to 690 times higher than the short-term reference dose. Changes to the spleen, in rat, were observed between levels of thiamethoxam 700 to 1,400 times higher than the subchronic reference dose. Beagles were a more sensitive species, with thymus and spleen changes occurring at levels 72 times higher than the short-term reference dose. White blood cell changes occurred at levels around 400 times higher than the subchronic reference dose.

[3] The short-term reference dose is based on the developmental effect of reduced pup body weight, an effect that occurred in multiple studies. Reductions in fetal body weights and skeletal abnormalities occurred at levels 700 times higher than the short-term reference dose in rats and 300 times higher than the short-term reference dose in rabbits.

[4] The subchronic reference dose is based on adverse reproductive effects occurring in adult male beagles. There were no reproductive effects in pregnant rats exposed to levels of thiamethoxam up to 700 times higher than the short-term reference dose. Pregnant rabbits were more sensitive, demonstrating reproductive effects at levels 300 times higher than the short-term reference dose. Adult female mice experienced reproductive changes at levels up to 1,400 times higher than the subchronic reference dose, and male mice at levels over 3,000 times higher than the subchronic reference dose. Studies in adult rats varied, with reports of no adverse reproductive events at thiamethoxam levels 500 times higher than the subchronic reference dose, to changes in sperm concentrations at levels 16 times higher than the subchronic reference dose.

[5] Thiamethoxam exposure in rodents produced transient neurotoxicity at high doses over 250 - 500 times greater than the short-term and subchronic reference doses. Altered activity and changes in the brain were noted in these studies. The mouse was more sensitive than the rat, with adverse effects in the mouse (reduced locomotor activity, convulsions, prostration) occurring at thiamethoxam levels 250 times higher than the short-term reference dose. The rat experienced adverse effects from thiamethoxam levels beginning at levels 450 times higher than the short-term reference dose. There were no adverse effects on pups when pregnant rats were exposed to thiamethoxam at levels up to 300 times higher than the short-term reference dose.

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Minnesota Department of Health

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Toxicological Summary for: 1,1,1-Trichloroethane

CAS**: 71-55-6**
Synonyms: Methyl chloroform, 1,1,1-TCA

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 9,000 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(3.0 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 8,571 rounded to **9,000 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 3.0 mg/kg-d (B6C3F1 mouse)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	2155 mg/kg-d ($BMDL_{10}$, NTP, 2000)
Dose Adjustment Factor (DAF):	0.14 (Body weight scaling, subchronic female B6C3F1 mouse) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 2155 mg/kg-d x 0.14 = 302 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (inadequate evaluation of neurological endpoint (identified as critical endpoint in inhalation studies))
Critical effect(s):	Decreased adult body weight
Co-critical effect(s):	Decreased adult body weight/weight gain, decreased relative liver weight, decreased epididymal spermatozoal concentration

Additivity endpoint(s):	Hepatic (liver) system, Male reproductive system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 5,000 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(1.0 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044L/kg-d)}^{**}}$$

= 4,545 rounded to **5,000 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 1.0 mg/kg-d (B6C3F1 mouse)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	2155 mg/kg-d ($BMDL_{10}$, NTP, 2000; subchronic exposure)
Dose Adjustment Factor (DAF):	0.14 (Body weight scaling, subchronic female B6C3F1 mouse) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 2155 mg/kg-d x 0.14 = 302 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for sub-chronic to chronic extrapolation, and 3 for database uncertainty (inadequate evaluation of neurological endpoint (identified as critical endpoint in inhalation studies))
Critical effect(s):	decreased adult body weight
Co-critical effect(s):	Decreased adult body weight/weight gain, Decreased relative liver weight, decreased epididymal spermatozoal concentration
Additivity endpoint(s):	Hepatic (liver) system, Male reproductive system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Group D: not classifiable as to human carcinogenicity (USEPA, 2007)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (high)

Summary of Guidance Value History:

