MINNESOTA

February 1, 2023

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St. Paul, Minnesota 55155

Re: In The Matter of the Proposed Rules of the Department of Health about the Health Risk Limits in Groundwater; Revisor's ID Number 4587

Dear Librarian:

The Minnesota Department of Health intends to adopt rules about the Health Risk Limits in Groundwater. We plan to publish a Notice of Hearing in the February 6, 2023, edition of the State Register.

The Department 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 Hearing.

If you have questions, please contact me at 651-201-4923 or nancy.rice@state.mn.us.

Sincerely,

Nancy Rice Digitally signed by Nancy Rice
Date: 2023.02.01 13:35:10 -06'00'

Nancy Rice
Research Scientist
Health Risk Assessment Unit

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, Part 7850, and Part 7860.
Revisor's ID Number: 04587

STATEMENT OF NEED AND REASONABLENESS

January 2023

1/26/2023
Date

Daniel Huff
Assistant Commissioner
Minnesota Department of Health

Abbreviations and Acronyms

(See also the Glossary at the end of this SONAR)

aci	as cited in (Used when a publication is cited in a second document)
ADAF	Age-Dependent Adjustment Factor
$AF_{lifetime}$	Lifetime Adjustment Factor
AMPA	Aminomethylphosphonic acid
APA	Administrative Procedures Act
ATSDR	Agency for Toxic Substances and Disease Registry
BDCM	Bromodichloromethane
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower-confidence Limit
CAS	Chemical Abstract Service Number
CEC	Contaminant of Emerging Concern
cHRL	cancer Health Risk Limit
DAF	Dosimetric Adjustment Factors
DWEL	Drinking Water Equivalent Levels (issued by EPA)
(E)	Endocrine
EPA	U.S. Environmental Protection Agency
ESA	Ethanesulfonic acid
HA	Health Advisory (issued by EPA)
HBV	Health-Based Value
HED	Human Equivalent Dose
HRA	Health Risk Assessment
HRL	Health Risk Limit
IRIS	Integrated Risk Information System
IR	Intake Rate
LOAEL	Lowest Observed Adverse Effect Level
MCL	Maximum Contaminant Level (created by EPA)
MDA	Minnesota Department of Agriculture
MDH	Minnesota Department of Health
µg/L	microgram/Liter (also parts per billion)
mg/kg-day	milligrams (of a chemical) per kilogram (of body-weight) per day
MPCA	Minnesota Pollution Control Agency
MMB	Minnesota Management and Budget
NA	Not Applicable
ND	Not Derived
nHRL	noncancer Health Risk Limit
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OEHHA	California Office of Environmental Health Hazard Assessment
OXA	Oxanilic Acid

PFAS	Per- and Polyfluoroalkyl Substances
PFBS	Perfluorobutane sulfonate
PFHxA	Perfluorohexanoate
PFHxS	Perfluorohexane sulfonate
PBPK	Physiological based pharmacokinetic
POD	Point of Departure
RfD	Reference Dose
RSC	Relative Source Contribution
SF	Slope Factor
SONAR	Statement of Need and Reasonableness
UF	Uncertainty Factor
WHO	World Health Organization

STATEMENT OF NEED AND REASONABLENESS

Proposed Amendments to the Rules on Health Risk Limits for Groundwater

(Minnesota Rules, Chapter 4717, parts 7500, 7850 and 7860)

About this Document

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

Rules Amendments: Overview and Links
https://www.health.state.mn.us/communities/environment/risk/rules/water/overview.html

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

MDH will publish the Notice of Intent to Adopt Rules with a Hearing regarding the proposed rules in Minnesota's *State Register*. Subscribers of MDH's Groundwater Rules, Guidance and Chemical Review email subscription list will receive a notice of publication. To sign up for the emails, see Email Updates https://public.govdelivery.com/accounts/MNMDH/subscriber/new?topic_id=MNMDH_39. For Minnesota's statutory procedure for adopting administrative rules, see Minnesota Statutes, chapter 14.

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

This Statement of Need and Reasonable (SONAR) concerns Health Risk Limit (HRL) Rules amendments. An HRL is the concentration of a groundwater contaminant, or a mixture of contaminants that can be consumed with little or no risk to health. An HRL can be used to determine if groundwater is acceptable to drink.

Groundwater provides about 75 percent of Minnesota's drinking water, making it an important resource for the state. In 1989, the Minnesota *Groundwater Protection Act* proclaimed that it "is the goal of the state that groundwater be maintained in its natural condition, free from degradation caused by human activities." (Minn. Stat. § 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 (Minn. Stat. § 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 37 groundwater contaminants. Specifically, the proposed amendments add new HRL values for 17 contaminants to part 4717.7860. (*See* Section V.B.1). The amendments also repeal 20 outdated HRL values in parts 4717.7500 or 4717.7860, update the list in part 4717.7850, and add 19 updated HRL values to 4717.7860 to replace the repealed values. (*See* Section V.B.2).

These proposed amendments for the 37 groundwater contaminants build on MDH's 2009 rule revision and subsequent rulemaking. (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: (https://www.health.state.mn.us/communities/environment/risk/rules/water/hrlrule.html). Details on the 2009 HRL rule revision and rule adoption are presented in Section II. MDH will not be amending any other parts of the HRL rules at this time.

The *Minnesota Administrative Procedure Act* (APA), Minnesota Statutes, chapter 14, 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). (*See* Minn. Stat. § 14.131). This document fulfills that requirement.

This SONAR is divided into five sections. Section I contains 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 uses to derive the HRL values. Section III includes the scope of the amendments MDH is proposing. 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.

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 uses to derive HRL values.

Note: A detailed description of the methods and the underlying principles is available in Appendix C of this SONAR and MDH's 2008/2009 SONAR (PDF) at https://www.leg.mn.gov/archive/sonar/SONAR-03733.pdf#page=30.

A. Statutory Authority

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

1. The Groundwater Protection Act of 1989

The *Groundwater Protection Act* of 1989—now codified at Minnesota Statutes, chapter 103H—created MDH's statutory authority to adopt HRL values for groundwater contaminants. Under these new statutes, "[i]f 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." (Minn. Stat. § 103H.201, subd. 1(a)).

An HRL is defined 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." (Minn. Stat. § 103H.005, subd. 3).

Minnesota Statutes, section 103H.201 authorizes the department to adopt and revise HRL values by rule (subds. 2(a), 3(b)).

MDH uses the following two methods to derive HRL:

> [1] 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.
>
> [2] 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 or determined by the commissioner to have undergone thorough scientific review.

(Minn. Stat. § 103H.201, subd. 1(c), (d)).

2. 2001 Health Standards Statute

Additional authority is implicit under the 2001 *Health Standards Statute* (Minn. Stat. § 144.0751), which applies to safe drinking water and air quality standards. It provides that 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 hypersensitization, 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.

(§ 144.0751(a)).

In cases of water degradation, the Health Standards Statute informs MDH's review, development, and adoption of HRL values for water contaminants based on scientific methods to protect sensitive populations. These above-cited statutes clearly establish MDH's authority to adopt the proposed rules.

B. Past MDH Rule Revisions

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 the 1993 methods (the 1993-1994 HRL values). The 1993-1994 HRL values were published in Minnesota Rules, part 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 interested parties to participate. MDH began formal rulemaking in 2008 by proposing an updated methodology to derive HRL values based on the United States Environmental Protection Agency's (EPA) algorithms and standard practices available at that time. In 2009, MDH adopted the new methods and the HRL values for 21 groundwater contaminants that it derived using the updated methodology. The 2008/2009 SONAR documents additional details on the nature and scope of MDH's 2009 HRL rule revision.

In 2007, Minnesota enacted two laws that required MDH to establish additional HRLs through rule. The first law directed MDH to adopt HRLs for perfluorooctanoic acid (PFOA), (also called perfluorooactanoate [PFOA]), and perfluorooctane sulfonate (PFOS) (Minn. Laws 2007, ch. 37, § 1). MDH did this in August 2007 using the legislation's good-cause exemption authority for rulemaking. MDH adopted the 2007 values via the full rulemaking process in 2009. In 2018, the HRL for PFOA was replaced with an updated value derived from new scientific data.

The second 2007 law required MDH to set HRLs as stringent (i.e., low) as the EPA Maximum Contaminant Levels (MCL) for various commonly detected groundwater contaminants (Minn. Laws 2007, ch. 147, art. 17, § 2). 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. Eight of these "MCL-HRLs," as they have been called, plus nitrate, initially appeared in Minnesota Rules, part 4717.7850. MDH updated three of the original eleven MCL-HRLs and adopted them into Minnesota Rules, part 4717.7860 in 2009. Three more MCL-HRLs were adopted into rule in 2015. To date, five of the original 11 MCL values adopted in 2007, plus nitrate, remain in Minnesota Rules, part 4717.7850, subpart 2. The MCL-HRL value for tetrachloroethylene is proposed for replacement during this rulemaking, which would leave four of the original eleven values, plus nitrate, listed in Minnesota Rules, part 4717.7850.

In 2011, MDH added HRL values for 14 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 repealed outdated HRL values for three chemicals in Minnesota Rules, part 4717.7500, and replaced the repealed values with updated guidance in part 4717.7860. Outdated HRL values for three additional chemicals already

in Minnesota Rules, part 4717.7860, were repealed and replaced with new values. In total, MDH adopted new or updated HRL values for 14 chemicals in 2015.

In 2018, MDH proposed to adopt new or updated HRL values for 22 contaminants. Of these, 18 contaminants had values that were previously adopted in 1993, 2009, or 2011. One of the contaminants, PFOS, was removed from the initial proposed updates, leaving 17 contaminants with update proposals. MDH repealed the 17 outdated values from Minnesota Rules, parts 4717.7500 or 4717.7860, and added the updated values to Minnesota Rules, part 4717.7860. MDH added four additional new values to Minnesota Rules, part 4717.7860.

With this rulemaking, MDH proposes to adopt new or updated HRL values for 36 contaminants. There are 17 contaminants for which no previously adopted HRL values exist, and 19 HRL values that MDH proposes to repeal and replace. There is one additional value for hexane that MDH proposes to repeal and replace with a type of water guidance (Risk Assessment Advice, (RAA)) that cannot be adopted into rule.

The table below summarizes the new and updated HRLs adopted into rule since 1993. Some HRLs have been updated more than once.

Table 1. Number of HRL updates by year

Year	Number of new HRLs	Number of updated HRLs	Number of chemicals repealed and not replaced	Total Number of Chemicals with new or updated HRLs, by year
1993	89	-	-	89
1994	31	-	-	31
2007	2	12	-	14
2009	5	16	-	21
2011	6	8	3	17
2013	6	6	-	12
2015	8	6	-	14
2018	4	17	-	21
2022 (proposed)	17	19	1*	37

* The HRL for n-hexane was adopted in 1994 and has since become outdated, and, as discussed below in Part III, MDH is replacing it with updated Risk Assessment Advice.

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 Groundwater Protection Act in Minnesota Statutes, 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 populations, and has been adopted into rule. The purpose of the HRLs is described in Minnesota Rules, part 4717.7810, subpart 2, item B, which provides that, “HRLs specify a minimum level of quality for water used for human

consumption, such as ingestion of water, and do not imply that allowing degradation of water supplies to HRL levels is acceptable."

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 as an HRL. An HRL is expressed as micrograms of a chemical per liter of water (µg/L).

In calculating water guidance values, MDH assumes people drink the water containing the contaminant. This assumption comports with the legislature's express policy 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 . . . ." (Minn. Stat. § 115.063(a)(2)). This furthers the stated intent of MDH's groundwater protection statutes to prevent degradation of groundwater from contaminants (Minn. Stat. § 103H.001) and the more general legislative intent (Minn. Stat. § 115.063(a)(1)) that the waters of the state are protected.

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 in a context specific to their programs.

Except for the requirements for water resources protection (*See* Minn. Stat. § 103H.275, subd. 1(c)(2)), neither Minnesota statute nor current HRL rules specify 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 a Relative Source Contribution (RSC) factor;
- 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.

For more information on RSC, see the 2008/2009 SONAR [Part IV.E.1, page 51] (PDF) at https://www.leg.mn.gov/archive/sonar/SONAR-03733.pdf#page=60 and Minnesota Rules, part 4717.7820, subpart 22.

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 above, 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 HRL Algorithm

The MDH Health Risk Assessment (HRA) Unit derives water guidance values. The HRA Unit 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's 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 (*See* Minn. R. 4717.7810 –.7900). The calculation used to 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 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., nonlinear carcinogens, as defined in Minnesota Rules, part 4717.7820). The algorithms and explanation of concepts used to derive HRL values are presented in Appendix C of this SONAR. Additional information is available in MDH's 2008/2009 SONAR (PDF). (Part IV.A at page 30, *https://www.leg.mn.gov/archive/sonar/SONAR-03733.pdf#page=30*).

III. Proposed Rules

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

Scope

The 2022 proposed rule amendments are limited to Minnesota Rules, parts 4717.7500, 4717.7850, 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 36 groundwater contaminants with guidance developed using the 2009 methodology and 2019 EPA intake rates. Of these 36 contaminants, 17 contaminants have not previously had an adopted water guidance value in HRL rule and 19 contaminants have previously adopted HRL values in rule. The proposed HRL values, as shown in Section V.B.1 will be added to Minnesota Rules, part 4717.7860); and

- Repeal outdated guidance in Minnesota Rules, parts 4717.7500 or 4717.7860 for 20 contaminants. This includes 19 values to replace and one value, n-hexane, that will only be repealed. (See below).

    - seven contaminants for which HRL values were adopted in 1993 or 1994;

    - two contaminants for which HRL values were adopted in 2009;

    - 10 contaminants for which HRL values were adopted in 2011; and

    - One contaminant for which an HRL value was adopted 2013.

    Except for hexane in Minnesota Rules, part 4717.7500, subpart 58a, the repealed values will be replaced with values proposed to be added to Minnesota Rules, parts 4717.7860, as noted above.

    For hexane, a health-based guidance called Risk Assessment Advice (RAA) was derived in 2022 and posted on the MDH website. An RAA for hexane was created because there was insufficient information for creating an HBV that could be adopted into rule. While not eligible for rule, RAAs are protective of public health and can be applied like HBVs or HRLs. More information is available in the Toxicological Summary for Hexane (PDF) https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/nhexane.pdf or by contacting MDH at health.risk@state.mn.us.

- Update the list in Minnesota Rules, part 4717.7850, by removing subpart 2, item E (1,1,2,2-Tetrachloroethylene (PCE or PERC)) to reflect the proposed update to part 4717.7860, subpart 18 (Tetrachloroethylene (PCE or PERC)).

Table 2. Contaminants included in the proposed HRL amendments

Number	Chemical Abstract Service (CAS) Number	Contaminant Name	Previously adopted values in HRL Rule? (year adopted)
1	67-64-1	Acetone	Yes (2011)
2	1066-51-9	Aminomethylphosphonic acid (AMPA)	No
3	50-32-8	Benzo[a]pyrene	No
4	119-61-9	Benzophenone	No
5	95-14-7	1H-Benzotriazole	No
6	92-52-4	Biphenyl	Yes (1993)
7	75-27-4	Bromodichloromethane	Yes (1993)
8	106-46-7	1,4-Dichlorobenzene	Yes (1994)
9	156-60-5	trans-1,2-Dichloroethene	Yes (2013)
10	75-35-4	1,1-Dichloroethylene	Yes (2011)
11	78-87-5	1,2-Dichloropropane	Yes (1994)
12	57-63-6	17α-Ethinylestradiol	No
13	100-41-4	Ethylbenzene	Yes (2011)
14	107-21-1	Ethylene Glycol	Yes (2011)
15	86-73-7	Fluorene	Yes (1993)
16	72178-02-0	Fomesafen	No
17	110-54-3	Hexane (repeal only)	Yes (1994)
18	138261-41-3	Imidacloprid	No
19	7439-96-5	Manganese	Yes (1993)
20	51218-45-2; 87392-12-9	Metolachlor and s-Metolachlor	Yes (2011)
21	171118-09-5	Metolachlor ESA	Yes (2011)
22	152019-73-3	Metolachlor OXA	Yes (2011)

Number	Chemical Abstract Service (CAS) Number	Contaminant Name	Previously adopted values in HRL Rule? (year adopted)
23	84852-15-3	Nonylphenol	No
24	140-66-9	4-tert-Octylphenol	No
25	45187-15-3; 375-73-5; 29420-49-3; 68259-10-9; 60453-92-1	Perfluorobutane sulfonate (PFBS)	Yes (2011)
26	108427-53-8; 355-46-4; 3871-99-6	Perfluorohexane sulfonate (PFHxS)	No
27	92612-52-7; 307-24-4; 21615-47-4; 2923-26-4	Perfluorohexanoate (PFHxA)	No
28	91-22-5	Quinoline	No
29	127-18-4	Tetrachloroethylene (PERC or PCE)	Yes (HRL-MCL)
30	108-88-3	Toluene	Yes (2011)
31	526-73-8	1,2,3-Trimethylbenzene	No
32	95-63-6	1,2,4-Trimethylbenzene	No
33	108-67-8	1,3,5-Trimethylbenzene	Yes (2009)
34	78-51-3	Tris(2-butoxyethyl) phosphate (TBEP)	No
35	13674-87-8	Tris(1,3-dichloroisopropyl)phosphate (TDCPP)	No
36	93413-69-5; 99300-78-4	Venlafaxine	No
37	1330-20-7	Xylenes	Yes (2011)

Selection of Contaminants for Review

MDH selected the contaminants for the 2022 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 aims to periodically re-evaluate post-2009 adopted HRLs to ensure that they incorporate the latest scientific findings and continue to be relevant. 20 contaminants that were adopted into rule from 2009 to 2013 were re-evaluated from 2017 to 2022. These HRL re-evaluations are included in the proposed rule.

As MDH reviewed or re-evaluated each contaminant, it posted the following information on MDH's Chemicals Under Review webpage, available at: Chemicals Under Review (https://www.health.state.mn.us/communities/environment/risk/review.html). This page contains each chemical's name, its Chemical Abstracts Service (CAS) Registry Number, and the date it was posted. After completing each review or re-evaluation, MDH posted the guidance values and the chemical-specific summary sheets on the webpage called Human-Health Based Water Guidance Table (https://www.health.state.mn.us/communities/environment/risk/guidance/gw/table.html). MDH also notified subscribers to MDH's Groundwater Rules, Guidance and Chemical Review email notification account about the new or updated guidance. Electronic subscriptions to this account may be requested at https://public.govdelivery.com/accounts/MNMDH/subscriber/new?topic_id=MNMDH_39.

IV. Applying MDH-derived Methods

For a full explanation of components of MDH's guidance derivation process (i.e., how the guidance is calculated) please see Appendix C.

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 2022 proposed amendments. However, MDH uses the most recent intake rates from the EPA Exposure Factors Handbook. Water intake rate values were updated in 2019.

When MDH proposed updated water-guidance methods in 2008, EPA was planning to revise the U.S. water-consumption intake rates but had not published them in time for MDH's 2009 rule-making process. MDH used the draft intake rate values for ages of less than one year, and intake rates from the 2004 EPA Per Capita report (EPA, 2004b) for all

other ages. EPA finalized the intake rates for all ages in the 2011 Exposure Factors Handbook. In 2016, MDH updated the intake rates used to calculate the water guidance for each duration to match EPA's intake rates in the 2011 Exposure Factors Handbook (EPA, 2011a, ch. 3). This was announced to subscribers of MDH's email subscription service account called Groundwater Rules, Guidance, and Chemical Review via a message sent on June 15, 2016. In 2019, EPA published an updated set of water intake rates (EPA, 2019, Tables 3-1, 3-3, and 3-5). MDH began using these water intake rates in 2020, as announced in an email subscription service notice sent on September 22, 2020. All the proposed rules amendments in this SONAR include water guidance calculated using EPA's 2019 intake rates. The intake rates were calculated using data from US EPA, 2019 Table 3-1 (for ages 2 to 70 years), Table 3-5 (for birth up to 2 years of age), and Table 3-3 (for pregnant or lactating women). The intake rates that MDH uses, expressed as liters of water consumed per kilogram of bodyweight per day (L/kg-d), are shown below:

Table 3. Comparison of Draft and Finalized Intake Rates

Duration	2008 Intake Rate (L/kg-d)	2011 Intake Rate (L/kg-d)	2019 Intake Rate (L/kg-d)
Acute/Short-term	0.289	0.285	0.290
Subchronic	0.077	0.070	0.074
Chronic	0.043	0.044	0.045
Cancer: Age-Dependent Adjustment Factor (ADAF)Cancer: lifetime adjustment factor ($AF_{lifetime}$)	<2 yrs - 0.137 2 < 16yrs - 0.047 16 yrs & over - 0.039 0.043	<2 yrs - 0.125 2 - < 16yrs - 0.045 16 yrs & over - 0.041 0.044	<2 yrs - 0.155 2 - < 16yrs - 0.040 16 yrs & over - 0.042 0.045
Pregnant Women	0.043	0.043	0.038
Lactating Women	0.055	0.055	0.047

As noted above, MDH re-evaluates HRLs adopted since 2009 to ensure that they incorporate the latest scientific findings and continue to be relevant. During a re-evaluation, MDH may apply updated methods and water intake rates as well as incorporate more recent toxicity and exposure information. As a result, the new HRL values 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 dosimetric adjustment factors (DAFs) to derive human equivalency doses (HEDs). 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; and
- Changes in water intake rates within the guidance algorithms to consider the effect on sensitive populations (e.g., infants and children).

See Table 4, below, for a summary of differences between the proposed HRL value and existing HRL values.

Table 4. Comparison of Lowest Current HRL and Lowest Proposed HRL, by Chemical

Chemical Abstract Service number	**Chemical Name**	**Current Lowest HRL (µg/L), (Duration) (HRL Year)**	**Proposed Lowest HRL (µg/L)**	**Change**
67-64-1	Acetone	4,000 (Chronic) (HRL 2011)	3,000 (Chronic)	Lower
92-52-4	Biphenyl	300 (Chronic) (HRL 1993)	10 (Cancer)	Lower
75-27-4	Bromodichloromethane	6 (Cancer) (HRL 1993)	3 (Cancer)	Lower
106-46-7	1,4-Dichlorobenzene	10 (Cancer) (HRL 1994)	50 (Short-term)	Higher
156-60-5	trans-1,2-Dichloroethene	40 (Chronic) (HRL 2013)	9 (Chronic)	Lower
75-35-4	1,1-Dichloroethylene	200 (Chronic) (HRL 2011)	200 (Chronic)	No change
78-87-5	1,2-Dichloropropane	5 (Cancer) (HRL 1994)	3 (Cancer)	Lower
100-41-4	Ethylbenzene	50 (Short-term) (HRL 2011)	40 (Short-term)	Lower
107-21-1	Ethylene Glycol	2000 (Chronic) (HRL 2011)	2000 (Chronic)	No change
86-73-7	Fluorene	300 (Chronic) (HRL 1993)	80 (Chronic)	Lower
7439-96-5	Manganese	100 (Chronic) (HRL 1993)	100 (Short-term)	No change (duration change)

Chemical Abstract Service number	Chemical Name	Current Lowest HRL (µg/L), (Duration) (HRL Year)	Proposed Lowest HRL (µg/L)	Change
51218-45-2; 87392-12-9	Metolachlor and s-Metolachlor	300 (Subchronic) (HRL 2011)	300 (Short-term)	No change
171118-09-5	Metolachlor ESA	800 (Chronic) (HRL 2011)	1,000 (Chronic)	Higher
152019-73-3	Metolachlor OXA	800 (Chronic) (HRL 2011)	1,000 (Chronic)	Higher
45187-15-3; 375-73-5; 29420-49-3; 68259-10-9; 60453-91-4	Perfluorobutane sulfonate (PFBS)	7 (Chronic) (HRL 2011)	0.1 (Short-term)	Lower
127-18-4	Tetrachloroethylene	5 (Chronic) (HRL_{MCL} 2009)	4 (Cancer)	Lower
108-88-3	Toluene	200 (Short-term) (HRL 2011)	70 (Short-term)	Lower
108-67-8	1,3,5-Trimethylbenzene	100 (Short-term) (HRL 2009)	30 (Short-term)	Lower
1130-20-7	Xylenes	300 (Short-term) (HRL 2011)	300 (Subchronic)	No change

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

MDH uses 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 dose or exposure below 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 (i.e., higher than the threshold). That is, at a dose lower than the threshold dose, the chemical does not cause cancer or other

harmful effects. Therefore, the threshold is protective of harmful effects, including for cancer. MDH's threshold method, historically called a "non-linear 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 (Section IV.E.2., p. 52). MDH's non-threshold method has only been used by MDH for carcinogens that do not show a threshold. (*See* also Appendix C for more information).

Among the 37 contaminants for which HRL values are proposed during this rulemaking, there are twelve carcinogenic or possible carcinogenic contaminants (*See* Carcinogen in Glossary). Five contaminants (benzophenone, 1,4-dichlorobenzene, 17alpha-ethyinylestradiol, metolachlor and s-metolachlor,) are considered nonlinear carcinogens. For these chemicals, the chronic non-cancer values are considered protective of public health. Seven of these carcinogens or possible carcinogens are not considered to have thresholds (benzo[a]pyrene, biphenyl, bromodichloromethane, 1,2-dichlorobenzene, quinoline, tetrachloroethylene, and TDCPP) and therefore a linear approach was used to derive a cancer guidance value.

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 populations, 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, MDH provides the following information in a table:

Heading section:

- The chemical name;
- The CAS Registry Number that uniquely identifies each chemical;
- The year the rule will be adopted; 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 daily (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 and that should be grouped together for evaluation when more than one chemical is present (additivity endpoint). This can also include endocrine system involvement. (See also Endocrine (E) in the glossary).

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 for 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:

- "(2)" indicates the calculated HRL value is greater than the short-term HRL value, so the HRL is set equal to the short-term HRL value; and

- "(3)" indicates the calculated HRL is greater than the subchronic HRL, so the HRL is set to equal the subchronic HRL value.

Terminology:

Terms used in Section V.B. are defined below. A full glossary is available in Appendix A:

Additivity endpoint or 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.

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).

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).

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.

Human Equivalent Dose (HED): The oral human dose 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 ($BW^{3/4}$).

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 a dose-response curve where an effect or change in response is first estimated or observed, using benchmark dose response modeling or using a NOAEL or LOAEL obtained experimentally.

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).

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 2002). 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 ($10^{0.5} \times 10^{0.5} = 10^1$).

More information about each parameter can be found in Appendix C and in the 2008/2009 SONAR (PDF) (https://www.leg.mn.gov/archive/sonar/SONAR-03733.pdf#page=2).

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 section describes HRL Rules amendments proposed for 37 substances with new or updated guidance values: Changes to the current rule are reflected using [Delete] for deleted language and [Add] for new language.

Subpart. 3c. Acetone.

Change the Year Adopted from 2011 to 2023 in Minnesota Rules, 4717.7860, part 3c and change data in the table below as shown.

CAS number: 67-64-1
Year Adopted: [Delete:2011, Add: 2023]
Volatility: Moderate

	Acute	Short term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	[Delete: 9,000 Add: 5,000]	[Delete: 8,000 Add: 5,000 (2)]	[Delete: 4,000 Add: 3,000]	NA
RfD (mg/kg-day)	--	[Delete: 5.0 Add: 3.1]	[Delete: 3.0 Add: (2)]	[Delete: 0.90 Add: 0.69]	--
RSC	--	0.5	[Delete: 0.2 Add: (2)]	0.2	--

	Acute	Short term	Subchronic	Chronic	Cancer
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	[Delete: 0.289 Add: 0.290]	[Delete: 0.077 Add: (2)]	[Delete: 0.043 Add: 0.045]	--
Endpoints	--	renal (kidney) system	[Delete: hematological (blood) system] renal (kidney) system]	hematological (blood) system [Add: hepatic (liver) system], renal (kidney) system	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 5,000 µg/L, updated from 9,000 µg/L adopted into rule in 2011. The updated Reference Dose (RfD) is 3.1 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.5. The point of departure (POD) is a No Observed Adverse Effects Level (NOAEL) of 1,485 mg/kg-d (National Toxicology Program (NTP), 1991). The Dosimetric Adjustment Factor (DAF) for body weight scaling is 0.21, and the Human Equivalent Dose (HED) is 312 mg/kg-d. The total uncertainty factor (UF) is 100 (10 for intraspecies variability and 10 for database uncertainty, which includes lack of developmental studies, including multigenerational studies and neurotoxicity studies). No interspecies UF for toxicodynamic differences was applied as acetone plays a role in normal human metabolism, and it is not anticipated that humans will be more sensitive to acetone than laboratory animals. The critical effects are increased kidney weight (consistent with nephropathy seen in rats during the subchronic duration). There are no co-critical effects. The additivity endpoint is the renal (kidney) system.

Subchronic duration.
The proposed subchronic nHRL is 5,000 µg/L, updated from 8,000 µg/L adopted into rule in 2011. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 5,000 µg/L. The additivity endpoint is the renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 3,000 µg/L, updated from 4,000 µg/L adopted into rule in 2011. The updated RfD is 0.69 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 900 mg/kg-d based on subchronic exposure (NTP, 1991). The DAF is 0.23 using body weight scaling. Multiplying DAF by POD results in a HED of 207 mg/kg-d. The UF is 300 (10 for intraspecies variability and 10 for database uncertainty, which includes lack of adequate developmental studies, including multigenerational studies, neurotoxicity studies, and hematological studies. For using a subchronic duration POD in place of a chronic POD, 3 is also factored into the UF. The critical effects are nephropathy, increased relative kidney weight, and changes in blood parameters (increased leukocytes, increased mean corpuscular hemoglobin, increased mean cell volume, decreased erythrocyte count, and decreased reticulocyte counts). The co-critical effects are increased relative kidney weight, increased relative liver weight, increased incidence of hepatocellular hypertrophy, and tubular degeneration in the kidneys. The additivity endpoints are hematological (blood) effects, the hepatic (liver) system, and the renal (kidney) system.

Cancer.
Not applicable.

Subpart. 4a. **Aminomethylphosphonic acid (AMPA)**

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 4a. for AMPA:

CAS number: 1066-51-9
Year Adopted: 2023
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	3,000	1,000	NA
RFD (mg/kg-day)	--	**--**	0.96	0.32	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	0.074	0.045	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Endpoints	--	--	Hepatic (liver) system, Renal (kidney) system	Hepatic (liver) system, Renal (kidney) system	--

Acute duration.
Not derived because of insufficient information.

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

Subchronic duration.
The proposed subchronic nHRL is 3,000 µg/L. The RfD is 0.96 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2, and the POD is a NOAEL of 400 mg/kg-d (Estes et al. 1979 aci in World Health Organization (WHO), 1997, 2005). The DAF is 0.24 based on body weight scaling, and the HED is 96 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty (lack of multigenerational reproductive/developmental study). The critical effects are decreased body weight gain, bladder urothelial hyperplasia, increased serum lactate dehydrogenase. There are no co-critical effects. The additivity endpoint is the hepatic (liver) system and renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 1,000 µg/L. The RfD is 0.32 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2, and the POD is a NOAEL of 400 mg/kg-d (Estes et al., 1979). The DAF is 0.24 based on body weight scaling, and the HED is 96 mg/kg-d. The total UF is 300 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability,3 for database uncertainty due to a lack multigenerational reproductive/development study) 3 for subchronic -to-chronic extrapolation). The critical effects are decreased body weight gain, bladder urothelial hyperplasia, increased serum lactate dehydrogenase. There are no co-critical effects. The additivity endpoints are the hepatic (liver) system and renal (kidney) system.

Cancer:
Not applicable.

Subpart. 6c. Benzo[a]pyrene.

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 6c for Benzo[a]pyrene:

CAS number: 50-32-8
Year Adopted: 2023

Volatility: Low

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	0.5	0.5 (2)	0.5 (2)	0.1
RFD (mg/kg-day)	--	0.00031	(2)	(2)	--
RSC	--	0.5	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	1
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	--	0.290	(2)	(2)	$0.155_{(<2)}$ $0.040_{(2\ to\ <16)}$ $0.042_{(16+)}$
Endpoints	--	developmental, nervous system	developmental, nervous system	developmental, nervous system	cancer

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 0.5 µg/L. The RfD is 0.00031 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.5. The POD is a Benchmark Dose Lower Limit ($BMDL_{1SD}$) of 0.0917 mg/kg-d (Chen et al., 2012). A BMD is a 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 or one standard deviation). The DAF was not calculated due to the temporal differences in human and rodent brain development stages, and therefore the HED is not applicable. The total UF is 300 (10 for interspecies differences, 10 for intraspecies variability, and 3 for database uncertainty due to lack of adequate developmental and multigenerational studies that include exposure throughout gestation and early life). The critical effect is neurological changes in neonatal rats as documented in an elevated maze. The co-critical effect is neurological changes in neonatal rats as documented in open field and water maze testing. The additivity endpoints are developmental and the nervous system.

Subchronic duration.
The proposed subchronic nHRL is 0.5 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period. Therefore, the subchronic nHRL is set equal to the short-term nHRL of 0.5 µg/L. The additivity endpoints are developmental and the nervous system.

Chronic duration.
The proposed chronic nHRL is 0.5 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period. Therefore, the chronic nHRL is set equal to the short-term nHRL of 0.5 µg/L. The additivity endpoints are developmental and the nervous system.

Cancer.
The proposed cancer cHRL value is 0.1 µg/L. EPA's cancer classification is "carcinogenic to humans" (EPA, 2017b). The cancer slope factor is 1 $(mg/kg\text{-}d)^{-1}$ based on forestomach and oral cavity tumors in female mice (EPA, 2017b). The age-dependent adjustment factors and intake rates are 10 and 0.155 L/kg-d for an age under 2 years; 3 and 0.040 L/kg-d for an age between 2 years and less than 16 years; and 1 and 0.042 L/kg-d for ages above 16 years. The tumor sites are the digestive tract, liver, skin, and lung.

Subpart. 6d. Benzophenone.

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 6d for Benzophenone:

CAS number: 119-61-9
Year Adopted: 2023
Volatility: Low

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	900	100	100 (3)	NA
RFD (mg/kg-day)	--	0.52	0.053	(3)	--
RSC	--	0.5	0.2	(3)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	0.074	(3)	--
Endpoints	--	developmental	hepatic (liver) system, renal (kidney) system	hepatic (liver) system, renal (kidney) system	--

Acute duration.

Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 900 µg/L. The RfD is 0.52 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.5. The POD is a NOAEL of 67.4 mg/kg-d (Hoshino et al., 2005), the DAF is 0.23 for body weight scaling, and the HED is 15.5 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics and 10 for intraspecies variability). The critical effect and co-critical effect are both decreased pup body weight. The additivity endpoint is developmental.

Subchronic duration.
The proposed subchronic nHRL is 100 µg/L. The RfD is 0.053 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 6.4 mg/kg-d. The DAF is 0.25 using body weight scaling, and the HED is 1.6 mg/kg-d. The total UF is 30 (3 for interspecies toxicodynamics differences for and 10 for intraspecies variability). The critical effects are increased relative liver and kidney weights, proximal tubule regeneration, and proximal tubule dilatation. The co-critical effects are increased serum bile salts, relative liver weight, hepatocyte vacuolization, relative kidney weight, and renal tubule protein casts. The additivity endpoints are the hepatic (liver) system and the renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 100 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period and therefore, the chronic nHRL is set equal to the subchronic nHRL of 100 µg/L. The additivity endpoints are the hepatic (liver) system and the renal (kidney) system.

Cancer.
Not applicable.

Subpart. 6e. 1H-Benzotriazole.

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 6e for 1H-Benzotriazole:

CAS number: 95-14-7
Year Adopted: 2023
Volatility: Low

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	20	20 (2)	20 (2)	NA
RFD (mg/kg-day)	--	0.023	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	(2)	(2)	--
Endpoints	--	developmental	developmental	developmental	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 20 µg/L. The RfD is 0.023 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 30 mg/kg-d (Japan Bioassay Research Center, 2007). The DAF is 0.23, and the HED is 6.9 mg/kg-d. The total UF is 300 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 10 for database uncertainty due to lack of reproductive/developmental studies of sufficient exposure duration). The critical effect is reduced offspring body weight. There are no co-critical effects. The additivity endpoint is developmental.

Subchronic duration.
The proposed subchronic nHRL is 20 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 20 µg/L. The additivity endpoint is developmental.

Chronic duration.
The proposed chronic nHRL is 20 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 20 µg/L. The additivity endpoint is developmental.
Note: See the toxicological summary sheet in Appendix E for more information about the RfD selected for the chronic duration.

Cancer.
Not applicable

Subpart. 6f. Biphenyl.

New chemical for Minnesota Rules, part 4717.7860: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to part 4717.7860, subpart 6f, for Biphenyl. Repeal from part 4717.7500, subpart 11.

CAS number: 92-52-4
Year Adopted: 2023
Volatility: No

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	400	100	100 (2)	100 (2)	10
RFD (mg/kg-day)	0.58	0.18	(2)	(2)	--
RSC	0.2	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	0.008
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	0.290	0.290	(2)	(2)	$0.155_{(<2)}$ $0.040_{(2\ to\ <16)}$ $0.042_{\ (16+)}$
Endpoints	renal (kidney) system	renal (kidney) system	renal (kidney) system	renal (kidney) system	cancer

Acute duration.
The proposed acute nHRL is 400 µg/L. The RfD is 0.58 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 250 mg/kg-d (Kluwe, 1982). The DAF is 0.23 based on body weight scaling for male F344 rats in a subchronic study, and the HED is 57.5 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing). The critical effect is increased urine volume (polyuria) accompanied by increased excretion of urinary protein, glucose, and several renal enzymes. There are no co-critical effects. The additivity endpoint is renal (kidney) system.

Short-term duration.
The proposed short-term nHRL is 100 µg/L. The RfD is 0.18 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 83.7 mg/kg-d (Booth et al., 1961; Kluwe, 1982). The DAF is 0.21 based on body weight scaling for a female subchronic F344 rat, and the HED is 17.6 mg/kg-d. The total UF is 100 (3 for interspecies differences

for toxicodynamics, 10 for intraspecies variability, and 3 for database limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing). The critical effects are increased urine volume (polyuria); precipitable urinary sediment; and increased urinary glucose, protein, alkaline phosphatase and glutamic oxaloacetic transaminase excretion. There are no co-critical effects. The additivity endpoints are renal (kidney) system.

Subchronic duration.
The proposed subchronic nHRL is 100 µg/L. The Subchronic nHBV must be protective of shorter duration exposures that occur within the subchronic period. Therefore, the subchronic nHBV is set equal to the short-term nHBV of 100 µg/L. The additivity endpoint is the renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 100 µg/L. The chronic nHBV must be protective of shorter duration exposures that occur within the chronic period. Therefore, the chronic nHBV is set equal to the short-term nHBV of 100 µg/L. Additivity endpoint is the renal (kidney) system.