A noncancer chronic Health Risk Limit (HRL) of 600 µg/L was promulgated in 1993/1994. In 2007, as required by a Legislative Session Law (Chapter 147, Article 17, section 2), the HRL

was set equal to the MCL of 200 µg/L until MDH conducted a full review. Later in 2007, MDH derived subchronic and chronic noncancer Health Based Values (HBV) of 20,000 µg/L and 9,000 µg/L. The HBVs were adopted as HRLs in 2009. In 2016, MDH re-evaluated the noncancer HRLs resulting in new noncancer subchronic and chronic HBVs of 9,000 µg/L and 5,000 µg/L, respectively. The 2016 noncancer HBVs are lower than the previous HRLs as a result of 1) using MDH's most recent risk assessment methodology including the application of Human Equivalence Doses and 2) rounding to one significant digit. MDH intends to re-evaluate guidance values on an approximately five year cycle in order to keep guidance values current with scientific knowledge. Under this process, 1,1,1-Trichloroethane will undergo re-evaluation in 2022.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	Yes	Yes	Yes	Yes
Effects observed?	-	No[1]	No[2]	Yes [3]	Yes[4]

Comments on extent of testing or effects:

[1] There are no oral immunotoxicity studies. Inhalation exposure to moderate to high concentrations did not produce effects on spleen or thymus histopathology. Based on this limited inhalation data

1,1,1-TCA may not produce toxic effects on the immune system, however, sensitive immunological endpoints have not been evaluated.

[2] Epidemiological studies have not observed adverse pregnancy outcome. Low level, oral exposure did not produced adverse effects in laboratory animals. Minor developmental delays, accompanied by maternal toxicity, have been reported at high inhalation doses. A database uncertainty factor to, in part, address the absence of an established LOAEL for developmental effects has been incorporated into the derivation of the subchronic and chronic RfDs.

[3] Epidemiological studies have not observed adverse pregnancy outcome. Decreased sperm concentrations have been observed in laboratory animals exposed to concentrations similar to the critical study LOAEL. These effects are listed as co-critical effects.

[4] Inhalation of 1,1,1-TCA produces central nervous system depression, increasing with exposure concentration from mild motor impairment to euphoria, unconsciousness and death. Rats given a bolus oral dose exhibited a short period of hyperactivity followed by a period of prolonged narcosis. No clinical signs of neurotoxicity were seen in rats receiving similar doses from diet or drinking water. Since these studies did not evaluate subtle

neurological endpoints a database uncertainty factor was added to, in part, address this data gap.

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Minnesota Department of Health

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Toxicological Summary for: Vinyl Chloride

CAS**: 75-01-4**
Synonyms: Chloroethene, chloroethylene, ethylene monochloride, Monochloroethene, Monochloroethylene

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 90 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.033 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 94.3 rounded to **90 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.033 mg/kg-d (CD rat)
Source of toxicity value:	Determined by MDH in 2007
Point of Departure (POD):	10 ppm (NOAEL, CMA 1998 as cited by USEPA, 2000)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model (USEPA, 2000)
Human Equivalent Dose (HED):	1 mg/kg-d (HED from chemical-specific PBPK model (USEPA, 2000))
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased liver weight, hypertrophy, and hepatocellular foci
Co-critical effect(s):	Increased liver weight
Additivity endpoint(s):	Hepatic (liver) system

Chronic Non-Cancer Health Based Value/Risk Assessment Advice ($nHBV_{Chronic}$) = 10 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0030 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044L/kg-d)}^{**}}$$