Cancer.
The proposed cancer cHRL value is 10 µg/L. The cancer classification is "suggestive evidence of carcinogenic potential." The cancer slope factor is 0.008 $(mg/kg\text{-}d)^{-1}$ (Umeda et al., 2005). The age-dependent adjustment factors and intake rates are 10 and 0.155 L/kg-d for an age under 2 years; 3 and 0.040 L/kg-d for an age between 2 years and less than 16 years; and 1 and 0.042 L/kg-d for ages above 16 years. The tumor sites are liver adenomas and carcinomas.

Subpart. 6h. Bromodichloromethane (BDCM).

New chemical for Minnesota Rules, part 4717.7860: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to the rule to 4717.7860, subpart 6h for Bromodichloromethane. Repeal from part 4717.7500, subpart 15.

CAS number: 75-27-4
Year Adopted: 2023
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	400	30	30 (2)	30	3
RFD (mg/kg-day)	0.073	0.039	(2)	0.0075	--
RSC	0.2	0.2	(2)	0.2	--

	Acute	Short-term	Subchronic	Chronic	Cancer
SF (per mg/kg-day)	--	--	--	--	0.035
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	0.038	0.290	(2)	0.045	$0.155_{(<2)}$ $0.040_{(2\ to\ <16)}$ $0.042_{(16+)}$
Endpoints	female reproductive system (E)	immune system, spleen	immune system, spleen	hepatic (liver) system	cancer

Acute duration.
The proposed acute nHRL is 400 µg/L. The RfD is 0.073 mg/kg-d, and the intake rate is 0.038 L/kg-d. The RfD is based on full litter resorptions, which occurs in utero; therefore, the intake rate for a pregnant woman is used rather than the default infant intake rate as described in the 2008 SONAR (p. 46). The RSC is 0.2. The POD is a $BMDL_{0.5}$ of 10.4 mg/kg-d (Narotsky et al., 1997). The DAF is 0.21 based on body weight scaling, and the HED is 2.18 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability). The critical effect is full litter resorptions, associated with changes in female hormones that maintain pregnancy. There are no co-critical effects. The additivity endpoint is the female reproductive system (E).

Short-term duration.
The proposed short-term nHRL is 30 µg/L. The RfD is 0.039 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{10}$ of 30.3 mg/kg-d (Munson et al., 1982). The DAF is 0.13 based on body weight scaling, and the HED is 3.94 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty due to outstanding concerns related to BDCM-induced hormonal changes in females and immunotoxicity changes in a 2-generation study that is not confounded by vehicle, BDCM volatilization, water palatability, or animal dehydration issues). The critical effect is decreased spleen weight. The co-critical effect is full litter resorptions. Note that because an infant water ingestion rate exposure forms the basis of the short-term HBV calculation, and full litter resorptions is relevant only to pregnant women and is based on a pregnant woman's water ingestion rate exposure, the additivity endpoint for full litter resorptions is not necessary. The additivity endpoints are the immune system and the spleen.

Subchronic duration.
The proposed subchronic nHRL is 30 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore,

the subchronic nHRL is set equal to the short-term nHRL of 30 µg/L. The additivity endpoints are immune system and spleen.

Chronic duration.
The proposed chronic nHRL is 30 µg/L. The RfD is 0.0075 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{10}$ of 0.776 mg/kg-d (Aida, 1992). The DAF is 0.29 based on body weight scaling, and the HED is 0.225 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics, and 10 for intraspecies variability). The critical effect is fatty degeneration of the liver. There are no co-critical effects. The additivity endpoint is the hepatic (liver) system.

Cancer.
The proposed cancer cHRL value is 3 µg/L. The cancer classification is "likely to be carcinogenic to humans." The cancer slope factor is 0.035 $(mg/kg\text{-}d)^{-1}$ based on renal tumors in male B6C3F1 mice (NTP, 1987) and reported by EPA (2005a). The age-dependent adjustment factors and intake rates are 10 and 0.155 L/kg-d for an age under 2 years; 3 and 0.040 L/kg-d for an age between 2 years and less than 16 years; and 1 and 0.042 L/kg-d for ages above 16 years. The tumor sites are kidney, large intestine, liver, and lymphatic system.

Subpart. 8f. 1,4-Dichlorobenzene.

New chemical for Minnesota Rules, part 4717.7860: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to the rule to part 4717.7860, subpart 8f for 1,4-Dichlorobenzene. Repeal from part 4717.7500, subpart 34a.

CAS number: 106-46-7
Year Adopted: 2023
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	50	50 (2)	50 (2)	NA
RFD (mg/kg-day)	--	0.069	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Intake Rate (L/kg-day)	--	0.290	(2)	(2)	--
Endpoints	--	developmental, hepatic (liver) system, nervous system	developmental, hepatic (liver) system, nervous system	developmental, hepatic (liver) system, nervous system	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 50 µg/L. The RfD is 0.069 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 30 mg/kg-d (EPA, 2006). The DAF is 0.23 for body weight scaling, and the HED is 6.9 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty for lack of neurotoxicity studies and limitations in study reporting). The critical effects are reduced pup body weight, increased pup mortality, increased incidence postnatal dry and scaly skin, increased postnatal tail constriction, and a reduction in the number of pups with a positive reaction in the neurobehavioral draw-up test. The co-critical effects are increased liver weight and hepatocyte proliferation. The additivity endpoints are developmental, the hepatic (liver) system, and the nervous system.

Subchronic duration.
The proposed subchronic nHRL is 50 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 50 µg/L. The additivity endpoints are developmental, the hepatic (liver) system, and the nervous system.

Chronic duration.
The proposed chronic nHRL is 50 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 50 µg/L. The additivity endpoints are developmental, the hepatic (liver) system, and the nervous system.

Cancer.
Not applicable.

Subpart. 8i. trans-1,2-Dichloroethene.

Change the subpart for trans,1-2-Dichloroethane to Minnesota Rules, part 4717.7860, subpart 8i from subpart 8h. Change Year Adopted and data as shown in the table below.

CAS number: 156-60-5
Year Adopted: [Delete: 2013, Add: 2023]
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	[Delete: 200 Add: 50]	[Delete: 40 Add: 9]	NA
RFD (mg/kg-day)	--	--	[Delete: 0.091 Add: 0.020]	[Delete: 0.0091 Add: 0.0020]	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	[Delete: 0.077 Add: 0.074]	[Delete: 0043 Add:.045]	--
Endpoints	--	--	immune system	immune system	--

Acute duration.
Not derived because of insufficient information.

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

Subchronic duration.
The proposed subchronic nHRL is 50 µg/L. The RfD is 0.020 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2. The POD is a BMDL Administered Dose-1 Standard Deviation (ADM 1SD) of 14.5 mg/kg-d (OEHHA, 2018). The DAF is 0.14 for body weight scaling, and the HED is 2.03 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty due to lack of a multigenerational study and for supplementing the database with inhalation studies). The critical effect is the decreased ability to produce antibodies against sheep red blood cells in male spleen cells. The co-critical effects are decreased thymus weight and clinical chemistry effects. The additivity endpoint is the immune system.

Chronic duration.
The proposed subchronic nHRL is 9 µg/L. The RfD is 0.0020 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{ADM\text{-}1SD}$ of 14.5 mg/kg-d based on the 2018 OEHHA modeling of immunotoxicity data from a subchronic exposure from Shopp, 1985 (OEHHA, 2018). The DAF is 0.14 for body weight scaling, and the HED is 2.03 mg/kg-d. The total UF is 1000 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, 10 for subchronic to chronic extrapolation due to clear and

significant immunotoxicity in the subchronic study, and 3 for database uncertainty due to the lack of a multigenerational study and for supplementing the database with inhalation studies). The critical effect is the decreased ability to produce antibodies against sheep red blood cells in male spleen cells. The co-critical effects are decreased thymus weight and clinical chemistry effects. The additivity endpoint is the immune system.

Cancer.
Not applicable.

Subpart. 8j. 1,1-Dichloroethylene (Vinylidene chloride).

Change the subpart for 1,1-Dichloroethylene to Minnesota Rules, part 4717.7860, subpart 8j from subpart 8i. Change the Year Adopted and data as shown in the table below.

CAS number: 75-35-4
Year Adopted: [Delete: 2011, Add 2023]
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	200	200	NA
RFD (mg/kg-day)	--	--	[Delete: 0.090 Add: 0.069]	[Delete: 0.046 Add 0.040]	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	[Delete 0.077 Add: 0.074]	[Delete 0.043 Add 0.045]	--
Endpoints	--	--	hepatic (liver) system	hepatic (liver) system	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.

Not derived because of insufficient information.

Subchronic duration.
The proposed subchronic nHRL is 200 µg/L. The RfD is 0.069 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 9 mg/kg-d (Nitschke et al., 1983). The DAF is 0.23 for body weight scaling, and the HED is 2.07 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability). The critical effect is fatty changes in the liver. There are no co-critical effects. The additivity endpoint is the hepatic (liver) system.

Chronic duration.
The proposed chronic nHRL is 200 µg/L. The RfD is 0.040 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{10}$ of 4.6 mg/kg-d (Quast et al., 1983). The DAF is 0.26 for body weight scaling, and the HED is 1.20 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability). The critical effect and co-critical effect are both fatty changes in the liver. The additivity endpoint is the hepatic (liver) system.

Cancer.
Not applicable.

Subpart. 8k. **1,2-Dichloropropane.**

New chemical for Minnesota Rules, part 4717.7860: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to the rule to part 4717.7860, subpart 8k. Repeal from part 4717.7500, subpart 45a

CAS number: 78-87-5
Year Adopted: 2023
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	20	20 (2)	20 (2)	3
RFD (mg/kg-day)	--	0.029	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	0.037
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)

	Acute	Short-term	Subchronic	Chronic	Cancer
Intake Rate (L/kg-day)	--	0.290	(2)	(2)	$0.155_{(<2)}$ $0.040_{(2 \text{ to } <16)}$ $0.042_{(16+)}$
Endpoints	--	developmental	developmental	developmental	cancer

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed subchronic nHRL is 20 µg/L. The RfD is 0.029 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{05}$ of 12.8 mg/kg-d (Kirk, et al., 1995). The DAF is 0.23 for body weight scaling, and the HED is 2.94 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty due to the absence of an adequate 2-generational study and a developmental neurotoxicity study in offspring). The critical effect is delayed ossification of the fetal skull. There are no co-critical effects. The additivity endpoint is developmental.

Subchronic duration.
The proposed subchronic nHRL is 20 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 20 µg/L. The additivity endpoint is developmental.

Chronic duration.
The proposed chronic nHRL is 20 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 20 µg/L. The additivity endpoint is developmental.

Cancer.
The proposed cancer cHRL value is 3 µg/L. The cancer classification is "carcinogenic to humans." The US EPA cancer slope factor is 0.037 $(mg/kg\text{-}d)^{-1}$ based on liver tumors in male mice (NTP, 1986). The age-dependent adjustment factors and intake rates are 10 and 0.155 L/kg-d for an age under 2 years; 3 and 0.040 L/kg-d for an age between 2 years and less than 16 years; and 1 and 0.042 L/kg-d for ages above 16 years. The tumor site is liver.

Subpart. 12a. **17α – Ethinylestradiol.**

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility classification and all data in the table below to the rule to Minnesota Rules, part 4717.7860, subpart 12a, for 17α-Ethinylestradiol.

CAS number: 57-63-6
Year Adopted: 2023
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	0.0005	0.0002	0.0002	NA
RFD (mg/kg-day)	--	1.7×10^{-7}	1.4×10^{-8}	1.4×10^{-8}	--
RSC	--	0.8	0.8	0.8	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	0.074	0.045	--
Endpoints	--	developmental (E), female reproductive system (E), male reproductive system (E)	developmental	developmental	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 0.0005 µg/L. The RfD is 1.7×10^{-7} mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.8. Typically, an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations, and an RSC of 0.2 is used for subchronic and chronic durations. Given the limited potential for exposure from other sources, an RSC of 0.8 was selected rather than applying the default RSC value. For individuals who take 17α-ethinylestradiol by prescription, the additional exposure from drinking water will be negligible. The POD is a LOAEL of 0.00050 mg/kg-d (Delclos et al., 2014). The HED was not applied because the doses directly given to neonatal animals were not adjusted due to interspecies and life-stage differences in toxicokinetics. The total UF is 3000 (10 for interspecies differences, 10 for intraspecies variability, 10 for using a LOAEL in place of a NOAEL, and 3 for database uncertainty regarding potential latent effects). The critical effects are male mammary gland hyperplasia, decreased ovary weight, increased uterine weight, and delayed vaginal opening. The co-critical effects in humans are reduced fertility via prevention of

ovulation, increased sex hormone binding globulin, decreased corticosteroid-binding globulin, decreased follicle-stimulating hormone, decreased luteinizing hormone, and breast development (gynecomastia) in infants. The co-critical effects in laboratory animals are decreased body weight gain in adults, post-implantation loss, increased resorptions, decreased number of live pups/litter, decreased fetal/neonatal survival, reduced pup body weight and body weight gain, histopathology in female sex organs (uterus, ovaries and clitoral gland), latent uterine atypical focal hyperplasia, increased malformations in female external genitalia, increased number of female nipples, changes in sexually dimorphic behaviors, decreased fertility, early female pubertal onset, effects on estrous cyclicity, ovarian dysfunction, increased gestation length, changes in male reproductive organ weights, histopathology effects in various male reproductive organs, increased male mammary gland terminal end buds and density, decreased testosterone, decreased epididymal sperm counts, and increased pituitary gland weight. The additivity endpoints are developmental (E), the female reproductive system (E), and the male reproductive system (E).

Subchronic duration.
The proposed subchronic nHRL is 0.0002 µg/L. The RfD is 1.4×10^{-8} mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.8. Typically, an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations, and an RSC of 0.2 is used for subchronic and chronic durations. Given the limited potential for exposure from other sources, an RSC of 0.8 was selected rather than applying the default RSC value. For individuals who take 17α-ethinylestradiol by prescription, the additional exposure from drinking water will be negligible. The POD is a $BMDL_{10}$ of 4.2×10^{-5} mg/kg-d (NTP, 2010). The chemical-specific DAF is 0.01 and the HED is 4.2×10^{-7} mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics, and 10 for intraspecies variability). The critical effect is mammary gland hyperplasia in adult males. There are no co-critical effects. The additivity endpoint is developmental.

Chronic duration.
The proposed chronic nHRL is 0.0002 µg/L. The RfD is 1.4×10^{-8} mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.8. Typically, an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations, and an RSC of 0.2 is used for subchronic and chronic durations. Given the limited potential for exposure from other sources, an RSC of 0.8 was selected rather than applying the default RSC value. For individuals who take 17α-ethinylestradiol by prescription, the additional exposure from drinking water will be negligible. The POD is a $BMDL_{10}$ of 4.2×10^{-5} mg/kg-d (NTP, 2010). The chemical-specific DAF is 0.01 and the HED is 4.2×10^{-7} mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics, and 10 for intraspecies variability). The critical effect is mammary gland hyperplasia in adult males. There are no co-critical effects. The additivity endpoint is developmental.

Cancer.
Not applicable.

Subpart. 12b. **Ethylbenzene.**

Change the subpart for Ethylbenzene to Minnesota Rules, part 4717.7860, subpart 12b. from subpart 12a. Change the Year Adopted and data as shown in the table below

CAS number: 100-41-4
Year Adopted: [Delete: 2011, Add: 2023]
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	[Delete: 50 Add: 40]	[Delete: 50 (2) Add: 40 (2)]	[Delete: 50 (2) Add: 40 (2)]	NA
RFD (mg/kg-day)	--	[Delete**:** 0.075 Add: 0.06]	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	[Delete: 0.289 Add: 0.290]	(2)	(2)	--
Endpoints	--	hepatic (liver) system, renal (kidney) system	hepatic (liver) system, renal (kidney) system	hepatic (liver) system, renal (kidney) system	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 40 µg/L, updated from 50 µg/L. The RfD is 0.06 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 75 mg/kg-d (Mellert, Deckhardt, and Kaufmann, (2007). The DAF is 0.24 based on body weight scaling, and the HED is 18 mg/kg-d. The total UF is 300 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 10 for database uncertainty due to lack of studies via oral exposure including developmental and reproductive studies and toxicity data in multiple species). The critical effects are changes in liver and kidney weight in males with corresponding histological changes and blood chemistry changes at higher doses. There are no co-critical effects. The additivity endpoints are the hepatic (liver) system and the renal (kidney) system.

Subchronic duration.
The proposed subchronic nHRL is 40 µg/L, updated from 50 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period. Therefore, the subchronic nHRL is set equal to the short-term nHRL of 40 µg/L. The additivity endpoints are the hepatic (liver) system and the renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 40 µg/L, updated from 50 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 40 µg/L. The additivity endpoints are the hepatic (liver) system and the renal (kidney) system.

Cancer.
Not applicable.

Subpart 12d. Ethylene Glycol.

Change the subpart for Ethylene Glycol to Minnesota Rules, part 4717.7860, subpart 12d, from subpart 12e. Change the Year Adopted and data as shown in the table below.

CAS number: 107-21-1
Year Adopted: [Delete: 2011, Add: 2023]
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	[Delete: 4,000 Add: ND]	[Delete: 4,000 Add: 2,000]	2,000	2,000	NA
RFD (mg/kg-day)	[Delete: 0.76 Add: --]	[Delete: 0.76 Add: 0.33]	[Delete: 0.72 Add: (2)]	[Delete: 0.5 Add: (2)]	--
RSC	[Delete: 0.2 Add: --]	0.2	[Delete: 0.2 Add: (2)]	[Delete: 0.2 Add: (2)]	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or AFlifetime	--	--	--	--	--
Intake Rate (L/kg-day)	[Delete: 0.043 Add: --]	[Delete: 0.043 Add: 0.038]	[Delete: 0.077 Add: (2)]	[Delete: 0.043 Add: (2)]	--
Endpoints	[Delete: developmental Add: --]	developmental	developmental, renal (kidney) system	developmental [Add: male reproductive system] renal (kidney) system	--

Acute duration.
Not derived because of insufficient information. Previous values for the Acute duration are proposed to be deleted.

Short-term duration.
The proposed short-term nHRL is 2,000 µg/L, updated from 4,000 µg/L. The RfD is 0.33 mg/kg-d, and the intake rate is 0.038 L/kg-d. Note that the RfD is based on malformations that occur in utero, therefore, MDH used an intake rate for a pregnant woman rather than the default infant intake rate, as described in the MDH 2008/2009 SONAR (PDF) (p. 46) (https://www.leg.mn.gov/archive/sonar/SONAR-03733.pdf#page=55). Effects relevant to post-natal development occurred at higher dose levels. As the short-term duration intake is based on pregnant women, not infants, the RSC is 0.2. The POD is a $BMDL_{10}$ of 75.6 mg/kg-d (ATSDR, 2010). The DAF is 0.13 based on body weight scaling, and the HED is 9.83 mg/kg-d. The total UF is 30 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effect is increased fetal skeletal malformations. There are no co-critical effects. The additivity endpoint is developmental.

Subchronic duration.
The proposed subchronic nHRL is 2,000 µg/L. The calculated subchronic RfD (0.57 mg/kg-d) is higher than the short-term RfD (0.33 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. Therefore, the short-term RfD is used in place of the calculated subchronic RfD, and the water intake rate for a pregnant woman is used. The calculated subchronic nHBV, before consideration of the short-term RfD and HBV, resulted in the same water guidance value after rounding to one significant digit. Therefore, the subchronic duration additivity endpoint of renal (kidney) system is added to developmental, resulting in additivity endpoints of developmental and renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 2,000 µg/L. The calculated chronic RfD (0.44 mg/kg-d) is higher than the short-term RfD (0.33 mg/kg-d), which is based on developmental effects. The chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including short-term effects. Therefore, the short-term RfD is used in place of the calculated chronic RfD, and the water intake rate for a pregnant woman is used. The calculated chronic nHBV, before consideration of the short-term RfD and HBV, resulted in the same water guidance value after rounding to one significant digit. Therefore, the chronic duration additivity endpoints of male reproductive system and renal (kidney) system are added to developmental. The additivity endpoints therefore are developmental, the male reproductive system, and the renal (kidney) system.

Cancer.
Not applicable.

Subpart. 12f. **Fluorene (9H-Fluorene).**

New chemical for Minnesota Rules, part 4717.7860: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 12f, for Fluorene. Repeal from part 4717.7500, subpart 54.

CAS number: 86-73-7
Year Adopted: 2023
Volatility: Moderate

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	200	80	NA
RFD (mg/kg-day)	--	--	0.058	0.018	--
RSC	--	--	0.2	0.2	--

	Acute	Short-term	Subchronic	Chronic	Cancer
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	0.074	0.045	--
Endpoints	--	--	hematological (blood) system, spleen	hematological (blood) system, spleen	--

Acute duration.
Not derived because of insufficient information.

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

Subchronic duration.
The proposed subchronic nHRL is 200 µg/L. The RfD is 0.058 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 125 mg/kg-d (EPA, 1989). The DAF is 0.14 based on body weight scaling, and the HED is 17.5 mg/kg-d. The total UF is 300 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 10 for database uncertainty to account for the absence of adequate developmental, reproductive, and neurotoxicity studies). The critical effects are decreased red blood cells in female mice, decreased packed cell volume in female and male mice, and increased relative spleen weight in male and female mice. There are no co-critical effects. The additivity endpoints are the hematological (blood) system and spleen.

Chronic duration.
The proposed chronic nHRL is 80 µg/L. The RfD is 0.018 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 125 mg/kg-d from a subchronic exposure (EPA, 1989). The DAF is 0.14 for body weight scaling, and the HED is 17.5 mg/kg-d. The total UF is 1000 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, 3 for subchronic-to-chronic extrapolation, and 10 for database uncertainty to account for the absence of adequate developmental, reproductive, and neurotoxicity studies in the database). The critical effects are decreased red blood cells in female mice, decreased packed cell volume in female and male mice, and increased relative spleen weight in male and female mice. There are no co-critical effects. The additivity endpoints are the hematological (blood) system and spleen.

Cancer.
Not applicable.

Subpart. 12g. **Fomesafen.**

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility classification and all data in the table below to the rule to Minnesota Rules, part 4717.7860, subpart 12g for Fomesafen.

CAS number: 72178-02-0
Year Adopted: 2023

Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	200	200 (2)	20	NA
RFD (mg/kg-day)	--	0.12	(2)	0.005	--
RSC	--	0.5	(2)	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	(2)	0.045	--
Endpoints	--	developmental, hepatic (liver) system, immune system	developmental, hepatic (liver) system, immune system	hepatic (liver) system	--

Acute duration.
Not derived.

Short-term duration.
The proposed short-term nHRL is 200 µg/L. The RfD is 0.12 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.5. The POD is a NOAEL of 12.5 mg/kg-d from a 2-generation reproductive study (EPA, 1984). The DAF is 0.28 based on body weight scaling, and the HED is 3.50 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics and 10 for intraspecies variability). The critical effects are decreased litter weight gain, decreased pup survival, and reduced number of pups born alive. The co-critical effects are decreased plasma cholesterol and triglycerides, reduced IgM antibody and lymph node enlargement. The additivity endpoints are developmental, the hepatic (liver) system, and immune system.

Subchronic duration.
The proposed subchronic nHRL is 200 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 200 µg/L. The additivity endpoints are developmental, the hepatic (liver) system, and immune system.

Chronic duration.
The proposed chronic nHRL is 20 µg/L. The RfD is 0.005 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 0.96 mg/kg-d from a two-year toxicity study (EPA, 1981). The DAF is 0.16 for study-specific body weight scaling, and the HED is 0.15 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability). The critical effects are increased liver weight, enlarged and discolored liver; the presence of pigmented macrophages and/or Kupffer cells in the liver (inflammation), liver masses, increased serum alkaline phosphatase activity, and increased glutamic pyruvic transaminase activity. There are no co-critical effects. The additivity endpoint is the hepatic (liver) system.

Cancer.
Not applicable.

Subpart. 12h. **Imidacloprid.**

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility classification and all data in the table below to the rule to Minnesota Rules, part 4717.7860, subpart 12h, for Imidacloprid.

CAS number: 138261-41-3
Year Adopted: 2023
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	100	2	2 (2)	2 (2)	NA
RFD (mg/kg-day)	0.15	0.0036	(2)	(2)	--
RSC	0.2	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.290	0.290	(2)	(2)	--
Endpoints	nervous system	immune system	immune system	immune system	--

Acute duration.
The proposed acute nHRL is 100 µg/L. The RfD is 0.15 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2 because MDH deviated from the default RSC of 0.5, based on assessments from California EPA (California EPA, 2006) and EPA (EPA, 2017a) indicating that infant dietary exposures and infant exposures from residential pesticide treatments, including pet treatments, are high enough to warrant allocation of only 20% of the RfD to drinking water. The POD is a NOAEL of 8 mg/kg-d (California EPA, 2006). The DAF is 0.55 based on body weight scaling, and the HED is 4.4 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics and 10 for intraspecies variability). The critical effects are tremors. There are no co-critical effects. The additivity endpoint is the nervous system.

Short-term duration.
The proposed short-term nHRL is 2 µg/L. The RfD is 0.0036 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. MDH deviated from the default RSC of 0.5 based on assessments from California EPA (California EPA, 2006) and EPA (EPA, 2017a) indicating that infant dietary exposures and infant exposures from residential pesticide treatments, including pet treatments, are high enough to warrant allocation of only 20% of the RfD to drinking water. The POD is a $BMDL_{-1SD}$ of 0.820 mg/kg-d. The DAF is 0.13 for body weight scaling, and the HED is 0.107 mg/kg-d. The total UF is 30 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effect is the reduced delayed-type hypersensitivity response. There are no co-critical effects. The additivity endpoint is the immune system.

Subchronic duration.
The proposed subchronic nHRL is 2 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 2 µg/L. The additivity endpoint is the immune system.

Chronic duration.
The proposed chronic nHRL is 2 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 2 µg/L. The additivity endpoint is the immune system.

Cancer.
Not applicable.

Subpart. 12i **Manganese.**

New chemical for Minnesota Rules, part 4717.7860:: Add the chemical name, CAS number, Year Adopted, Volatility classification and all data in the table below to the rule to Minnesota Rules, part 4717.7860, subpart 12i, for Manganese. Repeal from part 4717.7500, subpart 61.

CAS number: 7439-96-5
Year Adopted: 2023
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	100	ND	ND	NA
RFD (mg/kg-day)	--	0.083	--	--	--
RSC	--	0.5	--	--	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	--	--	--
Endpoints	--	developmental, nervous system	--	--	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 100 µg/L. The RfD is 0.083 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.5. The POD is a LOAEL of 25 mg/kg-d (Kern, Sanwood, and Smith, 2010). The DAF is not applicable, because there was insufficient data to support the use of DAFs for the neonatal period. The HED is also not applicable. The total UF is 300 (10 for interspecies differences, 10 for intraspecies variability, and 3 for LOAEL-to-NOAEL extrapolation due to mild effects seen at the LOAEL). The critical effects are neurological effects including increased distance traveled in an open arena, decreased number of animals meeting learning criteria, increased learning errors, a shift in goal-oriented behavior, and altered dopamine receptor levels. The co-critical effects are neurological effects including an increased startle response. The additivity endpoints are developmental and the nervous system.

Subchronic duration.
Not derived because of insufficient information.
MDH recommends the US Environmental Protection Agency's (EPA) health advisory value of 300 µg/L for older children and adults experiencing subchronic or chronic duration exposures. The EPA health advisory value is based on a high end dietary intake level at which no health effects were observed. For additional information see: Manganese in Drinking Water https://www.health.state.mn.us/communities/environment/water/docs/contaminants/mangnsefctsht.pdf.

Chronic duration.
Not derived because of insufficient information.
MDH recommends the US Environmental Protection Agency's (EPA) health advisory value of 300 µg/L for older children and adults experiencing subchronic or chronic duration exposures. The EPA health advisory value is based on a high end dietary intake level at which no health effects were observed. For additional information see: Manganese in Drinking Water https://www.health.state.mn.us/communities/environment/water/docs/contaminants/mangnsefctsht.pdf.

Cancer.
Not applicable.

Subpart. 12j. **Metolachlor and s-Metolachlor.**

Change the subpart for Metolachlor and s-Metolachlor to Minnesota Rules, part 4717.7860, subpart 12j, from subpart 12e. Change the Year Adopted and data as shown in the table below.

CAS number: 51218-45-2; 87392-12-9
Year Adopted: [Delete: 2011, Add: 2023]
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	[Delete: 400 Add: ND]	[Delete: 400 Add: 300]	300 [Add: (2)]	300 [Delete: (3) Add: (2)]	NA
RFD (mg/kg-day)	[Delete: 0.24 Add: --]	[Delete: 0.24 Add: 0.19]	[Delete: 0.097 Add: (2)]	[Delete: (3) Add: (2)]	--
RSC	[Delete: 0.5 Add: --]	0.5	[Delete: 0.2 Add: (2)]	[Delete: (3) Add: (2)]	--
SF (per mg/kg-day)	--	--	--	--	--

	Acute	Short-term	Subchronic	Chronic	Cancer
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	[Delete: 0.289 Add: --]	[Delete: 0.289 Add: 0.290]	[Delete: 0.077 Add: (2)]	[Delete: (3) Add: (2)]	--
Endpoints	[Delete: developmental Add: --]	developmental	[Delete: none Add: developmental]	[Delete: none Add: developmental]	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 300 µg/L, updated from 400 µg/L. The RfD is 0.19 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.5. The POD is a NOAEL of 26 mg/kg-d. The DAF is 0.22, and the HED is 5.72 mg/kg-d, based on body weight scaling. The total UF is 30 (3 for interspecies differences for toxicodynamics and 10 for intraspecies variability). The critical effect is decreased body weight in pups. There are no co-critical effects. The additivity endpoint is developmental.

Subchronic duration.
The proposed subchronic nHRL is 300 µg/L, which is the same as the 2011 HRL. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 300 µg/L. The additivity endpoint is developmental.

Chronic duration.
The proposed chronic nHRL is 300 µg/L, which is the same as the 2011 HRL. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 300 µg/L. The additivity endpoint is developmental.

Cancer.
Not applicable.
At this time, MDH's non-cancer health-based guidance values are considered to be protective for possible cancer risks associated with metolachlor in drinking water. Neither the International Agency for Research on Cancer nor the National Toxicology Program (NTP) have classified metolachlor as a carcinogen. Metolachlor has been identified as a nonlinear carcinogen by the EPA. Three long-term animal studies have been conducted with metolachlor, and tumors were reported in only one of these studies at the highest dose level tested (over 200 times higher than the MDH Chronic RfD). Additionally, as part of the 2008 HRL revision, the MDH Group C review committee evaluated the weight of evidence regarding the carcinogenicity and determined that no Group C UF was needed and agreed that the data do not support derivation of a cancer specific value.

Subpart. 12k. **Metolachlor ESA.**

Change the subpart for Metolachlor ESA to Minnesota Rules, part 4717.7860, subpart 12k, from subpart 12f. Change the Year Adopted and data as shown in the table below.

CAS number: 171118-09-5
Year Adopted: [Delete: 2011, Add: 2023]
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	[Delete: 4,000 Add: 7,000]	[Delete: 800 Add: 1,000]	NA
RFD (mg/kg-day)	--	--	[Delete: 1.7 Add: 2.7]	[Delete: 0.17 Add: 0.27]	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	[Delete: 0.077 Add: 0.074]	[Delete: 0.043 Add: 0.045]	--
Endpoints	--	--	hepatic (liver) system	hepatic (liver) system	--

Acute duration.
Not derived because of insufficient information.

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

Subchronic duration.
The proposed subchronic nHRL is 7,000 µg/L, updated from 4,000 µg/L. The RfD is 2.7 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 500 mg/kg-d (EPA, 2000a). The DAF is 0.53, and the HED is 265 mg/kg-d using body weight scaling. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty because of lack of a two-generation study). The critical effects are increased liver weight and increased serum liver enzymes. There are no co-critical effects. The additivity endpoint is the hepatic (liver) system.

Chronic duration.
The proposed chronic nHRL is 1,000 µg/L, updated from 800 µg/L. The RfD is 0.27 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a NOAEL of

500 mg/kg-d. The DAF is 0.53 based on body weight scaling, and the HED is 265 mg/kg-d. The total UF is 1,000 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, 10 for subchronic-to-chronic extrapolation, and 3 for database uncertainty due to the lack of a two-generation study). The critical effects are increased liver weight and increased serum liver enzymes. There are no co-critical effects. The additivity endpoint is the hepatic (liver) system.

Cancer.
Not applicable.

Subpart. 12l. **Metolachlor OXA.**

Change the subpart for Metolachlor OXA to Minnesota Rules, part 4717.7860, subpart 12l, from subpart 12g. Change the Year Adopted and data as shown in the table below.

CAS number: 152019-73-3
Year Adopted: [Delete: 2011, Add: 2023]
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	[Delete: 3,000 Add: 5,000]	[Delete: 3,000 Add: 5,000] (2)	[Delete: 800 Add: 1,000]	NA
RFD (mg/kg-day)	--	[Delete: 1.7 Add: 2.7]	(2)	[Delete: 0.17 Add: 0.27]	--
RSC	--	0.5	(2)	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	[Delete: 0.289 Add: 0.290]	(2)	[Delete: 0.043 Add: 0.045]	--
Endpoints	--	none	none	none	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 5,000 µg/L, changed from 3,000 µg/L. The RfD is 2.7 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.5. The POD is a NOAEL of 500 mg/kg-d (Syngenta, 2004). The DAF is 0.53 based on body weight scaling, and the HED is 265 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty for a lack of a two-generation

study). The critical effects are changes in blood chemistry parameters without identified specific target organs. There are no co-critical effects. There is no additivity endpoint.

Subchronic duration.
The proposed subchronic nHRL is 5,000 µg/L, changed from 3,000 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 5,000 µg/L. There is no additivity endpoint.

Chronic duration.
The proposed chronic nHRL is 1,000 µg/L, changed from 800 µg/L. The RfD is 0.27 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 500 mg/kg-d from subchronic exposure (Syngenta, 2004). The DAF is 0.53 based on body weight scaling, and the HED is 265 mg/kg-d. The total UF is 1,000 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, 10 for subchronic-to-chronic extrapolation, and 3 for database uncertainty for lack of a two-generation study). The critical effects are changes in blood chemistry parameters without identified specific target organs. There are no co-critical effects. There is no additivity endpoint.

Cancer.
Not applicable.

Subpart. 13a. **p-Nonylphenol (4-Nonylphenol).**

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility classification and all data in the table below to Minnesota Rules, part 4717.7860, subpart 13a, for p-Nonylphenol (4-Nonylphenol):

CAS number: 84852-15-3
Year Adopted: 2023
Volatility: Low

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	100	40	20	NA
RFD (mg/kg-day)	--	0.21	0.016	0.0049	--
RSC	--	0.2	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Intake Rate (L/kg-day)	--	0.290	0.074	0.045	--
Endpoints	--	developmental, female reproductive system	renal (kidney) system	renal (kidney) system	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 100 µg/L. The RfD is 0.21 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2 because the available data indicate that infant exposures from sources such as breast milk and baby food are not lower than adult exposures. Infant exposures are equal to or exceed adult exposures based on the available exposure data, so a relative source contribution of 0.2 has been selected for all durations. The POD is a NOAEL of 33 mg/kg-d (Chapin et al., 1999; NTP, 1997). The DAF is 0.19 based on body weight scaling, and the HED is 6.27 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics and 10 for intraspecies variability). The critical effect is accelerated vaginal opening. The co-critical effects are decreased pup body weight and increased duration of the estrous cycle. The additivity endpoints are developmental and the female reproductive system.

Subchronic duration.
The proposed short-term nHRL is 40 µg/L. The RfD is 0.016 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{10}$ of 1.94 mg/kg-d (Chapin et al., 1999; NTP, 1997). The DAF is 0.25 based on body weight scaling, and the HED is 0.485 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics and 10 for intraspecies variability). The critical effect is renal mineralization in male rats. There are no co-critical effects. The additivity endpoint is the renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 20 µg/L. The RfD is 0.0049 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{10}$ of 1.94 mg/kg-d (Chapin et al., 1999; NTP, 1997) The DAF is 0.25 based on body weight scaling and the HED is 0.485 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for subchronic to chronic extrapolation). The critical effect is renal mineralization in male rats. There are no co-critical effects. The additivity endpoint is the renal (kidney) system.

Cancer.
Not applicable.

Subpart. 13b. 4-*tert*-Octylphenol.

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 13b, for 4-tert-Octylphenol:

CAS number: 140-66-9
Year Adopted: 2023
Volatility: Low

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	100	100 (2)	100 (2)	NA
RFD (mg/kg-day)	--	0.17	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	(2)	(2)	--
Endpoints	--	developmental	developmental	developmental	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 100 µg/L. The RfD is 0.17 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2 because the available data indicate that infant exposures from sources such as breast milk and baby food are not lower than adult exposures. Infant exposures are equal to or exceed adult exposures based on the available exposure data, so a relative source contribution of 0.2 has been selected for all durations. The POD is a NOAEL of 22 mg/kg-d (Tyl et al., 1999). The DAF is 0.23 based on body weight scaling, and the HED is 5.06 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics and 10 for intraspecies variability). The critical effects are decreased pup body weight and increased time to preputial separation. The co-critical effect is decreased adult body weight. The additivity endpoint is developmental.

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

Chronic duration.
The proposed chronic nHRL is 100 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and therefore the chronic nHRL is set equal to the short-term nHRL of 100 µg/L. The additivity endpoint is developmental.

Cancer.
Not applicable.

Subpart. 14a. **Perfluorobutane sulfonate (PFBS).**

Add CAS numbers 45187-15-3; 29420-49-3; 68259-10-9; and 60453-92-1 to Minnesota Rules, part 4717.7860, subpart 14a, change Year Adopted from 2011 to 2023, and change data as shown in the table below.

CAS number: 375-73-5; [Add: 45187-15-3 (anion);] 375-73-5 (free acid); [Add: 29420-49-3 (potassium salt);] 68259-10-9 (ammonium salt); [Add: 60453-92-1 (sodium salt)]
Year Adopted: [Delete: 2011, Add: 2023]
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	[Delete: ND Add: 0.1]	[Delete: 9 Add: 0.1 (2)]	[Delete: 7 Add: 0.1 (2)]	NA
RFD (mg/kg-day)	--	[Delete: -- Add: 0.000084]	[Delete: 0.0042 Add: (2)]	[Delete: 0.0014 Add: (2)]	--
RSC	--	[Delete: -- Add: 0.5]	[Delete: 0.5 Add: (2)]	[Delete: 0.2 Add: (2)]	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	[Delete: -- Add: 0.290]	[Delete: 0.245 Add: (2)]	[Delete: 0.043 Add: (2)]	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Endpoints	--	[Delete: -- Add: thyroid (E)]	[Delete: hepatic (liver) system, hematological (blood) system, renal (kidney) system, Add: thyroid (E)]	[Delete: hepatic (liver) system, hematological (blood) system, Add: thyroid (E)]	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.

The proposed new short-term nHRL is 0.1 µg/L. The RfD is 0.000084 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.5. The POD is a $BMDL_{1SD}$ of 6.97 mg/kg-d (NTP, 2019b). The DAF is 0.0012 based on a chemical- and study-specific toxicokinetic adjustment, resulting in an HED of 0.0084 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty due to lack of available immunotoxicity and developmental neurotoxicity studies (known sensitive effects of other per- and polyfluoroalkyl substances (PFAS)) as well as lack of a 2-generation study in a more appropriate species). The critical effect is decreased total T4. There are no co-critical effects. The additivity endpoint is thyroid (E).

Subchronic duration.
The proposed subchronic nHRL is 0.1 µg/L, updated from 9 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period. Therefore, the subchronic nHRL is set equal to the short-term nHRL of 0.1 µg/L. The additivity endpoint is thyroid (E).

Chronic duration.
The proposed chronic nHRL is 0.1 µg/L, updated from 7 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period. Therefore, the chronic nHRL is set equal to the short-term nHRL of 0.1 µg/L. The additivity endpoint is thyroid (E).

Cancer.
Not applicable.

Subpart. 14c. **Perfluorohexane sulfonate (PFHxS).**

New chemical: Add the chemical name, CAS numbers, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 14c, for perfluorohexane sulfonate:

CAS number: 108427-53-8 (anion); 355-46-4 (acid); 3871-99-6 (potassium salt)
Year Adopted: 2023
Volatility: Moderate

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	0.047	0.047	0.047	NA
RFD (mg/kg-day)	--	0.0000097	0.0000097	0.0000097	--
RSC	--	0.5	0.5	0.5	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	*	*	*	--
Endpoints	--	hepatic (liver) system, thyroid (E)	hepatic (liver) system, thyroid (E)	hepatic (liver) system, thyroid (E)	--

Note: Due to the highly bioaccumulative nature of PFHxS, short-term exposures have the potential to stay in the body for an extended period of time. In addition, accumulated maternal PFHxS is transferred to offspring (i.e., placental and breastmilk transfer). A single HBV has therefore been recommended for short-term, subchronic, and chronic durations. See the Toxicological Summary sheet for Perfluorohexane sulfonate in Appendix E for more information.

Acute duration.
Not applicable.

Short-term, Subchronic and Chronic durations.
The proposed short-term, subchronic and chronic nHRL value is 0.047 µg/L. The RfD is 0.0000097 mg/kg-d (corresponding serum concentration is 0.108 mg/L). In keeping with MDH's promulgated methodology, 95th percentile water intake rates (EPA 2019 at Tables 3-1, 3-3, and 3-5) or upper percentile breastmilk intake rates (EPA 2011 at Table 15-1) were used. A placental transfer factor of 70% was used to calculate infant serum levels at birth. Breastmilk concentrations were calculated by multiplying the maternal

serum concentration by a serum to breastmilk transfer factor of 1.4%. 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. Based on local and national biomonitoring data an RSC of 0.5 was used. The POD is a $BMDL_{20\%}$ serum concentration of 32.4 µg/L (NTP, 2018). The DAF of 0.000090 L/kg-day is a toxicokinetic adjustment based on the chemical-specific clearance rate, and the HED is 0.00292 mg/kg-d. The total UF is 300 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 10 for database uncertainty to address concerns regarding early life sensitivity to decreased thyroxine (T4) levels as well as lack of 2 generation or immunotoxicity studies). The critical effect is decrease of free T4. The co-critical effects are decreased of free and total T4, triiodothyronine (T3), and changes in cholesterol levels and increased hepatic focal necrosis. The additivity endpoints are the hepatic (liver) system and the thyroid (E).

Cancer:
Not applicable.

Subpart. 14d. Perfluorohexanoate (PFHxA) and salts).

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 14d, for PFHxA:

CAS number: 92612-52-7 (anion); 307-24-4 (free acid); 21615-47-4 (ammonium salt); 2923-26-4 (sodium salt)
Year Adopted: 2023
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	0.2	0.2 (2)	0.2 (2)	NA
RFD (mg/kg-day)	--	0.00032	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	(2)	(2)	--
Endpoints	--	developmental, thyroid (E)	developmental, thyroid (E)	developmental, thyroid (E)	--

Acute duration.
Not derived.

Short-term duration.
The proposed short-term nHRL is 0.2 µg/L. The RfD is 0.00032 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2 was used for all exposure durations due to concerns about infant exposures from house dust and diet, potential exposures from the breakdown of precursor chemicals, and uncertainty about infant exposure levels. The POD is a $BMDL_{1SD}$ of 25.9 mg/kg-d (NTP, 2019a). The DAF is Chemical and Study-Specific Toxicokinetic Adjustment calculated with a Half-life for Male Rat of 2.87 hours/Half-life for Human of 768 hrs, which equals 0.0037 (based on Dzierlenga et al 2020, for male rats, and Russell et al., 2013, for humans). The HED is 0.0958 mg/kg-d. The total UF is 300 (3 for interspecies differences [for toxicodynamics] and 10 for intraspecies variability, and 10 for database uncertainty for a lack of a 2-generation study, lack of thyroid hormone measurements or neurodevelopmental toxicity in young offspring in a development/reproductive study, and lack of immunotoxicity studies as well as evidence of pup body weight effects near the selected POD)). The critical effect is decreased total T4. The co-critical effect is decreased pup body weight. The additivity endpoints are developmental and thyroid (E).

Subchronic duration.
The proposed subchronic nHRL is 0.2 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period and therefore the subchronic nHRL is set equal to the short-term nHRL of 0.2 µg/L. The additivity endpoints are developmental and thyroid (E).

Chronic duration.
The proposed chronic nHRL is 0.2 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and therefore the chronic nHRL is set equal to the short-term nHRL of 0.2 µg/L. The additivity endpoints are developmental and thyroid (E).

Cancer.
Not applicable.

Subpart. 16b. **Quinoline.**

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 16b, for Quinoline:

CAS number: 91-22-5
Year Adopted: 2023
Volatility: Low

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	ND	4	0.03
RFD (mg/kg-day)	--	--	--	0.00079	--
RSC	--	--	--	0.2	--
SF (per mg/kg-day)	--	--	--	--	3
ADAF or $AF_{lifetime}$	--	--	--	--	10 (ADAF<2) 3 (ADAF2 to <16) 1 (ADAF16+)
Intake Rate (L/kg-day)	--	--	--	0.045	$0.155_{(<2)}$ $0.040_{(2\ to\ <16)}$ $0.042_{(16+)}$
Endpoints	--	--	--	hematological (blood) system, hepatic (liver) system, renal (kidney) system, respiratory system, and spleen	cancer

Acute duration.
Not derived because of insufficient information.

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

Subchronic duration.
Not derived because of insufficient information

Chronic duration.
The proposed chronic nHRL is 4 µg/L. The RfD is 0.00079 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a LOAEL of 8.8 mg/kg-d (Matsumoto et al., 2018). The DAF is 0.27 based on body weight scaling, and the HED is 2.38 mg/kg-d. The total UF is 3000 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, 10 for using a LOAEL in place of a NOAEL, and 10 for database uncertainty for lack of reproductive, developmental, immunotoxicity, and neurotoxicity studies). The critical effects are increased cellular changes in the liver and kidney including necrosis; increased hematopoiesis in the bone marrow of both sexes; and increased extramedullary hematopoiesis in the spleen of male rats. The co-critical effects are

central degeneration of the liver; increased immature blood cells in the liver and lungs; increased erythropoiesis/hematopoiesis in the bone marrow, spleen, and liver; increased inflammatory infiltration in the lungs; and hemosiderin deposits in the kidney in both male and female mice; increased eosinophilic changes in the respiratory epithelium and increased Kupffer cell mobilization in the liver of female mice. The additivity endpoints are the hematological (blood) system, the hepatic (liver) system, the renal (kidney) system, the respiratory system, and the spleen.

Cancer.
The proposed cancer cHRL value is 0.03 µg/L. The cancer classification is "likely carcinogenic to humans" (EPA, 2001). The cancer slope factor is 3 $(mg/kg\text{-}d)^{-1}$ based on hepatic hemangioendotheliomas or hemangiosarcomas in Sprague dawley rats. The age-dependent adjustment factors and intake rates are 10 and 0.155 L/kg-d for an age under 2 years; 3 and 0.040 L/kg-d for an age between 2 years and less than 16 years; and 1 and 0.042 L/kg-d for ages above 16 years. The tumor site is the liver.

Subpart. 18. Tetrachloroethylene (PCE or PERC).

Change the name to remove "1,1,2,2-", change the Year Adopted and add all data in the table below to Minnesota Rules, part 4717.7860, subpart 18, for Tetrachloroethylene. Change the entry as shown below.

CAS number: 127-18-4
Year Adopted: [Delete: 2009, Add: 2023]
Volatility: High
[Delete: MCL-Based HRL: 5 µg/L]

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	7	7 (3)	4
RFD (mg/kg-day)	--	--	0.0026	(3)	--
RSC	--	--	0.2	(3)	--
SF (per mg/kg-day)	--	--	--	--	0.0249
ADAF or $AF_{lifetime}$	--	--	--	--	10 (ADAF<2) 3 (ADAF2 to <16) 1 (ADAF16+)

	Acute	Short-term	Subchronic	Chronic	Cancer
Intake Rate (L/kg-day)	--	--	0.074	(3)	$0.155_{(<2)}$ $0.040_{(2 \text{ to } <16)}$ $0.042_{(16+)}$
Endpoints	--	--	nervous system	nervous system	cancer

Acute duration.
Not derived because of insufficient information.

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

Subchronic duration.
The proposed subchronic nHRL is 7 µg/L. The RfD is 0.0026 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2. The POD is a LOAEL of 2.6 mg/kg-d (Cavalleri et al., 1994). The total UF is 1000 (10 for intraspecies variability, 10 for LOAEL-to-NOAEL because results from residential studies suggest points of departure 3 to 15 times lower than the current LOAEL, and 10 for database uncertainty due to lack of data regarding immune, hematological and developmental neurotoxicity). The critical effects are impacts on visual color domain –dyschromatopsia. There are no co-critical effects The additivity endpoint is the nervous system.

Chronic duration.
The proposed chronic nHRL is 7 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 7 µg/L. The additivity endpoint is the nervous system.

Cancer.
The proposed cancer cHRL value is 4 µg/L. The cancer classification is "likely carcinogenic to humans by all routes of exposure" (EPA, 2012). The cancer slope factor is 0.0249 $(mg/kg\text{-}d)^{-1}$. The age-dependent adjustment factors and intake rates are 10 and 0.155 L/kg-d for an age under 2 years; 3 and 0.040 L/kg-d for an age between 2 years and less than 16 years; and 1 and 0.042 L/kg-d for ages above 16 years. The cancer type is leukemia.

Subpart. 18c. **Toluene.**

Change the Year Adopted from 2011 to 2023 in Minnesota Rules, part 4717.7860, subpart 18c, and change data as shown in the table below.

CAS number: 108-88-3
Year Adopted: [Delete: 2011, Add: 2023]

Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	[Delete: 200 Add: 70]	[Delete: 200 (2) Add: 70 (2)]	[Delete: 200 (2) Add: 70 (2)]	NA
RFD (mg/kg-day)	--	[Delete: 0.22 Add: 0.10]	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	[Delete: 0.289 Add: 0.290]	(2)	(2)	--
Endpoints	--	immune system, nervous system	immune system, nervous system	immune system, nervous system	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 70 µg/L. The RfD is 0.10 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 22 mg/kg-d (Hsieh, Sharma, and Parker, 1989), the DAF is 0.14 based on body weight scaling, and the HED is 3.08 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics and 10 for intraspecies variability). The critical effect is immunosuppression. The co-critical effects are behavior changes due to nervous system effects, neurotransmitter level changes in the brain, and changes in the immune response. The additivity endpoints are the immune system and the nervous system.

Subchronic duration.
The proposed subchronic nHRL is 70 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 70 µg/L. The additivity endpoints are the immune system and the nervous system.

Chronic duration.
The proposed chronic nHRL is 70 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 70 µg/L. The additivity endpoints are the immune system and the nervous system.

Cancer.
Not applicable.

Subpart. 21b. **1,2,3-Trimethylbenzene.**

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 21b, for 1,2,3-Trimethylbenzene.

CAS number: 526-73-8
Year Adopted: 2023
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	30	30 (2)	30 (2)	NA
RFD (mg/kg-day)	--	0.042	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	(2)	(2)	--
Endpoints	--	nervous system	nervous system	nervous system	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 30 µg/L. The RfD is 0.042 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2, and the POD is a NOAEL of 22.0 mg/m^3 (Gralewicz et al., 1997 aci EPA, 2016). The DAF is 0.19, from a chemical-specific physiological based pharmacokinetic (PBPK) model-based on route-to-route extrapolation, using the ratio of subchronic oral POD_{HED} (3.5 mg/kg-d) to inhalation POD_{HEC} (18.15 mg/m^3) from EPA, 2016. The HED is 4.2 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty related to the lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study). The critical effects are central nervous system changes (increased open field grooming), and decreased pain sensitivity (lowered step down

latency and paw lick latency). The co-critical effects are central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), and decreased pain sensitivity (paw lick latency). The additivity endpoint is the nervous system.

Subchronic duration.
The proposed subchronic nHRL is 30 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 30 µg/L. The additivity endpoint is the nervous system.

Chronic duration.
The proposed chronic nHRL is 30 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 30 µg/L. The additivity endpoint the is nervous system.

Cancer:
Not applicable.

Subpart. 21c. **1,2,4-Trimethylbenzene.**

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 21c, for 1,2,4-Trimethylbenzene:

CAS number: 95-63-6
Year Adopted: 2023
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	30	30 (2)	30 (2)	NA
RFD (mg/kg-day)	--	0.042	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	(2)	(2)	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Endpoints	--	nervous system	nervous system	nervous system	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 30 µg/L. The RfD is 0.042 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2, and the POD is a NOAEL of 22.0 mg/m^3 (Gralewicz et al., 1997 aci EPA, 2016). The DAF is 0.19, from chemical-specific PBPK model-based route-to-route extrapolation, using the ratio of subchronic oral POD_{HED} (3.5 mg/kg-d) to inhalation POD_{HEC} (18.15 mg/m^3) from EPA, 2016. The HED is 4.2 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics,10 for intraspecies variability, and 3 for database uncertainty related to the lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study). The critical effects are central nervous system changes (increased open field grooming), and decreased pain sensitivity (lowered step down latency and paw lick latency). The co-critical effects are central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), and decreased pain sensitivity (paw lick latency). The additivity endpoint is the nervous system.

Subchronic duration.
The proposed subchronic nHRL is 30 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 30 µg/L. The additivity endpoint is the nervous system.

Chronic duration.
The proposed chronic nHRL is 30 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 30 µg/L. The additivity endpoint is the nervous system.

Cancer:
Not applicable.

Subpart. 22. **1,3,5-Trimethylbenzene.**

Change the Year Adopted and data as shown in the table below.

CAS number: 108-67-8
Year Adopted: [Delete: 2009, Add: 2023]
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	[Delete: 100 Add: 30]	[Delete: 100 (2) Add: 30 (2)]	[Delete: 100 (2) Add: 30 (2)]	NA
RFD (mg/kg-day)	ND --	[Delete: 0.14 Add: 0.042]	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	[Delete: 0.289 Add: 0.290]	(2)	(2)	--
Endpoints	--	[Delete: hepatic (liver) system, Add: nervous system]	[Delete: hepatic (liver) system, renal (kidney) system Add: nervous system]	[Delete: hepatic (liver) system, renal (kidney) system Add: nervous system]	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 30 µg/L. The RfD is 0.042 mg/kg-d ,and the intake rate is 0.290 L/kg-d. The RSC is 0.2, and the POD is a NOAEL of 22.0 mg/m^3 (Gralewicz et al., 1997 aci EPA, 2016). The DAF is 0.19, from chemical-specific PBPK model-based route-to-route extrapolation, using a ratio of subchronic oral POD_{HED} (3.5 mg/kg-d) to inhalation POD_{HEC} (18.15 mg/m^3) from EPA, 2016. The HED is 4.2 mg/kg-d. The total UF is 100 (3 for interspecies differences [for toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty related to lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study). The critical effects are central nervous system changes (increased open field grooming), and decreased pain sensitivity (lowered step down latency and paw lick latency). The co-critical effects are central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), and decreased pain sensitivity (paw lick latency). The additivity endpoint is the nervous system.

Subchronic duration.
The proposed subchronic nHRL is 30 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore,

the subchronic nHRL is set equal to the short-term nHRL of 30 µg/L. The additivity endpoint is the nervous system.

Chronic duration.
The proposed chronic nHRL is 30 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 30 µg/L. The additivity endpoint is the nervous system.

Cancer:
Not applicable.

Subpart. 22a. Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)

New chemical. Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 22a, for Tris(1,3-dichloroisopropyl) phosphate:

CAS number: 13674-87-8
Year Adopted: 2023
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	20	8	0.8
RFD (mg/kg-day)	--	--	0.0067	0.0019	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	0.13
ADAF or $AF_{lifetime}$	--	--	--	--	10 (ADAF<2) 3 (ADAF2 to <16) 1 (ADAF16+)
Intake Rate (L/kg-day)	--	--	0.074	0.045	$0.155_{(<2)}$ $0.040_{(2 \text{ to } <16)}$ $0.042_{(16+)}$
Endpoints	--	--	hepatic (liver) system; kidney system	renal (kidney) system; male reproductive system	cancer

Acute duration.
Not derived because of insufficient information.

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

Subchronic duration.
The proposed chronic nHRL is 20 µg/L. The RfD is 0.0067 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 15 mg/kg-d (Kamata et al., 1989). The total UF is 300 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 10 for database uncertainty to address no or inadequate information regarding developmental/reproductive function, neurological, immune and endocrine effects). The critical effects are increased liver and kidney weights. There are no co-critical effects. The additivity endpoints are the hepatic (liver) system and the renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 8 µg/L. The RfD is 0.0019 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{10\%}$ of 1.94 mg/kg-d (ATSDR, 2012). The total UF is 300 (3 for interspecies differences for toxicodynamics and 10 for database uncertainty to address no or inadequate information regarding developmental/reproductive function, neurological, immune and endocrine effects). The critical effects are renal tubule epithelial hyperplasia and seminal vesicle atrophy There are no co-critical effects. The additivity endpoints are the renal (kidney) system and the male reproductive system.

Cancer.
The proposed cancer cHRL value is 0.8 µg/L. The cancer slope factor is 0.13 (mg/kg-d)-1 based on 2-year dietary study in rats by Freudenthal and Henrich (2000). The age-dependent adjustment factors and intake rates are 10 and 0.155 L/kg-d for an age under 2 years; 3 and 0.040 L/kg-d for an age between 2 years and less than 16 years; and 1 and 0.042 L/kg-d for ages above 16 years. The tumor sites are liver, kidney, and testes.

Subpart. 22b. Tris(2-butoxyethyl) phosphate (TBEP).

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 22b, for Tris (2-butoxyethyl) phosphate (TBEP):

CAS number: 78-51-3
Year Adopted: 2023
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	30	30 (2)	30	NA
RFD (mg/kg-day)	--	0.043	(2)	0.0074	--
RSC	--	0.2	(2)	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	(2)	0.045	--
Endpoints	--	hepatic (liver) system	hepatic (liver) system	hepatic (liver) system	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 30 µg/L. The RfD is 0.043 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2, and the POD is a $BMDL_{10}$ of 18.08 mg/kg-d (HRI, 1996). The DAF is 0.24 based on body weight scaling, and the HED is 4.34 mg/kg-d. The total UF is 100 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 3 for database uncertainty due to a lack of any 2-generational study and additional studies in a second test species). The critical effect is liver cell vacuolization. There are no co-critical effects. The additivity endpoint is the hepatic (liver) system.

Subchronic duration.
The proposed subchronic nHRL is 30 µg/L. The subchronic nHRL must be protective of the shorter duration exposures that occur within the subchronic period, and, therefore, the subchronic nHRL is set equal to the short-term nHRL of 30 µg/L. The additivity endpoint is the hepatic (liver) system.

Chronic duration.
The proposed chronic nHRL is 30 µg/L. The RfD is 0.0074 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2, and the POD is a $BMDL_{10}$ of 8.92 mg/kg-d (subchronic exposure) (Reyna and Thake, 1987). The DAF is 0.25 based on body weight scaling, and the HED is 2.23 mg/kg-d. The total UF is 300 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, 3 for database uncertainty due to a lack of any 2-generational study and additional studies in a second test species, and 3 for use of a subchronic study for chronic guidance). The critical effect is liver cell vacuolization. There are no co-critical effects. The additivity endpoint is the hepatic (liver) system.

Cancer:
Not applicable.

Subpart. 22d. Venlafaxine.

New chemical: Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 22d, for Venlafaxine:

CAS number: 93413-69-5 (free base), 99300-78-4 (HCl salt)
Year Adopted: 2023
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	10	10 (2)	10 (2)	NA
RFD (mg/kg-day)	--	0.0054	(2)	(2)	--
RSC	--	0.8	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.290	(2)	(2)	--
Endpoints	--	developmental, gastrointestinal system, male reproductive system, nervous system (E)	developmental, gastrointestinal system, male reproductive system, nervous system (E)	developmental, gastrointestinal system, male reproductive system, nervous system (E)	--

Acute duration.
Not derived because of insufficient information.

Short-term duration.
The proposed short-term nHRL is 10 µg/L. The RfD is 0.0054 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.8, and the POD is a LOAEL of 0.54 mg/kg-d (Wyeth Pharmaceuticals, 2014). Because this is a human pharmaceutical, the DAF or HED are not applicable. The total UF is 100 (10 for intraspecies variability, and 10 for use of a LOAEL). The critical effects include developmental (persistent pulmonary hypertension

and nervous system effects), gastrointestinal system (nausea, constipation), male reproductive effects (decreased libido, abnormal orgasm, erectile dysfunction, ejaculation failure/disorder), and nervous system effects (effects on serotonin hormone receptor interaction, sweating, abnormal dreams, and dizziness, and neuroendocrine-mediated increases in blood pressure). There are no co-critical effects. The additivity endpoints are developmental, gastrointestinal system, male reproductive system, nervous system (E).

Subchronic duration.
The proposed chronic nHRL is 10 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 10 µg/L. The additivity endpoints are developmental, gastrointestinal system, male reproductive system, nervous system (E).

Chronic duration.
The proposed chronic nHRL is 10 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 10 µg/L. The additivity endpoints are developmental, gastrointestinal system, male reproductive system, nervous system (E).

Cancer:
Not applicable.

Subpart. 23a. Xylenes.

Change the Year Adopted from 2011 to 2023 and change all data in the table below as shown in Minnesota Rules, part 4717.7860, subpart 23a.

CAS number: 1330-20-7
Year Adopted: [Delete: 2011, Add: 2023]
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	[Delete: 800 Add: 700]	300	300 [Delete: (2)]	[Delete: 300 (2) Add: 300 (3)]	NA
RFD (mg/kg-day)	[Delete: 1.2 Add: 1.0]	[Delete: 0.50 Add: 0.38]	[Delete: (2) Add: 0.12]	[Delete: (2) Add: (3)]	--
RSC	0.2	0.2	[Delete: (2) Add: 0.2]	[Delete: (2) Add: (3)]	--

	Acute	Short-term	Subchronic	Chronic	Cancer
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	[Delete: 0.289 Add: 0.290]	[Delete: 0.289 Add: 0.290]	[Delete: (2) Add: 0.074]	[Delete: (2) Add: (3)]	--
Endpoints	nervous system	[Add: developmental] nervous system	[Add: developmental] nervous system, renal (kidney) system	[Add: developmental] nervous system, renal (kidney) system	--

Xylenes are a mixture of three isomers: meta-xylene (m-xylene), ortho-xylene (o-xylene), and para-xylene (p-xylene) with the meta-isomer usually being the dominant part of the mixture at 40-70%. The exact composition of the commercial xylene grade depends on the source, but a typical mixture will also contain ethylbenzene at 6 - 20% in addition to the three isomers. The environmental fate (transport, partitioning, transformation, and degradation) is expected to be similar for each of the xylene isomers based on the similarities of their physical and chemical properties (ATSDR, 2007). The metabolism of each individual isomer is thought to be similar, and the EPA's 2003 Integrated Risk Information System (IRIS)Toxicological Review states that, "although differences in the toxicity of the xylene isomers have been detected, no consistent pattern following oral or inhalation exposure has been identified.".

Acute duration.
The proposed acute nHRL is 700 µg/L, updated from 800 µg/L. The RfD is 1.0 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 125 mg/kg-d (ATSDR, 2007). The DAF is 0.24 using body weight scaling, and the HED is 30 mg/kg-d. The total UF is 30 (3 for interspecies differences for toxicodynamics, and 10 for intraspecies variability). The critical effect is altered visual evoked potentials. There are no co-critical effects. The additivity endpoint is the nervous system.

Short-term duration.
The proposed short-term nHRL is 300 µg/L. The RfD is 0.38 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2, and the POD is a NOAEL of 500 mg/kg-d (ATSDR, 2007). The DAF based on body weight scaling is 0.23, and the HED is 115 mg/kg-d. The total UF is 300 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 10 for database uncertainty due to the lack of a multigenerational reproductive study as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was

identified as a sensitive endpoint from inhalation studies). The critical effect is decreased body weight gain. The co-critical effects are altered visual evoked potentials, decreased fetal body weight, and increased fetal malformations. The additivity endpoints are developmental and the nervous system.

Subchronic duration.
The proposed subchronic nHRL is 300 µg/L. The RfD is 0.12 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2, and the POD is a NOAEL of 150 mg/kg-d (NTP, 1986). The DAF is 0.23 based on body weight scaling, and the HED is 34.5 mg/kg-d. The total UF is 300 (3 for interspecies differences for toxicodynamics, 10 for intraspecies variability, and 10 for database uncertainty due to the lack of a multigenerational reproductive study as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies). The critical effects are increased kidney weights and minimal chronic nephropathy. The co-critical effects are altered visual evoked potentials, decreased fetal body weight, decreased adult body weight gain, increased fetal malformations, and hyperactivity. The additivity endpoints are developmental, the nervous system, and the renal (kidney) system.

Chronic duration.
The proposed chronic nHRL is 300 µg/L. The chronic nHRL must be protective of the shorter duration exposures that occur within the chronic period, and, therefore, the chronic nHRL is set equal to the short-term nHRL of 300 µg/L. The additivity endpoints are developmental, the nervous system, and the renal (kidney) system.

Cancer:
Not applicable.

2. Proposed Deletions: Health Risk Limits: (Minnesota Rules, parts 4717.7500, 4717.7850 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 seven outdated HRLs adopted into rule in 1993 or 1994, two of the HRLs adopted into rule in 2009, 10 HRLs adopted into rule in 2011, and one HRL adopted in 2013, for a total of 20 values to repeal. The specific subparts to be repealed are noted below:

Subparts to be repealed from part 4717.7500. (updated values for these chemicals, shown in Section V B. of this SONAR, will be added to part 4717.7860, with the exception of n-Hexane. MDH has replace the n-Hexane HRL value with Risk Assessment Advice):

Subpart. 11 1,1'-Biphenyl (1993)

Subpart. 15. Bromodichloromethane (1993)

Subpart. 34a. 1,4-Dichlorobenzene (1994)

Subpart. 45a. 1,2-Dichloropropane (1994)

Subpart. 54. Fluorene (9H-Fluorene) (1993)

Subpart. 58a. Hexane (n-hexane) (1994)

Subpart. 61. Manganese (1993)

Subpart to be updated in part 4717.7850, subpart2e. 1,1,2,2-Tetrachloroethylene will be repealed. This removal is because the value for 1,1,2,2-Tetrachloroethylene will be updated in 4717.7860, subpart 18, which will eliminate the need for the HRL_{MCL} value for this chemical that was set by the Minnesota Legislature in 2007.

Subparts to be updated in part 4717.7860. Old guidance values will be repealed and 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. The year the rule was adopted is shown in parentheses after the chemical name.

Subpart 3c. Acetone (2011)

Subpart 8h. trans-1,2-Dichloroethene (2013)

Subpart 8i. 1,1-Dichloroethylene (2011)

Subpart 12a. Ethylbenzene (2011)

Subpart 12c. Ethylene Glycol (2011)

Subpart 12e. Metolachlor and s-Metolachlor (2011)

Subpart 12f. Metolachlor ESA (2011)

Subpart 12g. Metolachlor OXA (2011)

Subpart 12g. Perfluorobutane sulfonate (PFBS) (2011)

Subpart 18. 1,1,2,2-Tetrachloroethylene (HRL_{MCL} 2009)

Subpart 18c. Toluene (2011)

Subpart 22. 1,3,5-Trimethylbenzene (2009)

Subpart. 23a. Xylenes (2011)

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 chooses to estimate 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. Other agencies might choose to implement and enforce these amendments. Other 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 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 previously adopted specific methodology 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 subdivision 1, 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 subdivision 1, 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 or 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 to four-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.

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 MDH has not used resources to 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 HRL 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 quantify the 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 eleven of the contaminants are lower than their previously adopted HRL values (i.e., acetone, biphenyl, bromodichloromethane, trans-1,2-dichloroethene, 1,2-dichloropropane, ethylebenzene, fluorene, perfluorobutane sulfonate, tetrachloroethylene, toluene, 1,3,5-trimethylbenzene), the cost of remediating or preventing water contamination might increase. The proposed HRL values for the chemicals that lack previously adopted HRL values would be new HRL values. Costs associated with implementing 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 safety and quality. 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 proposed HRLs does not in and of themselves prevent degradation. Some water resources have already been unintentionally contaminated by accidental or intentional 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. When contamination is discovered, authorities often need a way to provide context to a sample's contaminant concentration and the implication for human health. HRL values allow authorities to evaluate drinking water sources to ensure that there is minimal risk to human health from using the water source for drinking, or to pursue cleanup more quickly if a risk exists. 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

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, 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 considers more durations than EPA, allowing for protection of critical lifestages;
- 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. 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 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. Nominations may be submitted via the MDH website at Nominate Contaminants (https://www.health.state.mn.us/communities/environment/risk/guidance/dwec/nominate.html). Anyone may submit a nomination.

MDH reviews and prioritizes the 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 142 chemicals that have been found in Minnesota groundwater; there are 91 chemicals for which EPA has MCLs. This proposed update for 19 existing HRL values and addition of 17 new HRL values, plus the removal of the n-hexane HRL, when added to the existing 146 HRLs, will bring HRLs to a total of 162 in Minnesota.

Minnesota's water guidance also protects more sensitive populations, especially infants and children, as required by the Health Standards Statute of 2021 and supported by the EPA 2021 Policy of Children's Health, recommends plans to "identify and integrate data to conduct risk assessments of children's health to inform decisions" (EPA, 2021). 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 EPA. At times, 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. However, those who consume or work to protect the water from a private well may seek to comply with an HRL 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 Plan

The Minnesota APA has requirements for the publication of official notices in the *State Register* and related procedures. In addition to these basic notification requirements, MDH has or will complete additional notice activities, as follows:

- Throughout the process of water guidance derivation and updates from 2011 to present, MDH has used the practice of sending email subscription service messages through an account called Groundwater Rules, Guidance, and Chemical Review, hosted by a commercial service called GovDelivery, to communicate with stakeholders about updates to the value or processes. Anyone may sign up for free to receive messages via this service directly from MDH webpages or by phoning or emailing Health Risk Assessment staff. As of the date this SONAR was signed, this account had 4958 subscribers. Subscribers to this account include most of the stakeholders known to be active or interested in this topic, such as trade associations and industry advocates like the American Chemistry Council and the Minnesota Chamber of Commerce, several State agencies, several advocacy groups, and chemical manufacturers such as 3M, Bayer, and other companies.

  MDH's HRA Unit sent an email notice from its email subscription service account on September 22, 2020, to notify subscribers that MDH is considering HRL rulemaking, and to provide information about an update to the intake rates used by MDH, following EPA's update to intake rate. The message also included a link to a webpage with a list of guidance values for contaminants eligible for rulemaking. MDH encouraged comments. This email was sent to 4,045 subscribers expressed interest in water guidance or the work of the Health Risk Assessment Unit.

- **Request for Comments:** The Request for Comments was published on January 19, 2021. The morning of January 19th, MDH sent emails directly to 12 industry representatives, environmental advocacy organization staff, or trade organization staff who had requested notice about HRL rulemaking activity. The same day, MDH also sent emails to 11 interested staff members of other State agencies about the pending Request for Comments. Further, MDH sent out an email notice to the 4,169 subscribers (as of January 19, 2021) of the Water Rules, Guidance, and Chemical Review email subscription service account. The email notices provided information about publication of the Request for Comments, a link to the announcement in the State Register, and links to MDH's rules webpage that contains information about each chemical with water guidance eligible for rulemaking.

  Additionally, information about the Request for Comments was published in the Spring 2021 issue of an MDH publication called the *Waterline*. As of August 24, 2022, this publication had been viewed 901 times from the MDH website. Paper copies are also sent to 5,200 subscribers of the Waterline. There is also a GovDelivery account that delivers this information electronically to 5,700 subscribers, but there might be some overlap among people who subscribe to the paper copies and the electronic copy.

- **HRL rule amendment public meeting:** MDH hosted a virtual public meeting on February 2, 2022. MDH sent notification to the 4667 people subscribed to the email service about the public meeting via its email subscription service account for Water Rules, Guidance, and Chemical Review over two weeks prior to the meeting. Fifty-four people registered for the meeting and 53 people attended, though some of the attendees did not register and received the meeting link from other registered participants.

  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; and 3) the proposed HRL amendments. MDH encouraged attendees to ask questions, engage in discussion with staff, and submit written comments.

  MDH posted all meeting materials, including answers to the questions asked at the meeting, available on its HRL rule amendments webpages after the public meeting. Materials and handouts for MDH's meeting on the amendments to the rules will be available on the webpage called Public Meeting https://www.health.state.mn.us/communities/environment/risk/rules/water/publicmeeting.html)

  As of August 22, 2022 MDH has received comments about Ethylene glycol from one party, a request to be informed about the Notice of Intent from second party, a comment about PFAS from a third party, and a comment about nonylphenol from a fourth party. MDH acknowledged the comments from the first, third, and fourth party, and added the second party to the contact list for notifications.

- Notice of Intent to Adopt Rules: MDH plans to publish the *Notice of Intent to Adopt Rules* 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* and a copy of the SONAR to the Legislature and the Legislative Reference Library. Further, MDH will send a notice to the over 5273 (as of November 1, 2022) subscribers of its Water Rules, Guidance and Chemical Review email subscription service account. Sign up to the email subscription service is offered on the website or by phoning or emailing MDH staff members. MDH will also send information to the offices of interested parties such as water resource interest 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.

However, Department of Agriculture staff are included in the direct email notifications that MDH will send.

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

- HRL rule amendment website: MDH created webpages for the HRL rule amendment, which is available at: Overview and Links (https://www.health.state.mn.us/communities/environment/risk/rules/water/overview.html) 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's Groundwater Rules, Guidance, and Chemical Review email subscription account is a free email subscription list for sending updates on water rules and guidance on the chemicals reviewed. Anyone may subscribe through links on the 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 January 5, 2023, this account had 5,532 subscribers.

- Direct communication: MDH will directly contact, by phone or email, parties to have expressed interest or concern about the HRL rulemaking

F. Impact of Proposed Rules

Consultation with MMB on Local Government Impact

As required by Minnesota Statutes, section 14.131, MDH consulted with Minnesota Management and Budget (MMB) about the impact the proposed rules might have on local governments. MDH did this by sending to the MMB Commissioner copies of the proposed rule and SONAR before MDH published the *Notice of Intent to Adopt Rules*. A copy of our correspondence with MMB is attached as Appendix F.

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 groundwater quality. Local units of government have consulted with MDH on the use of HRL values for interpreting the results of well monitoring.

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, including those at other agencies, 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 Hearing" and anticipates having no outside witnesses testify. All witnesses will likely be MDH staff members.

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."(Minn. Stat. § 115.063(a)(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 EPA risk-assessment guidelines, and provide protections to vulnerable populations as required by Minnesota Statutes, sections 103H.201 and 144.0751. MDH used reasonable and well-established methods adopted in 2009, as found in 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. MDH 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 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 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, 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 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 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 2005c) as "Carcinogenic to Humans" or "Likely to be carcinogenic to humans."

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

Chemical Abstract Service (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 postnatally 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," EPA, Risk Assessment Forum (December 2002, https://www.epa.gov/osa/review-reference-dose-and-reference-concentration-processes).

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," 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 should be included in the same Health Risk Index calculation.

Epidemiological Study: Epidemiology is the method used to find the causes of health outcomes and diseases in populations. An epidemiologic study is a way to analyze the community's health using data on risk factors and health outcomes to look for causes of health issues. The community is a population such as the whole state, a county, or another group of people. There are several types of epidemiologic studies. Some examples include: case-control, cohort, and cross-sectional studies.

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.

Groundwater: 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."

Human Equivalent Dose (HED): The oral human dose 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 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 (also referred to as physiologically based pharmacokinetic 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.

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 a dose-response curve where an effect or change in response is first estimated or observed, using benchmark dose response modeling or using a NOAEL or LOAEL obtained experimentally.

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 EPA's Exposure Decision Tree approach contained in Chapter 4 of the Ambient Water Quality Criteria document (EPA, 2000b) 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 2002). 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 EPA RfC/RfD Technical Panel (EPA, 2002) 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, 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 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,* EPA recommends the derivation of acute, short-term, subchronic, and

chronic RfDs (EPA, 2002). 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).

In 2021, the Minnesota Legislature passed an amendment to the Groundwater Protection Act that allows MDH to use slope factors published by EPA or determined by the Commissioner to have undergone sufficient scientific review. To derive a cancer HRL, MDH accounts for the potential for increased cancer potency when exposure occurs early in life by using methodology contained in the EPA *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA, 2005b). 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:

- 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 Drinking Water Contaminant Candidate List (CCL) and Regulatory Determination (https://www.epa.gov/ccl) 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 (https://inchem.org/pages/cicads.html); 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).

$$\text{nHRL}\left(\frac{\text{L}}{\text{kg}-\text{d}}\right) = \frac{\text{RfD}\left(\frac{\text{mg}}{\text{kg}-\text{d}}\right) \text{ x } (1000\ \mu\text{g/mg})}{\text{Intake rate}\left(\frac{\text{L}}{\text{kg}-\text{d}}\right)}$$

The initial 2008 default values were time-weighted averages based on the data reported in U.S. EPA's Per Capita Report (EPA, 2004b) and a draft assessment prepared for the Child-Specific Exposure Factors Handbook (EPA, 2008). In 2016, MDH began using the water intake rates from the finalized EPA 2011 Exposure Factors Handbook. In 2019, EPA published another update to water intake rates (Chapter 3, US EPA, 2019). MDH staff calculated and used the following default time-weighted-average intake rates for non-cancer health-based guidance from the 2019 EPA values. MDH began using those rates in 2020 and updated all guidance prepared for rulemaking, using the intake rates, shown below:

- Acute: 0.290 L/kg-day
- Short-term: 0.290 L/kg-day
- Subchronic: 0.074 L/kg-day
- Chronic: 0.045 L/kg-day

- Pregnant Women: 0.038 L/kg-day
- Lactating Women: 0.047 L/kg-d

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 [Time Weighted Average] TWA of the 95th percentile intake rate for each age range. MDH staff calculated and used the following default time-weighted-average intake rates, based on the 2019 EPA values, for cancer health-based guidance: 0.155 L/kg-day (up to 2 years of age), 0.040 L/kg-day (2 to up to 16 years of age), and 0.042 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 RSC was used to allocate a portion of the total daily RfD to exposure from ingestion of water. This apportionment is to ensure that exposure from ingestion of water combined with 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 will not result in exceeding the RfD. 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 an Exposure Decision Tree from the EPA Ambient Water Quality Criteria document (EPA, 2000b) 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 EPA's Exposure Decision Tree (EPA, 2000b), 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 × 10^{-7} to 1 × 10^{-5} atm-m^3/mol
- Moderate volatility – Henry's Law constant >1 × 10^{-5} to 1 × 10^{-3} atm-m^3/mol
- High volatility – Henry's Law constant > 1 × 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, 2011b) 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 populations, 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, 2002). 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 EPA RfC/RfD Technical Panel (EPA, 2002) 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:

$$\mathrm{nHRL_{duration}} = \frac{\mathrm{RfD_{duration}} \times \mathrm{RSC} \times 1000}{\mathrm{IR_{duration}}}$$

Where:

$\mathrm{nHRL_{duration}}$ = 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).