= 13.6 rounded to **10 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF= 0.003 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2007
Point of Departure (POD):	0.13 mg/kg-d (NOAEL, Til et al. 1991 as cited by USEPA, 2000)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model (USEPA, 2000)
Human Equivalent Dose (HED):	0.09 mg/kg-d (HED from chemical-specific PBPK model (USEPA, 2000))
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Liver cell polymorphism, liver cyst formation
Co-critical effect(s):	Increased liver weight
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Based Value (cHBV) = 0.2 µg/L

$$\frac{\text{(Additional Lifetime Cancer Risk, 1 x } 10^{-5}\text{) x (Conversion Factor,1000 µg/mg)}}{\text{(Slope Factor, per mg/kg-d) x (Lifetime Adjustment Factor) x (Lifetime Intake Rate, L/kg-d)}}$$

$$= \frac{(1\text{x}10^{-5}) \text{ x } 1{,}000}{[(1.4 \text{ x } 1^{*}) \text{ x } 0.044 \text{ L/kg-day}]^{*}}$$

= 0.162 rounded to **0.2 µg/L**

* Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Cancer classification:	Known Human Carcinogen (USEPA, 2000) Group 1: Carcinogenic to Humans (IARC, 2012)
Slope factor (SF):	1.4 mg/kg-d (total of liver angiosarcoma, hepatocellular carcinoma, and neoplastic nodules - adjusted for continuous lifetime exposure from birth) (female Wistar rats, Feron et al. 1981)
Source of cancer slope factor (SF):	USEPA, 2000
Tumor site(s):	Hepatic (liver)

Volatile: Yes (high)

Summary of Guidance Value History:

A cancer Health Risk Limit (HRL) of 0.2 µg/L was promulgated in 1993. Sub-chronic and chronic Non-cancer Health Based Values (HBVs) of 80 µg/L and 10 µg/L were derived in 2007. The HBVs were adopted as HRLs in 2009 along with a cancer value of 0.2 µg/L, which was the same as the previous HRL. In 2016, MDH re-evaluated the HRLs resulting in noncancer subchronic and chronic HBVs of 90 µg/L and 10 µg/L and a cancer HBV of 0.2 µg/L. The 2016 noncancer subchronic HBV is higher than the previous HRL as a result of 1) using MDH's most recent risk assessment methodology and 2) rounding to one significant digit. The 2016 re-evaluation did not result in changes to the chronic noncancer HBV or the cancer HBV. MDH intends to re-evaluate guidance values on an approximately five year cycle in order to keep guidance values current with scientific knowledge. Under this process Vinyl Chloride will undergo re-evaluation in 2022.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	Yes	Yes	Yes	Yes
Effects observed?	No[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Vinyl chloride has not been directly evaluated for endocrine effects. A study of workers exposed to vinyl chloride in PVC manufacturing plants reported that most workers who presented with scleroderma were shown to have thyroid insufficiency. No histopathology effects on the adrenals were reported in guinea pigs exposed to 400,000 ppm for 30 minutes. Rats were found to have colloid goiter and markedly increased numbers of perifollicular cells.

[2] Stimulation of spontaneous lymphocyte transformation was observed in mice following inhalation exposure. There is some evidence to suggest that an adaptive process may lead to a reduction or elimination of this effect over time. Also, it is not clear from the evidence that a clear adverse effect to the immune system is taking place.

[3] Developmental toxicity occurred in inhalation experiments at doses that caused maternal toxicity. These effects occurred at exposure levels significantly higher than those producing liver toxicity (i.e., the basis of the RfD)

[4] Testicular histopathological changes and decreased male fertility have been reported in inhalation studies. These effects occur at exposure levels significantly higher than those producing liver toxicity (i.e., the basis of the RfD).

[5] Nervous system toxicity has been observed in inhalation studies at high exposure levels. Vinyl chloride was once considered for use as an inhalation anesthetic. Investigators studying the effects of vinyl chloride exposure frequently report central nervous system symptoms that are consistent with the anesthetic properties of vinyl chloride. The most commonly reported central nervous system effects are ataxia or dizziness, drowsiness or fatigue, loss of consciousness, and/or headache. Other central nervous system effects that have been reported by vinyl chloride workers include euphoria and irritability, visual and/or hearing disturbances, nausea, memory loss, and nervousness and sleep disturbances.

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