$\mathrm{RfD_{duration}}$ = 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 EPA Exposure Decision Tree (EPA, 2000b) 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 95^{th} percentile intake rate during the relevant duration: acute and short-term - 0.290 L/kg-day, based on intake for 1 up to 3 months of age; subchronic - 0.074 L/kg-day, based on a TWA up to 8 years of age; and chronic - 0.045 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 these proposed rules are presented in Section V.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:

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

$$nHRL_{short\ term} = \frac{(0.0037\ mg/kg/d) \times (0.2) \times (1000\ \mu g/mg)}{(0.290\ L/kg\text{-}d)}$$

$$= 2.55 \text{ rounded to } 3\ \mu g/L$$

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

$$nHRL_{subchronic} = \frac{(0.0098\ mg/kg/d) \times (0.2) \times (1000\ \mu g/mg)}{(0.074\ L/kg\text{-}d)}$$

= 26.48 rounded to 26 µg/L

The calculated subchronic nHRL (26 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 endpoint is the hepatic (liver) 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 shown above and specified in Minnesota Rules, part 4717.7830, subpart 2:

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

- 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:

$$cHRL = \frac{(1 \times 10^{-5}) \times 1{,}000\ \frac{\mu g}{mg}}{\left[(SF \times ADAF_{<2} \times IR_{<2} \times D_{<2}) + (SF \times ADAF_{2\ to<16} \times IR_{2\ to<16} \times D_{2\ to<16}) + (SF \times ADAF_{16+} \times IR_{16+} \times D_{16+})\right] \div 70\ years}$$

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..155L/kg-day, for up to 2 years of age ($IR_{<2}$); 0.040 L/kg-day, for 2 up to 16 years of age ($IR_{2<16}$); and 0.042 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 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:

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

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.

0.045 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 CONTAMINANTS

MDH selected the contaminants for these amendments based on input from several sources. Examples include programs within MDH, such as the Site Assessment and Consultation Unit, Drinking Water Protection Section, and CEC initiative, as well as 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. Some of the contributing programs and agencies collect input from the public. Further, MDH initiated a system to re-evaluate previously adopted HRLs to ensure that values remain up-to-date. Listed below are chemicals with proposed HRLs and the origin of the guidance requests. All HBVs were updated in September 2020 to include updated water intake rates from EPA.

Table D-1. Request for Guidance on Groundwater Contaminants

CAS Number	Chemical Name	HBV year	Origin of Request
67-64-1	Acetone	2017	Scheduled re-evaluation
50-32-8	Benzo[a]pyrene	2018	MPCA HRL nomination
119-61-9	Benzophenone	2019	MPCA CEC nomination
95-14-7	1H-Benzotriazole	2019	MPCA CEC nomination
92-52-4	Biphenyl	2021	MDH CEC nomination
75-27-4	Bromodichloromethane	2018	MPCA HRL nomination
106-46-7	1,4-Dichlorobenzene	2019	MPCA HRL nomination
156-60-5	trans-1,2-Dichloroethene	2020	MPCA special review
75-35-4	1,1-Dichloroethylene (Vinylidene chloride	2019	Scheduled re-evaluation
78-87-5	1,2-Dichloropropane	2021	MPCA HRL nomination

CAS Number	Chemical Name	HBV year	Origin of Request
57-63-6	17α-Ethinylestradiol	2016	MPCA CEC nomination
100-41-4	Ethylbenzene	2019	Scheduled re-evaluation
107-21-1	Ethylene Glycol	2017	Scheduled re-evaluation
86-73-7	Fluorene (9H-Fluorene)	2019	MPCA HRL nomination
72178-02-0	Fomesafen	2020	MDA HRL nomination
110-54-3	n-Hexane	1994	MPCA, Special request, 2019
138261-41-4	Imidacloprid	2019	MDA HRL nomination
7439-96-5	Manganese	2018	MDH, Special review
51218-45-2; 87392-12-9	Metolachlor and s-Metolachlor	2018	Scheduled re-evaluation
171118-09-5	Metolachlor ESA	2018	Scheduled re-evaluation
152019-73-3	Metolachlor OXA	2018	Scheduled re-evaluation
84852-15-3	p-Nonylphenol	2015	MPCA CEC nomination
140-66-9	4-tert-Octylphenol	2015	MPCA CEC nomination
45187-15-3; 375-73-5	Perfluorobutane sulfonate (PFBS)	2017	Scheduled re-evaluation
108427-53-8; 355-46-4	Perfluorohexane sulfonate (PFHxS)	2019	Re-evaluation triggered by new studies
92612-52; 307-24-4;	Perfluorohexanoate (PFHxA)	2018	MPCA and MDH CEC nomination

CAS Number	Chemical Name	HBV year	Origin of Request
21615-47-4; 2923-26-4			
91-22-5	Quinoline	2019	MPCA HRL nomination
127-18-4	Tetrachloroethylene	2014	MPCA HRL nomination
108-88-3	Toluene	2019	Scheduled re-evaluation
526-73-8	1,2,3-Trimethylbenzene	2019	Scheduled re-evaluation
95-63-6	1,2,4-Trimethylbenzene	2019	Scheduled re-evaluation
108-67-8	1,3,5-Trimethylbenzene	2019	Scheduled re-evaluation
78-51-3	Tris(2-butoxyethyl) phosphate (TBEP)	2020	MPCA CEC nomination
13674-87-8	Tris(1,3-dichloroisopropyl)phosphate (TDCPP)	2013	MPCA CEC nomination
1330-20-7	Xylenes	2019	Scheduled re-evaluation

APPENDIX E. TOXICOLOGICAL SUMMARY SHEETS

Copies of all 37 of the Toxicological Summary sheets can also be viewed online by clicking on the following link: Health Risk Limits SONAR Appendix E.
https://www.health.state.mn.us/communities/environment/risk/docs/rules/appende.pdf

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

Web Publication Date: August 2020

Toxicological Summary for: Acetone

CAS: **67-64-1**

Synonyms: 2-propanone, propan-2-one, β-ketopropane, dimethyl ketone, dimethylformaldehyde, DMK

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 5,000 µg/L

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

$$= \frac{\text{(3.1 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0. 290 L/kg-d)}^{**}}$$

= 5,344 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 312/100 = 3.1 mg/kg-d (F344N rats)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	1485 mg/kg-d (NOAEL, (NTP, 1991) (Dietz, 1991))
Dose Adjustment Factor (DAF):	0.21 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 1485 mg/kg-d x 0.21 = 312 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for intraspecies variability, and 10 for database uncertainty (lack of adequate developmental studies, including multigeneration studies, and neurotoxicity studies). No interspecies UF for toxicodynamics differences was applied as acetone plays a role in normal human metabolism and it is not anticipated that humans will be more sensitive to acetone than laboratory animals.
Critical effect(s):	Increased kidney weight (consistent with nephropathy seen in rats during the subchronic duration)
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 5,000 µg/L

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

$$= \frac{\text{(2.1 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 5,675 rounded to 6,000 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 207/100 = 2.1 mg/kg-d (F344N rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	900 mg/kg-d (NOAEL (NTP, 1991) (Dietz, 1991))
Dose Adjustment Factor (DAF):	0.23 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 900 mg/kg-d x 0.23 = 207 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for intraspecies variability, and 10 for database uncertainty (lack of adequate developmental studies, including multigenerational studies, neurotoxicity studies, and hematological studies). No interspecies UF of toxicodynamics differences was applied as acetone plays a role in normal human metabolism and it is not anticipated that humans will be more sensitive than laboratory animals.
Critical effect(s):	Nephropathy, increased relative kidney weight, changes in blood parameters (increased leukocytes, increased mean corpuscular hemoglobin, increased mean cell volume, decreased erythrocyte count, and decreased reticulocyte counts)
Co-critical effect(s):	Increased relative kidney weight, increased relative liver weight, increased incidence of hepatocellular hypertrophy, tubular degeneration in the kidneys
Additivity endpoint(s):	Hematological (blood) effects; Hepatic (liver) system; Renal (kidney) system

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 5000 µg/L. Additivity endpoints: Renal (kidney) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 3,000 µg/L

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

$$= \frac{\text{(0.69 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 3,066 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 207/300= 0.69 mg/kg-d (F344N rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	900 mg/kg-d (NOAEL, (NTP, 1991) (Dietz, 1991), subchronic exposure)
Dose Adjustment Factor (DAF):	0.23 (Body weight scaling, default) (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 900 mg/kg-d x 0.23 = 207 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	10 for intraspecies variability, and 10 for database uncertainty (lack of adequate developmental studies, including multigenerational studies, neurotoxicity studies, and hematological studies), and 3 for subchronic to chronic extrapolation. No interspecies UF of toxicodynamics differences was applied as acetone plays a role in normal human metabolism and it is not anticipated that humans will be more sensitive than laboratory animals.
Critical effect(s):	Nephropathy, increased relative kidney weight, changes in blood parameters (increased leukocytes, increased mean corpuscular hemoglobin, increased mean cell volume, decreased erythrocyte count, and decreased reticulocyte counts)
Co-critical effect(s):	Increased relative kidney weight, increased relative liver weight, increased incidence of hepatocellular hypertrophy, tubular degeneration in the kidneys
Additivity endpoint(s):	Hematological (blood) effects; Hepatic (liver) system; Renal (kidney) system

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: Yes (moderate)

Summary of Guidance Value History:

In 1993/1994, MDH derived a chronic noncancer Health Risk Limit (HRL) of 700 µg/L. In 2011, MDH derived short-term, subchronic, and chronic noncancer Health Based Values (HBV) of 9,000, 8,000, and 4,000 µg/L, respectively. These HBVs were adopted as HRLs in 2011. In 2017, MDH re-evaluated the noncancer HRLs, resulting in new noncancer short-term, subchronic, and chronic HBVs of 5,000, 5,000, and 3,000 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 Human Equivalence Doses (HED), and 2) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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]

Comments on extent of testing or effects:

[1] No immunotoxicity effects were observed in drinking water studies of mice at doses more than 200 fold higher than the chronic reference dose. Changes in thymus weight were observed in rats at doses nearly 300 fold higher than the short-term reference dose, but were not accompanied by other immunotoxicity effects.

[2] Offspring exposed to acetone through inhalation during gestation experienced decreased fetal weight and increased incidence of fetal malformations. During another inhalation study in mice, no developmental effects were seen in the offspring. A database uncertainty factor was incorporated into the derivation of short-term, subchronic, and chronic reference doses due to

lack of adequate multigenerational and developmental studies assessing developmental effects after oral exposure.

[3] Male rats exposed to acetone through drinking water for 13 weeks experienced an increase in relative testes weight, decreased caudal and epididymis weights, depressed sperm motility, and increased incidence of abnormal sperm at doses greater than 1000 fold higher than the chronic reference dose. No reproductive effects were seen when male rats were exposed to acetone in drinking water for six weeks prior to mating. A database uncertainty factor was incorporated into the derivation of short-term, subchronic, and chronic reference doses due to lack of an adequate multigenerational study assessing reproductive effects after oral exposure.

[4] A couple of neurotoxicity studies were conducted for oral exposure to acetone with only one reporting slightly altered vision in rats at a dose greater than 200 fold higher than the chronic reference dose. Excessive salivation was also observed in rats exposed to acetone in drinking water at a dose greater than 800 fold higher than the chronic reference dose, but it is unclear whether this is a neurological response or due to gavage administration. Narcotic-like effects have been reported after humans have inhaled or ingested acetone which include lethargy, minimal responsiveness, and comatose condition. A database uncertainty factor was incorporated into the derivation of short-term, subchronic, and chronic reference doses due to lack of adequate data addressing neurotoxic effects after oral exposure. Neurotoxicity observed in animals following inhalation of acetone include: inhibition of avoidance behavior, effects on fixed ratio and fixed interval response rates, and central nervous system depression measured by tests of unconditioned performance and reflexes.

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

Web Publication Date: March 2022

Toxicological Summary for: Aminomethylphosphonic acid

CAS: **1066-51-9**

Synonyms: AMPA, 1-Aminomethylphosphonic acid; 1-Aminomethylphosphonate

NOTE: AMPA (CAS# 1066-51-9), the glyphosate metabolite/degradate, is not to be confused with AMPA, the neurotoxic agent, which is a different chemical with CAS# 74341-63-2 with the same acronym. The neurotoxic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) is a specific agonist for the AMPA receptor where it mimics the effects of the neurotransmitter glutamate.

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 ($nHBV_{Subchronic}$) = 3,000 µg/L

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

$$= \frac{\text{(0.96 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 2,594 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5

Reference Dose:	HED/Total UF = 0.96 mg/kg-d (CD rats)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	400 mg/kg-d (administered dose NOAEL, Estes et al. 1979, Monsanto unpublished test report, as cited in WHO 1997, 2005)
Dose Adjustment Factor (DAF):	0.24 (Body weight scaling, male rats (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 400 mg/kg-d x 0.24 = 96 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 (lack of multigenerational reproductive/developmental study)
Critical effect(s):	Decreased body weight gain, bladder urothelial hyperplasia, increased serum lactate dehydrogenase
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 1,000 µg/L

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

$$= \frac{(0.32 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 1,422 rounded to **1,000 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5

Reference Dose:	HED/Total UF = 0.32 mg/kg-d (CD rats)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	400 mg/kg-d (administered dose NOAEL, Estes et al. 1979, Monsanto unpublished subchronic study, as cited in WHO 1997, 2005)
Dose Adjustment Factor (DAF):	0.24 (Body weight scaling, male rats (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 400 mg/kg-d x 0.24 = 96 mg/kg
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (lack of multigenerational reproductive/development study), 3 for subchronic-to-chronic extrapolation
Critical effect(s):	Decreased body weight gain, bladder urothelial hyperplasia, increased serum lactate dehydrogenase
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

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:

There are no current MDH HBVs or HRLs for AMPA. MDH developed a non-cancer pesticide rapid assessment value of 2,000 µg/L in 2016. The 2017 $nHBV_{Subchronic}$ is higher than the 2016 Pesticide Rapid Assessment due to use of a different intake rate. The 2017 $nHBV_{Chronic}$ is lower than the 2016 Pesticide Rapid Assessment Value due to use of a different relative source contribution and addition of a database uncertainty factor in the RfD derivation. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	No	No
Effects observed?	-	- [1]	Yes [2]	-	- [3]

Comments on extent of testing or effects:

[1]AMPA has not been tested for immunotoxicity via oral ingestion. However, AMPA was negative for dermal sensitization in guinea pig tests.

[2]Decreased fetal body weight was reported in a gestational exposure study in rats at a dose which also produced overt maternal toxicity (including decreased bw gain, food consumption, soft stools, hair loss). This dose was 230 times higher than the subchronic RfD and findings were inconsistent with another developmental study that reported no maternal or fetal effects at a dose approximately 240 times higher than the subchronic RfD.

[3]AMPA has not been tested for neurotoxicity. However, there were no clinical signs of neurotoxicity in any of the short-term or subchronic tests in rats or dogs (i.e., no twitching, salivation or seizures, etc.).

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

Web Publication Date: August 2020

Toxicological Summary for: Benzo[a]pyrene

CAS: **50-32-8**
Synonyms: BaP, Benzo[pqr]tetraphene, 3,4-Benz[a]pyrene, Benzo(d,e,f)chrysene

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 0.5 µg/L

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

$$= \frac{\text{(0.00031 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 0.53 rounded to **0.5 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	Administered Dose/Total UF = 0.0917/300 = 0.00031 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	0.0917 mg/kg-d ($BMDL_{1SD}$, Chen, 2012)
Dose Adjustment Factor (DAF):	Not calculated due to temporal differences in human and rodent brain developmental stages
Human Equivalent Dose (HED):	Not applicable
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	10 for interspecies differences, 10 for intraspecies variability, and 3 for database uncertainty due to lack of adequate developmental and multigenerational studies that include exposure throughout gestation and early life.
Critical effect(s):	Functional test of neurological changes in neonatal rats (elevated maze)
Co-critical effect(s):	Functional test of neurological changes in neonatal rats (open field and water maze testing)
Additivity endpoint(s):	Developmental, Nervous system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 0.5 µg/L

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

$$= \frac{\text{(0.00031 mg/kg-d)}^{\#} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 0.83 rounded to 0.8 µg/L

[#]No Subchronic RfD was calculated due to study limitations. Therefore, the developmental-based Short-term RfD was applied to the subchronic duration.
[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

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 0.5 µg/L. Additivity endpoints: Developmental and Nervous system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 0.5 µg/L

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

$$= \frac{\text{(0.00031 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 1.37 rounded to 1 µg/L

[#]No Chronic RfD was calculated due to study limitations. Therefore, the developmental-based Short-term RfD was applied to the chronic duration.
[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

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 0.5 µg/L. Additivity endpoints: Developmental and Nervous system

Cancer Health Based Value (cHBV) = 0.1 µg/L

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2\text{-}<16\ yr} \times IR_{2\text{-}<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(1 \times 10^{*} \times 0.155\ \text{L/kg-d}^{**} \times 2) + (1 \times 3^{*} \times 0.040\ \text{L/kg-d}^{**} \times 14) + (1 \times 1^{*} \times 0.042\ \text{L/kg-d}^{**} \times 54)] / 70}$$

= 0.099 rounded to **0.1 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Cancer classification:	Carcinogenic to humans (US EPA, 2017a)
Slope factor (SF):	1 $(mg/kg\text{-}d)^{-1}$ (Forestomach and oral cavity tumors in female mice, Beland and Culp, 1998 aci US EPA, 2017a)
Source of cancer slope factor (SF):	US EPA, 2017a
Tumor site(s):	Digestive tract, liver, skin, lung

Volatile: Yes (low)

Summary of Guidance Value History:

A cancer HBV of 0.05 µg/L was derived in 1995. Acute, Short-term, Subchronic, and Chronic nHBVs of 2, 0.3, 0.3, and 0.3 µg/L were derived in 2012, along with a cancer HBV of 0.06 µg/L. In 2018, MDH derived nHBVs of 0.5 µg/L for Short-term, Subchronic, and Chronic durations and a cHBV of 0.1 µg/L. The 2018 values changed as a result of: 1) using MDH's most recent risk assessment methodology; 2) incorporating more recent toxicological information; and 3) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the final 2018 HBVs.

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 were assessed following laboratory exposures to BaP. Changes in testosterone, estradiol, and estrous cycles were noted at doses far in excess (greater than1,800 times) of the Short-term RfD.

[2] Immune system effects were seen at high doses in comparison to the short-term RfD. Changes in immune cell populations and decreased thymic weights were noted in multiple studies at doses greater than 5,000 times higher than the Short-term RfD.

[3] A developmental neurobehavioral effect forms the basis of the Short-term RfD. Altered blood pressure and heart rate following in utero exposure were reported at doses 400-800 times higher than the Short-term RfD. Other observed developmental toxicities include decreased weight gain in early life, stillbirth, and birth defects. These effects occurred at the lowest dose tested, however, these doses are greater than 30,000 times higher than the Short-term RfD. A database uncertainty factor of 3

was applied in deriving the Short-term RfD in order to address outstanding concerns regarding developmental effects.

[4] Most reproductive effects were noted at doses much higher than the Short-term RfD. Histopathological changes in the cervix and sperm alterations of mice were observed at the lowest doses tested in two studies (300-400 times higher than the Short-term RfD). In other studies, reduced fertility, decreased ovary weights, and decreased follicle number were reported at doses over 1,800 times higher than the Short-term RfD. A database uncertainty factor of 3 was applied in deriving the Short-term RfD in order to address concerns regarding reproductive effects that would be tested in a standard multigenerational study.

[5] Neurodevelopmental effects form the basis of the Short-term RfD. Neurotoxicity was also observed after high dose acute exposure. Three acute oral studies observed suppressed motor activity and other changes at doses nearly 2,000 times higher than the Short-term RfD. A study in adult animals reported alterations in mobility during tail suspension testing at a dose 10 times higher than the Short-term RfD, however this effect's significance was unclear and did not display a dose response. Other studies examining neurotoxicity in adult laboratory animals noted effects at doses greater than 1,000 times higher than the Short-term RfD.

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

Web Publication Date: August 2020

Toxicological Summary for: Benzophenone

CAS: **119-61-9**

Synonyms: Diphenylmethanone; Methanone, diphenyl-, diphenyl ketone, benzoyl benzene, alpha-oxo-diphenyl methane, alpha oxoditane, phenyl ketone

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

Short-term Non-Cancer Health-Based Value ($nHBV_{Short\text{-}term}$) = 900 µg/L

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

$$= \frac{\text{(0.52 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 896 rounded to **900 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 15.5/30 = 0.52 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	67.4 mg/kg-d (administered dose NOAEL, Hoshino et al. 2005)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 67.4 mg/kg-d x 0.23 = 15.5 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight
Co-critical effect(s):	Decreased pup body weight
Additivity endpoint(s):	Developmental

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

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

$$= \frac{(0.053 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 143 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 1.6/30 = 0.053 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	6.4 mg/kg-d (administered dose NOAEL, Hoshino et al., 2005)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 6.4 mg/kg-d x 0.25 = 1.6 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased relative liver weight, relative kidney weight, proximal tubule regeneration, proximal tubule dilatation
Co-critical effect(s):	Increased serum bile salts, relative liver weight, hepatocyte vacuolization, relative kidney weight, renal tubule protein casts
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

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

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

$$= \frac{(0.053 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 235 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 1.58/30 = 0.053 mg/kg-d (Fischer 344 rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	5.86 mg/kg-d (administered dose BMDL calculated by MDH from (National Toxicology Program, 2006))
Dose Adjustment Factor (DAF):	0.27, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 5.86 mg/kg-d x 0.27 = 1.58 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 renal tubule hyperplasia
Co-critical effect(s):	Increased renal pelvis transitional hyperplasia, severity of nephropathy, and bile duct hyperplasia
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

The Chronic nHBV must be protective of the subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Subchronic nHBV of 100 µg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	2B – Possibly carcinogenic to humans (IARC 2013)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	In male mice: hepatocellular adenoma, combined hepatocellular adenoma, carcinoma and hepatoblastoma. In female mice: histiocytic sarcoma. In male rats: renal tubule adenoma.

Statement for non-linear carcinogens:
Benzophenone was reported to be neither mutagenic nor genotoxic in various *in vivo* and *in vitro* experiments, and is likely to be a nonlinear carcinogen. The chronic RfD is considered to be protective against cancer.

Volatile: Yes (low)

Summary of Guidance Value History:

In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in changes to the subchronic and chronic duration water guidance values from 200 µg/L to 100 µg/L.

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

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

Comments on extent of testing or effects:

[1] One study identified estrogenic activity of orally-administered benzophenone based on increased uterine weight in ovariectomized rats at doses 200-fold higher than the Short-Term RfD. *In vivo* studies based on other routes of exposure did not show estrogenic effects. Based on *in vitro* studies, it appears that benzophenone and its main metabolite benzhydrol do not possess estrogenic activity, whereas a minor metabolite 4-hydroxybenzophenone is weakly estrogenic.

[2] There were no specific immunotoxicity studies available. Subchronic and chronic studies in rodents did not note any abnormalities in immune cell blood parameters or immune organ histopathology after oral benzophenone exposure at levels up to 300-fold higher than the Short-Term RfD.

[3] A two-generation reproductive/developmental study in rats noted a decrease in pup body weight close to weaning; this effect served as the basis of the Short-Term RfD. Other studies in rats and rabbits found that developmental toxicity only occurred at doses higher than those causing maternal toxicity.

[4] A two-generation reproductive/developmental study in rats did not note any reproductive abnormalities in the following tested parameters: reproductive serum hormones (testosterone, FSH, LH), estrous cycles, sperm morphology and motility and spermatid head count, mating behavior, conception, gestation, parturition, lactation, and weaning at doses up to 100-fold higher than the Short-Term RfD. Additionally, organ weights and histopathology of the testes, epididymes, prostate, seminal vesical, ovary, and uterus were unchanged.

[5] No neurotoxicity studies were found. A two-generation reproductive/developmental study in rats found no changes in reflex or pain response in pups at doses up to 100-fold higher than the Short-Term RfD.

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

Web Publication Date: August 2020

Toxicological Summary for: 1H-Benzotriazole

CAS: **95-14-7**

Synonyms: 1,2,3-Benzotriazole, Benzotriazole, 1H-Benzo[d][1,2,3]triazole, 1H-1,2,3-benzotriazole

Note: 1H-benzotriazole is the surrogate for water guidance values for 5-methyl-1H-benzotriazole and Tolyltriazole (https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/5mebtttr.pdf)

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

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

$$= \frac{\text{(0.023 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 15.8 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 6.9/300 = 0.023 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	30 mg/kg-d (administered dose NOAEL, JBRC, 2007)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 30 mg/kg-d x 0.23 = 6.9 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 due to the lack of reproductive/developmental studies of sufficient exposure duration
Critical effect(s):	Reduced offspring body weight
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

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

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

$$= \frac{\text{(0.017 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 45.9 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 5.15/300 = 0.017 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	22.4 mg/kg-d (administered dose $BMDL_{10\%}$, JBRC, 2007)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 22.4 mg/kg-d x 0.23 = 5.15 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 due to the lack of adequate subchronic toxicity studies and lack of reproductive/developmental studies of sufficient exposure duration
Critical effect(s):	Proximal tubule regeneration in kidney of female rats
Co-critical effect(s):	None
Additivity endpoint(s):	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 20 µg/L. Additivity endpoints: Developmental

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

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

$$= \frac{\text{(0.017 mg/kg-d)}^{***} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 75.5 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5
[***] The candidate Chronic RfD is significantly higher than the Subchronic RfD (0.017 mg/kg-d). Although, both identify kidney as the sensitive effect, the chronic study does not include information in the lower part of the dose-response range. Given the significant limitations of the chronic database, MDH has selected the Subchronic RfD as the final Chronic RfD.

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 20 µg/L. Additivity endpoints: Developmental

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: Yes (low)

Summary of Guidance Value History:
No previous guidance has been developed for 1H-Benzotriazole. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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
Effects observed?	--	--	Yes[1]	Yes[2]	--

Comments on extent of testing or effects:
[1] The short-term reference dose is based on developmental toxicity in offspring (decreased body weight). A lack reproductive/developmental studies of sufficient duration form a major part of the basis for the selection of a 10-fold database uncertainty factor.

[2] Changes in reproductive organs were noted in a two-year study in males (prostate inflammation) and females (uterus/endometrium inflammation and cystic hyperplasia) at doses over 8,000 times higher than the short-term and subchronic reference doses. A lack of reproductive/developmental studies of sufficient duration form a major part of the basis for the selection of a 10-fold database uncertainty factor.

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

Web Publication Date: February 2021

Toxicological Summary for: 1,1'-Biphenyl

CAS: **92-52-4; DTXSID4020161**

Synonyms: Biphenyl; Phenylbenzene; Diphenyl

Acute Non-Cancer Health-Based Value ($nHBV_{Acute}$) = 400 µg/L

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

$$= \frac{\text{(0.58 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 400 µg/L

*Relative Source Contribution: Because inhalation is the predominant route of exposure, and infant exposure does not appear to be significantly less than exposures to older children or adults, an RSC value of 0.2 was used for all exposure durations. MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 57.5/100 = 0.58 mg/kg-d (F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	250 mg/kg-d (administered dose NOAEL, Kluwe et al 1982)
Dose Adjustment Factor (DAF):	0.23 subchronic male F344 rats, body weight scaling default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 250 mg/kg-d x 0.23 = 57.5 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 limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Increased urine volume (polyuria) accompanied by increased excretion of urinary protein, glucose, and several renal enzymes
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

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

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

$$= \frac{\text{(0.18 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 124 rounded to **100 µg/L**

*Relative Source Contribution: Because inhalation is the predominant route of exposure, and infant exposure does not appear to be significantly less than exposures to older children or adults, an RSC value of 0.2 was used for all exposure durations. MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.6/100 = 0.18 mg/kg-d (female F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	83.7 mg/kg-d (administered dose NOAEL, Booth et al 1961. LOAEL based on Booth et al 1961 and Kluwe et al 1982.)
Dose Adjustment Factor (DAF):	0.21 female subchronic F344 rat based on body weight scaling, default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 83.7 mg/kg-d x 0.21 = 17.6 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 limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Increased urine volume (polyuria), precipitable urinary sediment, and increased urinary glucose, protein, alkaline phosphatase (AP) and glutamic oxaloacetic transaminase (GOT) excretion
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

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

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

$$= \frac{\text{(0.18 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 486 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.6/100 = 0.18 mg/kg-d (female F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	83.7 mg/kg-d (administered dose NOAEL, Booth et al 1961)
Dose Adjustment Factor (DAF):	0.21 female subchronic F344 rats body weight scaling, default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 83.7 mg/kg-d x 0.21 = 17.6 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 limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Increased urine volume and precipitable sediment accompanied by limited renal histological changes
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

The Subchronic nHBV must be protective of shorter duration 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: Renal (kidney) system.

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

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

$$= \frac{\text{(0.073 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 324 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 7.31/100 = 0.073 mg/kg-d (female F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	30.45 mg/kg-d (administered dose $BMDL_{10\%}$, Umeda et al 2002)
Dose Adjustment Factor (DAF):	0.24 female chronic F344 rats body weight scaling, default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 30.45 mg/kg-d x 0.24 = 7.31 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 limitations,

	including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Renal transitional cell simple hyperplasia
Co-critical effect(s):	Increased hemosiderin deposits in the kidney and mineralization of outer renal medulla and pelvis
Additivity endpoint(s):	Renal (kidney) system

The Chronic nHBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 100 µg/L. Additivity endpoints: Renal (kidney) system.

Cancer Health-Based Value (cHBV) = 10 µg/L

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\ yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.008 \times 10^{*} \times 0.155\ L/kg\text{-}d^{**} \times 2) + (0.008 \times 3^{*} \times 0.040\ L/kg\text{-}d^{**} \times 14) + (0.008 \times 1^{*} \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 12.4 rounded to **10 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer classification:	Suggestive evidence of carcinogenic potential
Slope factor (SF):	0.008 per mg/kg-d (female BDF1 mice, Umeda et al 2005)
Source of cancer slope factor (SF):	U.S. EPA 2013
Tumor site(s):	Liver adenomas and carcinomas

Volatile: No (moderate)

Summary of Guidance Value History:
MDH promulgated a chronic nHRL of 300 µg/L in 1993. In 2020 MDH conducted a full review and derived nHBVs of 400 µg/L for acute duration and 100 µg/L for short-term, subchronic and chronic durations as well as a cHBV of 10 µg/L for cancer. The 2020 chronic and cancer HBVs are lower than the 1993 HRL value due to the use of MDH's multiduration methodology, more recent toxicological data, and updated water intake rates (U.S. EPA 2019).

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
Effects observed?	-[1]	-	Yes[2]	Yes[3]	-[4]

Comments on extent of testing or effects:

[1] Endocrine effects have not been specifically tested in animals. *In vitro* estrogenic assays indicate that biphenyl does not exhibit estrogenic activity, however, hydroxylated metabolites of biphenyl do exhibit estrogenic activity. This activity was mainly observed when cultures contained cells from induced rat livers as little effect was observed when cells from untreated rats were used.

[2] Decreased fetal or pup body weights, delayed ossification, and increased dead or resorbed fetuses have been reported at HED doses ~600-fold higher than the short-term and subchronic RfDs. The developmental studies are old and do not include the more extensive evaluation of current study protocols. A database uncertainty factor of 3 was incorporated into the RfD derivation, in part, to address the need for more comprehensive developmental and reproductive toxicity testing.

[3] Decreased fertility in laboratory animals has been reported at HED doses ~1000-fold higher than the short-term and subchronic RfDs. The reproductive studies are old and do not include the more extensive evaluation of current study protocols. A database uncertainty factor of 3 was incorporated into the RfD derivation, in part, to address the need for more comprehensive developmental and reproductive toxicity testing.

[4] Occupational studies in humans have reported neurological effects when exposed to air levels in excess of occupational exposure limits. No animal neurotoxicity testing has been conducted. A database uncertainty factor of 3 was incorporated into the RfD derivation, in part, to address this data gap.

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

Web Publication Date: August 2020

Toxicological Summary for: Bromodichloromethane

CAS: **75-27-4**

Synonyms: Dichlorobromomethane, Monobromodichloromethane, BDCM

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = 400 µg/L

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

$$= \frac{\text{(0.073 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.038 L/kg-d)}^{**}}$$

= 384 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5. The RfD is based on full litter resorptions, which occurs in utero; therefore, the intake rate for a pregnant woman is used rather than the default infant intake rate as described in the 2008 SONAR (p. 46).

Reference Dose/Concentration:	HED/Total UF = 2.18/30 = 0.073 mg/kg-d (F344 rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	10.4 mg/kg-d (administered dose $BMDL_{05}$, Narotsky 1997 with support from Bielmeier 2001 as an acute effect)
Dose Adjustment Factor (DAF):	0.21, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 10.4 mg/kg-d x 0.21 = 2.18 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Full litter resorptions, associated with changes in female hormones that maintain pregnancy
Co-critical effect(s):	None
Additivity endpoint(s):	Female Reproductive system (E)

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

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

$$= \frac{(0.039 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}}$$

= 26.8 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 3.94/100 = 0.039 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	30.3 mg/kg-d (administered dose $BMDL_{10}$, Munson 1982)
Dose Adjustment Factor (DAF):	0.13, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 30.3 mg/kg-d x 0.13 = 3.94 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	e.g. 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (due to outstanding concerns related to BDCM-induced hormonal changes in females and immunotoxicity changes in a 2-generation study that is not confounded by vehicle, BDCM volatilization, water palatability, or animal dehydration issues)
Critical effect(s):	Decreased spleen weight
Co-critical effect(s):	Full litter resorptions***
Additivity endpoint(s):	Immune system, Spleen

***Since an infant water ingestion rate exposure forms the basis of the Short-term HBV calculation, and full litter resorptions is relevant only to pregnant women and is based on a pregnant woman water ingestion rate exposure, an additivity endpoint for full litter resorptions is not necessary.

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

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

$$= \frac{(0.039 \text{ mg/kg-d})^{\#} \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 105 rounded to 100 µg/L

#No Subchronic RfD was calculated due to study limitations. Therefore, the Short-term RfD was applied to the subchronic duration.

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

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 30 µg/L. Additivity endpoints: Immune system, Spleen

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

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

$$= \frac{\text{(0.0075 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 33 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 0.225/30 = 0.0075 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	0.776 mg/kg-d (administered dose $BMDL_{10}$, Aida 1992)
Dose Adjustment Factor (DAF):	0.29, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.776 mg/kg-d x 0.29 = 0.225 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 degeneration of the liver
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Based Value (cHBV) = 3 µg/L

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\ yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.035 \times 10^{*} \times 0.155\ \text{L/kg-d}^{**} \times 2) + (0.035 \times 3^{*} \times 0.040\ \text{L/kg-d}^{**} \times 14) + (0.035 \times 1^{*} \times 0.042\ \text{L/kg-d}^{**} \times 54)] / 70}$$

= 2.8 rounded to **3 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Cancer classification: Likely to be carcinogenic to humans

Slope factor (SF): 0.035 per mg/kg-d, renal tumors in male B6C3F1 mice (NTP 1987)
Source of cancer slope factor (SF): (US EPA 1998) as cited in US EPA 2005
Tumor site(s): Kidney, Large intestine, Liver, Lymphatic system

Volatile: Yes (high)

Summary of Guidance Value History: In 1993, MDH promulgated a cancer HRL of 6 µg/L. The new 2018 HBV for cancer (3 µg/L) is lower because of 1) the use of a more recent slope factor; 2) the use of MDH's most recent risk assessment methodology; and 3) rounding to one significant digit. In 2018 MDH also derived noncancer HBVs of 300 µg/L for Acute and 30 µg/L for Short-term, Subchronic, and Chronic durations. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in an increase of the Acute duration HBV from 300 µg/L to 400 µg/L.

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]A hormone profile was conducted on pregnant rats exposed to BDCM during pregnancy that resulted in full litter resorptions (acute critical effect). Maternal hormone changes occurred at levels 200-300 times higher than the acute RfD and 400-500 times higher than the short-term RfD.

[2]The short-term RfD is based on reduced spleen weights in mice exposed to BDCM. Altered immune cell levels and function occurred at doses 300-400 times higher than the RfD. Other studies in rodents demonstrated changes in thymus weights at levels 100 times higher than the short-term RfD and lymphoid atrophy of the thymus, spleen, and lymph nodes at levels 1,000 times higher than the short-term RfD.

[3]The acute-duration RfD is based on maternally-mediated full litter resorptions in rats, which was noted in a reproductive and developmental study. At doses 300 times higher than the short-duration RfD, fetal skeletal anomalies were also reported in rats. However, there were no fetal or pup developmental effects noted in rabbits at doses between 50 to 900 times higher than the short-term RfD.

[4]The acute RfD is based on maternally-mediated full litter resorptions in rats, and this effect is also identified as a co-critical effect for the short-term duration, occurring at a dose approximately 200 times higher than the Short-term RfD. Ovarian abscesses were reported in mice at doses

200 times higher than the short-term RfD, and sperm velocity in rats was observed to decrease at BDCM doses 300 times higher than the short-term RfD, although with no supporting histology.

[5]Neurotoxic effects appear to be minimal after BDCM exposure. At levels 400 times higher than the short-term RfD, rats in one study had slightly altered behavior. At BDCM doses 3,000 times higher than the short-term RfD, another study reported hyperactivity in rats.

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

Web Publication Date: August 2020

Toxicological Summary for: 1,4-Dichlorobenzene

CAS: **106-46-7**

Synonyms: p-Dichlorobenzene, paradichlorobenzene, para-Dichlorobenzene

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

Short-term Non-Cancer Health-Based Value ($nHBV_{Short\text{-}term}$) = 50 µg/L

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

$$= \frac{\text{(0.069 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 47.5 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 6.9/100 = 0.069 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	30 mg/kg-d (administered dose NOAEL, Bornatowicz 1994 cited in US EPA 2006.)
Dose Adjustment Factor (DAF):	0.23 Body weight scaling, default for female Sprague-Dawley rat, subchronic (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 30 mg/kg-d x 0.23 = 6.9 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 for lack of neurotoxicity studies and limitations in study reporting.
Critical effect(s):	Reduced pup body weight, increased pup mortality, increased incidence postnatal dry and scaly skin, increased postnatal tail constriction, and a reduction in the number of pups with a positive reaction in the neurobehavioral draw-up test.
Co-critical effect(s):	Increased liver weight and hepatocyte proliferation
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Nervous system

Subchronic Non-Cancer Health-Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 50 µg/L

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

$$= \frac{\text{(0.042 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 113 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 4.21/100 = 0.042 mg/kg-d (Beagle)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	7.14 mg/kg-d (administered time-weighted-average dose NOAEL, Naylor 1996, cited in EPA, 1996.)
Dose Adjustment Factor (DAF):	0.59 Body weight scaling, default for female beagle in 1-yr toxicity study (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 7.14 mg/kg-d x 0.59 = 4.21 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 for lack of neurotoxicity studies and limitations in study reporting.
Critical effect(s):	Increased liver weight, hepatocellular hypertrophy, hepatocyte pigment deposition, hepatic portal inflammation, increased serum alkaline phosphatase, and decreased serum albumin; increased kidney weight and incidence of collecting duct epithelial vacuolation; increased blood platelet count; and increased thyroid weight
Co-critical effect(s):	Reduced pup body weight, increased pup mortality, increased incidence postnatal dry and scaly skin, increased postnatal tail constriction, and a reduction in the number of pups with a positive reaction in the neurobehavioral draw-up test; increased hepatocyte proliferation, increased bile duct/ductile hyperplasia, increased serum alanine aminotransaminase, and increased gamma-glutamyl transferase; increased incidence of renal discoloration; increased incidence of anemia and hyperplastic changes in hematopoietic tissues; and increased adrenal gland weight

Additivity endpoint(s):	Adrenal, Developmental, Hematological (blood) system, Hepatic (liver) system, Nervous system, Renal (kidney) system, Thyroid

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 50 µg/L. Additivity endpoints: **Developmental, Hepatic (liver) system, Nervous system**

Chronic Non-Cancer Health-Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 50 µg/L

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

$$= \frac{\text{(0.032 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 32.1/1000 = 0.032 mg/kg-d ($B6C3F_1$ mouse)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	214 mg/kg-d (administered time-weighted-average dose LOAEL, NTP 1987)
Dose Adjustment Factor (DAF):	0.15 Body weight scaling, default for male and female $B6C3F_1$ mouse, chronic (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 214 mg/kg-d x 0.15 = 32.1 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, and 3 for database uncertainty for lack of neurotoxicity studies and limitations in study reporting.
Critical effect(s):	Hepatocellular degeneration; lymphoid hyperplasia; nephropathy and renal tubular regeneration; and adrenal gland hyperplasia
Co-critical effect(s):	Reduced pup body weight, increased pup mortality, increased incidence postnatal dry and scaly skin, increased postnatal tail constriction, and a reduction in the number of pups with a positive reaction in the neurobehavioral draw-up test; increased liver weight, hepatocyte proliferation, hepatocyte hypertrophy, hepatocellular pigment deposition, hepatic portal inflammation, bile

	duct/ductile hyperplasia, increased serum alanine aminotransaminase, increased gamma-glutamyl transferase, increased serum alkaline phosphatase, and decreased serum albumin; increased kidney weight, changes in renal proximal tubule cell proliferation, increased incidence collecting duct epithelial vacuolation, and renal discoloration; anemia, increased blood platelet count, and hyperplastic changes in hematopoietic tissues; increased adrenal weight; and increased thyroid weight
Additivity endpoint(s):	Adrenal, Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Renal (kidney system), Thyroid

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 50 µg/L. Additivity endpoints: Developmental, Hepatic (liver) system, Nervous system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	"Not likely to be carcinogenic to humans based on evidence that a non-mutagenic mode-of-action involving mitogenesis was established for *p*-dichlorobenzene-induced liver tumors in mice, and that the carcinogenic effects are not likely below a defined dose that does not perturb normal liver homeostasis (*e.g.* increased liver cell proliferation)". (US EPA 2018) Group 2B, possibly carcinogenic to humans (IARC 1999 cited in IARC 2019) Reasonably anticipated to be a human carcinogen (ATSDR 2006; NTP 2016)
Slope factor (SF):	Not applicable
Source of cancer slope factor (SF):	Not applicable
Tumor site(s):	Liver

Statement for non-linear carcinogens:
Based on the available information, MDH has determined that 1,4-dichlorobenzene is a nonlinear carcinogen. The MDH Short-term, Subchronic, and Chronic nHBVs of 50 µg/L are based on preventing hepatocellular proliferation, the key event in 1,4-dichlorobenzene carcinogenicity.

Volatile: Yes (high)

Summary of Guidance Value History:
A cancer HRL of 10 µg/L was promulgated in 1994. A revised non-cancer HBV of 50 µg/L was derived in 2019. This value is higher than the 1994 cancer HRL and is protective of cancer effects as the result of: 1) the use of MDH's most recent risk assessment methodology; 2) better understanding of the mode-

of-action for 1,4-dichlorobenzene toxicity (hepatocellular proliferation); and 3) an updated cancer classification from EPA (not likely to be carcinogenic to humans at doses that do not perturb normal liver homeostasis). In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Increased thyroid and adrenal gland weights were observed in exposed laboratory animals and were identified as critical and co-critical effects for the subchronic duration. The dose levels at which these effects were observed were 300 to 1,000-fold higher than the derived reference doses (RfDs). Adrenal gland hyperplasia was an effect of the chronic critical study and occurred at levels 500 to 1,000 times higher than the derived RfDs. Thyroid hyperplasia occurred at levels 900 to 2,000 times higher than the derived RfDs. 1,4-Dichlorobenzene is currently on the EPA Endocrine Disruptor Screening Program's List 2 for endocrine activity testing.

[2] Although one short-term immunotoxicity study in male mice did not detect any immunological effects at doses greater than 2,000 to 4,000 times higher than the derived RfDs, other toxicity studies did note secondary immunological effects during longer exposures at lower doses. The chronic duration RfD is partly based on a secondary immune effect (lymphoid hyperplasia). This effect, along with hypoplasia of the bone marrow, reduced spleen weights, and lymphoid depletion of the spleen and thymus were observed at doses 250 to 2,000-fold higher than the derived RfDs.

[3] Developmental effects (reduced body weight at birth, increased mortality, dry and scaly skin, tail constriction, and a reduction in positive reactions in a neurodevelopmental test) in rat pups forms the basis of the short-term RfD. Additional developmental effects were also observed as dose levels increased, with increased incidence of delayed eye opening and ear erection, skeletal variations, and cyanosis occurring at doses greater than 900-fold higher than the short-term RfD. Reduced fetal weight was also reported at doses greater than 3,000 times higher than the short-term RfD.

[4] In developmental and 2-generational studies no reproductive effects were reported at doses greater than 900 fold higher than the short-term RfD. In subchronic and chronic studies, uterine hyperplasia and changes in female reproductive organ weights were reported at dose levels 700 to 2,000 times higher than the derived RfDs.

[5] The short-term RfD is based in part on a neurodevelopmental effect (positive reaction to the "draw-up" test) in rat pups. The decision to apply a database uncertainty factor of "3" in part is due to the lack of any other neurotoxicity tests in the 1,4-dichlorobenzene database.

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

Web Publication Date: August 2020

Toxicological Summary for: trans-1,2-Dichloroethene

CAS: **156-60-5**

Synonyms: 1,2-Dichloroethylene (trans); 1,2-trans-dichloroethylene; (E)-1,2-dichloroethene; (E)-1,2-Dichloroethylene; trans-1,2-Dichloroethene; trans-1,2-dichloroethylene; trans-1,2-dichloroethylene ; trans-1,2-DCE; trans-acetylene dichloride; trans-dichloroethylene

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/Risk Assessment Advice ($nHBV_{Subchronic}$) = 50 µg/L

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

$$= \frac{\text{(0.020 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 54 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 2.03/100 = 0.020 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	14.5 mg/kg-d ($BMDL_{ADM\text{-}1SD}$ based on 2018 OEHHA modeling of immunotoxicity data from Shopp et al 1985)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 14.5 mg/kg-d x 0.14 = 2.03 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 due to lack of a multigenerational study and supplementing database with inhalation studies
Critical effect(s):	Decreased ability to produce antibodies against sheep RBCs in male spleen cells

Co-critical effect(s):	Decreased thymus weight, clinical chemistry effects
Additivity endpoint(s):	Immune system

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

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

$$= \frac{\text{(0.0020 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 8.8 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 2.03/1000 = 0.0020 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	14.5 mg/kg-d ($BMDL_{ADM\text{-}1SD}$ based on 2018 OEHHA modeling of immunotoxicity data from Shopp et al 1985, subchronic exposure)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 14.5 mg/kg-d x 0.14 = 2.03 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for subchronic-to-chronic extrapolation due to clear and significant immunotoxicity in the subchronic study, and 3 for database uncertainty due to lack of a multigenerational study and supplementing database with inhalation studies
Critical effect(s):	Decreased ability to produce antibodies against sheep RBCs in male spleen cells
Co-critical effect(s):	Decreased thymus weight, clinical chemistry effects
Additivity endpoint(s):	Immune system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	*"Inadequate information to assess the carcinogenic potential"* of trans-1,2-DCE
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	EPA IRIS 2010
Tumor site(s):	Not Applicable

Volatile: Yes (High)

Summary of Guidance Value History:

A chronic HRL of 100 µg/L was promulgated in 1993. In 2011, subchronic and chronic Health-Based Values (HBVs) of 600 and 100 µg/L, respectively, were derived. In 2012, MDH re-evaluated the HBVs to incorporate HED methodology, resulting in subchronic and chronic HBVs of 200 and 40 µg/L, respectively. The 2012 HBVs were adopted as HRLs in 2013 and the 1993 HRL was repealed. In 2020, MDH re-evaluated the 2013 HRLs and derived subchronic and chronic HBVs of 60 and 9 µg/L, respectively. The re-evaluation resulted in values that were 3 to 4-fold lower as the result of using the most recent risk assessment methodology (specifically, improvements in benchmark dose modeling for POD calculation). In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a decrease in the Subchronic HBV from 60 µg/L to 50 µg/L.

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	No	No
Effects observed?	No	Yes[1]	Yes[2]	No[3]	Secondary observations[4]

Comments on extent of testing or effects:

[1]Shopp et al. (1985) measured depression in humoral immune status following 90 days of exposure via drinking water. These effects form the basis of the subchronic and chronic HBVs.
[2]A single inhalation developmental study exists. Decreased fetal body weight was observed at doses estimated to be over 400-fold higher than the minimal short-term critical Human Equivalent Dose. A database uncertainty factor has been applied, in part, due to the lack of oral developmental/reproductive studies.
[3]Examination of the reproductive organs of animals in the 90-day study did not report any histological changes. A database uncertainty factor has been applied, in part, due to the absence of a multigenerational study.
[4]Neurological effects have not been adequately studied. Acute exposures (e.g., a single high dose) have reported effects.

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

Web Publication Date: August 2020

Toxicological Summary for: 1,1-Dichloroethylene

CAS: **75-35-4**

Synonyms: Vinylidene chloride, 1,1-Dichloroethene

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

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

$$= \frac{\text{(0.069 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 186 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 2.07/30 = 0.069 mg/kg-d (Sprague Dawley Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	9 mg/kg-d (NOAEL, Nitschke et al. 1983 supported by Quast et al. 1977)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 9 mg/kg-d x 0.23 = 2.07 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 changes in the liver
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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

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

$$= \frac{\text{(0.040 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 1.20/30 = 0.040 mg/kg-d (Sprague Dawley Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	4.6 mg/kg-d ($BMDL_{10}$, Quast et al. 1983 as calculated by USEPA, 2002)
Dose Adjustment Factor (DAF):	0.26, Body weight scaling, default (USEPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 4.6 mg/kg-d x 0.26 = 1.20 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 changes in the liver
Co-critical effect(s):	Fatty changes in the liver
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Data are inadequate for an assessment of human carcinogenic potential (oral route); Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential (inhalation route) (USEPA, 2002)
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 non-cancer Health Risk Limit (HRL) of 6 µg/L was promulgated in 1993/1994. Subchronic and chronic health-based values (HBV) of 200 µg/L were derived in 2009 and were promulgated as Health Risk Limits (HRL) in 2011. In 2019, MDH re-evaluated the noncancer HRLs using the most recent risk assessment methodology, resulting in no changes to the subchronic and chronic guidance values. In

2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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
Effects observed?	-	-	Yes[1]	Yes[2]	-[3]

Comments on extent of testing or effects:

[1]Two developmental studies with oral exposure have been conducted in laboratory animals. No developmental effects were observed at doses up to 100 times higher than the subchronic reference dose. Developmental effects were tested and observed in inhalation studies, however, maternal toxicity was evident at levels that resulted in developmental toxicity.

[2]One multi-generation reproductive study with oral exposure has been conducted in laboratory animals. No reproductive effects were observed at doses up to 100 times higher than the subchronic reference dose. No reproductive effects were observed in developmental inhalation studies in laboratory animals.

[3]Neurotoxicity of 1,1-dichloroethylene has not been studied. However, neurotoxicity endpoints were included in a developmental inhalation study in laboratory animals. No evidence of developmental neurotoxicity was observed up to the highest dose tested.

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

Web Publication Date: September 2021

Toxicological Summary for: 1,2-Dichloropropane

CAS: **78-87-5**
Synonyms: Propylene dichloride

Individuals with inherited glucose-6-phosphate dehydrogenase (G6PDH) deficiency may be more susceptible to the negative health effects associated with 1,2-dichloropropane toxicity, particularly hemolytic anemia (ATSDR 2019). According to the g6pd Deficiency Foundation, the overall frequency of G6PDH deficiency is 4-7% in the US, almost exclusively in males, with higher rates (~12%) in African American males. Due to lack of data, a quantitative estimate of sensitivity associated with G6PDH deficiency could not be conducted. However, MDH has applied a 10-fold uncertainty factor to account for human variability in the response to 1,2-dichloropropane toxicity. People who have questions about G6PDH deficiency should contact their physician.

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

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

$$= \frac{\text{(0.029 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

$$= \mathbf{20\ \mu g/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 2.94/100 = 0.029 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	12.8 mg/kg-d (administered dose $BMDL_{05}$, developmental toxicity study by Kirk 1995)
Dose Adjustment Factor (DAF):	0.23, body weight scaling, default (US EPA 2011 and MDH 2017)

Human Equivalent Dose (HED):	POD x DAF = 12.8 mg/kg-d x 0.23 = 2.94 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 due to the absence of an adequate 2-generational study and a developmental neurotoxicity study in offspring
Critical effect(s):	Delayed ossification of the fetal skull
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

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

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

$$= \frac{(0.029 \text{ mg/kg-d})^{***} \text{ x } (0.2)^{*} \text{ x } (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 78 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.
*** The calculated subchronic RfD (0.059 mg/kg-d) is higher than the Short-term RfD (0.029 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.

The Subchronic HBV must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic HBV is set equal to the Short-term nHBV of 20 µg/L. Additivity endpoint: Developmental

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

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

$$= \frac{(0.018 \text{ mg/kg-d}) \text{ x } (0.2)^{*} \text{ x } (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 80 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.8/1000 = 0.018 mg/kg-d (Sprague-Dawley rat)

Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	71 mg/kg-d (administered dose LOAEL; Bruckner 1989, subchronic exposure)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 71 mg/kg-d x 0.25= 17.8 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for database uncertainty due to the absence of an adequate 2-generational study and a developmental neurotoxicity study in offspring, 3 for using a LOAEL in place of a NOAEL, and 3 for using a subchronic study for a chronic duration
Critical effect(s):	Hemolytic anemia (increased bilirubin and increased hemosiderosis and hyperplasia of erythropoietic elements of the spleen)
Co-critical effect(s):	Increased absolute and relative liver weights, fatty change of the liver, hepatocytomegaly, increased cholesterol and glycerin, and liver necrosis; mammary gland hyperplasia; transient neurotoxicity in pregnant dams, and delayed ossification of the fetal skull.
Additivity endpoint(s):	Developmental, Female Reproductive system, Hematological (blood) system, Hepatic (liver) system, and Nervous system

The Chronic nHBV must be protective of shorter duration 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 endpoint: Developmental

Cancer Health-Based Value (cHBV) = 3 µg/L

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\ yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{1E\text{-}5) \times (1000\ \mu g/mg)}{[(0.037 \times 10^{*} \times 0.155\ L/kg\text{-}d^{**} \times 2) + (0.037 \times 3^{*} \times 0.040\ L/kg\text{-}d^{**} \times 14) + (0.037 \times 1^{*} \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 2.68 rounded to **3 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer classification: Carcinogenic to humans (WHO 2017)

Slope factor (SF): 0.037 $(mg/kg\text{-}d)^{-1}$ based on liver tumors in male mice (NTP 1986)
Source of cancer slope factor (SF): (EPA 2016)
Tumor site(s): Liver

Volatile: Yes (high)

Summary of Guidance Value History:

In 1994, MDH developed a cancer HRL (cHRL) of 5 µg/L. The 2021 cHBV (3 µg/L) is based on the same NTP 1986 study (liver tumors in male mice), however, MDH used an updated EPA slope factor (EPA 2016) and incorporated age dependent adjustment factors (ADAFs) to determine the 2021 cHBV. Updated EPA water intake rates also contributed to a lower MDH 2021 cHBV.
Noncancer guidance values previously did not exist, therefore, the short-term, subchronic, and chronic noncancer HBVs derived in 2021 represent new values.

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?	-[1]	-	Yes[2]	Yes[3]	Yes[4]

Comments on extent of testing or effects:

[1] Thyroid follicular cell adenoma or carcinoma occurred in female mice (NTP 1986) at a dose 900 times higher than the short-term RfD.
[2] The short-term duration RfD is based on delayed skull ossification in fetal rats. This effect was also observed in rabbits at a dose approximately 2.4-fold higher than the dose in rats. A database UF of 3 was applied due to the lack of a developmental neurotoxicity study in offspring.
[3] Reproductive effects include complete litter resorptions in rabbits at a level 4,000 times higher than the short-term duration RfD. Testicular degeneration and declines in sperm number in rats occurred at levels 3,000 to 5,000 times the short-term RfD. Mammary gland hyperplasia occurred in rats at a dose 700 times higher than the short-term RfD. A database UF of 3 was added in part due to the absence of an adequate 2-generational study. A 2-generation study exists in rats, however, 1,2-dichloropropane was added to the drinking water and due to palatability issues as the dose increased, dams drank significantly less water. This obscured the results of the study, as effects could be attributed, in part, to dehydration from lower water ingestion.

[4] Transient central nervous system (CNS) depression was a common occurrence in test animals after exposure to 1,2-dichloropropane and occurred at levels starting at 100 times higher than the short-term RfD. Only one study was specifically designed to test neurotoxicity in adult animals and aside from transient CNS depression, found no other effects. However, neurodevelopmental data are lacking, especially for offspring of exposed parental animals, and therefore a database UF of 3 was applied to account for the uncertainty around developmental neurotoxicity.

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

Web Publication Date: August 2020

Toxicological Summary for: 17α-Ethinylestradiol

CAS: **57-63-6**

Synonyms: Ethinyl estradiol; Ethinylestradiol; 17-α ethinyl estradiol; 17-α EE; EE2; 17-ethinylestradiol; ethynylestradiol; 17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol;19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol (IUPAC)

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 0.0005 µg/L

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

$$= \frac{(1.7 \times 10^{-7}\ \text{mg/kg-d}) \times (0.8^{*}) \times (1000\ \mu\text{g/mg})}{(0.290\ \text{L/kg-d})^{**}}$$

= 0.000468 rounded to **0.0005 µg/L**

* Relative Source Contribution: MDH 2008, Section IV.E.1. MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate Relative Source Contributions (RSCs) (MDH 2008, Appendix K). Typically an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations and an RSC of 0.2 is used for subchronic and chronic durations. Given the limited potential for exposure from other sources, an RSC of 0.8 was selected rather than applying the default RSC value. For individuals who take 17α-ethinylestradiol by prescription, the additional exposure from drinking water will be negligible.

** Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	(POD x DAF)/Total UF = 1.7×10^{-7} mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	0.00050 mg/kg-d (LOAEL, Delclos et al. 2014)
Human Equivalent Dose (MDH, 2011):	Not applied (doses directly given to neonatal animals were not adjusted due to interspecies and life-stage differences in toxicokinetics)
Total uncertainty factor:	3000
Uncertainty factor allocation:	10 for interspecies differences, 10 for intraspecies variability, and 10 for LOAEL-to-NOAEL, 3 for database uncertainty regarding potential latent effects
Critical effect(s):	Male mammary gland hyperplasia, decreased ovary weight, increased uterine weight, delayed vaginal opening
Co-critical effect(s):	In humans: reduced fertility (prevention of ovulation), increased sex hormone binding globulin, decreased corticosteroid-binding globulin, decreased follicle-stimulating hormone, decreased luteinizing hormone, breast development (gynecomastia) in infants

	In laboratory animals: Decreased body weight gain in adults, post-implantation loss, increased resorptions, decreased number of live pups/litter, decreased fetal/neonatal survival, reduced pup body weight and body weight gain, histopathology in female sex organs (uterus, ovaries and clitoral gland), latent uterine atypical focal hyperplasia, increased malformations in female external genitalia, increased number of female nipples, changes in sexually dimorphic behaviors, decreased fertility, early female pubertal onset, effects on estrous cyclicity, ovarian dysfunction, increased gestation length, changes in male reproductive organ weights and histopathology effects in various male reproductive organs, increased male mammary gland terminal end buds and density, decreased testosterone, decreased epididymal sperm counts, increased pituitary gland weight
Additivity endpoint(s):	Developmental (E), Female reproductive system (E), Male reproductive system (E)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 0.0002 µg/L

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

$$= \frac{(1.4 \times 10^{-8} \text{ mg/kg-d}) \times (0.8^{*}) \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 0.000151 rounded to **0.0002 µg/L**

*Rationale for selecting RSC of 0.8 – same explanation as that provided for the short-term duration (see above)
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	(POD x DAF)/Total UF = 1.4×10^{-8} mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	determined by MDH in 2016
Point of Departure (POD):	4.2×10^{-5} mg/kg-d ($BMDL_{10}$, NTP 2010a)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 4.2×10^{-5} mg/kg-d x 0.01 = 4.2×10^{-7} mg/kg-d (DAF chemical-specific basis)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Mammary gland hyperplasia in adult males
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 0.0002 µg/L

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

$$= \frac{(1.4 \times 10^{-8} \text{ mg/kg-d}^{**}) \times (0.8^{*}) \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{***}}$$

= 0.000248, rounded to **0.0002 µg/L**

Additivity endpoint(s): Developmental

*Rationale for selecting RSC of 0.8 – same explanation as that provided for the short-term duration (see above)
**See the subchronic information above for details about the reference dose
*** Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer Health Based Value (cHBV) = Not Derived

After carefully reviewing the available data MDH concluded that the non-cancer HBVs are sufficiently protective for potential cancer effects.

Cancer classification:	IARC Group 1, Carcinogenic to humans
Slope factor:	Not available
Source of slope factor:	Not Applicable
Tumor site(s):	Endometrium, ovary, mammary

Volatile: No

Summary of Guidance Value History:
The HBVs for 17α-ethinylestradiol are new. No previous values exist. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in the Chronic duration HBV no longer being set to the Subchronic duration HBV. However, the Chronic duration HBV remains the same value.

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]Ethinylestradiol is used as a human contraceptive for its ability to disrupt the human endocrine system at human contraceptive doses over 260 times higher than the short-term RfD and over 9,000 times higher than the sub/chronic RfD. Endocrine-mediated effects on a variety of male and female endocrine-responsive tissues form the basis for all of the RfDs. In humans, hormonal effects including increased sex hormone binding globulin and angiotensinogen with decreased corticosteroid binding globulin and follicle-stimulating hormone were reported at doses more than 300 times higher than all of the RfDs. In laboratory animal studies, steroid hormonal effects including reduced testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin, progesterone and increased serum estradiol have been reported at doses more than 100 times higher than all of the RfDs. Thyroid hormones were affected in adult rats at doses more than 350 times higher than the subchronic RfD.

No effects on thyroid hormones were found in neonatal animals. Increased pituitary gland weight was reported at doses more than 2,800 times higher than the subchronic RfD.

[2]Ethinylestradiol produced decreased bone marrow DNA synthesis and blood cell progenitor cells in rats, indicating a potential impact on the immune system at doses over 2,000 times higher than all of the RfDs. Other immune system effects occurring at doses more than 1,000 times higher than the subchronic RfD included increased natural killer cell activity, increased spleen cell proliferation related to cell-mediated immunity, decreased spleen cell numbers (B, T, and NK cells), and increased relative spleen weight. Significant, but inconsistent increases in thymus weight were reported in adult rat offspring at doses over 140 times higher than the subchronic RfD.

[3]The short-term RfD is based, in part, on male and female developmental effects reported in laboratory animal studies. The sub/chronic RfDs are based on male mammary gland hyperplasia, considered an aberrant developmental effect for males. Epidemiological studies have found no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy and also do not suggest any overt birth defects effects when taken inadvertently during early pregnancy. However, potential for subtle, long-term effects from gestational exposure in humans has not been fully evaluated. In a clinical study of children whose mothers used oral contraceptives during lactation (starting at age 2 months), no effects on intellectual or behavioral development were found when children were followed up to age 8 years. A few adverse effects in nursing infants whose mothers were taking ethinylestradiol have been reported, including jaundice and breast enlargement. These effects in nursing infants occurred at maternal doses more than 2,000 times higher than the short-term RfD and more than 30,000 times higher than the subchronic RfD.

[4]Ethinylestradiol is a human contraceptive drug that is used deliberately for its ability to disrupt human reproduction by inhibiting ovulation. Oral contraceptives given during nursing may also interfere with lactation by decreasing the quantity and quality of breast milk. The lowest human contraceptive dose is 260 times higher than the short-term RfD and over 9,000 times higher than the sub/chronic RfDs. The short-term RfD is based, in part, on female reproductive system effects in laboratory animals.

[5]Neurobehavioral developmental effects related to feminization or masculinization of behaviors were reported in rats exposed to doses more than 100 times higher than the short-term RfD and 30,000 higher than the subchronic RfD. Effects included changes in saccharin and sodium preferences and decreased female rearing behavior. Increased activity and startle responses were reported in rat offspring. In a clinical study of children whose mothers used oral contraceptives during lactation (starting at age 2 months), no effects on intellectual or behavioral development were found when children were followed up to age 8 years.

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

Web Publication Date: August 2020

Toxicological Summary for: Ethylbenzene

CAS**: 100-41-4**
Synonyms: Phenylethane, ethylbenzol, EB, 1-Ethylbenzene

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 40 µg/L

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

$$= \frac{\text{(0.06 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 41 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 18/300 = 0.06 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	75 mg/kg-d (administered dose NOAEL, Mellert 2007)
Dose Adjustment Factor (DAF):	0.24, Body weight scaling, default (USEPA 2011) (MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 75 mg/kg-d x 0.24 = 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 database uncertainty (lack of studies via oral exposure including a lack of developmental and reproductive studies and toxicity data in multiple species)
Critical effect(s):	Changes in liver and kidney weight in males with corresponding histological changes; and blood chemistry changes at higher doses
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 40 µg/L

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

$$= \frac{\text{(0.036 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 97 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 10.68/300 = 0.036 mg/kg-d (Wistar rat)
Source of toxicity value:	ATSDR 2010
Point of Departure (POD):	6.61 µmol/L (Liver serum concentration $BMDL_{10}$, ATSDR 2010 analysis of Mellert 2007)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model (ATSDR 2010)
Human Equivalent Dose (HED):	10.68 mg/kg-d HED from PBPK modelling conducted by ATSDR 2010
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 studies via oral exposure including a lack of developmental and reproductive studies and toxicity data in multiple species)
Critical effect(s):	Centrilobular hepatocyte hypertrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) 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 40 µg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 40 µg/L

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

$$= \frac{\text{(0.011 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 48 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	HED/Total UF = 10.68/1000 = 0.011 mg/kg-d (Wistar rat)
Source of toxicity value:	ATSDR 2010
Point of Departure (POD):	6.61 µmol/L ($BMDL_{10}$ based on concentration of ethylbenzene in the liver, ATSDR 2010 analysis of Mellert 2007) (subchronic exposure)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model (ATSDR 2010)
Human Equivalent Dose (HED):	10.68 mg/kg-d HED from PBPK modelling conducted by ATSDR 2010
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for database uncertainty (lack of studies via oral exposure including a lack of developmental and reproductive studies and toxicity data in multiple species), and 3 for extrapolation to a chronic duration from a subchronic duration study
Critical effect(s):	Centrilobular hepatocyte hypertrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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 40 µg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	2B - possibly carcinogenic to humans (IARC 2000); D - not classifiable as to human carcinogenicity (USEPA 1991)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	liver and kidney

Volatile: Yes (high)

Summary of Guidance Value History:

A noncancer chronic Health Risk Limit (HRL) of 700 µg/L was promulgated in 1993. In 2011, MDH derived short-term, subchronic, and chronic HRLs of 50 µg/L. In 2015, MDH evaluated the potential of incorporating an oral slope factor into the assessment. There was no new

information to support derivation of a cancer water guidance value. In 2018, MDH re-evaluated the existing HRLs, resulting in slightly lower Health Based Values (HBV). The 2018 HBVs are lower than the previous HRLs as a result of 1) use of MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	Yes	Yes
Effects observed?	-[1]	-[2]	-[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Endocrine activity of ethylbenzene has not been tested. However, an acute oral study noted decreases in peripheral hormone levels and possible effects on the estrus cycle in rats at doses 2000 or more times higher than the short-term reference dose. Rats and mice exposed to ethylbenzene in an inhalation exposure study showed an increased incidence of follicular cell hyperplasia in the thyroid gland and hyperplasia in the pituitary gland over the two-year study period.

[2] Immunotoxicity of ethylbenzene has only been studied by inhalation in laboratory animals. Some studies noted changes in immune cell numbers and increased spleen weights, but these results were not consistently seen across all studies. One general toxicity oral study noted decreased thymus weights in rats exposed at doses over 900 times higher than the short-term reference dose.

[3] Developmental effects have not been studied in laboratory animals exposed through the oral route. Effects observed in rat inhalation exposure studies include reduced fetal weight and skeletal and urogenital anomalies observed in the presence of maternal toxicity.

[4] Very limited information is available on reproductive effects following oral exposures. Decreases in hormone levels affecting the estrus cycle and uterine effects were indicated in a single acute reproductive study in laboratory animals with oral exposure at doses 2000 or more times higher than the short-term reference dose. Adverse reproductive effects were not observed in laboratory animals studies with inhalation exposure.

[5] Significant ototoxic effects have been reported, including loss of the outer hair cells in a part of the ear. This effect was observed in male rats at a single oral dose over 3000 times higher than the short-term reference dose. Ototoxicity has also been seen following inhalation exposure to ethylbenzene.

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

Web Publication Date: August 2020

Toxicological Summary for: Ethylene Glycol

CAS: **107-21-1**

Synonyms: Ethane-1,2-diol, Monoethylene glycol (MEG), 1,2-Ethanediol, Glycol

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 2000 µg/L

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

$$= \frac{\text{(0.33 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.038 L/kg-d)}^{**}}$$

= 1,736 rounded to **2,000 µg/L**

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

** The RfD is based on malformations that occur *in utero*, therefore, the intake rate for a pregnant woman is utilized rather than the default infant intake rate as described in the MDH 2008 SONAR (page 46). Effects relevant to post-natal development occurred at higher dose levels. As the short-term duration intake is based on pregnant women, not infants, a Relative Source Contribution of 0.2 is utilized. (Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.)

Reference Dose/Concentration:	HED/Total UF = 9.83/30 = 0.33 mg/kg-d (CD-1 mice)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	75.6 mg/kg-d ($BMDL_{10}$; derived by ATSDR 2010, using data from Neeper-Bradley, 1995)
Dose Adjustment Factor (DAF):	0.13 (Body weight scaling, default) (MDH, 2017) (US EPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 75.6 mg/kg-d x 0.13 = 9.83 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 fetal skeletal malformations
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 2000 µg/L

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

$$= \frac{\text{(0.33 mg/kg-d)}^{**} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.038 L/kg-d)}^{**}}$$

= 1,736 rounded to **2,000 µg/L**

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

** The calculated Subchronic RfD (0.57 mg/kg-d) is higher than the Short-term RfD (0.33 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 Short-term RfD is used in place of the calculated subchronic RfD and the water intake rate for a pregnant woman is used. (Intake rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5).

The calculated Subchronic nHBV, before consideration of the Short-term RfD and HBV, resulted in the same water guidance value after rounding to one significant digit. Therefore, the subchronic duration additivity endpoint of Renal (kidney) system is added to Developmental. **Additivity endpoints: Developmental, Renal (kidney) system**

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 2000 µg/L

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

$$= \frac{\text{(0.33 mg/kg-d)}^{**} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.038 L/kg-d)}^{**}}$$

= 1,736 rounded to **2,000 µg/L**

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

** The calculated Chronic RfD (0.44 mg/kg-d) is higher than the Short-term RfD (0.33 mg/kg-d), which is based on developmental effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including short-term effects (MDH, 2008). Therefore, the Short-term RfD is used in place of the calculated Chronic RfD and the water intake rate for a pregnant woman is used. (Intake rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5)

The calculated Chronic nHBV, before consideration of the Short-term RfD and HBV, resulted in the same water guidance value after rounding to one significant digit. Therefore, the chronic duration additivity endpoints of Male Reproductive system and Renal (kidney) system are added to Developmental. **Additivity endpoints: Developmental, Male Reproductive system, Renal (kidney) system**

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 1993/1994, MDH promulgated a Health Risk Limit (HRL) of 10,000 µg/L. In 2011, MDH derived acute, short-term, subchronic, and chronic noncancer Health Based Values (HBV) of 4,000 µg/L, 4,000 µg/L, 2,000 µg/L, and 2,000 µg/L, respectively. These HBVs were adopted as HRLs in 2011. In 2017, MDH re-evaluated the noncancer HRLs, resulting in the removal of the acute guidance, and the derivation of new noncancer short-term, subchronic, and chronic HBVs of 2,000 µg/L. The revisions were a result of 1) using MDH's most recent risk assessment methodology including the application of Human Equivalent Doses (HED) and updated intake rates; and 2) rounding to one significant digit. In 2020, MDH incorporated updated intake rates (USEPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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?	-[1]	-[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Studies assessing endocrine function have not been conducted, however, secondary observations from histological examinations of endocrine organs in existing studies of ethylene glycol showed no effects in rats or mice.

[2] Repeat-dose studies assessing immunotoxicity and immune function have not been conducted. However, one study reported decreased leukocyte levels in rats at a dose 400 times higher than the short-term RfD.

[3] The short-term RfD is based on skeletal malformations observed in mouse fetuses following *in utero* exposure. Numerous developmental studies have been conducted, and mice have been shown to be

more sensitive than rats or rabbits regarding developmental effects. In addition to skeletal effects in mice, decreased fetal and pup body weights were observed at doses approximately 300 and 600 times higher than the short-term RfD.

[4] Reproductive and multi-generational studies have been conducted. Decreased reproductive success was observed at dose levels more than 600 times higher than the short-term RfD. Decreased sperm counts were observed at doses approximately 400 times higher than the short-term RfD, while sperm motility and morphology were altered at doses over 700 times higher than the short-term RfD.

[5] Following acute ingestion (poisoning incidents) of very high doses approximately 8000 times higher than the short-term RfD, ethylene glycol has a direct toxic effect on the nervous system with effects including ataxia, convulsion, and coma. In animal studies at doses 3000 times higher than the short-term RfD, calcium oxalate crystals have been observed in brain and nervous system tissue.

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

Web Publication Date: August 2020

Toxicological Summary for: Fluorene

CAS: **86-73-7**

Synonyms: 9H-fluorene, 2,2'-methylenebiphenyl, diphenylenemethane, O-biphenylenemethane

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

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

$$= \frac{\text{(0.058 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 156 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.5 / 300 = 0.058 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	125 mg/kg-d (administered dose NOAEL, US EPA, 1989)
Dose Adjustment Factor (DAF):	0.14 from body weight scaling, study specific (US EPA, 2011 and MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 125 mg/kg-d x 0.14 = 17.5 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 to account for the absence of adequate developmental, reproductive, and neurotoxicity studies in the database.
Critical effect(s):	Decreased red blood cells in female mice, decreased packed cell volume in female and male mice, and increased relative spleen weight in male and female mice
Co-critical effect(s):	None identified
Additivity endpoint(s):	Hematological (blood) system, Spleen

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 80 µg/L

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

$$= \frac{\text{(0.018 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

$$= \mathbf{80\ \mu g/L}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.5/1000 = 0.018 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	125 mg/kg-d (administered dose NOAEL, US EPA, 1989 subchronic exposure)
Dose Adjustment Factor (DAF):	0.14 from body weight scaling, study specific (US EPA, 2011 and MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 125 mg/kg-d x 0.14 = 17.5 mg/kg-d (study specific body weight scaling basis)
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 to account for the absence of adequate developmental, reproductive, and neurotoxicity studies in the database.
Critical effect(s):	Decreased red blood cells in female mice, decreased packed cell volume in female and male mice, and increased relative spleen weight in male and female mice
Co-critical effect(s):	None identified
Additivity endpoint(s):	Hematological (blood) system, Spleen

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: Yes (moderate)

Summary of Guidance Value History:
A non-cancer chronic HRL of 300 µg/L was promulgated in 1993. The 2019 chronic and subchronic nHBVs are lower than the previous HRL as a result of using MDH's most recent risk assessment

methodology. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	No	No	Yes
Effects observed?	-	No[1]	-	-	No[2]

Comments on extent of testing or effects:

[1] Very little information relating to immunotoxicity is available. One limited acute oral gavage study in male mice did not find any reduction in humoral or cell mediated immunity following exposure to fluorene.

[2] Results from a limited neurobehavioral gavage study in adult male rats did not indicate any adverse effects on locomotor activity or learning ability. A slight, but significant, decrease in anxiety-related behavior was observed in rats exposed to fluorene at a dose approximately 13-fold higher than the current chronic reference dose when tested in the elevated plus maze, although there was no dose response and the biological significance of this finding is unknown. In the subchronic/chronic critical study, increased incidence of salivation and hypoactivity were noted in the fluorene-exposed rats, however, there was no statistical analysis performed on these endpoints and they are not clear indicators of neurotoxicity but may point to central nervous system effects. No other neurotoxicity studies were available. A database uncertainty factor of 10 was applied, in part, to account for possibility of neurotoxic effects.

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

Web Publication Date: August 2020

Toxicological Summary for: Fomesafen

CAS: **72178-02-0**

Synonyms: IUPAC 5-[2-chloro-4-(trifluoromethyl)phenoxy]-N-methanelsulfonyl-2-nitrobenzamide; 5-(-2-chloro-α-α-α-trifluoro-4-tolyloxy)-N-methylsulphonyl-2-nitro benzamide; PP021

Acute Noncancer Health-Based Value ($nHBV_{Acute}$) = Not Derived

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

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

$$= \frac{\text{(0.12 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 206 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 3.50/30 = 0.12 mg/kg-d (Alderley Park Wistar rat)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	12.5 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, MRID 00144862, US EPA 1984a)
Dose Adjustment Factor (DAF):	0.28 study-specific, Body weight scaling, default (US EPA 2011c and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 12.5 mg/kg-d x 0.28 = 3.50 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased litter weight gain, decreased pup survival, and reduced number of pups born alive
Co-critical effect(s):	Decreased plasma cholesterol and triglycerides, increased liver weight and hepatocyte hypertrophy; reduced IgM antibody and lymph node enlargement
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Immune system

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

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

$$= \frac{\text{(0.14 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 378 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 14/100 = 0.14 mg/kg-d (beagle)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	25 mg/kg-d (administered dose LOAEL, 26-week toxicity study, MRID 00103014, US EPA 1981a)
Dose Adjustment Factor (DAF):	0.56, Body weight scaling, default (US EPA 2011c and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 25 mg/kg-d x 0.56 = 14 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for using a LOAEL in place of a NOAEL because of wide dose spacing
Critical effect(s):	Blood changes (decreased hemoglobin, hematocrit, red blood cell count accompanied by an increased number of platelets); Decreased plasma cholesterol and triglycerides
Co-critical effect(s):	Reduced litter weight gain and pup survival, and a reduction in the number of pups born alive; Reduced plasma triglycerides and cholesterol, increased liver weight, hepatocyte hypertrophy, liver inflammation, and liver necrosis; Decreased IgM antibody and increased lymph node enlargement
Additivity endpoint(s):	Developmental, Hematological (blood) system, Hepatic (liver) system, Immune 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 200 µg/L. Additivity endpoints: Developmental, Hepatic (liver) system, Immune system

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

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

$$= \frac{(0.005 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 22.2 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.15/30 = 0.005 mg/kg-d (CD-1 mouse)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	0.96 mg/kg-d (administered dose NOAEL, 2-year toxicity study, MRID 00131491, US EPA 1983);
Dose Adjustment Factor (DAF):	0.16 study-specific, Body weight scaling, default (US EPA 2011c and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.96 mg/kg-d x 0.16 = 0.15 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 liver weight, enlarged and discolored liver; the presence of pigmented macrophages and/or Kupffer cells in the liver (inflammation), liver masses, increased serum alkaline phosphatase activity, and increased glutamic pyruvic transaminase activity
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	Not likely to be carcinogenic to humans (US EPA 2018)
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 2018, MDH derived a Pesticide Rapid Assessment value of 3 µg/L, which used an infant water intake rate with a chronic RfD and an RSC of 0.5 (MDH Pesticide Rapid Assessment Results Table, updated 2020). The 2020 nHBV is based on MDH's duration-specific methodology, which matches the RfD and intake rate, resulting in a higher value of 20 µg/L. In 2020, MDH also incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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]	Yes[5]

Comments on extent of testing or effects:

[1] Although, there are no *in vivo* toxicity studies that tested specifically for endocrine changes after fomesafen treatment, the EPA's Endocrine Disruptor Screening Program tested fomesafen for endocrine activity *in vitro*. Fomesafen was found to have activity in a small fraction of *in vitro* tests (EPA Chemical Dashboard).

[2] The short duration co-critical effects of reduced antibody response and lymph node enlargement are based on an immunotoxicity assay in mice.

[3] The short-term duration critical study is based on developmental effects in rat pups whose mothers were exposed to fomesafen. The reference dose is based on decreased litter weight gain, decreased pup survival, and a reduction in the number of pups born alive. In another developmental study in rats, post-implantation loss and decreased litter weight occurred at a dose approximately 400 times higher than the short-term reference dose.

[4] A reduction in the number of rat pups born alive was a critical effect for the short-term duration study, and is also listed as a developmental effect. Additionally, in a separate experiment, increased post-implantation loss occurred in pregnant rats at a dose approximately 400 times higher than the short-term reference dose. Small uteri was observed in female mice at a dose 300 times higher than the short-term reference dose, and pale uteri occurred at a dose 1,000 times higher than the short-term reference dose.

[5] Neurotoxicity was evaluated in an acute toxicity study in rats. Motor activity was briefly reduced beginning at a dose 500 times higher than the short-term duration reference dose. However, a 13-week neurotoxicity study in rats found no neurotoxic effects at levels 400 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

Web Publication Date: February 2022

Toxicological Summary for: n-Hexane

CAS: **110-54-3**
Synonyms: hexane

Acute Non-Cancer Risk Assessment Advice (RAA_{Acute}) = Not Derived (Insufficient Data)

Short-term Non-Cancer Risk Assessment Advice ($RAA_{Short\text{-}term}$) = 100 µg/L

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

$$= \frac{\text{(0.19 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 131 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 188/1000 = 0.19 mg/kg-d (male Wistar rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	785 mg/kg-d (administered dose LOAEL, neurotoxicity study by Ono et al. 1981)
Dose Adjustment Factor (DAF):	0.24, body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 785 mg/kg-d x 0.24 = 188 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for toxicodynamic differences between species; 10 for intraspecies variation; 3 for use of a LOAEL; 10 for database limitations, including the lack of multigenerational and neurodevelopmental studies
Critical effect(s):	Reduced motor nerve conduction velocity
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Subchronic Non-Cancer Risk Assessment Advice ($RAA_{Subchronic}$) = $RAA_{Short-term}$ = 100 µg/L

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

$$= \frac{\text{(0.063 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 170 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 188/3000 = 0.063 mg/kg-d (male Wistar rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	785 mg/kg-d (administered dose LOAEL, neurotoxicity study by Ono et al., 1981)
Dose Adjustment Factor (DAF):	0.24 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 785 mg/kg-d x 0.24 = 188 mg/kg-d
Total uncertainty factor (UF):	3000
Uncertainty factor allocation:	3 for toxicodynamic differences between species; 10 for intraspecies variation; 3 for use of a LOAEL; 3 for extrapolation from a short-term duration study; 10 for database limitations, including lack of multigenerational and neurodevelopmental studies
Critical effect(s):	Reduced motor nerve conduction velocity
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

The Subchronic RAA must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic RAA is set equal to the Short-term RAA of 100 µg/L. Additivity endpoints: Nervous system

Chronic Non-Cancer Risk Assessment Advice ($RAA_{Chronic}$) = 80 µg/L

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

$$= \frac{\text{(0.019 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 84.4 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 188/10000 = 0.019 mg/kg-d (male Wistar rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	785 mg/kg-d (administered dose LOAEL, neurotoxicity study by Ono et al. 1981, short-term exposure)
Dose Adjustment Factor (DAF):	0.24 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 785 mg/kg-d x 0.24 = 188 mg/kg-d
Total uncertainty factor (UF):	10000
Uncertainty factor allocation:	3 for toxicodynamic differences between species; 10 for intraspecies variation; 3 for use of a LOAEL; 10 for the use of a shorter duration study.; 10 for database limitations, including lack of multigenerational and neurodevelopmental studies
Critical effect(s):	Reduced motor nerve conduction velocity
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Cancer Risk Assessment Advice (cRAA) = Not Applicable

Cancer classification:	Not Classified—Inadequate information (EPA, 2005)
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 HRL of 400 µg/L was promulgated in 1994. MDH derived short-term, subchronic and chronic noncancer RAAs in 2021 that are lower than the 1994 HRL as a result of: 1) using MDH's most recent assessment methodology; and 2) incorporation of additional toxicological information.

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]	Yes[3]	Yes[4]

Comments on extent of testing or effects:

1. In one rat study, animals had increased levels of white blood cells, lymphocytes, granulocytes, and eosinophils in the blood and inflammatory cells and macrophages in the lung following oral exposure to levels 380 times higher than the short-term RfD.
2. One developmental mouse study reported decreased fetal body weight at doses more than 5,400 times the short-term reference dose. Absence of multigenerational developmental and neurodevelopmental study data is addressed with the application of a database uncertainty factor.
3. Oral rat studies reported decreased prostate weight and increased seminal vesicle weight at doses more than 13,000 and 26,000 times higher than the short-term reference dose, respectively. No histopathological changes were noted; however, testicular sperm count was decreased following a single exposure to a dose over 26,000 times higher than the short-term reference dose. Additionally, in a subchronic neurotoxicity study in rats, testicular atrophy was observed following exposure to doses more than 3,700 times the short-term reference dose. The absence of a multigenerational reproductive study contributed to the application of a database uncertainty factor.
4. The reference dose for short-term, subchronic, and chronic durations is based on neurotoxicity (i.e., reduced motor nerve conduction velocity). Uncertainty regarding the effects of n-hexane on a developing organism's nervous system are addressed with the addition of a database uncertainty factor.

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

Web Publication Date: September 2020

Toxicological Summary for: Imidacloprid

CAS: **138261-41-3**

Synonyms: N-[1-[(6-chloropyridin-3-yl)methyl]-4,5-dihydroimidazol-2-yl]nitramide; 1-((6-chloro-3-pyridinyl)methyl)-N-nitro-2-imidazolidinimine; [N-(6-chloropyridin-3-ylmethyl)-2-nitroiminoimidazolidine]; *(E)* -1-(6-Chloro-3-pyridinylmethyl)-*N*-nitroimidazolidin-2-ylideneamine; NTN; 2-Imidazolidinimine

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

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

$$= \frac{\text{(0.15 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 103 rounded to **100 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. MDH deviated from the default RSC of 0.5 based on assessments from California EPA (2006) and U.S. EPA (2017) indicating that infant dietary exposures and infant exposures from residential pesticide treatments, including pet treatments, are high enough to warrant allocation of only 20% of the RfD to drinking water.

**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 4.4/30 = 0.15 mg/kg-d (Beagle dogs)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	8 mg/kg-d (administered dose NOAEL, Ruf 1990 cited in California EPA 2006)
Dose Adjustment Factor (DAF):	0.55, Body weight scaling based on dog body weights at start of study (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 8 mg/kg-d x 0.55 = 4.4 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Tremors
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 2 µg/L

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

$$= \frac{\text{(0.0036 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 2.48 rounded to **2 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. MDH deviated from the default RSC of 0.5 based on assessments from California EPA (2006) and U.S. EPA (2017) indicating that infant dietary exposures and infant exposures from residential pesticide treatments, including pet treatments, are high enough to warrant allocation of only 20% of the RfD to drinking water.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.107/30 = 0.0036 mg/kg-d (BALB/c mice)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	0.820 mg/kg-d (administered dose $BMDL_{1SD}$, Badgujar 2013)
Dose Adjustment Factor (DAF):	0.13, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 0.820 mg/kg-d x 0.13 = 0.107 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 delayed-type hypersensitivity response
Co-critical effect(s):	None
Additivity endpoint(s):	Immune system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 2 µg/L

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

$$= \frac{\text{(0.0036 mg/kg-d)}^{***} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 9.72 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

***The calculated Subchronic RfD (0.073 mg/kg-d) is higher than the Short-term RfD (0.0036 mg/kg-d), which is based on immune 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.

The Subchronic nHBV must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 2 µg/L. Additivity endpoints: Immune system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 2 µg/L

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

$$= \frac{\text{(0.0036 mg/kg-d)}^{***} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 16 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

***The calculated Chronic RfD (0.019 mg/kg-d) is higher than the Short-term RfD (0.0036 mg/kg-d), which is based on immune effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including subchronic and short-term effects (MDH 2008, page 34). Therefore, the Short-term RfD is used in place of the calculated Chronic RfD.

The Chronic HBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic HBV is set equal to the Short-term HBV of 2 µg/L. Additivity endpoints: Immune system

Cancer Health Based Value (cHBV) = "Not Applicable"

Cancer classification:	Evidence of non-carcinogenicity for humans (U.S. EPA 2017a)
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 2014, MDH derived a pesticide rapid assessment value for imidacloprid (90 µg/L) based on a US EPA risk assessment from 2010 (US EPA 2010) and the thyroid as a critical health endpoint. The 2019 HBVs for short-term, subchronic, and chronic durations (this assessment) are lower than the pesticide rapid assessment due to the incorporation of a toxicologically more sensitive health endpoint that occurred in a shorter-duration study than the chronic thyroid effects. The 2019 MDH risk assessment methodology includes BMD modeling for the delayed-type hypersensitivity response in mice. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a change in the short-term duration water guidance value from 3 µg/L to 2 µg/L. As in the 2019 MDH risk assessment, the subchronic and chronic guidance values were set to equal the short-term guidance value (2 µg/L).

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] At an imidacloprid exposure 1,000 times higher than the short-term RfD, reduced ovarian weight was associated with increased ovarian lipid peroxidation, decreased ovarian antioxidant activity, and changes in ovarian hormones and ovarian morphology in the female rat 90-days after exposure. At a dose 2,500 times higher than the short-term RfD, male rats had increased adrenal weight, increased adrenal cholesterol, and increased hypothalamic and pituitary acetylcholinesterase activity. Changes in male hormones were observed in two lower quality, single dose studies in both rat pups and adults at doses 25 – 70 times higher than the short-term RfD. Thyroid lesions were observed in male rats after 2 years of exposure at doses 300 times higher than the short-term RfD. Thyroid changes occurred in female beagles at doses 4,000 times higher than the short-term RfD.

[2] The short-term RfD is based on immunotoxicity (decreased delayed-type hypersensitivity response) in female mice in a 28-day immunotoxicity study. In the same study, a five-fold higher dose resulted in reduced T-cell stimulation and a reduction in the number of lymphocytes. In a longer-duration study, the spleen weight in mice was reduced at a dose 17,000 times higher than the short-term RfD. Immunotoxicity was also observed in other study animals. Rat pups had a reduced hemagglutination titer and phagocytic index at a dose 150 times higher, and had a delayed-type hypersensitivity response at imidacloprid levels 400 times higher than the short-term RfD. At levels 1,000 times higher than the short-term RfD, rat pups had a decreased number of white blood cells. Beagles after a one-month exposure, had atrophy of the bone marrow, involution of the thymus, and a drop in serum α-1 globulin M at a dose 7,000 times higher than the short-term RfD.

[3] Skeletal abnormalities were observed in both rat and rabbit fetuses at doses 6,000 and 9,000 times higher than the short-term RfD, respectively. Reduced body weight in rat pups occurred at doses 2,000 to 6,000 times higher than the short-term RfD. Some of these pups also had morphometric changes in the brain, learning delays, or changes in motor activity. A lower quality, single dose study using a commercial formulation in mice reported changes in neuronal branching and neuronal density in the brain at doses 25 times higher than the short-term RfD.

[4] Maternal death, abortion, total resorption, and post-implantation loss were only observed in rabbits; and at imidacloprid doses 10,000 times higher than the short-term RfD. Despite no apparent change in reproductive outcomes, female rats had reduced ovarian weight along with changes in ovarian

morphology, and increased lipid peroxidation and decreased anti-oxidant activity in the ovaries at doses 1,000 times higher than the short-term RfD. Male rats, at doses 70 to 500 times higher than the short-term RfD, had reduced seminal vesicle and testicular weight, testicular atrophy, reduced sperm concentration, reduced sperm mobility and viability, increased sperm abnormalities, and changes in male reproductive hormones. Conversely, increased testicular weight was noted in rats after one-year of exposure at imidacloprid levels 8,000 times higher than the short-term RfD, and increased ovarian weight was noted after two-years exposure at levels 10,000 times higher than the short-term RfD. Testicular degeneration was observed in the beagle at imidacloprid doses 7,500 times higher than the short-term RfD.

[5] The acute duration RfD is based on tremors in beagles after imidacloprid exposure. This occurred at imidacloprid concentrations 3,500 times higher than the short-term RfD. In the rat, tremors (at 1,000 times higher than the short-term RfD), occurred in addition to uncoordinated gait, reduced motor and locomotor activity, reduced hindlimb grip strength, and the absence of response to human touch or a tail pinch at levels 5,000 to 10,000 times higher than the short-term RfD. Rat fetuses, at maternal doses 3,000 times higher than the short-term RfD, had changes in brain thickness. Rat pups had a delay in learning and a decrease in memory consolidation at imidacloprid levels 2,000 times higher than the short-term RfD, and adults were affected at levels 100 to 500 times higher than the short-term RfD in the same study. Chemical changes in the brain were measured in female rat at levels 60 times higher than the short-term RfD. Tremors in mice occurred at levels 4,000 times higher than the short-term RfD. A lower quality, single dose study using a commercial formulation found that male mice had changes in brain thickness at levels 25 times higher than the short-term RfD.

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

Web Publication Date: August 2020

Toxicological Summary for: Manganese

CAS: **7439-96-5**

MDH has updated manganese guidance to a Health Based Value (HBV), and is removing the tiered Risk Assessment Advice. The Short-term Health-Based Value for Manganese is 100 ug/L. This value is protective of bottle-fed infants less than one year of age, the most sensitive population, as well as other populations.

MDH continues to support the U.S. Environmental Protection Agency (EPA) Lifetime Health Advisory (HA) of 300 µg/L for children older than one year of age and adults See Drinking Water Health Advisory for Manganese (PDF) (https://www.epa.gov/sites/production/files/2014-09/documents/support_cc1_magnese_dwreport_0.pdf)

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

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

$$= \frac{\text{(0.083 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 143 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 25/300 = 0.083 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2012
Point of Departure (POD):	25 mg/kg-d (LOAEL, Kern 2010)
Dose Adjustment Factor (DAF):	Not applicable (Insufficient data to support use of DAFs for neonatal period) (MDH, 2017) (U.S. EPA, 2011)
Human Equivalent Dose (HED):	Not applicable
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	10 for interspecies differences, 10 for intraspecies variability, and 3 for LOAEL-to-NOAEL extrapolation (due to mild effects seen at LOAEL)
Critical effect(s):	Neurological effects including increased distance traveled in open arena, decreased number of animals meeting

	learning criteria, increased learning errors, shift in goal-oriented behavior, altered dopamine receptor levels
Co-critical effect(s):	Neurological effects including increased startle response
Additivity endpoint(s):	Developmental, Nervous System

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = Not Derived (Insufficient Information)*

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = Not Derived (Insufficient Information)*

*MDH recommends the US Environmental Protection Agency's (EPA) health advisory value of 300 µg/L for older children and adults experiencing subchronic or chronic duration exposures. The EPA health advisory value is based on a high end dietary intake level at which no health effects were observed. For additional information see: https://www.health.state.mn.us/communities/environment/water/docs/contaminants/mangnsefctsht.pdf.

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	Group D – Not classifiable as to human carcinogenicity (U.S. EPA, 2011)
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:

A non-cancer Health Risk Limit (HRL) of 100 µg/L was promulgated in 1993. New guidance of 1,000 µg/L based on an updated U.S. EPA assessment was developed in 1997. A Health Based Value (HBV) of 300 µg/L based on U.S. EPA's Lifetime Health Advisory value of 300 µg/L was developed in 2008. In 2011, based on new information and risk assessment methodology, MDH reverted to recommending the 1993 HRL value of 100 µg/L for infants until guidance could be re-evaluated. In 2012, MDH again reviewed manganese and established Risk Assessment Advice (RAA) of 100 µg/L that used tiered guidance based on age instead of MDH's typical duration-specific guidance. In 2017, MDH re-evaluated the available information and updated the risk assessment methodology, which resulted in no change to the existing RAAs. In 2018, the tiered guidance methodology was removed and the guidance value was converted from RAA of 100/300 µg/L to an HBV of 100 µg/L for the short-term duration. The toxicological information available supports guidance at the level of HBV. MDH also continues to support the U.S. EPA HA of 300 µg/L for adult, infants older than one year of age, and children. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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?	No	No	Yes[1]	Yes[2]	Yes[3]

Comments on extent of testing or effects:

Note: Effects reported in dietary animal studies have limited relevance to humans because humans are known to have tightly regulated controls that limit absorption and excretion of manganese from the diet.

[1] There was some evidence of delayed fetal skeletal and organ development in offspring born to pregnant rats exposed to manganese by gavage at a dose of 33 mg/kg-day, which is similar to the critical short-term LOAEL of 25 mg/kg-day. However, these effects were not present in the same offspring when they were observed at 100 days old, so these effects may be transient. Neurodevelopmental effects are a concern following manganese exposure from drinking water during early life. Neurodevelopmental effects were selected as the basis of the short-term RfD in this assessment and are discussed in footnote 3.

[2] Some male and female reproductive effects were reported in subchronic duration rodent studies (and one developmental study) following oral exposures to manganese. The information available about these effects is very limited, which makes it difficult to establish a strong level of confidence in the results. Male reproductive effects (decreased testicular weight and increased testicular degeneration) were reported at doses 2 times to 5 times higher than the short-term critical LOAEL. Most toxicity studies did not report female reproductive toxicity. Post-implantation loss was observed in female rats as a dose slightly above the short-term critical LOAEL but this effect was not reported in other rodent studies.

[3] Neurodevelopmental effects in animals form the basis of the short-term RfD. Subtle neurodevelopmental effects (biochemical, behavioral, and cognitive changes) have been observed in neonatal rats and non-human primates following oral manganese exposure at exposure levels equal to and above the short-term critical LOAEL of 25 mg/kg-day. Manganese is well established as a neurotoxin following inhalation by humans in occupational settings with the central nervous system appearing to be the primary target for manganese toxicity.

Several epidemiology studies have suggested there could be subtle IQ and memory effects in children exposed to manganese in drinking water at concentrations >200 µg/L. Manganese has also been associated with neurological effects in adults exposed to manganese in drinking water for over 10 years at concentrations of 1,800 to 2,300 µg/L.

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

Web Publication Date: August 2020

Toxicological Summary for: Metolachlor and s-Metolachlor

CAS: **51218-45-2 and 87392-12-9**

Synonyms: Metolachlor: **2-Chloro-N-(2-ethyl-6-methylphenyl)-N-(1-methoxypropan-2-yl)acetamide)**
s-Metolachlor: **2-Chloro-N-(2-ethyl-6-methylphenyl)-N-[(2S)-1-methoxypropan-2-yl]acetamide**

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 300 µg/L

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

$$= \frac{\text{(0.19 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 327 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.72/30 = 0.19 mg/kg-d (laboratory rat)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	26 mg/kg-d (NOAEL, MRID 00080897 (Smith, 1981 (Ciba-Geigy)) aci (EPA, 1995))
Dose Adjustment Factor (DAF):	0.22 (Body weight scaling, default) (EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 26 mg/kg-d x 0.22 = 5.72 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased body weight in pups
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 300 µg/L

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

$$= \frac{\text{(0.19 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 513 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5

Reference Dose/Concentration:	HED/Total UF = 5.72/30= 0.19 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	9.7 mg/kg-d (NOAEL, MRID 409807 (Hazelette, 1989) aci (USEPA, 1995))
Dose Adjustment Factor (DAF):	0.59 (Body weight scaling, default) (EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 9.7 mg/kg-d x 0.59 = 5.72 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased body weight gain in adults
Co-critical effect(s):	Decreased body weight in pups
Additivity endpoint(s):	Developmental

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 300 µg/L. Additivity endpoints: Developmental

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

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

$$= \frac{\text{(0.19 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 844 rounded to 800 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5

Reference Dose/Concentration:	HED/Total UF = 5.72/30 = 0.19 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2017
Point of Departure (POD):	9.7 mg/kg-d (NOAEL, MRID 409807 (Hazelette, 1989) aci (EPA, 1995)) (subchronic exposure)
Dose Adjustment Factor (DAF):	0.59 (Body weight scaling, default) (EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 9.7 mg/kg-d x 0.59 = 5.72 mg/kg-d
Total uncertainty factor (UF):	30

Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability (subchronic-to-chronic uncertainty factor not selected as toxicity did not increase with longer durations of related studies)
Critical effect(s):	Decreased body weight gain in adults
Co-critical effect(s):	Decreased body weight in pups
Additivity endpoint(s):	Developmental

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 300 µg/L. Additivity endpoints: Developmental

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Group C (possible human carcinogen) (EPA, 2006)
Slope factor (SF):	Non-linear approach recommended by US EPA 0.0092 $(mg/kg\text{-}d)^{-1}$ (EPA, 1995) (EPA, 2002) (EPA, 2006)
Source of cancer slope factor (SF):	US EPA, 2006
Tumor site(s):	liver tumors in rats

Statement for non-linear carcinogens:
At this time, MDH's non-cancer health-based guidance values are considered to be protective for possible cancer risks associated with metolachlor in drinking water. Neither the International Agency for Research on Cancer (IARC) nor the National Toxicology Program (NTP) have classified metolachlor as a carcinogen. Metolachlor has been identified as a nonlinear carcinogen by the US Environmental Protection Agency (EPA). Three long-term animal studies have been conducted with metolachlor, and tumors were reported in only one of these studies at the highest dose level tested (over 200 times higher than the MDH Chronic RfD). Additionally, as part of the 2008 HRL revision, the MDH Group C review committee evaluated the weight of evidence regarding the carcinogenicity and determined that no Group C uncertainty factor was needed and agreed that the data do not support derivation of a cancer specific value. (MDH, 2008)

Volatile: No

Summary of Guidance Value History:
A noncancer chronic Health Risk Limit (HRL) of 100 µg/L was promulgated in 1993. Acute, Short-term, Subchronic, and Chronic Health-Based Values (HBV) of 400, 400, 300, and 300 µg/L were derived in 2009 and promulgated as HRLs in 2011. In 2017, MDH re-evaluated the non-cancer HRLs, resulting in the removal of the acute HRL, an updated short-term HBV of 300 µg/L, and updated subchronic and chronic HBVs set to the short-term HBV of 300 µg/L. The short-term, subchronic, and chronic values were updated and the acute guidance removed as a result of 1) using MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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] Serum levels of testosterone, estradiol, and other hormones were altered in rats after pubertal exposure (PND 23-53) at levels 60 times higher than the short-term RfD. Increased relative thyroid weights were observed in F1 males in a multigenerational study in rats. A related compound, Acetochlor, caused thyroid effects in laboratory studies.

[2] The short-term reference dose is based on developmental effects (decreased body weight in pups) observed in the critical study.

[3] Decreased implantations, increased resorptions, decreased litter size, and increased post-implantation loss has been observed at doses ~1,000 higher than the short-term reference dose.

[4] Neurotoxicity of metolachlor has not be studied. However, a related compound, acetochlor, causes neurological effects.

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

Web Publication Date: August 2020

Toxicological Summary for: Metolachlor ESA

CAS: **171118-09-5**

Synonyms: Ethanesulfonate degradate of metolachlor; Metolachlor ethane sulfonic acid

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

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

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 7,000 µg/L

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

$$= \frac{\text{(2.7 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 7,297 rounded to **7,000 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 265/100 = 2.7 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, MRID 44931709 Data Evaluation Report, US EPA 2000)
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 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 (lack of two-generation study)
Critical effect(s):	Increased liver weight and increased serum liver enzymes
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 1,000 µg/L

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

$$= \frac{\text{(0.27 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 1,200 rounded to **1,000 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 265/1000 = 0.27 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, MRID 44931709 Data Evaluation Report, US EPA 2000, subchronic exposure)
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for subchronic-to-chronic extrapolation, and 3 for database uncertainty (lack of two-generation study)
Critical effect(s):	Increased liver weight and increased serum liver enzymes
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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

A noncancer Health Based Value (HBV) of 1,000 µg/L was derived in 2004. Updated noncancer subchronic and chronic Health Risk Limits (HRL) of 4,000 and 800 µg/L, respectively, were promulgated in 2011. In 2018, MDH re-evaluated the noncancer HRLs, resulting in updated values for the subchronic and chronic durations of 8,000 and 1,000 µg/L, respectively. The noncancer HBVs are higher as a result of 1) using MDH's most recent risk assessment methodology, and 2) rounding to one significant digit. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a decrease in the subchronic duration water guidance value from 8,000 µg/L to 7,000 µg/L. The chronic water guidance value did not change.

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	No	No
Effects observed?	-	-	No[1]	-	-

Comments on extent of testing or effects:

[1] The single available developmental study reported no treatment related effects to pregnant animals or fetuses at the highest dose tested, a dose 80 times higher than the subchronic RfD. However, the database for the parent compound demonstrated that developmental toxicity observed in the two-generation reproductive study occurred at lower doses than the standard developmental study. As no two-generation reproductive study has been conducted for metolachlor ESA, a database uncertainty factor was incorporated into the RfD derivation to address this data gap.

Resources Consulted During Review:

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

Web Publication Date: August 2020

Toxicological Summary for: Metolachlor OXA

CAS: **152019-73-3**

Synonyms: Oxanilic acid degradates of metolachlor, metolachlor OA, Metolachlor oxanilic acid

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 5,000 µg/L

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

$$= \frac{\text{(2.7 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 4,655 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 265/100 = 2.7 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, Syngenta, 2004)
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 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 (lack of two generation study)
Critical effect(s):	Changes in blood chemistry parameters without identified specific target organs
Co-critical effect(s):	None
Additivity endpoint(s):	None

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 5,000 µg/L

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

$$= \frac{\text{(2.7 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 7,297 rounded to 7,000 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 265/100 = 2.7 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, Syngenta, 2004)
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 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 (lack of a two-generation study)
Critical effect(s):	Changes in blood chemistry parameters without identified specific target organs
Co-critical effect(s):	None
Additivity endpoint(s):	None

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 5,000 µg/L. Additivity endpoints: None

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 1,000 µg/L

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

$$= \frac{\text{(0.27 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 1,200 rounded to **1,000 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5

Reference Dose/Concentration:	HED/Total UF = 265/1000 = 0.27 mg/kg-d (beagle dog)
Source of toxicity value:	Determined by MDH in 2009
Point of Departure (POD):	500 mg/kg-d (NOAEL, Syngenta, 2004 (subchronic exposure))
Dose Adjustment Factor (DAF):	0.53 (Body weight scaling, default) (US EPA, 2011) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.53 = 265 mg/kg-d
Total uncertainty factor (UF):	1000

Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for subchronic-to-chronic extrapolation, and 3 for database uncertainty (lack of two-generation study)
Critical effect(s):	Changes in blood chemistry parameters without identified specific target organs
Co-critical effect(s):	None
Additivity endpoint(s):	None

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:

A noncancer Health Based Value (HBV) of 1,000 µg/L was derived in 2004. Updated noncancer short-term, subchronic and chronic Health Risk Limits (HRL) of 3,000, 3,000, and 800 µg/L, respectively, were promulgated in 2011. In 2018, MDH re-evaluated the noncancer HRLs, resulting in updated values for the short-term, subchronic, and chronic durations of 5,000, 5,000, and 1,000 µg/L, respectively. The noncancer HBVs are higher as a result of 1) using MDH's most recent risk assessment methodology, and 2) rounding to one significant digit. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	No	No
Effects observed?	-	-	No[1]	-	-

Comments on extent of testing or effects:

[1] The single available developmental study reported no treatment related effects to pregnant animals or fetuses at the highest dose tested, a dose 80 times higher than the short-term RfD. However, the database for the parent compound demonstrated that developmental toxicity observed in the two-

generation reproductive/developmental study occurred at lower doses than the standard developmental study. As no two generation reproductive study has been conducted for metolachlor OXA, a database uncertainty factor was incorporated into the RfD derivation to address this data gap.

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

Web Publication Date: September 2020

Toxicological Summary for: *p*-Nonylphenol, branched isomers

CAS: **84852-15-3**

Synonyms: 4-Nonylphenol; Phenol, *p*-nonyl-; 4-*p*-Nonyl phenol; Phenol, 4-nonyl-; *para* Nonyl phenol, branched (mixed isomers)

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

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

$$= \frac{\text{(0.21 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 144 rounded to **100 µg/L**

*The available data indicate that infant exposures, from sources such as breast milk and baby food, are not lower than adult exposures. As infant exposures are equal to or exceed adult exposures based on the available exposure data, a relative source contribution of 0.2 has been selected for all durations

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 6.27/30 = 0.21 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	33 mg/kg-d (administered dose NOAEL; NTP 1997/Chapin 1999)
Dose Adjustment Factor (DAF):	0.19, Body weight scaling, study-specific (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 33 mg/kg-d x 0.19 = 6.27 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Accelerated vaginal opening
Co-critical effect(s):	Decreased pup body weight and increased duration of estrous cycle
Additivity endpoint(s):	Developmental, Female Reproductive system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 40 µg/L

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

$$= \frac{\text{(0.016 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{}$$

(0.074 L/kg-d)**

= 43.2 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.485/30 = 0.016 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	1.94 mg/kg-d (administered dose $BMDL_{10}$, NTP 1997/Chapin 1999)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.94 mg/kg-d x 0.25 = 0.485 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Renal mineralization in male rats
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

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

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

$$= \frac{\text{(0.0049 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 21.7 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.485/100 = 0.0049 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	1.94 mg/kg-d (administered dose $BMDL_{10}$, NTP 1997/Chapin 1999, subchronic exposure)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.94 mg/kg-d x 0.25 = 0.485 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability and 3 for subchronic to chronic extrapolation
Critical effect(s):	Renal mineralization in male rats

Co-critical effect(s): None
Additivity endpoint(s): Renal (kidney) system

Cancer Health-Based Value (cHBV) = Not Applicable

Volatile: Yes (low)

Summary of Guidance Value History:
MDH developed non-cancer Health-Based Values for Short-term, Subchronic and Chronic durations of 100, 40, and 20 ug/L, respectively, for p-nonylphenol in 2015. In 2020, MDH incorporated updated intake rates (US EPA 2019) and performed a re-evaluation of p-Nonylphenol. Use of the updated intake rates and results from the re-evaluation did not result in any changes to the 2015 guidance values. Recent detections of *p*-nonylphenol in Minnesota's groundwater make it eligible for promulgation as a Health Risk Limit.

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]The short-term reference dose (RfD) is based on a developmental and endocrine-mediated effect (accelerated vaginal opening). Endocrine effects have been well studied. Hormone level changes in adult rats have been observed at approximately 60 times higher than the current short-term reference dose. Endocrine-mediated alterations in development and reproduction were not observed, at doses up to 160 times the short-term reference dose, in three multiple generation studies.

[2]Immunotoxicity has been evaluated in two studies. Subtle alterations in immune cell populations were observed at a dose approximately 30 times higher than the current subchronic reference dose. More overt effects on immune system organ weights and immune cellular parameters were not observed until doses reached over 2000 times the current subchronic reference dose.

[3]Development effects have been well studied. The critical effect for the short-term duration is accelerated vaginal opening, a developmental effect. The only other consistent developmental effect seen was decreased pup body weight at weaning occurring at doses over 150 times higher than the current short-term reference dose.

[4]Reproductive effects have been well studied. Altered hormone levels in female rats, identified as a co-critical effect, was observed at 50 times higher than the short-term reference dose. Male reproductive toxicity noted as altered sperm and decreased testes weight was observed at 800 times up to 3500 times the subchronic reference dose.

[5]Both neurotoxicity and developmental neurotoxicity have been studied. Small alterations in maze performance tests on rodents were noted at 800 times the subchronic reference dose. At doses 2000 times the subchronic reference dose, no effects were seen on neurobehavioral endpoints. Certain gender-specific behaviors may be altered by nonylphenol exposure, but not until doses reach over 900 times the subchronic reference dose.

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

Web Publication Date: August 2020

Toxicological Summary for: 4-*tert*-Octylphenol

CAS: **140-66-9**

Synonyms: 4-(1,1,3,3-Tetramethylbutyl)phenol, *p*-(1,1,3,3-Tetramethylbutyl)phenol, *p-tert*-Octylphenol, 4-(2,4,4-trimethylpentan-2-yl)phenol

Acute Non-Cancer Health Based Value (nHBVAcute) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value (nHBVShort-term) = 100 µg/L

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

$$= \frac{\text{(0.17 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.290 L/kg-d)**}}$$

= 117 rounded to **100 µg/L**

*The available data indicate that infant exposures, from sources such as breast milk and baby food, are not lower than adult exposures. As infant exposures are equal to or exceed adult exposures based on the available exposure data, a relative source contribution of 0.2 has been selected for all durations.

** Intake rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.06/30 = 0.17 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	22 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, Tyl *et al.* 1999)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD X DAF = 22 mg/kg-d x 0.23 = 5.06 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight and increased time to preputial separation
Co-critical effect(s):	Decreased adult body weight
Additivity endpoint(s):	Developmental

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

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

$$= \frac{\text{(0.17 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.074 L/kg-d)**}}$$

= 459 rounded to 500 µg/L

** Intake rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.06/30 = 0.17 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	22 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, Tyl *et al.* 1999)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD X DAF = 22 mg/kg-d x 0.23 = 5.06 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Decreased uterine weight
Co-critical effect(s):	Decreased adult body weight
Additivity endpoint(s):	Female 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 100 µg/L. Additivity endpoints: Developmental

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

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

$$= \frac{\text{(0.051 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.045 L/kg-d)**}}$$

= 226 rounded to 200 µg/L

** Intake rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	HED/Total UF = 5.06/100 = 0.051 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	22 mg/kg-d (administered dose NOAEL, 2-generation reproductive study, Tyl *et al.* 1999, subchronic exposure)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (US EPA 2011, MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 22 mg/kg-d x 0.23 = 5.06 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for subchronic to chronic extrapolation
Critical effect(s):	Decreased uterine weight
Co-critical effect(s):	Decreased adult body weight
Additivity endpoint(s):	Female Reproductive system

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 100 µg/L. Additivity endpoints: Developmental

Cancer Health Based Value (cHBV) = **Not Applicable**

Volatile: Yes (low)

Summary of Guidance Value History:
An HBV of 100 µg/L for all durations was developed in 2015. In 2020, MDH re-evaluated 4-tert-octylphenol resulting in no changes to the guidance value, however, the recent detections of 4-tert-octylphenol in Minnesota groundwater made it eligible for rule. Also in 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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	Yes
Effects observed?	Yes[1]	--[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:
[1]Endocrine effects such as increased uterine weights, increased vaginal and uterine thickness, and changes in estrus cyclicity were reported in female rats receiving doses approximately 35-275 times

higher than the short-term RfD. In addition, male animals receiving doses approximately 225 times higher than the short-term RfD had increased prolactin levels.

[2] No oral studies specifically evaluating immunotoxicity have been conducted. Studies examining other endpoints reported reduced thymus and spleen weights at approximately 300 times higher than the short-term RfD, and increased white blood cell/platelet counts around 650-700 times higher than the short-term RfD.

[3]The short-term RfD is based on reduced pup body weights and delayed preputial separation after rats were exposed to 4-*tert*-Octylphenol through their diet. Precocious vaginal patency was observed at doses more than 250 times the short-term RfD.

[4]The subchronic and chronic reference doses are based on reduced uterine weights of rats exposed to 4-*tert*-Octylphenol through their diet. In other studies, doses more than 650 times higher than the short-term RfD resulted in changes in epididymis and prostate weights. In addition, an increase in post-implantation loss and the reduction of number of live fetuses per litter were observed at doses 41-160 times higher than the short-term RfD.

[5]Neurobehavioral effects, including effects on a variety of sexually dimorphic behaviors and water maze performance, were evaluated in a single oral study. The effects occurred at an estimated dose approximately 150 times higher than the short-term RfD.

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

Web Publication Date: March 2022

Toxicological Summary for: Perfluorobutane sulfonate

CAS: **45187-15-3 [anion]**
375-73-5 [free acid]
29420-49-3 [potassium salt]
68259-10-9 [ammonium salt]
60453-92-1 [sodium salt]

Synonyms: PFBS ion; Perfluorobutanesulfonate; 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (IUPAC name); Perfluorobutyl sulfonate

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

Short-term Non-Cancer Health-Based Value ($nHBV_{Short\text{-}term}$) = 0.1 µg/L

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

$$= \frac{\text{(0.000084 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 0.14 rounded to **0.1 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.0084/100 = 0.000084 mg/kg-d (Hsd:Sprague Dawley Rats)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	6.97 mg/kg-d (administered dose $BMDL_{1SD}$, (National Toxicology Program 2019))
Dose Adjustment Factor (DAF):	Chemical- and Study-Specific Toxicokinetic Adjustment $Half\text{-}life_{FemaleRat}/Half\text{-}life_{Human}$ = 1.3 hr/1050 hr = 0.0012, based on MDH analysis of (Huang, Dzierlenga et al. 2019) for female rats and (Xu, Fletcher et al. 2020) for humans.
Human Equivalent Dose (HED):	POD x DAF = 6.97 mg/kg-d x 0.0012 = 0.0084 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 due to a lack of available immunotoxicity and developmental neurotoxicity studies (known sensitive effects of other

	PFAS) as well as lack of a 2-generation study in a more appropriate species
Critical effect(s):	Decreased total T4
Co-critical effect(s):	None
Additivity endpoint(s):	Thyroid (E)

Subchronic Non-Cancer Health-Based Value ($nHBV_{Subchronic}$) = 0.1 µg/L

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

$$= \frac{(0.000084 \text{ mg/kg-d})^{\#} \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 0.23 rounded to 0.2 µg/L

[#]The calculated Subchronic RfD (0.00054 mg/kg-d) is higher than the Short-Term RfD (0.000084 mg/kg-d), which is based on thyroid 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 when deriving subchronic water guidance.

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

The Subchronic nHBV must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 0.1 µg/L. Additivity endpoints: Thyroid (E)

Chronic Non-Cancer Health-Based Value ($nHBV_{Chronic}$) = 0.1 µg/L

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

$$= \frac{(0.000084 \text{ mg/kg-d})^{\#} \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 0.37 rounded to 0.4 µg/L

[#]The calculated Chronic RfD (0.00018 mg/kg-d) is higher than the Short-Term RfD (0.000084 mg/kg-d), which is based on thyroid effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of shorter exposures, including short-term effects (MDH 2008, page 34). Therefore, the Short-Term RfD is used in place of the calculated Chronic RfD when deriving chronic water guidance.

[*]Relative Source Contribution: MDH 2008, Section IV.E.1.
[**]Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

The Chronic nHBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-Term nHBV of 0.1 µg/L. Additivity endpoints: Thyroid (E)

Cancer Health-Based Value (cHBV) = Not Applicable

Chemical Mixtures: Exposure to chemicals in combination may cause adverse effects that would not be predicted based on separate exposures to individual chemicals. When multiple contaminants occur as a mixture in water, the cumulative risk should be assessed (MDH 2008, Section IV.E.3). To download the calculator, see MDH's Water Guidance and Additivity Calculator https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/guidance.xlsx

Volatile: No

Summary of Guidance Value History:
In 2009, Health-Based Values (HBVs) for PFBS were first derived: 9 µg/L for Subchronic durations and 7 µg/L for Chronic durations. These HBVs were adopted as HRLs in 2011.

In 2017, MDH re-evaluated the 2011 guidance and derived new HBVs of 3 µg/L for Short-Term and Subchronic durations and 2 µg/L for Chronic durations based on new toxicokinetic information in mice, a reassessment of toxicokinetic information in rats, and a new developmental toxicity study in mice.

In 2020, MDH updated the intake rates used in the calculation of water guidance values based on the most recent EPA Exposure Factors Handbook. This update did not change the PFBS 2017 guidance values.

In 2022, MDH re-evaluated the 2020 guidance and derived new HBVs of 0.1 µg/L for Short-Term, Subchronic, and Chronic durations. The 2022 values are lower than the previous values as a result of: 1) new toxicokinetic information in humans and rats, and 2) a new toxicity study in rats evaluating sensitive thyroid endpoints.

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	Yes
Effects observed?	Yes[1]	-[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] Male and female rats exposed to PFBS orally had large decreases in various thyroid hormones at a dose 900-fold higher than the Short-Term RfD; the effect on one thyroid hormone (tT4) served as the basis for the Short-Term RfD. A decrease in serum thyroid hormones is an effect consistently observed in other PFAS compounds.

An oral developmental study evaluated female mice exposed in utero to PFBS. Delays in vaginal opening and changes in estrus cycling as well as changes in uterine and ovarian size were reported. Pubertal and adult female offspring exhibited decreases in serum estrogen and progesterone levels with elevation of luteinizing hormone levels. Decreases in serum tT4 and T3 were observed in conjunction with slight increases in TSH in female offspring as well as their mothers. These effects all occurred at doses at least 1400-fold higher than the Short-Term RfD.

[2]An study evaluated the association between 11 PFAS chemicals and immunological markers in children from Taiwan. Associations of several PFAS chemicals, including PFBS, with asthma and asthma related biomarkers were found. Associations for PFBS were fewer and weaker than those for several other PFAS chemicals. Concentrations of individual PFAS were positively correlated, and therefore it is not possible to determine whether associations apply to multiple PFASs or to only a subset of individual PFAS. A more recent study following a cohort of several hundred children in Shanghai, China found an association between PFBS concentration in maternal cord blood with increased frequency of respiratory tract infections and decreased IgG concentration in 5-year-old children, suggesting that pre/perinatal exposures to PFBS impacts future immune function in children.

No PFBS immunotoxicity studies have been conducted in laboratory animals. Immunotoxicity has been identified as a sensitive endpoint for several other PFAS. A database uncertainty factor of 3 was incorporated, in part, to address the need for immunotoxicity testing.

[3] Two oral developmental studies (one in rats and one in mice) and a 2-generation study in rats have been conducted. The developmental effects reported in the mouse study included decreased pup body weight, decreased serum thyroid hormones, delayed eye opening, delayed vaginal opening and first estrus as well as smaller ovarian and uterine size in adult offspring. These effects were observed at doses 1400-fold higher than the Short-Term RfD. The developmental study in rats reported decreased fetal body weight at doses >14000-fold higher than the Short-term RfD. In the 2-generation study in rats, no developmental effects were identified at the highest dose tested (14000-fold higher than the Short-Term RfD). However, female rats excrete PFBS much more quickly than humans, which may limit the applicability of this 2-generation study. A database uncertainty factor of 3 was incorporated, in part, to address the lack of a 2-generation study in a more appropriate species.

[4]Researchers examined the association between PFAS chemicals and endometriosis-related infertility among Chinese reproductive-age women in a case-control study. Women with endometriosis-related infertility had significantly higher median levels of PFBS compared with those without the disease. PFBS was the only PFAS identified with a significant positive association, while several other PFAS chemicals exhibited an inverse association. Limitations of this study include no identification of the time course,

disease survey reported levels may not reflect actual exposure, and no physical exam data was measured for controls.

An oral 2-generation study in rats has been conducted. No treatment related effects on female reproductive parameters were noted. Decreased number of spermatids per gram testes (P0) and increased incidence of abnormal sperm (F1) were noted at HED dose levels 37000-fold higher than the Short-term RfD.

[5]Neurological alterations were reported in the 28-day but not the 90-day oral study in adult rats. The results of the study are difficult to interpret. The longer study did not report any treatment related effects. The effects in the 28-day study occurred at HED dose levels 1400-fold higher than the Short-term RfD.

A database UF was incorporated, in part, to address the need for additional neurological testing, particularly in developmental life stages.

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

Web Publication Date: August 2020

Toxicological Summary for: Perfluorohexane sulfonate

CAS: 108427-53-8 (anion)
355-46-4 (acid)
3871-99-6 (potassium salt)

Synonyms: PFHxS; perfluorohexanesulfonic acid; 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane-1-sulfonate

Short-term, Subchronic and Chronic* Non-Cancer Health Based Value (nHBV) = 0.047 µg/L**

*Due to the highly bioaccumulative nature of PFHxS within the human body, serum concentrations are the most appropriate dose metric and the standard equation to derive the HBV is not appropriate. Short-term exposures have the potential to stay in the body for an extended period of time. In addition, accumulated maternal PFHxS is transferred to offspring (i.e., placental and breastmilk transfer). A single HBV has therefore been recommended for short-term, subchronic, and chronic durations. The HBV was derived using a toxicokinetic (TK) model previously developed by MDH (Goeden 2019). Model details and results are presented below.

**Relative Source Contribution (RSC): Using the most recent published biomonitoring results (CDC, accessed February 2019) and USEPA's Exposure Decision Tree (USEPA 2000) as outlined in MDH 2008, Section IV.E.1., an RSC of 0.5 (50%) was selected for the peak serum concentration during infancy. The RSC of 0.5 during infancy resulted in chronic (steady-state) serum concentrations at approximately 0.2 of the 'reference' serum concentration.

Intake Rate: In keeping with MDH's peer-reviewed and promulgated methodology, 95th percentile water intake rates (Table 3-1, 3-3 and 3-5, USEPA 2019) 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 PFHxS breastmilk transfer factor of 1.4%. 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. [Note: "exclusively breast-fed" intake rates refers to infants whose sole source of milk comes from human breastmilk, with no other milk substitutes (USEPA 2011, page 15-2).]

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 PFHxS showed that serum concentrations are 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 = 0.00292/300 = 0.0000097 mg/kg-d (or 9.7 ng/kg-d) (adult Sprague Dawley rats). [The corresponding serum concentration is 32.4/300 = 0.108 µg/mL. Note: this serum concentration is inappropriate to use for individual or clinical assessment.***]
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	32.4 µg/mL (or mg/L) serum concentration (male rats - NTP 2018, MDH modeled $BMDL_{20\%}$)

Dose Adjustment Factor (DAF):	Toxicokinetic Adjustment based on Chemical-Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half-life, days) = 0.25 L/kg x (0.693/1935 days) = 0.000090 L/kg-day. (Half-life from Li et al 2018)
Human Equivalent Dose (HED):	POD x DAF = 32.4 mg/L x 0.000090 L/kg-d = 0.00292 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 to address concerns regarding early life sensitivity to decreased thyroxine (T4) levels as well as lack of 2 generation or immunotoxicity studies.
Critical effect(s):	decreased free T4
Co-critical effect(s):	decreased free and total T4, triiodothyronine (T3), and changes in cholesterol levels and increased hepatic focal necrosis
Additivity endpoint(s):	Hepatic (Liver) System and Thyroid (E)

***The serum concentration is useful for informing public health policy and interpreting population-based exposure potential. 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 (Goeden 2019):

PFHxS is well absorbed and is not metabolized. Serum concentrations can be calculated from the dose and clearance rate using the following equation.

$$Serum\ Concentration\ \left(\frac{mg}{L}\right) = \frac{Dose\left(\frac{mg}{kg \cdot day}\right)}{Clearance\ Rate\left(\frac{L}{kg \cdot day}\right)}$$

Where:

Dose (mg/kg-day) = Water or Breastmilk Intake (L/kg-day) x Water or Breastmilk Concentration (mg/L)
and
Clearance (L/kg-day) = Volume of distribution (L/kg) x (Ln 2/human half-life, days)

Two exposure scenarios were evaluated: 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. In both scenarios the simulated individuals began life with a pre-existing body burden through placental transfer of PFHxS (maternal serum concentration x 70%) based on median 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 and was calculated by using the equation above with a time-weighted 95th percentile intake from birth to 30 years of age (0.048 L/kg-d). During lactation a 95th percentile water intake rate

of 47 mL/kg-d and a body weight of 65.1 kg ((USEPA 2019), Table 3-3) was used to calculate daily maternal serum concentrations.

Consistent with MDH methodology, 95th percentile water intake and upper percentile breastmilk intake rates were used to simulate a reasonable maximum exposed individual. A PFHxS breastmilk transfer factor of 1.4%, 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, dropping to 41% at twelve months. MDH chose to use the breastmilk intake rates for exclusively breastfed infants, as reported in USEPA 2011, for 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 Reasonable Maximum Exposure (RME) Scenario Model Parameters

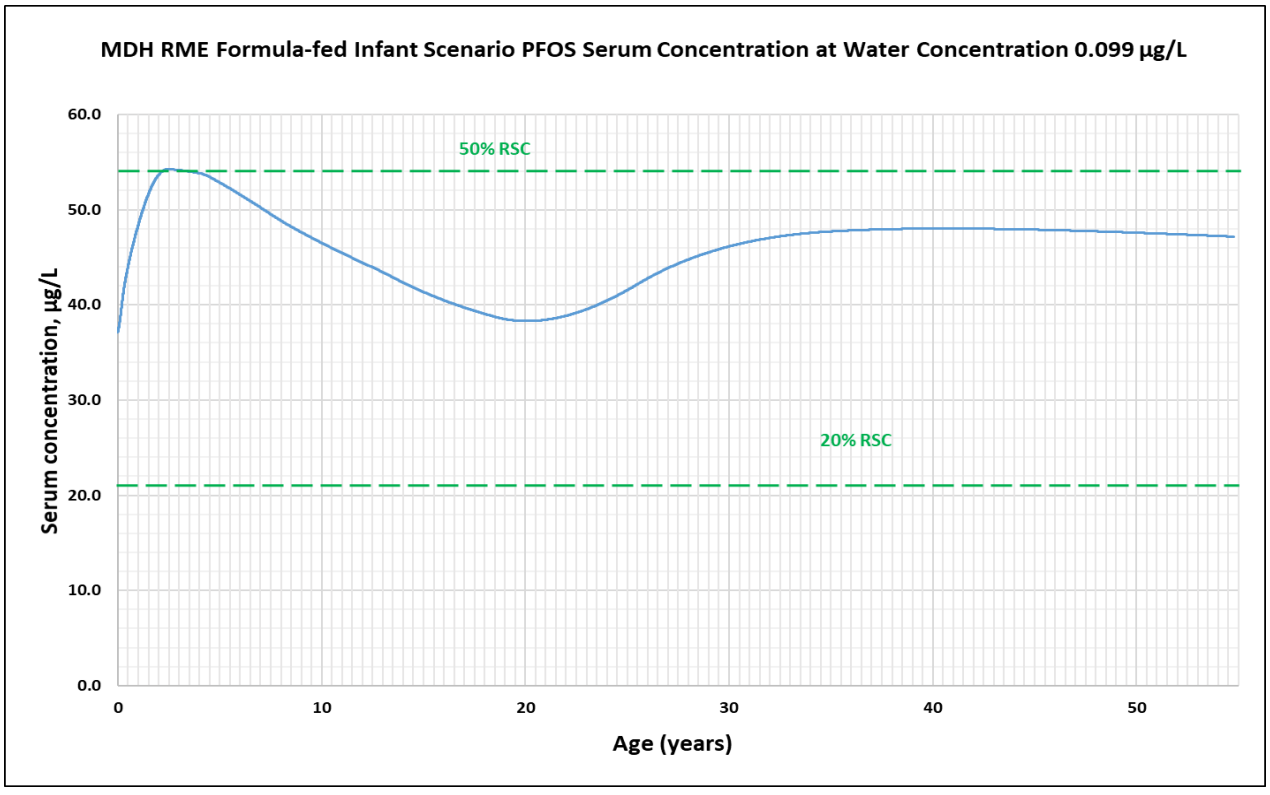
Model Parameter	Value Used
Volume of distribution (Vd)	0.25 L/kg (average of male (0.287) and female (0.213) nonhuman primate Vd, Sundstrom, 2012)
Vd Age Adjustment Factor	2.1 age 1-30 days decreasing to 1.2 age 5-10 years and 1.0 after age 10 years (Friis-Hansen 1961)
Half-life	1935 days (mean value for all ages, Li et al 2018) (5th to 95th percentile range: 1095 – 3358 days)
Elimination rate constant (k)	Calculated from Ln 2/half-life
Placental transfer factor *(% of maternal serum level)*	70% (mean of median paired maternal:cord blood ratios reported in the literature. Range of mean values 43 – 95%.) (Mean 95th percentile value 110%, range 69 – 168%.)
Breastmilk transfer factor *(% of maternal serum level)*	1.4% (mean of mean paired maternal serum:breastmilk ratios reported in the literature. Range of mean values 0.8 – 2%.) (No 95th percentile values reported in literature.)
Water Intake Rate (L/kg-d)	95th percentile consumers only (default values, MDH 2008) (Table 3-1 (for ages $\geq$ 2 yrs), 3-3 (for lactating women), and 3-5 (for ages < 2yr)) (USEPA 2019)
Breastmilk Intake Rate (L-kg-d)	Upper percentile exclusively breast-fed infants (Table 15-1, USEPA 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 USEPA 2000 to derive appropriate RSCs. Determination of an appropriate RSC must recognize the long elimination half-life of PFHxS, 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.

Human biomonitoring data provide a quantitative description of the ongoing widespread exposure, but the serum data are not informative as to the specific pathways and exposure routes. The most recently reported 95th percentile serum concentrations from CDC (February 2019) range from 1.62 µg/L serum for young children to nearly 5 µg/L serum for older children and adults. This suggests that 'background' exposures, when compared to the 'reference' serum concentration (108 µg/L serum) would not represent significant sources of exposure. Using the most recent published biomonitoring results and USEPA's Exposure Decision Tree (USEPA 2000) as outlined in MDH 2008, an RSC of 0.5 (50%) was selected.

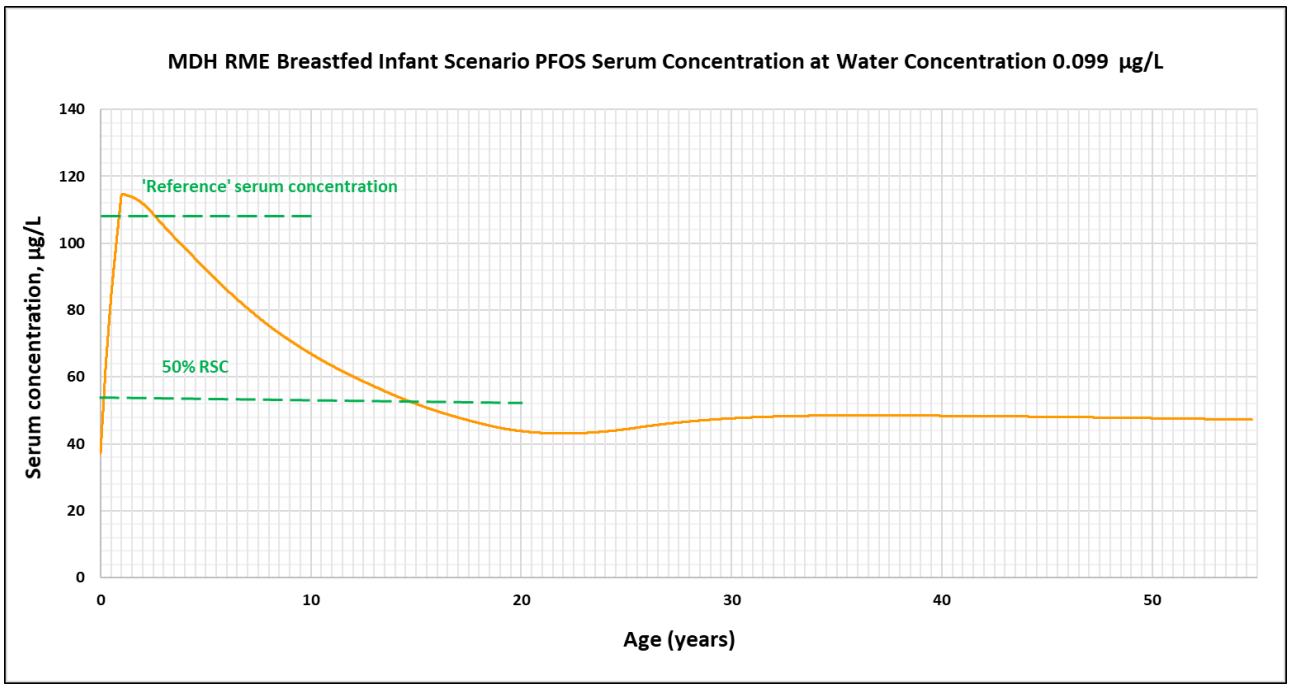
As mentioned above, two exposure scenarios were examined: 1) an infant fed formula reconstituted with PFHxS-contaminated water starting at birth and continuing ingestion of contaminated water throughout life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking PFHxS-contaminated water throughout life. For the first scenario, the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water at or below an RSC of 50% is 0.099 µg/L (Figure 1).

Figure 1. Exclusively formula-fed infant scenario serum concentrations over a lifetime, based on MDH's RME and an RSC of 50%.



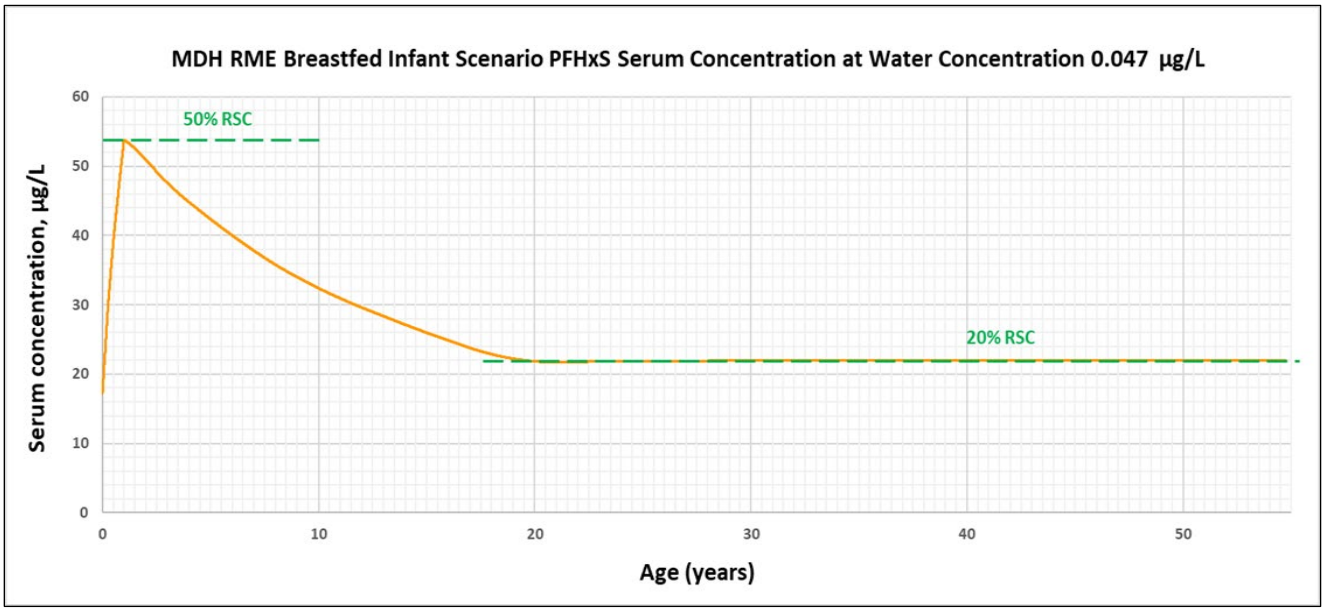
Applying this water concentration (0.099 µg/L) in the context of the breast-fed infant resulted in serum PFHxS concentrations exceeding the 'reference' serum concentration for nearly 2 years, and the 50% RSC threshold for nearly 14 years. See Figure 2.

Figure 2. Breast-fed infant scenario serum concentrations over a lifetime, based on MDH's RME and a water concentration of 0.099 µg/L.



In order to maintain serum concentrations at or below an RSC of 50% for breast-fed infants, the water concentration should not exceed 0.047 µg/L; see Figure 3. This water concentration also produces steady state serum concentrations at approximately 20% of the 'reference' serum concentration.

Figure 3. Exclusively breast-fed infant scenario serum concentrations over a lifetime, based on MDH's RME, and a water concentration of 0.047 µg/L.



To ensure protection of all segments of the population, the final health-based value for PFHxS is set at 0.047 µg/L.

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: Yes (moderate)

Summary of Guidance Value History:

MDH first reviewed PFHxS in 2009 and determined that there was insufficient data to derive a value. In 2013, MDH's Site Assessment and Consultation Unit began using the guidance value for PFOS as a surrogate to assess potential risks from exposure to PFHxS, in the absence of adequate chemical specific data. In 2018 additional toxicokinetic and toxicity information became available. In 2019, MDH derived a noncancer HBV (applicable to short-term, subchronic, and chronic durations) of 0.047 µg/L. In 2020 MDH incorporated updated water intake rates (US EPA 2019). Use of the updated intake rates did not result in changes to the 2018 value.

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	Yes
Effects observed?	Yes[1]	-[2]	No[3]	Yes[4]	No[5]

Comments on extent of testing or effects:

[1] Several human epidemiological studies have evaluated the possible association between serum PFHxS and alterations in thyroid hormone levels. Two studies found an association in women between serum PFHxS and thyroid hormone levels, however, other studies did not find this association. Two general population epidemiology studies have evaluated associations between PFHxS and reproductive hormones, finding no association.

Based on studies in laboratory animals, alterations in serum thyroid hormone levels, in particular thyroxine (T4), appear to be a sensitive effect. The POD is based on decreased serum T4 levels in adult male rats however, decreased serum T4 levels have also been reported in pregnant and lactating rats and pups. Unfortunately, serum PFHxS levels were not measured in pregnant or lactating rats or pups at the NOAEL and LOAEL dose levels, however, study results suggest that pups may be more sensitive than adult nonpregnant animals. A database uncertainty factor (DB UF) has been incorporated into the RfD derivation, in part, due to concerns that early life stages may be more sensitive.

Androgenic effects have also been evaluated in laboratory animals to a limited extent. No changes in adult male reproductive organ weights or sperm parameters were observed at serum levels up to ~600-fold higher than the 'reference' serum concentration. Androgenic activity was also evaluated in pups exposed in utero and through lactation. No significant effects were observed on anogenital distance, nipple retention, or reproductive organ weights at serum levels ~1300-fold higher than the 'reference' serum concentration.

[2] Several epidemiology studies have examined the potential association between PFHxS and suppression of the immune system. Inverse or no associations were observed in these studies. In general, available studies have not found an association between PFHxS and infectious disease resistance or with hypersensitivity outcomes.

Immunotoxicity has not been studied in laboratory animals. A DB UF has been incorporated into the RfD derivation, in part, to address this data gap.

[3] General population epidemiology studies have evaluated potential associations between maternal PFHxS and a variety of birth outcomes. A couple of studies have reported associations with birth weight or neurobehavioral outcome but others found no association.

Reproductive/developmental screening studies in rats and mice have not found treatment related changes in development outcome, including neurobehavioral effects, at serum levels ≥ ~900-fold higher than the 'reference' serum concentration. Neurobehavioral outcomes were also evaluated in a study using a single oral exposure to neonatal mice on postnatal day 10. No serum levels were measured and therefore, the results could not be quantitatively incorporated into MDH's assessment. No 2-generation study has been conducted. A DB UF has been incorporated into the RfD derivation, in part, to address this data gap.

[4] In general, epidemiology studies evaluating potential associations between PFHxS and reproductive measures have not found any associations. A small number of studies have reported associations with earlier menopause or time to pregnancy. However, since menstruation, childbirth, and lactation are potential elimination routes for women this could confound the associations.

Laboratory studies in rats did not find changes in reproductive parameters at serum levels ≥ ~1600-fold higher than the 'reference' serum concentration. A decrease in the number of pups per litter has been reported in mice, however the dose-response curve was flat and there was no difference in the number of pups born to the implant ratio. The 'reference' serum concentration is ~500-fold lower than the serum concentrations at which this effect occurs in mice, therefore the RfD is protective for this potential effect.

[5] Two epidemiology studies have evaluated association between PFHxS serum levels and self-reported memory loss or periods of confusion. One study reported a decrease in risk at the fifth quintile whereas the second study found no association.

Laboratory animal studies have evaluated neurotoxicity using the functional observation battery (FOB) and motor activity assessment. No effects were observed on adult rats and mice at serum concentrations ≥~600-fold higher than the 'reference' serum concentration. Potential neurological effects have also been evaluated in rat pups using these same evaluation tools. No effects were observed at serum concentrations up to ~800-fold higher than the 'reference' serum concentration. A neurotoxicity evaluation following a single oral dose to neonatal animals has also been conducted. See footnote #3 above.

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

Web Publication Date: December 2021

Toxicological Summary for: Perfluorohexanoate

CAS: **92612-52-7 (anion)**
307-24-4 (free acid)
21615-47-4 (ammonium salt)
2923-26-4 (sodium salt)

Synonyms: PFHxA; Perfluorohexanoic acid

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

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

$$= \frac{\text{(0.00032 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 0.22 rounded to **0.2 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA, 2000) to select appropriate RSCs. For PFHxA, an RSC of 0.2 was used for all exposure durations due to concerns about infant exposures from house dust and diet, potential exposures from the breakdown of precursor chemicals, and uncertainty about infant exposure levels.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.0958/300 = 0.00032 mg/kg-d (laboratory animal – SD rats)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	25.9 mg/kg-d (administered dose $BMDL_{1SD}$, NTP 2019)
Dose Adjustment Factor (DAF):	Chemical and Study-Specific Toxicokinetic Adjustment $Half\text{-}life_{MaleRat}/Half\text{-}life_{Human}$ = 2.87 hrs/ 768 hrs = 0.0037 (based on Dzierlenga et al 2020, for male rats, and Russell et al 2013, for humans)
Human Equivalent Dose (HED):	POD x DAF = 25.9 mg/kg-d x 0.0037 = 0.0958 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 (e.g., lack of a 2-generation study, lack of thyroid hormone measurements or neurodevelopmental toxicity in young offspring in a development/reproductive study, and lack of immunotoxicity studies as well as evidence of pup body weight effects near the selected POD)

Critical effect(s):	Decreased total T4
Co-critical effect(s):	Decreased pup body weight
Additivity endpoint(s):	Developmental, Thyroid [E]

Subchronic Non-Cancer Health-Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 0.2 µg/L

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

$$= \frac{\text{(0.00015 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 0.405 rounded to 0.4 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 0.045/300 = 0.00015 mg/kg-d (laboratory animal – SD rats)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	22.5 mg/kg-d (administered dose $BMDL_{10\%}$, Loveless et al 2009)
Dose Adjustment Factor (DAF):	Chemical and Study-Specific Toxicokinetic Adjustment $\text{Half-life}_{MaleRat}/\text{Half-life}_{Human}$ = 1.5 hrs/ 768 hrs = 0.0020 (based on Gannon et al 2011, for male rats, and Russell et al 2013, for humans)
Human Equivalent Dose (HED):	POD x DAF = 22.5 mg/kg-d x 0.0020 = 0.045 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 (e.g., lack of a 2-generation study, lack of thyroid hormone measurements or neurodevelopmental toxicity in young offspring in a development/reproductive study, and lack of immunotoxicity studies as well as evidence of pup body weight effects near the selected POD)
Critical effect(s):	Nasal epithelium degeneration
Co-critical effect(s):	Decreased bilirubin
Additivity endpoint(s):	Hepatic (liver) system, Respiratory system

The Subchronic nHBV must be protective of shorter duration 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, Thyroid [E]

Chronic Non-Cancer Health-Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 0.2 µg/L

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

$$= \frac{\text{(0.00015 mg/kg-d)}^{***} \text{ x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 0.67 rounded to 0.7 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

***Reference Dose/Concentration: The calculated Chronic RfD was higher in magnitude than the Subchronic RfD. Therefore, the Chronic RfD is set to the Subchronic RfD, see information above for details on the RfD derivation.

The Chronic nHBV must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 0.2 µg/L. Additivity endpoints: Developmental, Thyroid [E]

Cancer Health-Based Value (cHBV) = Not Applicable

Volatile: Nonvolatile

Summary of Guidance Value History:
There are no previous guidance values for PFHxA. The 2021 derived values represent new guidance.

Additional Information on the MDH TK model (Goeden et al., 2019):
PFHxA water guidance was calculated using MDH's standard equations shown above. The Goeden et al. (2019) toxicokinetic model previously used to calculate guidance for PFOA, PFOS, and PFHxS was evaluated during this review because PFHxA crosses the placenta and is found in breastmilk. The toxicokinetic data that the model requires are quite limited for PFHxA (e.g., no information on breastmilk:maternal serum ratio, limited information on half-life). As a result, the model was not used quantitatively to derive PFHxA water guidance. However, the PFHxA modelling results, using the best available information for model parameters, indicate that water guidance of 0.2 µg/L developed using the standard equation is adequately protective.

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	Yes

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Effects observed?	Yes[1]	-[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1]A significant positive correlation between PFHxA exposure and TGAb (thyroglobin antibodies) and TMAb (thyroid microsomal antibody) was reported in an epidemiological study. Short-term studies in adult laboratory animals identified decreased serum thyroid hormone levels. These effects form the basis of the short-term RfD. A database uncertainty factor (DB UF) was incorporated into the RfD derivation, in part, to address the lack of thyroid evaluations in developing animals. Thyroid cellular hypertrophy in adult animals was also reported, but at doses ~3,000-fold higher than the Subchronic/Chronic RfD.

[2] No immunotoxicity studies have been conducted. Three general toxicity studies reported decreased thymus weight at dose levels ≥5800-fold higher than the Subchronic/Chronic RfD. At slightly higher dose levels atrophy and necrosis in spleen and thymus as well as a depletion of lymph nodes were observed.

[3]Decreases in pup body weight and increased pup mortality have been reported. These effects were observed at levels ~1500-fold higher than the Subchronic/Chronic RfD. A database uncertainty factor (DB UF) was incorporated into the RfD derivation, in part, to address the lack of a two-generation study.

[4] Significant decreases in maternal body weight gain during gestation and complete litter loss were reported at doses >3,000-fold higher than the Subchronic/Chronic RfD. Decreases in sperm count and seminiferous tubule spermatid retention were reported at doses 25,000-fold higher than the Subchronic/Chronic RfD.

[5] Acute studies reported ataxia and abnormal gait at dose levels ~1,000-fold higher than the Subchronic/Chronic RfD. No neurological changes, based on functional observation battery and locomotor activity evaluations, were reported in adult rats following 90 days of exposure at levels up to ~5,000-fold higher than the Subchronic/Chronic RfD.

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

Web Publication Date: August 2020

Toxicological Summary for: Quinoline

CAS: **91-22-5**
Synonyms: Leukol, quinoleine, 1-Azanaphthalene, benzo[b]pyridine

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 ($nHBV_{Subchronic}$) = Not Derived (Insufficient Data)

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 4 µg/L

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

$$= \frac{\text{(0.00079 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 3.51 rounded to **4 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 2.38/3000 = 0.00079 mg/kg-d (F344 rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	8.8 mg/kg-d (LOAEL, Matsumoto, 2018)
Dose Adjustment Factor (DAF):	Body weight scaling, default MDH 2017 and US EPA 2011
Human Equivalent Dose (HED):	POD x DAF = 8.8 mg/kg-d x 0.27 = 2.38 mg/kg-d
Total uncertainty factor (UF):	3000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for LOAEL to NOAEL, and 10 for database uncertainty (lack of reproductive, developmental, immunotoxicity, and neurotoxicity studies)
Critical effect(s):	Increased cellular changes in the liver and kidney including necrosis, increased hematopoiesis in the bone marrow of

	both sexes, increased extramedullary hematopoiesis in the spleen of male rats.
Co-critical effect(s):	Central degeneration of the liver, increased immature blood cells in the liver and lungs, increased erythropoiesis/hematopoiesis in the bone marrow, spleen, and liver, increased inflammatory infiltration in the lungs, and hemosiderin deposits in the kidney in both male and female mice; increased eosinophilic changes in the respiratory epithelium and increased Kupffer cell mobilization in the liver of female mice.
Additivity endpoint(s):	Hematological (blood) system, Hepatic (liver) system, Renal (kidney) system, Respiratory system, Spleen

Cancer Health Based Value cHBV= 0.03 µg/L

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\ yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(3 \times 10^{*} \times 0.155\ \text{L/kg-d}^{**} \times 2) + (3 \times 3^{*} \times 0.040\ \text{L/kg-d}^{**} \times 14) + (3 \times 1^{*} \times 0.042\ \text{L/kg-d}^{**} \times 54)] / 70}$$

= 0.033 rounded to **0.03 µg/L**

*ADAF (Age-dependent adjustment factor): MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer classification:	Likely to be carcinogenic in humans EPA, 2001
Slope factor (SF):	3 $(mg/kg\text{-}day)^{-1}$ (hepatic hemangioendotheliomas or hemangiosarcomas in SD rats, Hirao, 1976)
Source of cancer slope factor (SF):	EPA (2001)
Tumor site(s):	Liver

Volatile: Yes (low)

Summary of Guidance Value History:
In 2019 MDH derived chronic noncancer and cancer guidance values for quinolone. Quinolone had not been evaluated by MDH previously. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates lowered the cHBV to 0.03 from 0.04 µg/L but did not change the chronic noncancer value.

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?	–	–[1]	–	–	No[2]

[1] No studies directly testing immunotoxicity have been conducted, however, one study did note endpoints associated with immune system activation in the liver and respiratory system. While these effects did not indicate immune system toxicity, little information is currently available. The lack of available information on how quinoline may impact the immune system is part of the rationale for selecting a 10-fold database uncertainty factor.

[2] One aspect of neurotoxicity has been investigated in a limited study, which reported that quinoline was not a dopaminergic neurotoxicant. Lack of more complete neurotoxicity testing also contributed to the selection of a database uncertainty factor of 10.

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

Web Publication Date: December 2021

Toxicological Summary for: Tetrachloroethylene

CAS: 127-18-4
Synonyms: Perchloroethene; Perchloroethylene; PERC; PCE

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 ($nHBV_{Subchronic}$) = 7 µg/L

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

$$= \frac{\text{(0.0026 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 7.0 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0026 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	2.6 mg/kg-d (EPA calculated the LOAEL based on route-to-route extrapolation of Cavalleri et al. 1994)
Human Equivalent Dose (MDH, 2011):	NA
Total uncertainty factor:	1000
Uncertainty factor allocation:	10 for intraspecies variability, 10 for LOAEL-to-NOAEL because results from residential studies suggest points of departure 3 to 15 times lower than the current LOAEL, and 10 for database uncertainty due to lack of data regarding immune, hematological, and developmental neurotoxicity
Critical effect(s):	Impacts on visual color domain – dyschromatopsia
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Subchronic}$ = 7 µg/L

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

$$= \frac{\text{(0.0026 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 11.5 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0026mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	2.6 mg/kg-d (EPA calculated the LOAEL based on route-to-route extrapolation of Cavalleri et al. 1994)
Human Equivalent Dose (MDH, 2011):	NA
Total uncertainty factor:	1000
Uncertainty factor allocation:	10 for intraspecies variability, 10 for LOAEL-to-NOAEL because results from residential studies suggest points of departure 3 to 15 times lower than the current LOAEL, and 10 for database uncertainty due to lack of data regarding immune and hematological effects and concerns about early life sensitivity
Critical effect(s):	Impacts on visual color domain – dyschromatopsia
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

The Chronic nHBV must be protective of the shorter duration exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Subchronic nHBV of 7 µg/L. Additivity endpoint: Nervous system.

Cancer Health Based Value (cHBV) = 4 µg/L

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2\text{-}<16\ yr} \times IR_{2\text{-}<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.025 \times 10^{*} \times 0.155\ \text{L/kg-d}^{**} \times 2) + (0.025 \times 3^{*} \times 0.040\ \text{L/kg-d}^{**} \times 14) + (0.025 \times 1^{*} \times 0.042\ \text{L/kg-d}^{**} \times 54)] / 70}$$

= **4 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Cancer classification:	Likely to be carcinogenic in humans by all routes of exposure (EPA, 2012)
Slope factor:	2.49×10^{-2} (laboratory animal) (Japan Industrial Safety Association (JISA), 1993)
Source of slope factor:	Massachusetts Department of Environmental Protection 2014
Tumor site(s):	Leukemia

Volatile: Yes (high)

Summary of Guidance Value History:

The 2014 subchronic and chronic noncancer HBVs (7 µg/L) are new guidance. The 2014 cancer HBV (4 µg/L) is slightly lower than the 2009 Maximum Contaminant Level (MCL) based HRL of 5 µg/L due to: 1) new toxicity data, 2) application of age-dependent early life cancer sensitivity adjustment factors, 3) water intake rates that incorporate higher intakes during early life, and 4) rounding to one significant digit.

In 2021 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Yes
Effects?	No[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

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] Few studies in humans or animals have examined altered hormones, and those that did generally found no adverse effects or were inconsistent.

[2] There have been reports indicating potential associations between tetrachloroethylene exposure and immune suppression, allergy/hypersensitivity, and autoimmune disease in humans. Several occupational and environmental studies in humans have reported a statistically significant association with exposure to tetrachloroethylene and leukemia. The most sensitive target for tetrachloroethylene-induced cancer is an immune cell type, mononuclear cell leukemia. Other immune effects, such as increases in white blood cells, lymphocytes, and natural killer cells, have been reported in studies that evaluated dry cleaning worker exposures. Effects on T-cells, natural killer cells, IgE and interleukin-4 suggest a potential for hypersensitivity but limited studies in children do not support associations between tetrachloroethylene and allergy or asthma. However, there have been limited case reports of occupational hypersensitivity. One residential study reported increased incidence of kidney/urinary tract and respiratory infections associated with drinking well water containing tetrachloroethylene. There have been a few occupational case reports and a few case-control studies reporting non-significant associations with sclerosis, an autoimmune disease. There is some evidence suggesting the developing immune system could be susceptible from exposure to tetrachloroethylene. There are very limited data for the evaluation of immune effects in animal studies, but mice exposed via inhalation had

increased susceptibility to respiratory infections and greater mortality from infection. The noncancer immune effects generally occur at high doses greater than 200-fold above the RfD, while the cancer effect of induction of mononuclear cell leukemia is the basis of the cancer HBV.

[3] There is not conclusive evidence from human studies that tetrachloroethylene exposure is linked to developmental effects. Many human studies that have evaluated the association between tetrachloroethylene and developmental effects have confounders and the evaluation of effects is complicated by exposures to solvent mixtures. Most animal studies that evaluated developmental effects did not show specific adverse effects on offspring. Developmental effects have been reported in animal inhalation toxicity studies at high levels of exposure (at 1500 mg/m^3 or higher). The effects include impacts on the developing nervous system (impacts on behavior, impacts on motor activity, and developmental delays) as well as decreased fetal body weight at exposures greater than 4500 mg/m^3 and increased malformations in pups at exposures greater than 1500 mg/m^3.

[4]The evidence of reproductive effects from exposure to tetrachloroethylene is limited from both human and animal studies. Human studies in dry cleaning and laundry workers evaluated reproductive outcomes and showed evidence of impacts on menstrual cycles, altered sperm quality, and longer time to pregnancy in workers exposed to tetrachloroethylene through inhalation. Decreased sperm quality and reduced fertilization of extracted oocytes was also reported in an animal inhalation study at high levels of exposure (12,000 mg/m3).

[5] The nervous system is the most sensitive target following exposure to tetrachloroethylene. The visual and cognitive domains are the most sensitive neurological endpoints and impacts on vision and cognition have been reported in several human occupational and environmental studies. Subtle visual effects including impacts on visual color domain – dyschromatopsia; impacts on visual cognitive domain and reaction times - decrements in visual reproduction, pattern memory, and pattern recognition, were identified as critical endpoints and are the basis of the non-cancer reference dose (0.0026 mg/kg-d) derived in MDH's evaluation of tetrachloroethylene. Acute CNS depression has been reported in children and adults following inhalation and ingestion of high levels of tetrachloroethylene.

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

Web Publication Date: August 2020

Toxicological Summary for: Toluene

CAS: **108-88-3**

Synonyms: methyl-Benzene, methylbenzol, monomethyl benzene, phenylmethane, Tol, Toluol, tolu-sol

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

Short-term Non-Cancer Health-Based Value ($nHBV_{Short\text{-}term}$) = 70 µg/L

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

$$= \frac{\text{(0.10 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 68.9 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 3.08/30 = 0.10 mg/kg-d (CD-1 mice)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	22 mg/kg-d (NOAEL; Hsieh, 1989)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (USEPA, 2011b) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 22 mg/kg-d x 0.14 = 3.08 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Immunosuppression
Co-critical effect(s):	behavior changes due to nervous system effects, neurotransmitter level changes in the brain, changes in immune response
Additivity endpoint(s):	Immune system, Nervous system

Subchronic Non-Cancer Health-Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 70 µg/L

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

$$= \frac{(0.18 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 486 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 54.7/300 = 0.18 mg/kg-d (F344 rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	238 mg/kg-d ($BMDL_{10}$; USEPA, 2005 using NTP, 1990)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (USEPA, 2011b) (MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 238 mg/kg-d x 0.23 = 54.7 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 (concerns regarding lack of evaluation of immunological and neurotoxicity endpoints. Alterations in immune response and in behavior were reported in shorter-term studies at doses lower than the subchronic and chronic PODs.)
Critical effect(s):	Increased liver and kidney weights (with histological changes in higher doses)
Co-critical effect(s):	Increased liver weight, behavior changes due to nervous system effects, neurotransmitter level changes in the brain, changes in immune response and immunosuppression
Additivity endpoint(s):	Hepatic (liver) system, Immune system, Nervous system, 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 70 µg/L. Additivity endpoints: Immune system, Nervous system.

Chronic Non-Cancer Health-Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 70 µg/L

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

$$= \frac{(0.055 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 244 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 54.7/1000 = 0.055 mg/kg-d (F344 Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	238 mg/kg-d (BMDL; NTP, 1990; subchronic exposure)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (USEPA, 2011b)(MDH, 2017)
Human Equivalent Dose (HED):	POD x DAF = 238 mg/kg-d x 0.23 = 54.7 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for database uncertainty (For concerns regarding lack of evaluation of immunological and neurotoxicity endpoints. Alterations in immune response and in behavior were reported in shorter-term studies at doses lower than the subchronic and chronic PODs), and 3 for subchronic to chronic extrapolation
Critical effect(s):	Increased liver and kidney weights (with histological changes in higher doses)
Co-critical effect(s):	Increased liver weight, behavior changes due to nervous system effects, neurotransmitter level changes in the brain, changes in immune response and immunosuppression
Additivity endpoint(s):	Hepatic (liver) system, Immune system, Nervous system, Renal (kidney) system

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 70 µg/L. Additivity endpoints: Immune system, Nervous system.

Cancer Health-Based Value (cHBV) = Not Applicable

Cancer classification:	Inadequate information to assess the carcinogenic potential in humans (USEPA, 2005)
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 non-cancer health risk limit (HRL) of 1000 µg/L was promulgated in 1993/1994. Short-term, subchronic, and chronic health-based values (HBV) of 200 µg/L were derived in 2009 and were promulgated as HRLs in 2011. In 2019, MDH re-evaluated the non-cancer HRLs, resulting in lower

water guidance values of 70 µg/L for the short-term, subchronic, and chronic durations. The changes to existing guidance were the result of 1) using MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020 MDH updated intake rates (US EPA 2019). Use of the updated intake rates did not result in changes to the 2019 values.

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	No	Yes
Effects observed?	- [1]	Yes[2]	Yes[3]	- [4]	Yes[5]

Comments on extent of testing or effects:

[1]Endocrine activity of toluene has not been studied. However, increased adrenocorticotropic hormone (ACTH) was observed at the highest dose tested in a short-term drinking water study in mice. The biological significance of this limited data is uncertain.

[2]The short-term reference dose is based on immunosuppression (decreased lymphocyte culture responses and decreased antibody PFC responses) in male mice. The immunological effect of decreased IL-2 production was seen at similar doses in other studies, and was included as co-critical effect for the subchronic and chronic durations. In a single dose study, additional immunological effects were seen at doses approximately 800 times higher than the short-term RfD. A database uncertainty factor was added to the subchronic and chronic RfDs to account for a lack of immunological studies at longer durations.

[3]Neurodevelopmental behavioral effects as well as other developmental effects (fetal body weight and organ weight decreases, kidney pelvis dilation) have been seen at doses 1,000 (fetal body weight and organ weight decreases) and up to 3,000 (kidney pelvis dilation) times higher than the short-term RfD.

[4]Oral exposure multigenerational or reproductive studies have not been conducted. No functional reproductive effects were observed in single dose developmental studies at doses up to 3,000 times the short-term RfD. Increased testicular weights were observed at high doses in a systemic subchronic study, but reproductive performance was not evaluated.

[5]Several short-term and subchronic studies have reported changes in brain neurotransmitter levels, histological changes in the brain, and mild behavioral changes in rodents. Changes in neurotransmitter levels as well as mild behavior changes were observed at similar doses to the critical effects dose ranges, and were included as co-critical effects for the short-term, subchronic, and chronic durations. A database uncertainly factor was added to the subchronic and chronic RfDs to account for a lack of neurological studies at longer durations.

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

Web Publication Date: August 2020

Toxicological Summary for: 1,2,4-Trimethylbenzene; 1,3,5- Trimethylbenzene; and 1,2,3-Trimethylbenzene

CAS: **95-63-6; 108-67-8; 526-73-8**

1,2,4-Trimethylbenzene Synonyms: 1,2,4-TMB; pseudocumene; asymmetrical trimethylbenzene
1,3,5-Trimethylbenzene Synonyms: 1,3,5-TMB; mesitylene; symmetrical trimethylbenzene
1,2,3-Trimethylbenzene Synonyms: 1,2,3-TMB; hemimellitene; hemellitol; pseudocumol

The trimethylbenzene (TMB) isomers, 1,2,4-TMB, 1,2,3-TMB, and 1,3,5-TMB, have similar chemical structures and properties. Toxicological studies in laboratory animals demonstrate similar health effects at similar dose levels and durations (USEPA 2016). Based on these similarities, the Minnesota Department of Health (MDH) used the information provided in the 2016 USEPA IRIS review to derive HBVs for the short-term, subchronic, and chronic durations that are applicable for all three isomers.

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

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

$$= \frac{\text{(0.042 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 28.9 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 4.2/100 = 0.042 mg/kg-d (Wistar rat)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	22.0 mg/m^3 (MDH calculated continuous inhalation exposure based on Gralewicz et al 1997 for NOAEL of 123 mg/m^3 identified in USEPA, 2016)
Dose Adjustment Factor (DAF):	0.19 mg/kg-d per mg/m^3 (ratio of subchronic oral POD_{HED} (3.5 mg/kg-d) to inhalation POD_{HEC} (18.15 mg/m^3) from (USEPA, 2016). Chemical-Specific PBPK model-based route-to-route extrapolation.)

Human Equivalent Dose (HED):	POD x DAF = 22.0 mg/m^3 x 0.19 mg/kg-d per mg/m^3 = 4.2 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 (lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study)
Critical effect(s):	Central nervous system changes (increased open field grooming), decreased pain sensitivity (lowered step down latency and paw lick latency)
Co-critical effect(s):	Central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), decreased pain sensitivity (paw lick latency)
Additivity endpoint(s):	Nervous system

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

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

$$= \frac{\text{(0.035 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 94.5 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 3.5/100 = 0.035 mg/kg-d (Wistar rat)
Source of toxicity value:	USEPA, 2016
Point of Departure (POD):	POD_{ADJ} (0.099 mg/L) weekly average blood concentration resulting from an inhalation POD_{HEC} of 18.15 mg/m^3 (dose metric from Korsak and Rydzynski, 1996 calculated by EPA, Table 2-5, USEPA, 2016)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model as calculated by USEPA, 2016 (USEPA, 2016)
Human Equivalent Dose (HED):	3.5 mg/kg-d (PBPK basis as calculated by USEPA, 2016 (page 2-34))
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database

	uncertainty (lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study)
Critical effect(s):	Decreased pain sensitivity (paw lick latency)
Co-critical effect(s):	Central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), decreased pain sensitivity (paw lick latency)
Additivity endpoint(s):	Nervous system

The Subchronic nHBV must be protective of 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: Nervous system

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

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

$$= \frac{\text{(0.012 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 53.3 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 3.5/300 = 0.012 mg/kg-d (Wistar rat)
Source of toxicity value:	USEPA, 2016
Point of Departure (POD):	POD_{ADJ} (0.099 mg/L) weekly average blood concentration resulting from an inhalation POD_{HEC} of 18.15 mg/m^3 (dose metric from Korsak and Rydzynski, 1996 calculated by EPA, Table 2-5, USEPA, 2016) (subchronic exposure)
Dose Adjustment Factor (DAF):	Chemical-Specific PBPK model as calculated by USEPA, 2016 (USEPA, 2016)
Human Equivalent Dose (HED):	3.5 mg/kg-d (PBPK basis as calculated by USEPA, 2016 (page 2-34))
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for database uncertainty (lack of a multi-generation developmental/reproductive study and lack of a neurodevelopmental study), and 3 for subchronic

	to chronic extrapolation (use of subchronic study and slight potential for an increased severity of effects with increasing duration)
Critical effect(s):	Decreased pain sensitivity (paw lick latency)
Co-critical effect(s):	Central nervous system changes (impaired learning of passive avoidance and deleterious effects on locomotor activity), decreased pain sensitivity (paw lick latency)
Additivity endpoint(s):	Nervous system

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 30 µg/L. Additivity endpoints: Nervous system

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: Yes (high)

Summary of Guidance Value History:

Short-term, subchronic, and chronic duration health-based values (HBV) of 100 µg/L were derived for 1,3,5-TMB in 2008 and promulgated as health-risk limits (HRL) in 2009. Short-term, subchronic, and chronic duration risk assessment advice (RAA) of 100 µg/L was derived for 1,2,4-TMB in 2010, and was based on the MDH guidance values for 1,3,5-TMB. The derived guidance values for 1,3,5-TMB and 1,2,4-TMB were re-evaluated in 2018. The re-evaluation included one additional TMB isomer, 1,2,3-TMB. All three isomers were evaluated together for the purposes of updating and deriving guidance values. As a result of the 2018 re-evaluation, short-term, subchronic, and chronic HBVs of 30 µg/L were derived for all three TMB isomers (1,2,3-; 1,2,4-; and 1,3,5-). The values are lower than previous MDH guidance as a result of 1) incorporation of more recent toxicological information, 2) route-to-route extrapolation using US EPA PBPK results, and 3) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Using the updated intake rates did not result in changes to the 2018 values.

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?	-[1]	-[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1]Endocrine activity of the trimethylbenzene isomers has not been tested. There is some evidence that other alkylbenzenes may modulate endocrine function and signaling. Alkylbenzene alterations of hormone concentrations may be tied to alterations in fetal growth and the development of inflammatory responses.

[2]Immunotoxicity was not directly tested with trimethylbenzene isomers. Studies examining nonimmune endpoints reported increases in immune and inflammatory cells and alveolar macrophages in lung lavage fluid. The increased macrophages could potentially indicate immune suppression activity at high doses in laboratory animals.

[3]Limited information is available on the developmental effects of the trimethylbenzene isomers. Decreased fetal body weight in decreased maternal body weight was observed in laboratory animals at doses over 3000 times higher than the reference dose for the short-term duration. The lack of a multigenerational study is addressed with a database uncertainty factor for all three durations.

[4] Limited information is available on the reproductive effects of the trimethylbenzene isomers. Decreased maternal body weight in addition to decreased fetal body weight was observed in laboratory animals at doses over 3000 times higher than the reference dose for the short-term duration. The lack of a multi-generational study is addressed with a database uncertainty factor for all three durations.

[5]The reference doses for the short-term, subchronic, and chronic durations are based on neurotoxicity endpoints (central nervous system disturbances and decreased pain sensitivity) observed in inhalation studies. Co-critical effects are also based on the same nervous system effects at doses up to the non-PBPK adjusted dose associated with the reference dose.

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

Web Publication Date: August 2020

Toxicological Summary for: Tris(2-butoxyethyl) Phosphate

CAS: **78-51-3**
Synonyms: TBEP, Tributoxyethyl phosphate

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

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

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

$$= \frac{\text{(0.043 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 29.6 rounded to **30 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. Based on the potential for infants to be exposed at levels equal to a significant fraction of the short-term MDH RfD value from house dust (Fromme, 2014), an RSC of 0.2 has been used.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 4.34 / 100 = 0.043 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	18.08 mg/kg-d (administered dose $BMDL_{10}$, HRI, 1996)
Dose Adjustment Factor (DAF):	0.24 sex averaged body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 18.08 mg/kg-d x 0.24 = 4.34 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 due to a lack of any 2-generational study and additional studies in a second test species
Critical effect(s):	Liver cell vacuolization
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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

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

$$= \frac{\text{(0.022 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 59.4 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 2.23 / 100 = 0.022 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	8.92 mg/kg-d (administered dose $BMDL_{10}$, Reyna & Thake, 1987)
Dose Adjustment Factor (DAF):	Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 8.92 mg/kg-d x 0.25 = 2.23 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 due to a lack of any 2-generational study and additional studies in a second test species
Critical effect(s):	Liver cell vacuolization
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) 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: Hepatic (liver) system

Chronic Noncancer Health-Based Value ($nHBV_{Chronic}$) = 30 µg/L

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

$$= \frac{\text{(0.0074 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 32.8 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 2.23 / 300 = 0.0074 mg/kg-d (SD rats)
Source of toxicity value:	Determined by MDH in 2020

Point of Departure (POD):	8.92 mg/kg-d (administered dose $BMDL_{10}$, Reyna & Thake, 1987, subchronic exposure)
Dose Adjustment Factor (DAF):	Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 8.92 mg/kg-d x 0.25 = 2.23 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty due to a lack of any 2-generational study and additional studies in a second test species, and 3 for use of a subchronic study for chronic guidance
Critical effect(s):	Liver cell vacuolization
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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 2020 MDH derived guidance for TBEP. Previously no MDH guidance existed. Later in 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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?	-[1]	-[2]	No[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] No specific animal studies are available. A general toxicity study in rats noted a slight endocrine system organ weight change (thyroid) at a dose approximately 2,000 times higher than the subchronic reference dose. In cell culture studies, a small number of tests have been positive for endocrine activity.

[2] No specific animal studies are available. A general toxicity study in rats noted a slight decrease in spleen weight after five weeks of exposure at a dose over 10,000 times higher than the short-term reference dose. A small reduction in white blood cells has also been reported in two studies at doses over 6,000 times higher than the subchronic reference dose.

[3] Two studies have examined developmental effects in rats, and neither reported developmental effects at doses 1,700 and 8,000 times higher than the short-term reference dose. However, due to the lack of specific developmental studies and the lack of a second test species, a database uncertainty factor was applied.

[4] Male reproductive toxicity in adult rats was reported at a dose 1,700 times higher than the short-term reference dose. A slight increase in testis weight and a slight decrease in ovary weight has been reported at doses over 10,000 times higher than the subchronic reference dose. A database uncertainty factor has been applied due to the overall lack of reproductive studies.

[5] Neurotoxicity has been examined in two dated studies where effects were not seen until approximately 5,000 – 10,000 times higher than the short-term reference dose. Serum cholinesterase decreases have also been observed at doses 1,000 – 10,000 times higher than the subchronic reference dose.

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

Web Publication Date: December 2021

Toxicological Summary for: Tris - (1,3 - dicholorisopropyl) phosphate

CAS: **13674-87-8**

Synonyms: Tris(1,3-dichloro-2-propyl)phosphate; Tri[2-chloro-1-(chloromethyl)ethyl] phosphate; Fyrol FR 2; TDCPP; TDCP

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 ($nHBV_{Subchronic}$) = 20 µg/L

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

$$= \frac{\text{(0.0067 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 18 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0067 mg/kg-d (mice)
Source of toxicity value:	MDH, 2013
Point of Departure:	15 mg/kg-d (NOAEL from 3 month dietary study by Kamata et al 1989)
Human Equivalent Dose (MDH, 2011):	15 x 0.13 = 2.0 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (to address no or inadequate information regarding developmental/reproductive function, neurological, immune and endocrine effects)
Critical effect(s):	Increased liver and kidney weights
Co-critical effect(s):	None

Additivity endpoint(s): Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 8 µg/L

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

$$= \frac{\text{(0.0019 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Reference Dose/Concentration:	0.0019 mg/kg-d (rats)
Source of toxicity value:	MDH, 2013
Point of Departure:	1.94 mg/kg-d ($BMDL_{10\%}$ calculated by ATSDR 2012 based on renal tubule epithelial hyperplasia reported in Bio/dynamics 1981)
Human Equivalent Dose (MDH, 2011):	1.94 x 0.29 = 0.56 mg/kg-d (MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (to address no or inadequate information regarding developmental/reproductive function, neurological, immune and endocrine effects)
Critical effect(s):	Renal tubule epithelial hyperplasia and seminal vesicle atrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system; Male reproductive system

Cancer Health Based Value (cHBV) = 0.8 µg/L

$$= \frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\,yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\,yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\,yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.13 \times 10^{*} \times 0.155\ \text{L/kg-d}^{**} \times 2) + (0.13 \times 3^{*} \times 0.040\ \text{L/kg-d}^{**} \times 14) + (0.13 \times 1^{*} \times 0.042\ \text{L/kg-d}^{**} \times 54)] / 70}$$

= 0.764 rounded to **0.8 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3, and 3-5.

Cancer classification:	Has not been classified by US EPA Probable human carcinogen (Consumer Product Safety Commission 2006) Identified under Proposition 65 as a chemical known to cause cancer (CalEPA 2012)
Slope factor:	0.13 per mg/kg-d (2 year dietary study in rats, Freudenthal and Henrich 2000)
Source of slope factor:	CalEPA 2012
Tumor site(s):	Liver, kidney and testes

Volatile: **No**

Summary of Guidance Value History:

Guidance values for TDCPP were developed in 2013. In 2021 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in a change in the chronic duration water guidance value from 9 µg/L to 8 µg/L.

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

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

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] A recent epidemiological study reported significant associations between serum prolactin and free T4 levels and TDCPP levels in household dust. However, study limitations preclude drawing conclusions from these observations. Oral toxicity studies in laboratory animals have mainly been limited to organ weights and histological assessments. Chronic exposure resulted in effects on male reproductive organs and increased thyroid weights at higher doses (> 2,600-fold higher than the chronic RfD). Hormonal measurements, however, were not taken. Studies conducted *in vitro* and in zebrafish demonstrate that TDCPP affects steroidogenesis, acts as an estrogen receptor antagonist and alters thyroid hormone concentrations. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate dataset regarding endocrine activity.

[2] Oral studies of immunological effects have been limited to measurements of thymus and spleen organ weights which do not appear to be sensitive endpoints. However, a 4 day subcutaneous injection study reported changes in immune function. In addition immune effects have been observed following exposure to other triphosphate flame retardants. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate oral toxicity dataset regarding immunological assessment.

[3] Oral mammalian developmental studies are limited. No multigeneration studies have been conducted. Two

developmental studies reported increased incidence of fetal death as dose levels resulting in maternal toxicity. These dose levels were more than 3000-fold higher than the subchronic and chronic RfDs.

[4] Male reproductive organ effects were observed at the lowest dose tested in a 2 year dietary study in rats. These effects, in part, form the basis of the chronic RfD. Oral studies regarding functional reproductive effects are limited. No multigeneration studies have been conducted. Female reproductive effects have not been adequately assessed. Effects on male reproductive ability were not observed in a 12 week study in rabbits. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate dataset regarding reproductive toxicity.

[5] Oral studies regarding neurotoxicity are limited. A 2 year dietary study did not report clinical signs or morphological changes in the brain. Changes in red blood cell cholinesterase were measured but were inconsistent throughout the study. No developmental neurobehavioral effects were reported following *in utero* exposure but data reporting in that particular study were limited. Studies on other structurally related chemicals suggest the need for additional studies. A database uncertainty factor has been incorporated into the derivation of the RfD to address the inadequate dataset regarding neurological assessment.

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

Web Publication Date: March 2022

Toxicological Summary for: Venlafaxine

CAS: 93413-69-5 (free base)
99300-78-4 (HCl salt, Effexor XR)

Synonyms: Venlafaxine-HCl (Effexor XR); 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol (IUPAC)

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 10 ug/L

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

$$= \frac{\text{(0.0054 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.290 L/kg-d)**}}$$

= 14.9 rounded to **10 µg/L**

* MDH utilizes the U.S. EPA Exposure Decision Tree (U.S. EPA 2000) to select appropriate RSCs, ranging from 0.2 to 0.8. An RSC greater than 0.8 may be warranted for those who have no other route of exposure besides drinking water because of the unlikelihood of exposure from any other sources. However, without additional information a specific value cannot be determined at this time. Therefore, the recommended upper limit default of 0.8 was utilized. For those who take venlafaxine according to prescription the additional drinking water exposure will be negligible. For nursing infants whose mothers are taking venlafaxine, the drinking water exposure from supplemental bottle-feeding will also be negligible.
** Intake Rate: MDH, 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	0.0054 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.54 mg/kg-d (LOAEL, lowest starting dose of 37.5 mg/d from Wyeth Pharmaceuticals, 2014a)
Human Equivalent Dose (MDH, 2011):	n/a
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability and 10 for use of LOAEL
Critical effect(s):	Developmental (persistent pulmonary hypertension and nervous system effects), gastrointestinal system (nausea, constipation), male reproductive effects (decreased libido, abnormal orgasm, erectile dysfunction, ejaculation failure/disorder), and nervous system effects (effects on serotonin hormone receptor interaction, sweating, abnormal dreams, and dizziness, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	None

Additivity endpoint(s):	Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

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

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

$$= \frac{\text{(0.0054 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.074 L/kg-d)**}}$$

= 58 rounded to 60 µg/L

*Refer to RSC explanation provided for the short-term non-cancer health risk limit.
** Intake Rate: MDH, 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	0.0054 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.54 mg/kg-d (LOAEL, lowest starting dose of 37.5 mg/d and lowest dose tested in a 6-month clinical trial, Cobalt Pharmaceutical Co. 2014, Emslie et al. 2007a, Emslie et al. 2007b)
Human Equivalent Dose (MDH, 2011):	n/a
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability and 10 for use of LOAEL
Critical effect(s):	Cardiovascular system (neuroendocrine-mediated increases in blood pressure), developmental (persistent pulmonary hypertension and nervous system effects), gastrointestinal system (constipation), male reproductive effects (effects on orgasm, ejaculation failure, decreased libido), and nervous system (effects on serotonin hormone receptor interaction, abnormal dreams, sweating, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	Nervous system (mydriasis or dilation of pupils)
Additivity endpoint(s):	Cardiovascular system, Developmental, Gastrointestinal system, Male reproductive system, Nervous system (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 10 µg/L. Additivity endpoints: Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = Short-term HBV = 10 µg/L

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

$$= \frac{\text{(0.0054 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.045 L/kg-d)**}}$$

= 96 rounded to 100 µg/L

*Refer to RSC explanation provided for the short-term non-cancer health risk limit.
** Intake Rate: MDH, 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5

Reference Dose/Concentration:	0.0054 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.54 mg/kg-d (LOAEL, lowest starting dose of 37.5 mg/d, and lowest dose tested in a 6-month clinical trial Cobalt Pharmaceutical Co. 2014, Emslie et al. 2007a, Emslie et al. 2007b)
Human Equivalent Dose (MDH, 2011):	n/a
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability and 10 for use of LOAEL
Critical effect(s):	Cardiovascular system (neuroendocrine-mediated increases in blood pressure), developmental (persistent pulmonary hypertension in newborns and nervous system effects), gastrointestinal system (constipation), male reproductive effects (effects on orgasm, ejaculation failure, decreased libido), and nervous system (effects on serotonin hormone receptor interaction, abnormal dreams, sweating, and neuroendocrine-mediated increases in blood pressure)
Co-critical effect(s):	Nervous system (mydriasis or dilation of pupils)
Additivity endpoint(s):	Cardiovascular system, Developmental, Gastrointestinal system, Male reproductive system, Nervous system (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 10 µg/L. Additivity endpoints: Developmental, Gastrointestinal system, Male reproductive system, Nervous system (E)

Cancer Health Based Value (cHBV) = **Not Applicable**

Volatile: No

Summary of Guidance Value History:

There are no previous drinking water guidance values for venlafaxine. All values are new. In 2020, MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in any changes to the guidance values.

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

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

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]Neuroendocrine effects related to serotonin and norepinephrine are identified as critical effects. Serotonin receptor interactions are the basis for the intended pharmacological action of venlafaxine and many of the adverse effects. Significant neuroendocrine-mediated increases in systolic blood pressure related to norepinephrine have been reported in some clinical trials and are considered as a critical effect. Doses more than 200 times higher than the RfD have been associated with sustained hypertension (defined as supine diastolic blood pressure (SDBP) ≥90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive therapy visits). Other endocrine system effects have been described as "limited" and have generally occurred only at doses greater than those required for antidepressant therapeutic effects. Menstrual disorders in humans have been identified at doses over 200 times higher than the RfD. Inappropriate antidiuretic hormone secretion (SIADH) in the kidney has been reported as an adverse event in dehydrated patients. Rare reports of endocrine effects at therapeutic doses over 200 times higher than the RfD include galactorrhea, goiter, hyper- and hypothyroidism, thyroid nodule, thyroiditis, and increased prolactin.

[2]Venlafaxine has been reported to have only limited effects on the immune system that generally occur at doses greater than those required for therapeutic antidepressant effects (more than 200 times higher than the RfD). Since depression is associated with alterations in immune function, the effects of antidepressants on the immune system have been of interest, primarily from the perspective of restoring immune function in depressed patients. Some reports suggest that antidepressant treatment, including venlafaxine, may have a beneficial anti-inflammatory effect. In laboratory mice, effects on various pro-inflammatory cytokines were reported when mice were exposed to venlafaxine at HED doses more than 150 times higher than the RfD.

[3]Developmental toxicity in humans is identified as a critical endpoint with effects in newborns exposed during the third trimester of pregnancy as a result of maternal antidepressant therapy. Effects on newborns exposed to therapeutic doses during the third trimester can be life-threatening and require hospitalization. Effects may include respiratory distress at birth and/or tachypnea, persistent pulmonary hypertension, cyanosis, apnea, seizures, tremor, irritability, temperature instability, vomiting, hypoglycemia, and changes in muscle tone. Exposure during pregnancy at doses more than 200 times higher than the RfD did not adversely affect behavior or IQ of children at age 3 to 6 years. In laboratory animals, developmental toxicity including decreased fetal size and pup weight, increased stillborn pups, and increased pup deaths during early lactation were reported at doses over 1,400 times higher than the RfD.

[4]Male reproductive toxicity effects in humans are identified as critical effects for all durations. Female reproductive toxicity, including amenorrhea, dysmenorrhea or other menstrual disorders have been reported in humans at doses over 200 times higher than the RfD.

[5]Nervous system effects are identified as critical effects for all durations. Venlafaxine is a neurologically-active drug with intended pharmacological effects on the nervous system.

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

Web Publication Date: August 2020

Toxicological Summary for: Xylenes

CAS: **1330-20-7**

Synonyms: xylene; xylene mixture; o-,m-,p-xylene; xylenes mixed isomers; xylol; dimethylbenzene

Xylenes are a mixture of three isomers: meta-xylene (m-xylene), ortho-xylene (o-xylene), and para-xylene (p-xylene) with the meta-isomer usually being the dominant part of the mixture at 40-70%. The exact composition of the commercial xylene grade depends on the source but a typical mixture will also contain ethylbenzene at 6 - 20% in addition to the three isomers. The environmental fate (transport, partitioning, transformation, and degradation) is expected to be similar for each of the xylene isomers based on the similarities of their physical and chemical properties (ATSDR, 2007). The metabolism of each individual isomer is thought to be similar, and the U.S. Environmental Protection Agency, 2003 IRIS Toxicological Review states that, “although differences in the toxicity of the xylene isomers have been detected, no consistent pattern following oral or inhalation exposure has been identified” (USEPA, 2003).

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) =700 µg/L

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

$$= \frac{\text{(1.0 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 689 rounded to **700 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 30/30 = 1.0 mg/kg-d (Long Evans Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	125 mg/kg-d (NOAEL; Dyer, 1988 aci ATSDR 2007)
Dose Adjustment Factor (DAF):	0.24, Body weight scaling, default (MDH, 2017)(USEPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 125 mg/kg-d x 0.24 = 30 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Altered visual evoked potentials
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 300 µg/L

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

$$= \frac{\text{(0.38 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 262 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 115/300 = 0.38 mg/kg-d (F344/N Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	500 mg/kg-d (NOAEL; NTP, 1986 (14 day study))
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH, 2017) (USEPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 500 mg/kg-d x 0.23 = 115 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 as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies.)
Critical effect(s):	Decreased body weight gain
Co-critical effect(s):	Altered visual evoked potentials, decreased fetal body weight, increased fetal malformations
Additivity endpoint(s):	Developmental, Nervous System

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

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

$$= \frac{\text{(0.12 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 324 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 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 34.5/300 = 0.12 mg/kg-d (SD Rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	150 mg/kg-d (NOAEL; Condie, 1988)

Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH, 2017) (USEPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 150 mg/kg-d x 0.23 = 34.5 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 as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies.)
Critical effect(s):	Increased kidney weights, minimal chronic nephropathy
Co-critical effect(s):	Altered visual evoked potentials, decreased fetal body weight, decreased adult body weight gain, increased fetal malformations, hyperactivity
Additivity endpoint(s):	Developmental, Nervous system, Renal (kidney) system

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

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

$$= \frac{\text{(0.16 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 711 rounded to 700 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 48.3/300 = 0.16 mg/kg-d (F344/N rat)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	179 mg/kg-d (NOAEL; NTP, 1986 (2 year study))
Dose Adjustment Factor (DAF):	0.27, Body weight scaling, default (MDH, 2017) (USEPA, 2011)
Human Equivalent Dose (HED):	POD x DAF = 179 mg/kg-d x 0.27 = 48.3 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 as well as adequate ototoxicity and neurotoxicity studies. Neurotoxicity was identified as a sensitive endpoint from inhalation studies.)
Critical effect(s):	Decreased body weight gain

Co-critical effect(s):	Altered evoked visual potentials, decreased body weight gain, hyperactivity, minimal chronic nephropathy and increased kidney weights
Additivity endpoint(s):	Nervous system, Renal (kidney) 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 Subchronic nHBV of 300 µg/L. Additivity endpoints: Developmental, Nervous system, Renal (kidney) system.

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: Yes (high)

Summary of Guidance Value History:

A non-cancer Health Risk Limit (HRL) of 10,000 µg/L was promulgated in 1993/1994. Acute, short-term, subchronic, and chronic health-based values (HBV) of 800, 300, 300, and 300 µg/L, respectively, were derived in 2010 and were promulgated as HRLs in 2011. In 2019, MDH re-evaluated the non-cancer HRLs, resulting in a lower acute duration value of 700 µg/L and no changes to the values for short-term, subchronic, and chronic durations. The changes to existing guidance were due to 1) using MDH's most recent risk assessment methodology and 2) rounding to one significant digit. In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates did not result in changes to the 2019 guidance values.

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]	Yes[3]	Yes[4]

Comments on extent of testing or effects:

[1]Decreased thymus and spleen weights have been reported in laboratory animals at doses over 1,000 times higher than the current short-term reference dose.

[2]Developmental effects are included as co-critical effects for the short-term, subchronic, and chronic durations. Increased fetal malformations, mostly cleft palate malformations, were observed in laboratory animals in the absence of maternal toxicity at doses less than one fold higher than doses that caused increased kidney weights and mild nephropathy and decrease body weight gain in short-term, subchronic, and chronic duration studies.
[3]Decreased uterine weight and increased resorptions have been reported in laboratory animals at doses approximately 700 times higher than the current short-term reference dose. Other studies in laboratory animals at similar doses reported no adverse reproductive effects.
[4]The acute reference dose is based on neurotoxicity in male rats with observed effects of altered visual evoked potentials. Transient hyperactivity was observed in laboratory animals at doses at or less than one fold difference than doses observed to cause increased kidney weights and mild nephropathy in laboratory animals. Nervous system effects of altered visual evoked potentials and transient hyperactivity were listed as co-critical effects for the short-term, subchronic, and chronic durations. The nervous system was identified as a sensitive endpoint following inhalation exposure.

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APPENDIX F. MMB Correspondence

DEPARTMENT OF HEALTH

Protecting, Maintaining and Improving the Health of All Minnesotans

November 22, 2022

Mr. Thomas Carr
Executive Budget Officer
Minnesota Management and Budget
658 Cedar St., Ste. 400
St. Paul, MN 55155

Re: **Proposed Amendments to Rules Governing Health Risk Limits, *Minnesota Rules, Parts 4717.7500, .7850, .7860; Revisor's ID Number RD4587***

Dear Mr. Carr:

Minnesota Statutes, section 14.131, requires that an agency engaged in rulemaking consult with the Commissioner of Minnesota Management and Budget "to help evaluate the fiscal impact and fiscal benefits of the proposed rule on units of local government."

Enclosed for your review are copies of the following documents on the above-referenced rule revisions:

1. November 1, 2022, Revisor's draft of the proposed rule; and
2. November 17, 2022, draft SONAR.

If you or any other representative of the Commissioner of Minnesota Management & Budget has questions about the proposed rule revisions, please email me at *josh.skaar@state.mn.us*. If necessary, you can also call me at 651-368-0751.

Sincerely,

/s/ Josh Skaar

Josh Skaar
Senior Associate General Counsel
Rulemaking Coordinator
Minnesota Department of Health
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Enclosures: