VIA EMAIL
October 31, 2024

Legislative Reference Library
sonars@lrl.leg.mn

In the Matter of the Proposed Permanent Rules Relating to Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Parts 7500 and 7860; Revisor's ID Number 4803

Dear Legislative Reference Library:

The Minnesota Department of Health intends to adopt rules relating to Health Risk Limits for Groundwater. We plan to publish a Dual Notice on November 4, 2024, in the *State Register*.

We have prepared a Statement of Need and Reasonableness. As required under Minnesota Statutes, sections 14.131 and 14.23, we are sending the library an electronic copy of the Statement of Need and Reasonableness at the same time that we are sending our Notice of Intent to Adopt Rules.

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

Sincerely,

Nancy Rice Digitally signed by Nancy Rice Date: 2024.10.31 07:04:06 -05'00'

Nancy Rice
Research Scientist
Health Risk Assessment Unit

Enclosure: Statement of Need and Reasonableness

STATEMENT OF NEED AND REASONABLENESS

In the Matter of Proposed Revisions of
Minnesota Rules, Chapter 4717, Parts 7500 and 7860
Revisor's ID Number: 4803
OAH Docket number: 22-9000-40331

Division of Environmental Health

October 2024

General information

1) Availability: The State Register notice, this Statement of Need and Reasonableness (SONAR), and the proposed rule will be available during the public comment period on the Agency's Public Notices website: Health Risk Limits Rules for Groundwater Rules Amendments -Overview and Links https://www.health.state.mn.us/communities/environment/risk/rules/water/overview.html

2) View older rule records at: Minnesota Rule Statutes https://www.revisor.mn.gov/rules/status/

3) Agency contact for information, documents, or alternative formats: Upon request, this Statement of Need and Reasonableness can be made available in an alternative format, such as large print, braille, or audio. To make a request, contact Nancy Rice, Minnesota Department of Health, 625 North Robert St, St. Paul, MN 55164; telephone 651-201-4923 or 1-800-201-5000; nancy.rice@state.mn.us; or use your preferred telecommunications relay service.

Contents

Acronyms

aci	as cited in (Used when a publication is cited in a second document)
ADAF	Age-Dependent Adjustment Factor
$AF_{lifetime}$	Lifetime Adjustment Factor
APA	Administrative Procedures Act
ALJ	Administrative Law Judge
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower-Confidence Limit
CAS	Chemical Abstract Service Number
CEC	Contaminant of Emerging Concern
CFR	Code of Federal Regulations
cHRL	cancer Health Risk Limit
DAF	Dose Adjustment Factor
DWEL	Drinking Water Equivalent Levels (issued by EPA)
(E)	Endocrine
EPA	U.S. Environmental Protection Agency
HA	Health Advisory
HBV	Health-Based Value
HED	Human Equivalent Dose
HRA	Health Risk Assessment
HRL	Health Risk Limit
IR	Intake Rate
LOAEL	Lowest Observed Adverse Effect Level
MCL	Maximum Contaminant Level (created by EPA)
MCLG	Maximum Contaminant Level Goal (created by EPA)
µg/L	microgram/Liter (also parts per billion)
mg/kg-day	milligrams (of a chemical) per kilogram (of body-weight) per day
MDA	Minnesota Department of Agriculture
MDH	Minnesota Department of Health
MMB	Minnesota Management and Budget

MPCA	Minnesota Pollution Control Agency
Minn. R. pt	Minnesota Rules part
Minn. Stat.	Minnesota Statutes
MN	Minnesota
NA	Not Applicable
ND	Not Derived
nHRL	noncancer Health Risk Limit
NOAEL	No Observed Adverse Effect Level
OAH	Office of Administrative Hearings
PFAS	Per- and Polyfluoroalkyl Substances
PFOA	Perfluorooctanoate
PFOS	Perfluorooctane sulfonate
POD	Point of Departure
RfSC	Reference Serum Concentration
RfD	Reference Dose
RSC	Relative Source Contribution
SF	Slope Factor
SONAR	Statement of Need and Reasonableness
UF	Uncertainty Factor

Introduction and Overview

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. The value is usually expressed as micrograms of a chemical per liter of water (µg/L) though very low values are expressed as nanograms per liter of water (ng/L). MDH calculates HRL values for specific durations of exposure.

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 the 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).

This project proposes to amend Minnesota Rules, Chapter 4717, by revising and/or repealing HRLs for six groundwater contaminants. Specifically, the amendments repeal six outdated HRL values in Minnesota Rules part 4717.7500 or .7860 and add four updated HRL values to 4717.7860 to replace four of the repealed values (see Proposed Rules: The Health Risk Limits Table below). The two HRL values that will not be replaced are outdated, but there is insufficient data available to create updated water guidance values using methods adopted in 2009. However, using the information that is available, new Risk Assessment Advice (RAA) values (which can be used to develop water guidance but cannot be adopted into rule) have already been published on the MDH website at Human Health-Based Water Guidance Table (https://www.health.state.mn.us/communities/environment/risk/guidance/gw/table.html).

These proposed amendments for the six groundwater contaminants build on MDH's 2009 rule revision and subsequent rulemaking. The current rules on the Health Risk Limits in Minnesota Rules, Chapter 4717 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). 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. This Introduction and Overview section contains this introduction, a general scope of the proposed amendments, a description of the contents of the document, and a statement of general need and reasonableness. The Background section briefly describes the definition of HRLs, how they are calculated, past HRL Rule Revisions, and provides detail on MDH's statutory authority for adopting HRLs. The Proposed Rules section includes an overview of the scope of the proposed amendments, as well as detailed information on each proposed amendment in the Rule-by-Rule Analysis subsection. In the Public Participation and Interested Party Involvement section, MDH's process for selecting contaminants for water guidance development is discussed. Additional sections cover the Regulatory Analysis section, a Health Equity Statement, the Additional Notice Plan, the performance-based nature of the rules, consultation with Minnesota Management and Budget (MMB), and the impact of the proposed rules. Appendices A to E provide additional detail regarding term definitions, references cited, concepts used in calculating HRLs, contaminants selected, and a toxicological summary sheet for each contaminant included in this rulemaking.

Statement of General Need and Reasonableness

In general, the agency needs amendments to Minnesota Rules, parts 4717.7500 and .7860 to update outdated HRL values and to add new HRLs for newly detected groundwater contaminants.

In the case of these amendments, the Minnesota Legislature is requiring MDH to "adopt an updated HRL value of no greater than 0.015 ppm for PFOS" under a Session Law passed in 2023 (Laws of Minnesota 2023, Chapter 60, Article 3, Section 34).

Minnesota Statutes, section 103H.201 authorizes MDH to adopt HRLs and provides a general outline of how to derive the HRLs:

1) MDH, in partnership with other State of Minnesota agencies, have detected and identified contaminants in groundwater that cause the degradation of groundwater in some locations where the groundwater is or could be used as a source of drinking water.

2) The contaminants have been evaluated and found to pose potential health risks to humans when they are consumed in groundwater for over defined durations of time.

3) Recent studies of the contaminants have been reviewed by MDH staff and have resulted in updated water guidance values for some contaminants.

4) MDH will use its authority to propose adoption of new or updated HRLs when there is concern about human consumption of contaminated water.

Background

The following section for MDH's guidance on groundwater contaminants covers:

- Defining HRLs
- the MDH-derived HRL algorithm;
- past MDH HRL rule revisions; and
- the statutory authority to review, derive, adopt, and revise HRL values.

Defining Health Risk Limits (HRLs)

HRL values are a type of health-protective guidance MDH develops 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 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. HBVs and HRLs are 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 must 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.

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 the Regulatory analysis section 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 adverse 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).

Past MDH HRL 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 updated and adopted into rule in 2015. In 2023, an updated value for tetrachloroethylene was updated and added to part 4717.7860 and removed from part 4717.7850. To date, four of the original 11 MCL values adopted in 2007, plus nitrate, remain unchanged in Minnesota Rules, part 4717.7850, subpart 2.

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.

In 2023, MDH adopted 17 new HRL values and 19 updated HRL values. The 19 updated HRL values replaced values initially adopted in 1993, 1994, 2009, 2011, and 2013. In addition, one 1994 HRL value (n-hexane) was deleted and replaced with Risk Assessment Advice (RAA) which cannot be adopted into rule as they are not established using the same process and information as required under the laws and rules that govern HRL adoption.

For this rulemaking, MDH proposes to adopt an updated HRL value for PFOS. MDH also will propose to update values for three additional HRLs adopted in 1993, 1994, and 2018. In total, there are six contaminants included in this rulemaking (anthracene, chlorothalonil, 1,2-dibromoethane, dichlorodifluoromethane, PFOA, and PFOS), all of which have previous HRL values. MDH is proposing to repeal the HRLs for six contaminants and replace four of them. For

the two HRLs that will not be replaced (anthracene and dichlorodifluoromethane), MDH has already created new RAAs and posted them on the MDH website. This guidance can be used as a water guidance value but cannot be adopted into rule. MDH develops RAA guidance when there is insufficient data to develop a new Health-Based Value using the HRL methodology adopted in 2009.

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 HRLs repealed and not replaced	Total Number of Contaminants with new or updated or repealed 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
2023	17	19	1	37
2024 (Proposed)	0	4	2*	6

*The HRL value for anthracene adopted in 1993 is outdated. A newer RAA value was published on the MDH website in 2019. The HRL value for dichlorodifluoromethane was adopted in 2011, but it is now outdated. A RAA value for dichlorodifluoromethane was published on the MDH website in 2017.

Statutory Authority

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

Minnesota Session Law

During the 2023 Legislative Session, the Minnesota Legislature passed a session law that requires MDH to adopt a value for perfluorooctane sulfonate (PFOS) into HRL rule that is no greater than 0.015 ppb. Specifically, Laws of Minnesota 2023, Chapter 60, Article 3, Section 34 states:

> By July 1, 2026, the commissioner of health must amend the health risk limit for perfluorooctane sulfonate (PFOS) in Minnesota Rules, part 4717.7860, subpart 15, so that the health risk limit does not exceed 0.015 parts per billion. In amending the health risk limit for PFOS, the commissioner must comply with Minnesota Statutes, section 144.0751, requiring a reasonable margin of safety to adequately protect the health of infants, children, and adults.

The Groundwater Protection Act of 1989

The *Groundwater Protection Act* of 1989—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 HRLs:

> (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)).

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 laws clearly establish MDH's authority to adopt the proposed rules.

Proposed Rules

Scope of Amendments

The proposed rule amendments are limited to Minnesota Rules, parts 4717.7500 and 4717.7860, with specific subparts noted below.

Through the proposed rules, MDH intends to:

- Repeal outdated guidance in Minnesota Rules, parts 4717.7500 or 4717.7860 for six contaminants. This includes four values to replace and two values, anthracene and dichlorodifluoromethane, that will only be repealed, as discussed above. Specifically, the values to be repealed from Minnesota Rules parts 4717.7500 or 4717.7860 are:
    - Anthracene (repeal from part 4717.7500, Subp. 5; adopted in 1993)

- Chlorothalonil (repeal from part 4717.7500, Subp. 26a; adopted in 1994)
- 1,2-Dibromoethane (ethylene dibromide, EDB) (repeal from part 4717.7500, Subp. 31; adopted in 1993)
- Dichlorodifluoromethane (repeal from part 4717.7860, Subp. 8g; adopted in 2011)
- Perfluorooctanoate (PFOA) and salts (repeal from part 4717.7860, Subp. 16; adopted in 2018)
- Perfluorooctane Sulfonate (PFOS) and salts (repeal from part 4717.7860, Subp. 15; adopted in 2009)

- Adopt into rule HRL values for four groundwater contaminants with guidance developed using the 2009 methodology and 2019 EPA intake rates. All four contaminants have previously-adopted HRL values in rule. The proposed HRL values, as described in detail in the Rule-by-Rule Analysis section would be added to Minnesota Rules, part 4717.7860:
    - Chlorothalonil (Add updated HRL to renumbered Subp. 7b)
    - 1,2-Dibromoethane (ethylene dibromide, EDB) (Add updated HRL to renumbered Subp. 7e)
    - Perfluorooctane Sulfonate (PFOS) and salts (Add updated HRL to Subp. 15)
    - Perfluorooctanoate (PFOA) and Salts (Add updated HRL to Subp. 16)

More detail about these proposed changes is provided below in the Rule-by-Rule Analysis section.

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	120-12-7	Anthracene (Repeal only and not replace. Updated RAA values have already been published.)	Yes (1993)
2	1897-45-6	Chlorothalonil	Yes (1994)
3	106-93-4	1,2-Dibromoethane (ethylene dibromide, EDB)	Yes (1993)
4	75-71-8	Dichlorodifluoromethane (Repeal only and not replace. Updated RAA	Yes (2011)

Number	Chemical Abstract Service (CAS) Number	Contaminant Name	Previously adopted values in HRL Rule? (year adopted)
		values have already been published.)	
5	45285-51-6; 335-67-1; 3825-26-1; 2395-00-8; 335-93-3; 335-95-5	Perfluorooctanoate (PFOA) and salts	Yes (2018)
6	45298-90-6; 1763-23-1; 29081-56-9; 70225-14-8; 2795-39-3; 9457-72-5	Perfluorooctane Sulfonate (PFOS) and salts	Yes (2009)

Rule-by-Rule Analysis

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 of contaminant per liter of water.
- **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 95^{th} 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.

Terminology

Terms used in the Proposed Rules section 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).

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

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 No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (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).

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 (UF) 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).

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

Proposed HRL Rules Amendments for Updated Guidance

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

Subpart. 7b. Chlorothalonil.

Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 7b for Chlorothalonil. Repeal Subp. 26a. Chlorothalonil from Minnesota Rules, part 4717.7500.

CAS number: 1897-45-6
Year Adopted: 2025
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	20	2	1	6
RFD (mg/kg-day)	--	0.014	0.00067	0.00029	--
RSC	--	0.5	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	0.017
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	--	0.290	0.074	0.045	$0.155_{(<2)}$ $0.040_{(2\ to\ <16)}$ $0.042_{(16+)}$
Endpoints	--	gastrointestinal system	gastrointestinal system	gastrointestinal system, hepatic (liver) system, renal (kidney) system	cancer

Acute duration
Not derived because of insufficient information.

Short-term duration
The proposed short-term nHRL is 20 µg/L. The RfD is 0.014 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.5. The POD is a $BMDL_{BMR5\%}$ of 6.13 mg/kg-d (Myers, 1995, as cited in EPA, 1995a). The DAF for body weight scaling is 0.22, and the HED is 1.35 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 suggestive testicular effects reported in other animal studies and human epidemiology studies that have not been thoroughly assessed). The critical effect is forestomach roughening and thickening in F1 pups. There is no co-critical effect. The additivity endpoint is gastrointestinal system.

Subchronic duration
The proposed subchronic nHRL is 2 µg/L. The RfD is 0.00067 mg/kg-d, and the intake rate is 0.074 L/kg-d. The RSC is 0.2. The POD is a $BMDL_{BMR5\%}$ of 0.293 mg/kg-d (Spencer-Briggs, 1994, aci EPA, 1994). The DAF for body weight scaling is 0.23, and the HED is 0.067 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 suggestive testicular effects reported in other animal studies and human epidemiology studies that have not been thoroughly assessed). The critical effect is epithelial hyperplasia and hyperkeratosis at the limiting ridge of the stomach in female rats. The co-critical effect is epithelial hyperplasia and hyperkeratosis in the nonglandular region of the stomach in female rats. The additivity endpoint is gastrointestinal system.

Chronic duration
The proposed chronic nHRL is 1 µg/L. The RfD is 0.00029 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a LOAEL of 1.9 mg/kg-d (Spencer-Briggs, 1995, aci EPA, 1995b). The DAF is 0.15 using body weight scaling (US EPA, 2011b; MDH, 2017). Multiplying the DAF by the POD results in an HED of 0.29 mg/kg-d. The UF is 1000 (3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for using a LOAEL in place of a NOAEL, and 3 for database uncertainty due to suggestive testicular effects reported in other animal studies and human epidemiology studies that have not been thoroughly assessed). The critical effects are epithelial hyperplasia and hyperkeratosis at the limiting ridge and in the nonglandular regions of the stomach in male mice. The co-critical effects are epithelial hyperplasia and hyperkeratosis at the limiting ridge and in the nonglandular regions of the stomach in females, ulceration of the nonglandular region of the stomach, thickened appearance of the forestomach in males, renal uniform cortical scarring, renal karyomegaly in males, and centrilobular hepatocyte enlargement. The additivity endpoints are gastrointestinal system, the hepatic (liver) system, and the renal (kidney) system.

Cancer
The proposed cancer cHRL value is 6 µg/L. EPA's cancer classification is "likely to be a human carcinogen by all routes of exposure" (EPA, 2021b), and the IARC classification is "possibly

carcinogenic to humans (IARC, 1999). The cancer slope factor is 0.017 mg/kg-d^{-1} based on combined renal and forestomach tumors from the male rat (Wilson and Killeen, 1989 aci EPA, 1991; California EPA, 2012)). 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 forestomach, kidney, liver, and thyroid.

Subpart. 7e. 1,2-Dibromoethane (ethylene dibromide, EDB)

Add the chemical name, CAS number, Year Adopted, Volatility and all data in the table below to Minnesota Rules, part 4717.7860, subpart 7e for 1,2-Dibromoethane. Repeal Subp. 31. 1,2-Dibromoethane (ethylene dibromide, EDB) from Minnesota Rules, part 4717.7500.

CAS number: 106-93-4
Year Adopted: 2025
Volatility: High

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	10	10 (2)	9	0.03
RFD (mg/kg-day)	--	0.018	(2)	0.0021	--
RSC	--	0.2	(2)	0.2	
SF (per mg/kg-day)	--	--	--	--	3.6
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	--	0.290	(2)	0.045	$0.155_{(<2)}$ $0.040_{(2\ to\ <16)}$ $0.042_{(16+)}$
Endpoints	--	female reproductive system, hepatic (liver) system, immune system, male reproductive system, renal (kidney) system, respiratory system, spleen	female reproductive system, hepatic (liver) system, immune system, male reproductive system, renal (kidney) system, respiratory system, spleen	female reproductive system, hepatic (liver) system, immune system, male reproductive system, respiratory system	cancer

Acute duration
Not derived because of insufficient information.

Short-term duration
The proposed short-term nHRL is 10 µg/L. The RfD is 0.018 mg/kg-d, and the intake rate is 0.290 L/kg-d. The RSC is 0.2. The POD is a LOAEL of 125 mg/kg-d (Ratajczak et al., 1994). The DAF for body weight scaling is 0.14, and the HED is 17.5 mg/kg-d. The total UF is 1000 (3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for using a LOAEL in place of a NOAEL, and 10 for database uncertainty due to the lack of two-generation reproductive, developmental, and developmental immunotoxicity studies). The critical effects are increased liver weight, increased cholesterol, and reduced T-cell response. The co-critical effects are increased kidney weight, increased neutrophils, decreased immune function in the lung, decreased viable cells in the spleen, increased estrus cycle length, and increased percentage of abnormal sperm. The additivity endpoints are female reproductive system, hepatic (liver) system, immune system, male reproductive system, renal (kidney) system, respiratory system, and spleen.

Subchronic duration
The proposed subchronic nHRL is 10 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 10 µg/L. The additivity endpoints are female reproductive system, hepatic (liver) system, immune system, male reproductive system, renal (kidney) system, respiratory system, and spleen.

Chronic duration
The proposed chronic nHRL is 9 µg/L. The RfD is 0.0021 mg/kg-d, and the intake rate is 0.045 L/kg-d. The RSC is 0.2. The POD is a NOAEL of 44.6 mg/kg-d (Ratajczak et al., 1995). The DAF is 0.14 using body weight scaling (US EPA, 2011b and MDH, 2017). Multiplying the DAF by the POD results in a HED of 6.24 mg/kg-d. The UF is 3000 (3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for extrapolation to a chronic duration from a subchronic study, and 10 for database uncertainty for lack of two-generation reproductive, developmental, and developmental immunotoxicity studies). The critical effects are decreased T- and B-cell responses and increased cholesterol and triglycerides. The co-critical effects are increased relative liver weight, increased cholesterol, decreased T-cell response, decreased immune function in the lung, increased estrus cycle length, and increased percentage of abnormal sperm. The additivity endpoints are female reproductive system, hepatic (liver) system, immune system, male reproductive system, and respiratory system.

Cancer
The proposed cancer cHRL value is 0.03 µg/L. EPA's cancer classification is "likely to be carcinogenic to humans" (EPA, 2004), and the IARC classification is "2A - probably carcinogenic to humans" (IARC, 1999). The cancer slope factor is 3.6 $(mg/kg\text{-}d)^{-1}$ based on forestomach tumors in male and female rats and mice (NCI, 1978). 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 forestomach, esophagus, blood vessels, liver, lung, thyroid gland, and adrenal gland.

Subpart. 15. Perfluorooctane sulfonate (PFOS) and Salts:

Change the Year Adopted and the data for PFOS to Minnesota Rules, part 4717.7860, subpart 15, as shown in the table below.

CAS numbers: 45298-90-6; 1763-23-1; 29081-56-9; 2795-39-3; 70225-14-8; and 29457-72-5
Year Adopted: [Delete: 2009, Add: 2025]
Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	[Delete: ND; Add: 0.0023]	[Delete: ND; Add: 0.0023]	[Delete: 0.3; Add: 0.0023]	[Delete: NA; Add: 0.0076]
[Delete :RfD Add: RfSC] [Delete: (mg/kg-day) [Add: (ng/mL)*]	--	[Delete:--; Add: 2.6]	[Delete:--; Add: 2.6]	[Delete:0.00008; Add: 2.6]	--
RSC	--	[Delete:--; Add: 0.2]	[Delete:--; Add: 0.2]	0.2	--
SF (per mg/kg-day)	--	--	--	--	[Delete:--; Add: 13]
ADAF or $AF_{lifetime}$	--	--	--	--	[Delete:--; Add: 10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)]
Intake Rate (L/kg-day)	--	[Delete: --; Add: #]	[Delete: --; Add: #]	[Delete:0.049; Add: #]	[Delete: --; Add: $0.155_{(<2)}$ $0.040_{(2\ to\ <16)}$ $0.042_{(16+)}$]

	Acute	Short-term	Subchronic	Chronic	Cancer
Endpoints	--	[Delete: --; Add: developmental, hepatic (liver) system, immune system]	[Delete:--; Add: developmental, hepatic (liver) system, immune system]	[Delete: thyroid (E); Add: immune system]	[Delete: --; Add: cancer]

[Add: *A reference serum concentration (ng/mL) rather than a reference dose (mg/kg-d) was used in MDH's toxicokinetic model to calculate noncancer guidance values for PFOS.

95th percentile water intake rates (Tables 3-1, 3-3, and 3-5 in the Environmental Protection Agency, Exposures Factor Handbook, 2019), or upper percentile breastmilk intake rates (Table 15-1), Environmental Protection Agency Exposure Factors Handbook, 2011.]

Acute duration
Not derived because of insufficient information.

Short-term, Subchronic, and Chronic Durations
The proposed short-term, subchronic, and chronic nHRLs are 0.0023 µg/L. The RfSC for humans is 2.6 ng/mL, determined by MDH in 2023. The POD is a serum concentration of 7.7 ng/mL (equivalent to µg/L) (US EPA 2023a,b), based on a $BMDL_{5\%}$ for decreased birth weight from Wikström, 2020. The DAF and HED are not applicable in this case, as the POD is based on human data. The intake rate is the 95th percentile of water intake rates in Tables 3-1, 3-3, and 3-5 in the EPA's Exposures Factor Handbook (2019), or upper percentile breastmilk intake rates in Table 15-1 from Exposure Factors Handbook (2011). The RSC is 0.2. The total uncertainty factor (UF) is 3, which was applied to account for the remaining database uncertainties regarding potential adverse effects at or near the serum POD concentration. A UF for human toxicodynamics variability was not applied because the POD is based on a sensitive lifestage. Further, differences in human TK were determined to be adequately addressed through the exposure scenario and parameter values selected for use in the TK model. The critical effect is decreased birth weight. The co-critical effects are decreased antibody titers in children and increased cholesterol. The additivity endpoints are developmental system, hepatic (liver) system, and immune system.

Cancer
The proposed cancer cHRL value is 0.0076 µg or (7.6 ng/L) EPA's cancer classification is "likely to be carcinogenic to humans" (US EPA 2023a,b). The California EPA Office of Environmental Health Hazard Assessment (California EPA) (2023) has noted that PFOS "presents a carcinogenic hazard," and the IARC classification is "Group 2B (possibly carcinogenic to humans)" (IARC 2023)). The cancer slope factor is 13 per mg/kg-day for combined hepatocelluar adenomas and carcinomas in female rats (US EPA 2023a,b) and tumor data from Butenhoff et al.,2012. This

was derived from a US EPA cancer slope factor of 39.5 per mg/kg-d (US EPA 2023a,b) converted to 13 per mg/kg-d using a clearance rate of 0.39 mL/kg-d from California EPA, 2023. 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. 16. Perfluorooctanoate (PFOA) and salts

CAS numbers: 45285-51-6; 335-67-1; 3825-26-1; [Delete: 335-66-0;]2395-00-8; 335-93-3; 335-95-5

Year Adopted: [Delete: 2018, Add: 2025]

Volatility: Nonvolatile

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	[Delete: 0.035; Add: 0.00024]	[Delete: 0.035; Add 0.00024]	[Delete: 0.035; Add 0.00024]	[Delete: NA; Add 0.0000079]
[Delete :RfD Add: RfSC] [Delete: (mg/kg-day) Add: (ng/mL)*] R	--	[Delete 0.000018; Add: 0.93]	[Delete 0.000018; Add: 0.93]	[Delete 0.000018; Add: 0.93]	--
RSC	--	[Delete: 0.5; Add: 0.2]	[Delete: 0.5; Add: 0.2]	[Delete: 0.5; Add: 0.2]	--
SF (per ng/kg-day)	--	--	--	--	[Delete: --; Add: 0.0126]
ADAF or $AF_{lifetime}$	--	--	--	--	[Delete: --; Add: 10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)]
Intake Rate (L/kg-day)	--	[Delete: *; Add: #]	[Delete: *; Add: #]	[Delete: *; Add: #]	[Delete: --; Add: $0.155_{(<2)}$ $0.040_{(2\ to\ <16)}$ $0.042_{(16+)}$]
Endpoints	--	developmental, hepatic (liver) system, immune system [Delete: renal (kidney) system]	developmental, hepatic (liver) system, immune system [Delete: renal (kidney) system]	developmental, hepatic (liver) system, immune system [Delete: renal (kidney) system]	[Delete: --; Add: cancer]

[Add: * A reference serum concentration (ng/mL) rather than a reference dose (mg/kg-d) was used in MDH's toxicokinetic model to calculate noncancer guidance values for PFOA.]

[#] 95th percentile water intake rates (Tables 3-1 [Delete: and; Add: ,] 3-3 [Add: , and 3-5 in the Environmental Protection Agency, Exposures Factor Handbook, 2019)], or upper percentile breastmilk intake rates (Table 15-1), Environmental Protection Agency[Delete: (EPA)] Exposure Factors Handbook, 2011.

Acute duration
Not derived because of insufficient information.

Short-term, Subchronic, and Chronic Durations
The proposed short-term, subchronic, and chronic nHRLs are 0.00024 µg/L. The RfSC is 0.93 ng/mL, determined by MDH in 2023. The intake rate is the 95th percentile of water intake rates in Tables 3-1, 3-3, and 3-5 in the EPA Exposures Factor Handbook (2019), or upper percentile breastmilk intake rates in Table 15-1 from Exposure Factors Handbook (EPA, 2011). The RSC is 0.2. The POD is 2.8 ng/mL based on a $BMDL_{5\%}$ for decreased haemophilus influenzae Type B (Hib) antibodies (Abraham et al., 2020). There are no DAF or HED values for this calculation because the POD was based on human serum levels. The total UF is 3, which was applied to account for the remaining database uncertainties regarding potential adverse effects at or near the serum POD concentration. A UF for human toxicodynamics variability was not applied because the POD is based on a sensitive lifestage. The critical effect is decreased antibody titers in infants. The co-critical effects are decreased antibody titers in children, decreased birthweight, increased cholesterol, and increased ALT (liver enzyme). The additivity endpoints are developmental, hepatic (liver) system, and immune system.

Cancer
The proposed cancer cHRL value is 0.0000079 ug/L (or 0.0079 ng/L.). EPA's cancer classification is "likely to be carcinogenic to humans" (US EPA 2023 a,b). The California EPA (2023) has noted "strong evidence of carcinogenicity," and the IARC classification is "Group 1 (carcinogenic to humans)" (IARC 2023)). The cancer slope factor is 0.0126 per ng/kg-day based on renal cell carcinoma in humans (Shearer et al., 2021). The source of the cancer slope factor is a serum slope factor of 0.00325 per ng/mL (from US EPA 2023a,b), converted to 0.0126 per ng/kg-d using a clearance rate of 0.28 mL/kg-d (California EPA, 2023). 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 for human are kidney, which is the basis of this guidance, and testicle. For animals, the tumor sites are liver and pancreas.

Proposed HRL Rules for Deletion

Proposed Deletion: Health Risk Limit: Minnesota Rules, part 4717.7860)

Subp. 8g. Dichlorodifluoromethane (2011)

The outdated HRL for dichlorodifluoromethane, adopted in 2011, will be repealed only. MDH has replaced the dichlorodifluoromethane HRL with an RAA value.

Proposed Deletions: Health Risk Limits: (Minnesota Rules, part 4717.7500)

Based on MDH's recent review of health-based guidance values listed in Minnesota Rules, part 4717.7500, MDH intends to repeal three outdated HRLs adopted into rule in 1993 or 1994. The specific subparts to be repealed are noted below:

Subp. 5. Anthracene (1993)

Subp. 26a. Chlorothalonil (1993)

Subp. 31. 1,2-Dibromoethane (ethylene dibromide, EDB) (1994)

As discussed above in the Proposed Rules: The Health Risk Limits Table section, updated values for Chlorothalonil and 1,2-Dibromoethane will be added to part 4717.7860 at proposed subparts 7b and 7e. **The outdated HRL for anthracene, adopted in 1993, will be repealed only**. MDH has replaced the Anthracene HRL with Risk Assessment Advice (RAA).

Public participation and interested party involvement

Selection of Contaminants for Review

MDH selected the contaminants for the 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 for more information on selected contaminants).

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 periodically sends emails to the GovDelivery subscribers as reminder that nominations opportunities are available. MDH then screens these nominated 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. Three contaminants that were adopted into rule from 2009 to 2018 were re-evaluated from 2022 to 2023. These HRL re-

evaluations are included in the proposed rule.

As MDH reviewed or re-evaluated each contaminant, it posted the chemical's name, its Chemical Abstracts Service (CAS) Registry Number, and the date the review was started on MDH's Chemicals Under Review webpage, available at: Chemicals Under Review (https://www.health.state.mn.us/communities/environment/risk/review.html). A GovDelivery message is also sent to all interested parties subscribed to this account (8,139 number as of June 25, 2024). MDH invites questions, data submissions or comments throughout the review process.

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 Email Updates https://public.govdelivery.com/accounts/MNMDH/subscriber/new?topic_id=MNMDH_39.

Notice Plan

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

Notice

MDH will notify all parties listed on the current Minnesota Department of Health Rulemaking Notice List at least three days prior to the publication of Notice of Intent to Adopt Rules in the *State Register*. Further, MDH will complete all the additional activities listed below:

Additional notice plan

MDH attempts to notify as many parties with potential interest in HRLs as possible. Because the HRL Rules affect groundwater, which about 75% of Minnesotans consume for drinking water, there is a potentially a very large audience. However, not all affected parties will have interest in the topic. Therefore, MDH uses an email subscription service to communicate with interested parties about MDH's work on water guidance values and updates to the values. The account is called Groundwater Rules, Guidance, and Chemical Review and is hosted by a commercial service called GovDelivery (offered by the company Granicus). Anyone may sign up for these emails for free on MDH webpages or by phoning or emailing HRA Unit staff.

Another method that MDH uses to communicate detailed information about rulemaking is via its website where there are several pages dedicated to the HRL rulemaking activities. The home page for this collection of webpages is found at Health Risk Limits Rules for Groundwater Rules Amendments - Overview and Links (https://www.health.state.mn.us/communities/environment/risk/rules/water/overview.html).

Moreover, MDH often uses direct communication, via direct email or via phone call, to contact interested parties about developments with the HRL Rules, including announcing opportunities for comment.

Notifications completed or planned for each stage of this rulemaking are as follows:

Request for Comments

The Request for Comments was published on August 7, 2023. The morning of August 7th, MDH sent emails directly to 10 industry representatives or trade organization staff, seven environmental advocacy organization staff, two academic staff, and one corporate public affairs consultant who had requested notice about HRL rulemaking activity. The same day, MDH also sent emails to 14 interested staff members of other State agencies about the open Request for Comments. Further, MDH sent out an email notice to the 6,416 subscribers (as of August 7, 2023) to 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 webpages that provide information about each chemical with water guidance eligible for rulemaking.

In an attempt to reach a wider audience that may have interest in the HRL Rules, we also worked with the MDH Drinking Water Protection Section to publish a short announcement called "MDH proposing updates to health risk limits (https://www.health.state.mn.us/communities/environment/water/waterline/winter20232024.html#NaN)" in the Winter 2023-2024 Waterline, an MDH publication that is of interest to water operators and others. As of June 25, 2024, this publication had been viewed 744 times from the MDH website. Paper copies are also sent to 75 subscribers of the Waterline. There is also a GovDelivery account that delivers this information electronically to 7,700 subscribers (as of November 2023), but there might be some overlap among people who subscribe to the paper copies and who view the electronic copy.

Extended outreach

In past HRL rulemaking, many of the parties with comments have been either from large chemical manufacturers, chemical trade associations, chemical manufacturing lobbying groups, community advocacy groups, or state legislators. The PFAS chemicals (sometimes called "forever chemicals") are perhaps more recognizable by the public than some of the chemicals in past HRL rulemaking, and there may be more interest in them from groups with interest in health-equity or environmental justice. Our staff have had meetings with the Tribal Liaison and the Environmental Health's Health Equity Strategist to provide information about the Health Risk Limits Rules and to discuss ways to continue to conduct outreach for comment related to these rules.

Dual Notice of Intent to Adopt Rules

MDH will publish a Dual 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 8,537 subscribers (as of September 18, 2024) of its Water Rules, Guidance and Chemical Review email subscription service account. Subscribers to this account include most parties known to be 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, state legislators, and chemical manufacturers such as 3M, Bayer, and other companies. 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.

Regulatory analysis

This section discusses the department's consideration and implementation of performance-based rules and the impact of the proposed rules, as required by Minnesota Statutes, section 14.131.

The department's consideration of the eight factors for regulatory analysis that agencies must include in the SONAR under Minnesota Statutes, section 14.131 follows:

1) Description of the classes of persons who probably will be affected by the proposed rule, including classes that will bear the costs of the proposed rule and classes that will benefit from the proposed rule.

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 to some extent. Those who are affected depends more 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 of decisions by third parties 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." These decisions will impact who is affected by the HRL rules.

2) The probable costs to the agency and to any other agency of the implementation and enforcement of the proposed rule and any anticipated effect on state revenues.

The proposed amendments *do not* have any direct impact on state revenues, nor are there any costs to any state agencies related to the proposed rules' implementation or enforcement. There are no fees associated with the rules. The amendments simply provide health-based

levels for certain water contaminants. Some programs with enforcement or remediation authorities within MDH or other agencies might choose to implement and enforce their own authorities and rules in response to these amendments. Other programs and 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 methods 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. The HRA Unit staff calculate the water guidance values for the identified contaminants and the calculated values themselves are proposed for adoption into rule. As described in the section MDH-derived HRL Algorithm 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 that 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 outline how MDH 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 repeals old values and adds updated 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, as all HRLs must have been detected in Minnesota groundwater.

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, including the portion of the total costs that will be borne by identifiable categories of affected parties, such as separate classes of governmental units, businesses, or individuals.

HRL rules establish concentration levels of certain substances or chemicals in groundwater which may present health risks, but do not specify how to apply these health-protective numbers or what one must do in response to them. Neither MDH nor any other government entity can or will enforce compliance with HRLs, and there can be no cost, therefore, of complying with these unenforceable benchmarks.

While MDH cannot quantify the probable costs of complying with other legal requirements that refer to the HRLs proposed to be amended, MDH can describe generally how other regulations that incorporate 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. The values for the four contaminants proposed for rule are lower than the previous HRLs. Treatment of water to lower the concentration below the previous HRL level might increase the cost above the implementation of the previous HRL, but this can only be determined in each case by the enforcing agency.

6) The probable costs or consequences of not adopting the proposed rule, including those costs or consequences borne by identifiable categories of affected parties, such as separate classes of government units, businesses, or individuals.

Not adopting the proposed amendments would impose costs or consequences affecting water safety and quality that cannot be calculated. As stated above, Minnesota's groundwater is a primary source of drinking water for around 75% of 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 alone does 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) An assessment of any differences between the proposed rule and existing federal regulations and a specific analysis of 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
- 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 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 adopted into federal rule in 2001. While EPA currently has new MCLs proposed for six contaminants, two of which are included in this rulemaking (PFOA and PFOS, as described below), most MCLs were developed using outdated methods based only on adult intakes and body weight.

In April 2024, EPA announced finalized National Primary Drinking Water Regulation for PFOA and PFOS. The new Maximum Contaminant Levels (MCLs) for PFOA and PFOS are 4 ppt, while the Maximum Contaminant Level Goal (MCLG) for each is 0 ppt. As noted above, unlike the Minnesota HRLs, the EPA must consider several factors when deriving an MCL, such as the feasibility of detection, treatment, and cost of treatment. Minnesota Statute defines the mandate that MDH consider only health effects when deriving HRLs for groundwater

contaminants.

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 at industrial locations, 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 162 chemicals that have been found in Minnesota groundwater; there are 97 chemicals for which EPA has MCLs. This proposed update for 4 existing HRL values and the repeal of the anthracene HRL and 1,2-Dibromoethane (ethylene dibromide, EDB) HRL (1994) will make a total of 160 HRLs 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, 2021a). 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) Assessment of the cumulative effect of the rule with other federal and state regulations.

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.

Health Equity and Environmental Justice

Clean and safe drinking water is essential for good health for all people. MDH's methodology for assessing the potential health impacts from contaminants is designed to protect those who may be at higher risk for health impacts from potentially greater exposures to chemicals and intrinsic biological factors that potentially increase susceptibility to adverse effects of chemical exposure. MDH acknowledges that communities of color, those in some rural areas, and people with disabilities continue to experience higher rates of environmental contaminant exposure due to systemic polices that result in increased risk for adverse health effects. Further, there is growing awareness that non-chemical stressors associated with socioeconomic status, racism, discrimination associated with sexual orientation or disability status, genetic disposition, and others can converge with environmental exposures, or act on their own, to affect health. MDH strives to include information about socioeconomic and societal factors when developing water guidance.

Currently, within MDH's guidance development, higher exposure concerns are addressed by:

- Using the upper percentile drinking water intake rates in our duration-specific guidance calculations, as opposed to using a mean or median intake rates. This protects most of the population.

- Using intake rates for bottle-fed infants and children to calculate the acute and short-term duration guidance values. These are two of the most vulnerable populations to contaminant toxicity.

- Using a relative source contribution factor (RSC) in our guidance equation. This factor assigns a percentage of exposure that occurs only through water. If a certain population has other exposures to a specific contaminant (dermal, inhalation, food, etc.) the RSC is reduced to allow for these other exposures.

Data that would allow MDH to address potentially increased susceptibility to health effects related to biological/intrinsic factors such as genetics or metabolism is limited, but MDH continues to search for these data and incorporates findings into the guidance when possible. MDH also uses exposure information from communities, when available, to select contaminants for guidance development, particularly for Contaminants of Emerging Concern, and to develop the water guidance with contaminant exposure data incorporated into the calculations.

While there is still work to be done to determine how best to incorporate information about exposures and non-chemical stressors into MDH water guidance, especially as it relates to socioeconomic and societal factors, MDH is committed to working toward health and racial equity and environmental justice for all Minnesotans. This includes committing to thoughtfully calculating water guidance in a way that protects everyone, including those who are in sensitive developmental lifestages and individuals whose communities have been disproportionately impacted by inequities. MDH is also committed to sharing our methods for deriving guidance with communities around Minnesota through GovDelivery and meaningful engagement. MDH's ultimate goal is to ensure that all Minnesotans have access to clean, safe drinking water.

Performance-based rules

Minnesota Statutes, section 14.002, requires state agencies, whenever feasible, to develop rules that are not overly prescriptive and inflexible, and rules that emphasize achievement of the agency's regulatory objectives while allowing maximum flexibility to regulated parties and to the agency in meeting those objectives.

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 interested parties, including other regulatory agencies, may examine the options and make decisions on a course of action. After implementation, they may evaluate outcomes.

Consult 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.

Impact on local government ordinances and rules

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.

Costs of complying for small business or city

Minnesota Statutes, section 14.127, subdivisions 1 and 2, require an agency to "determine if the cost of complying with a proposed rule in the first year after the rule takes effect will exceed $25,000 for any one business that has less than 50 full-time employees, or any one statutory or home rule charter city that has less than ten full-time employees."

As described in detail above, there are no enforcement provisions associated with the proposed amendments to Minnesota Rules, parts 4717.7500 and .7860, or those rule parts themselves; thus, there are necessarily no costs associated with compliance with the proposed rule. As required by the plain language of Minnesota Statutes, section 14.127, the Department has determined that the cost of complying with the proposed rule in the first year after the rule takes effect will not exceed $25,000 for: (1) any one business that has less than 50 full-time employees; or (2) any one statutory or home rule charter city that has less than ten full-time employees.

Witnesses and other staff

The agency will publish a Dual Notice of Intent to Adopt Rules, meaning that if 25 or more people request a hearing, a hearing will be held. If less than 25 people request a hearing, a hearing will not be held. If a hearing is necessary, the agency anticipates having no outside witnesses testify.

All witnesses will likely be MDH staff members.

Conclusion

In this SONAR, the agency has established the need for and the reasonableness of each of the proposed amendments to Minnesota Rules, parts 4717.7500 and 4717.7860. The agency has provided the necessary notification documented in this SONAR its compliance with all applicable administrative rulemaking requirements of Minnesota statute and rules.

Based on the forgoing, the proposed amendments are both needed and reasonable.

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Wendy Underwood
Deputy Commissioner, Minnesota Department of Health

/s/ Wendy Underwood

Date 10/28/24

Appendix A: Glossary of Terms Used in Risk Assessment

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).

Reference Serum Concentration (RfSC): An estimate of the amount of a chemical in the serum of a 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 comparing the serum concentrations of the chemical 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 RfSC is typically expressed in units of nanograms of the chemical per milliliter of serum (ng/mL).

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 (https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=20003D2R.txt) 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 an 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 MDH-derived HRL Algorithm, 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 $>3 \times 10^{-7}$ to 1×10^{-5} atm-m^3/mol
- Moderate volatility – Henry's Law constant $>1 \times 10^{-5}$ to 1×10^{-3} atm-m^3/mol
- High volatility – Henry's Law constant $> 1 \times 10^{-3}$ atm-m^3/mol

Uncertainty Factors (UFs)

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

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

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

- Interspecies Extrapolation Factor – This factor accounts for the uncertainty or the difference between animals and humans when laboratory animal data are used as the source of the point of departure (POD). It is composed of two subfactors: 1) toxicokinetics (absorption, distribution, metabolism and elimination of the chemical) and 2) toxicodynamics (the body's response to the chemical). The current practice is to use either chemical-specific toxicokinetic data or a data-based adjustment for toxicokinetics rather than an uncertainty factor for toxicokinetics. If there is no chemical-specific information regarding quantitative differences between laboratory animals and humans, a body-weight scaling adjustment based on EPA guidance (EPA, 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 MDH-derived HRL Algorithm, 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 95th 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 rounded to 3 µg/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 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:

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

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.

Table D-1. Request for Guidance on Groundwater Contaminants

CAS Numbers	Chemical Name	HBV year	Origin of Request
120-12-7	Anthracene	(RAA 2019 HRL from 1993 to be repealed)	MPCA
1897-45-6	Chlorothalonil	2023	MDA
106-93-4	1,2-Dibromoethane (ethylene dibromide, EDB)	2023	MPCA
75-71-8	Dichlorodifluoromethane	(RAA 2017 HRL from 2011 to be repealed)	Scheduled Re-evaluation
45285-51-6; 335-67-1; 3825-26-1; 2395-00-8; 335-93-3; 335-95-5	Perfluorooctanoate (PFOA) and salts	2024	Scheduled re-evaluation
45298-90-6; 1763-23-1; 29081-56-9; 70225-14-8; 2795-39-3; 9457-72-5	Perfluorooctane sulfonate (PFOS) and salts	2024	Scheduled re-evaluation

Appendix E: Toxicological Summary Sheets

Copies of all four of the Toxicological Summary sheets can be viewed below.

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

Web Publication Date: January 2023

Toxicological Summary for: Chlorothalonil

CAS: **1897-45-6**
Synonyms: Tetrachloroisophthalonitrile; 1,3-Dicyanotetrachlorobenzene; 2,4,5,6-tetrachlorobenzene-1,3-dicarbonitrile (IUPAC)

Acute Non-Cancer Health-Based Value (nHBVAcute) = Not Derived (Insufficient Data)

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

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

$$= \frac{\text{(0.014 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 24.1 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 = 1.35/100 = 0.014 mg/kg-d (Crl:CD®BR VF/Plus Rat)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	6.13 mg/kg-d (administered dose $BMDL_{BMR5\%}$, Myers 1995)
Dose Adjustment Factor (DAF):	0.22 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 6.13 mg/kg-d x 0.22 = 1.35 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 suggestive testicular effects reported in other animal studies and human epidemiology studies that have not been thoroughly assessed
Critical effect(s):	Forestomach roughening and thickening in F1 pups
Co-critical effect(s):	None
Additivity endpoint(s):	Gastrointestinal system

Subchronic Non-Cancer Health-Based Value ($nHBV_{Subchronic}$) = 2 µg/L

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

$$= \frac{\text{(0.00067 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 1.8 rounded to **2 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 = 0.067/100 = 0.00067 mg/kg-d (Sprague-Dawley rat)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	0.293 mg/kg-d (administered dose $BMDL_{BMR5\%}$, Spencer-Briggs 1994)
Dose Adjustment Factor (DAF):	0.23 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 0.293 mg/kg-d x 0.23 = 0.067 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 suggestive testicular effects reported in other animal studies and human epidemiology studies that have not been thoroughly assessed
Critical effect(s):	Epithelial hyperplasia and hyperkeratosis at the limiting ridge of the stomach in female rats
Co-critical effect(s):	Epithelial hyperplasia and hyperkeratosis in the nonglandular region of the stomach in female rats
Additivity endpoint(s):	Gastrointestinal system

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

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

$$= \frac{\text{(0.00029 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 1.29 rounded to **1 µg/L**

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

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

Reference Dose/Concentration:	HED/Total UF = 0.29/1000 = 0.00029 mg/kg-d (Crl:CD(SD)BR mice)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	1.9 mg/kg-d (administered dose LOAEL, Spencer-Briggs 1995)
Dose Adjustment Factor (DAF):	0.15 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 1.9 mg/kg-d x 0.15 = 0.29 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for using a LOAEL in place of a NOAEL, and 3 for database uncertainty due to suggestive testicular effects reported in other animal studies and human epidemiology studies that have not been thoroughly assessed
Critical effect(s):	Epithelial hyperplasia and hyperkeratosis in the nonglandular and limiting ridge regions of the stomach in male mice
Co-critical effect(s):	Epithelial hyperplasia and hyperkeratosis at the limiting ridge and in the nonglandular regions of the stomach in females, ulceration of the nonglandular region of the stomach, thickened appearance of the forestomach in males, renal uniform cortical scarring, renal karyomegaly in males, and centrilobular hepatocyte enlargement
Additivity endpoint(s):	Gastrointestinal system, Hepatic (liver) system, Renal (kidney) system

Cancer Health-Based Value (cHBV) = 6 µg/L

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

$$\frac{= (1E\text{-}5) \times (1000\ \mu g/mg)}{[(0.017 \times 10^{*} \times 0.155\ L/kg\text{-}d^{**} \times 2) + (0.017 \times 3^{*} \times 0.040\ L/kg\text{-}d^{**} \times 14) + (0.017 \times 1^{*} \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 5.84 rounded to **6 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 a human carcinogen by all routes of exposure (EPA 2021); Possibly carcinogenic to humans (IARC 1999)
Slope factor (SF):	0.017 mg/kg-d^{-1} (Combined renal and forestomach tumors from the male rat, Wilson and Killeen 1989)

Source of cancer slope factor (SF): (California EPA 2012)
Tumor site(s): Forestomach, Kidney, Liver, Thyroid

Volatile: No

Summary of Guidance Value History:

Guidance for chlorothalonil was first developed by MDH in 1993/1994 with a cancer HRL = 30 µg/L. In 2014, MDH developed a cancer pesticide rapid assessment of 6 µg/L and a noncancer rapid assessment of 50 µg/L. The cancer guidance was lower in the pesticide rapid assessment than the 1993/1994 HRL due to the use of a newer slope factor (California EPA 2012). In 2022 MDH conducted an in-depth full review of chlorothalonil. The cancer guidance in the full review (6 µg/L) and the pesticide rapid assessment cancer value are the same because the slope factor and equation used are identical. The 2022 full review noncancer guidance (short-term, subchronic, and chronic) are lower than the 2014 noncancer rapid assessment as a result of using: 1) updated intake rates; 2) BMD modeling; and 3) selection of a more sensitive health endpoint (gastrointestinal).

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]	No[2]	Yes[3]	Yes[4]	No[5]

Comments on extent of testing or effects:

[1] A provocative but limited study in mice reported changes in the enzymes that make estradiol and progesterone at chlorothalonil levels equal to the short-term RfD, but 19 times higher than the subchronic RfD, and 45 times higher than the chronic RfD. At levels 460 times higher than the short-term RfD, chlorothalonil affected the maturation of ovarian follicles. Fertility in this study was not tested. In rats, increased pituitary gland weight was reported at levels 2,000 times higher than the short-term RfD and a decrease in T4 was reported at levels 3,000 times higher than the short-term RfD. Parathyroid hyperplasia was reported in rats beginning at levels 800 times higher than the short-term RfD. In beagles, increased thyroid weight occurred at chlorothalonil doses 16,000 times higher than the short-term RfD. Also at this dose an enlargement in adrenal cells was reported. In another beagle study, the absolute weight of the adrenal gland and its width were increased at chlorothalonil levels 22,000 times higher than the short-term RfD. Other animal studies also reported adrenal gland

enlargement and hyperplasia. In mice these changes occurred at levels 80 times higher than the short-term RfD. Testicular weight decrease occurred in male rats at levels 13,000 times higher than the short-term RfD while ovarian masses were observed in female rats at levels 1,300 times higher than the short-term RfD.

[2] EPA reported no effects from an immunologic study in laboratory animals. However, in a chronic toxicity study in female rats, a complete involution of the thymus occurred at levels 700 times higher than the short-term RfD.

[3] Early pregnancy resorptions occurred in both rats and mice at levels 7,000 and 4,000 times higher, respectively, than the short-term RfD. Reduced fetal and pup body weights were commonly reported in mouse and rat studies. Fetal mouse and rat pups were both reported to have reduced body weights at chlorothalonil levels beginning at 4,000 and 2,000 times higher, respectively, than the short-term RfD. In the rat, this was accompanied by reduced pup viability at 4,000 times higher than the short-term RfD. Skeletal variations were reported in fetal rats at levels 3,000 times higher than the short-term RfD. Delayed vaginal patency and preputial separation, most likely due to reduced body weights, were reported in developing rats at levels 4,000 times higher than the short-term RfD. In rabbits, reduced fetal bodyweights and skeletal variations were common at doses 700 times higher than the short-term RfD. Fetal malformations were also reported at levels 700 times higher than the short-term RfD. Abortions in rabbits occurred at chlorothalonil levels 300 times higher than the short-term RfD.

[4] The only reproductive effect reported from a sponsored study was reduced uterine weight in one rabbit study at a level of chlorothalonil 100 times higher than the RfD. A recent non-sponsored study in mice reported reduced sperm motility at the same level as the short-term RfD, but at levels 19 times higher than the subchronic RfD, and 45 times higher than the chronic RfD. At a chlorothalonil exposure 100 times higher than the short-term RfD were a reduction in sperm number and slower sperm maturation. The same laboratory reported the hormone and ovarian effects mentioned in the endocrine section, above. Adverse sperm effects have been reported in human epidemiology studies from exposure to chlorinated chemicals. Unfortunately, most of the animal studies in the chlorothalonil database did not test for sperm effects. This resulted in a data base uncertainty factor of "3" added to the chlorothalonil reference doses. Other reproductive effects in rats and mice include a decrease in the number of live fetuses at levels 4,000 times higher than the short-term RfD, and post-implantation loss and early resorptions at levels 4,000 times higher in mice and 7,000 times higher than the short-term RfD in rats.

[5] An acute neurotoxicity study in rats detected no effects at a chlorothalonil dose up to 33,000 times higher than the short-term RfD. In a subchronic neurotoxicity study, no effects were reported in rats up to 4,000 times higher than the short-term RfD. A decrease in brain weight was observed at a level 6,000 times higher than the short-term RfD in rats.

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Toxicological Summary for: 1,2-Dibromoethane

CAS: **106-93-4**
Synonyms: Ethylene dibromide; ethane, 1,2-dibromo-

Acute Non-Cancer Health-Based Value = Not Derived (Insufficient Data)

Short-term Non-Cancer Health-Based Value ($nHBV_{Short\text{-}term}$) = 10 µg/L

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

$$= \frac{\text{(0.018 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 12.4 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:	HED/Total UF = 17.5/1000 = 0.018 mg/kg-d (female B6C3F1 mice)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	125 mg/kg-d (LOAEL, Ratajczak, 1994)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (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):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for using a LOAEL in place of a NOAEL, and 10 for database uncertainty due to the lack of two-generation reproductive, developmental, and developmental immunotoxicity studies
Critical effect(s):	Increased liver weight, increased cholesterol, and reduced T-cell response
Co-critical effect(s):	Increased kidney weight, increased neutrophils, decreased immune function in the lung, decreased viable cells in the spleen, increased estrus cycle length, increased percentage of abnormal sperm
Additivity endpoint(s):	Female reproductive system, Hepatic (liver) system, Immune system, Male reproductive system, Renal (kidney) system, Respiratory system, Spleen

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

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

$$= \frac{\text{(0.021 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 56.8 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 = 6.24/300 = 0.021 mg/kg-d (female B6C3F1 mice)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	44.6 mg/kg-d (NOAEL, Ratajczak, 1995)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 44.6 mg/kg-d x 0.14 = 6.24 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 for lack of two-generation reproductive, developmental and developmental immunotoxicity studies
Critical effect(s):	Decreased T- and B-cell responses, increased cholesterol and triglycerides
Co-critical effect(s):	Increased liver weight, increased cholesterol, decreased T-cell response, decreased immune function in the lung, increased estrus cycle length, and increased percentage of abnormal sperm
Additivity endpoint(s):	Female reproductive system, Hepatic (liver) system, Immune system, Male reproductive 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 10 µg/L. Additivity endpoints: Female reproductive system, Hepatic (liver) system, Immune system, Male reproductive system, Renal (kidney) system, Respiratory system, Spleen

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

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

$$= \frac{\text{(0.0021 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 9.33 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 = 6.24/3000 = 0.0021 mg/kg-d (female B6C3F1 mice)
Source of toxicity value:	Determined by MDH in 2022
Point of Departure (POD):	44.6 mg/kg-d (NOAEL, Ratajczak et al. 1995, subchronic exposure)
Dose Adjustment Factor (DAF):	0.14, Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 44.6 mg/kg-d x 0.14 = 6.24 mg/kg-d
Total uncertainty factor (UF):	3000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for extrapolation to a chronic duration from a subchronic study, and 10 for database uncertainty for lack of two-generation reproductive, developmental, and developmental immunotoxicity studies
Critical effect(s):	Decreased T- and B-cell responses, increased cholesterol and triglycerides
Co-critical effect(s):	Increased relative liver weight, increased cholesterol, decreased T-cell response, decreased immune function in the lung, increased estrus cycle length, increased percentage of abnormal sperm
Additivity endpoint(s):	Female reproductive system, Hepatic (liver) system, Immune system, Male reproductive system, Respiratory system

Cancer Health-Based Value (cHBV) = 0.03 µg/L

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

$$\frac{= (1E\text{-}5) \times (1000\ \mu g/mg)}{[(3.6 \times 10^{*} \times 0.155\ L/kg\text{-}d^{**} \times 2) + (3.6 \times 3^{*} \times 0.040\ L/kg\text{-}d^{**} \times 14) + (3.6 \times 1^{*} \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 0.028 rounded to **0.03 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:	2A- probably carcinogenic to humans (IARC, 1999); Likely to be carcinogenic to humans (EPA, 2004)
Slope factor (SF):	3.6 $(mg/kg\text{-}day)^{-1}$ based on forestomach tumors in male and female rats and mice (NCI, 1978)
Source of cancer slope factor (SF):	Cal EPA (2003)

Tumor site(s): Forestomach, esophagus, blood vessels, liver, lung, thyroid gland, and adrenal gland

Volatile: Yes (high)

Summary of Guidance Value History:

A cancer HRL of 0.004 µg/L was promulgated in 1993. The new cancer HBV of 0.03 µg/L is higher than the previous cancer HRL as the result of: 1) use of MDH's most recent risk assessment methodology; 2) the use of a new slope factor derived by Cal EPA 2003; and 3) rounding to one significant digit.

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	No	Yes	No
Effects observed?	Yes[1]	Yes[2]	- [3]	Yes [4]	Yes[5]

[1] Testicular atrophy and degenerative changes to the adrenal cortex were observed in rats and mice exposed chronically to oral doses more than 400 times higher than the short-term RfD. An increased estrus cycle length was observed in mice exposed to levels nearly 700 times higher than the short-term RfD and is included as a co-critical effect for all durations.
[2] The short-term, subchronic, and chronic critical effects are based on immunotoxicity in female mice (decreased T- and B-cell response). Dose levels 1,200 times higher than the short-term RfD are associated with increased neutrophils, decreased bactericidal response in the lung, and decreased viable cells in the spleen. Dose levels 1,600 times higher than the short-term RfD are associated with decreased relative thymus weight, increased spleen weight, and decreased natural killer cell function. Chronic exposure in mice at levels 300 times higher than the short-term RfD resulted in increased splenic hematopoiesis.
[3] Developmental effects have not been studied using oral ingestion as a route of exposure. A database uncertainty factor is included in the guidance to account for the lack of developmental studies in the oral database.
[4] An occupational study in men exposed to 1,2-dibromoethane via inhalation and dermally for an average of 5 years found reductions in sperm count, viability, and motility and increases in sperm abnormalities at dose levels 10-fold higher than the short-term RfD. A shorter-duration study in men exposed via inhalation and dermally for 6 weeks reported reductions in sperm velocity and semen volume at a time weighted dose approximately 8 times higher than the short-term RfD.
Testicular atrophy, the male reproductive system chronic co-critical effect, was observed in rats and mice at more than 400 times higher than the short-term RfD. However, a subchronic study evaluating male reproductive toxicity did not observed any changes to fertility and sex organs using doses almost 700 times higher than the short-term RfD. The subchronic and chronic co-critical effect of lengthened estrus cycles in female mice was observed at doses 700 times higher than the short-term RfD. A database uncertainty factor is included in the RfD to account for the lack of a multigeneration or two-generation reproductive toxicity study.

[5] Neurotoxicity has been observed in human case studies involving ingestion, and manifests as confusion, coma, and brain lesions. Oral animal studies did not observe specific indications of neurotoxicity.

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

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Toxicological Summary for: Perfluorooctane sulfonate

CAS: **45298-90-6 (anion)**
1763-23-1 (acid)
29081-56-9 (ammonium salt)
70225-14-8 (diethanolamine salt)
2795-39-3 (potassium salt)
29457-72-5 (lithium salt)

DTXSID: DTXSID80108992

Synonyms: PFOS, Perfluorooctane sulfonic acid

In 2024, the Minnesota Department of Health (MDH) completed a re-evaluation of PFOS that focused on epidemiological data. Recent reviews from the European Food Safety Authority, California Environmental Protection Agency, US Environmental Protection Agency, and National Academies of Sciences, Engineering, and Medicine were utilized as resources. Many toxicity studies in laboratory animals also exist; however, the points of departure are significantly higher than those identified in epidemiology studies. MDH also conducted a literature search for epidemiological studies published between 2021 and December 2022, which focused on potential sensitive endpoints (e.g., development, immune, thyroid), to capture information that postdated the reviews by the agencies listed above.

Short-term, Subchronic, and Chronic Noncancer Health-Based Value (nHBV) = 0.0023 µg/L (equivalent to 2.3 ng/L or ppt)*

*Due to the highly bioaccumulative nature of PFOS, serum concentrations are the most appropriate dose metric. PFOS has a half-life of approximately 2.7 years, and the bioaccumulated levels within women of reproductive age can be passed on to fetuses and infants through placental and breastmilk transfer. The standard equation used to derive health-based values (HBVs) is not adequate to address the bioaccumulative nature nor the maternal transfer of PFOS. Since 2017, a single PFOS HBV for all durations has been derived using a toxicokinetic (TK) model developed by MDH (Goeden 2019), which assesses a formula-fed infant scenario as well as a breastfed infant scenario. The TK model accounts for the bioaccumulation and maternal transfer of PFOS and more accurately represents real-world exposure scenarios. MDH typically calculates HBVs at the part per billion level with the final concentration rounded to one significant digit. However, serum concentrations are impacted by changes in water concentrations at the part per trillion (ppt) level. As a result, the PFOS HBV is expressed with two significant digits.

Reference Serum Concentration:	POD/Total UF = 7.7/3 = 2.6 ng/mL (human) *This serum level was developed using population-based data and should not be used for clinical assessment or interpreting serum levels in individuals.*
Source of toxicity value:	Determined by MDH in 2024
Point of Departure (POD):	7.7 ng/mL (equivalent to µg/L) serum concentration (US EPA 2023a,b), $BMDL_{5\%}$ for decreased birth weight from (Wikström 2020)
Dose Adjustment Factor (DAF):	Not applicable (POD is based on human serum level)
Human Equivalent Dose (HED):	Not applicable (POD is based on human serum level)
Total uncertainty factor (UF):	3
Uncertainty factor allocation:	A database UF of 3 was applied to account for remaining database uncertainties regarding potential adverse effects at or near the serum POD concentration (e.g., immune effects, liver effects, thyroid effects). An UF for human toxicodynamic (TD) variability was not applied because the POD is based on a sensitive life stage (i.e., neonates). Differences in human TK were determined to be adequately addressed through the exposure scenario and parameter values selected for use in the TK model.[#]
Critical effect(s):	Decreased birth weight
Co-critical effect(s):	Decreased antibody titers in children, increased cholesterol
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Immune system

[#]The POD is based on birth weights paired with maternal serum levels at median gestation age 10 weeks. Very little information is available regarding PFOS half-life in infants; the half-life used in the TK model is based on a population (age 4-80 years of age) residing in a community with contaminated water (Li 2022). To evaluate the potential impact of TK variability, an upper-bounding scenario, in which all model parameters were set to upper percentile values, was evaluated. The maternal, peak infant, and lifetime steady-state serum levels produced by the upper-bounding scenario were ≤3-fold higher than MDH's selected Reasonable Maximum Exposure (RME) scenario. Since the upper-bounding scenario is considered worst-case and is very unlikely to represent a realistic scenario, the incorporation of an UF to address human TK variability was considered unnecessary. MDH's RME model parameter values used to derive the noncancer water guidance is considered adequately protective of the general population.

Toxicokinetic Model Description (Goeden 2019):

Serum concentrations can be calculated from the dose and clearance rate using the following equation:

$$Serum\ Concentration\left(\frac{\mu g}{L}\right) = \frac{Fluid\ IntakeRate\left(\frac{L}{kg \cdot day}\right) x\ Fluid\ Concentration\left(\frac{\mu g}{L}\right)}{Clearance\ Rate\left(\frac{L}{kg \cdot day}\right)}$$

Where:

Clearance Rate = Volume of Distribution (L/kg body weight) x (Ln2/half-life in days)

Two exposure scenarios were examined: 1) an infant fed with formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water throughout life; and 2) an infant exclusively breastfed 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. The serum concentration of the mother was calculated to be at steady state at the time of delivery, using the equation presented above and a time-weighted average (TWA) 95th percentile intake rate from birth to 30 years of age (sufficient time to attain steady-state).

Consistent with MDH methodology, a 95th percentile water and upper percentile (2 standard deviations above mean) breastmilk intake rates were used along with central tendency estimates for half-life, placental transfer, and breastmilk transfer. Breastmilk concentrations are calculated by multiplying the maternal serum concentration by a PFOS breastmilk transfer factor. For the breastfed exposure scenario, a one-year period of breastfeeding is used as representative of an RME scenario.

Daily post-elimination serum concentrations were calculated as:

$$Serum\ Concentration\left(\frac{\mu g}{L}\right) = \left[\frac{Previous\ day + Today's\ Intake(\mu g)}{V_d\left(\frac{L}{kg}\right) \times BW(kg)}\right] \times e^{-k}$$

Where:

V_d = volume of distribution
BW = body weight
e^{-k} = represents clearance

Note: MDH has made several improvements to the TK model published in 2019 (Goeden 2019), including the following:

- The PFOS mass transferred to the infant is now subtracted from the maternal steady-state concentration on day 0 (the day of delivery).
- The daily calculation of the infant's serum concentration is now fully mass-based by adjusting both the current day as well as the previous day's intake by the current day's body weight.
- Maternal lactation was phased in over the first four days of lactation based on data from Neville et al. (1991).
- Water intakes, breastmilk intakes, and body weights were updated with more current information.
- Chemical-specific parameter values (i.e., clearance, half-life, placental transfer, breastmilk transfer, and volume of distribution) were updated to include literature information up to December 2022.

Summary of TK Model Parameter Values Used to Derive Non-Cancer HBV for PFOS

Model Parameter	Value Used
Half-life ($t_{½}$)	Central Tendency = 996 days (2.73 years) (Mean value from (Li 2022) The TK model estimates serum levels from birth to approximately 50 years of age. Critical life-stage is <4 years of age for which serum half-life information is not available. The overall mean was used for the RME scenario. A 95th percentile half-life value of 4.75 years was used in the upper-bounding scenario evaluation.
Placental transfer	Central Tendency = 0.39 (mean of mean values from 27 studies) The mean upper percentile value (0.74) was selected as an upper-end value for the upper-bounding scenario evaluation.

<table>
<tr><th>Model Parameter</th><th>Value Used</th></tr>
<tr><td>Breastmilk transfer</td><td>Central Tendency = 0.03 (95th upper confidence limit (UCL) of the mean from 8 studies). Validation testing of model infant serum predictions indicated that use of the overall mean of the 8 studies (0.020) resulted in underestimating breastfed infant serum levels whereas the 95th UCL did not. A value of 0.065 was used as representative of an upper-end value for the upper-bounding scenario evaluation.</td></tr>
<tr><td>Breastmilk Intake Rate (mL/kg-day) and corresponding Body Weight (kg)</td><td>Upper Percentile intake for exclusively[1] breastfed infants ((US EPA 2019), Table 15-1). Body weight at birth was set at 3.38 kg (Donahue 2010). Remaining body weights (kg) were calculated from data presented in US EPA's Table 15-1 for each age group (i.e., mL/day ÷ mL/kg-day):
<table>
<tr><th>Age Group</th><th>Intake Rate (mL/kg-d)</th><th>Body Weight (kg)</th></tr>
<tr><td>>Birth to <1 month</td><td>220</td><td>4.3</td></tr>
<tr><td>1 to < 3 months</td><td>190</td><td>5.2</td></tr>
<tr><td>3 to < 6 months</td><td>150</td><td>6.7</td></tr>
<tr><td>6 to < 12 months</td><td>130</td><td>7.7</td></tr>
</table></td></tr>
<tr><td>Duration (months) of Breastfeeding</td><td>Upper percentile = 12 months (Breastfeeding Report Card for 2022 (CDC 2022)) reporting that nearly 70 percent of mothers in Minnesota report breastfeeding at six months, with 36.5 percent still exclusively breastfeeding at six months.</td></tr>
<tr><td>Water Intake Rate (mL/kg-day)</td><td>Upper Percentile Intake = Formula-fed infants (up to 2 years old, Table 3-5); for >2 years of age values (Table 3-1); and for lactating women (Table 3-3) (US EPA 2019) were used. Body weights (kg) were calculated from data presented in the aforementioned EPA tables (i.e., mL/day ÷ mL/kg-day):
<table>
<tr><th>Age Group</th><th>Intake Rate (mL/kg-d)</th><th>Body Weight (kg)</th></tr>
<tr><td><1 month</td><td>240</td><td>3.6</td></tr>
<tr><td>1 to < 3 months</td><td>290</td><td>3.8</td></tr>
<tr><td>3 to < 6 months</td><td>186</td><td>7.0</td></tr>
<tr><td>6 to < 12 months</td><td>151</td><td>8.9</td></tr>
<tr><td>1 to < 2 years</td><td>119</td><td>10.5</td></tr>
<tr><td>2 to < 3 years</td><td>67</td><td>13.4</td></tr>
<tr><td>3 to < 6 years</td><td>45</td><td>18.6</td></tr>
<tr><td>6 to < 11 years</td><td>41</td><td>30.7</td></tr>
<tr><td>11 to < 16 years</td><td>31</td><td>56.8</td></tr>
<tr><td>16 to < 21 years</td><td>31</td><td>71.4</td></tr>
<tr><td>21 to < 30 years</td><td>47</td><td>72.5</td></tr>
<tr><td>30 to < 40 years</td><td>44</td><td>74.5</td></tr>
<tr><td>40 to < 50 years</td><td>43</td><td>78.5</td></tr>
<tr><td>50 to < 60 years</td><td>42</td><td>80.7</td></tr>
</table>
For calculation of maternal serum concentration at time of delivery, a time-weighted average water intake rate was calculated from birth to 30 years of age, resulting in a 95th percentile water intake rate of 48 mL/kg-day.</td></tr>
</table>

Model Parameter	Value Used
Volume of Distribution (L/kg)	Central Tendency = 0.56 (calculated from human clearance rate of 0.39 mL/kg-d (California EPA Office of Environmental Health Hazard Assessment 2023)) and the mean half-life of 996 days (Li 2022): CR ÷ (Ln2/half-life) = V_d 0.39 mL/kg-d ÷ (Ln 2/996 d) = 560 mL/kg or rounded to 0.56 L/kg

[1]Note: Exclusively breastfed as defined by (US EPA 2019) refers to infants whose sole source of milk is breastmilk and not formula. Exclusively breastfed infants in the studies underlying these USEPA estimates were not excluded from other foods, typically after six months. This definition differs from other sources, which may define exclusive breastfeeding as breastmilk being the only source of nourishment (solid or liquid).

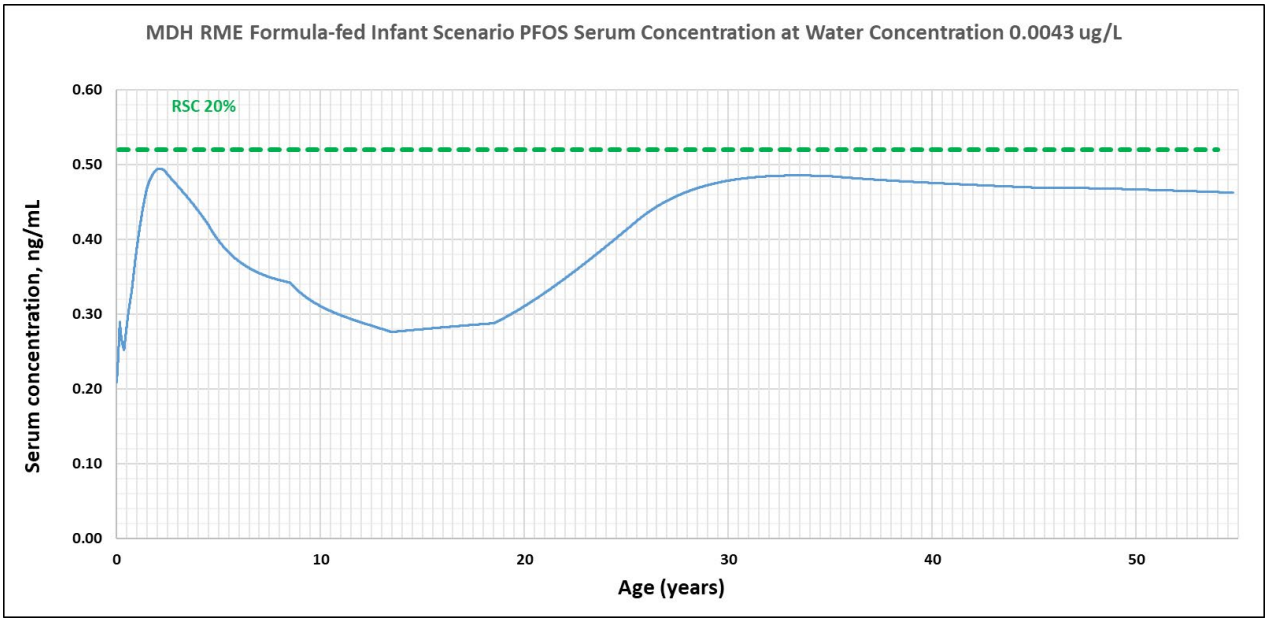
A relative source contribution factor (RSC) is incorporated into the derivation of HBV values to account for exposure sources other than drinking water. MDH utilizes the US EPA 2000 Exposure Decision Tree process to derive appropriate RSCs. The default duration-specific RSCs (0.5, 0.2, and 0.2 for short-term, subchronic and chronic, respectively) are based on the magnitude of contribution of non-drinking water exposures that occur during the relevant exposure duration (Minnesota Department of Health (MDH) 2008). However, in the case of PFOS, application of an RSC needs to account for the long elimination half-life, such that a person's serum concentration at any given age/duration is not only the result of current or recent exposures but also from years past and/or maternal transfer.

Serum concentrations are the best measure of cumulative exposure for PFOS and can be used in place of the reference dose in the Exposure Decision Tree process. Biomonitoring results for the general public reported in the most recent National Report on Human Exposure to Environmental Chemicals (CDC 2021) can be used to represent non-water exposures for older children and adults. The reference serum concentration is 2.6 ng/mL. Both the geometric mean (4.25 ng/mL) and the 95th percentile (14.6 ng/mL) PFOS serum concentration from the most recently available National Report exceed the reference serum concentration. Based on placental transfer data, newborn infants would have PFOS body burdens approximately half that of their mothers. Even at low levels of exposure, PFOS would accumulate in women of reproductive age. Studies assessing young infants (e.g., <6 months of age) who are exclusively breastfed exhibit serum levels that are similar to or slightly higher than their mothers (e.g., (Fromme 2010), (Gyllenhammar 2018)). Consequently, the RSC is set at the floor value of 20% for all life stages.

As mentioned above, two RME scenarios were examined: 1) an infant fed formula reconstituted with contaminated water starting at birth and continuing consumption of contaminated water throughout life; and 2) an infant exclusively breastfed for 12 months by a chronically-exposed mother, followed by consumption of contaminated water throughout life.

For the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water below an RSC of 20% throughout life is 0.0043 µg/L (equivalent to 4.3 ng/L or ppt). The infant peak is below the 20% RSC line as the maternal serum concentration was the limiting factor in the formula-fed scenario (Figure 1).

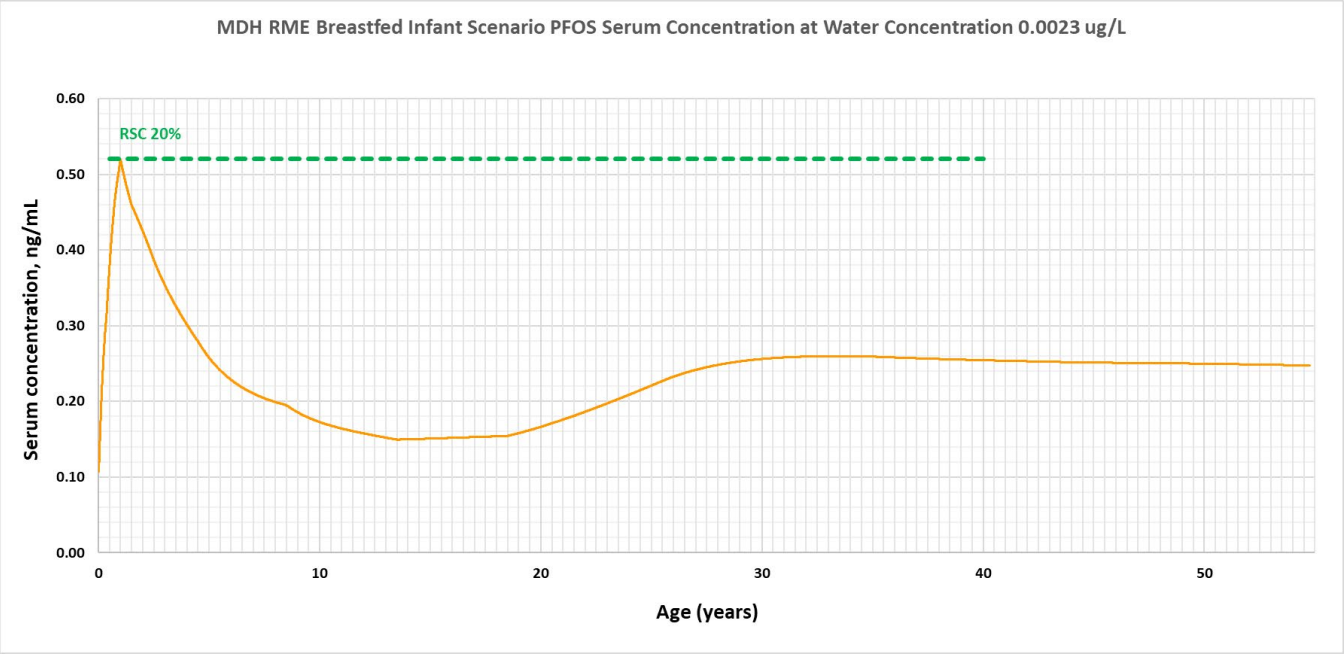
Figure 1. MDH RME Formula-fed Infant Scenario PFOS Serum Concentration at Water Concentration 0.0043 ug/L



A sharp decrease in the formula-fed infant serum levels between the 1 to < 3 month and 3 to <6 months is noted. The formula-fed infant water intake drops from 290 to 186 mL/kg-d as body weight increases from 3.8 to 7 kg across the same time period.

Applying this water concentration (4.3 ng/L) in the context of a breast-fed infant results in peak infant serum concentrations that significantly exceed the RSC of 20%. In order to maintain a serum concentration at or below an RSC of 20% for the breast-fed infant scenario, the water concentration should not exceed 0.0023 µg/L (or 2.3 ng/L or ppt) (Figure 2).

Figure 2. MDH RME Breastfed Infant Scenario PFOS Serum Concentration at Water Concentration 0.0023 µg/L



Due to bioaccumulation in the mother and subsequent transfer to breastmilk, the breast-fed infant exposure scenario produces the lower PFOS water concentration. To ensure protection of all segments of the population, the final noncancer HBV for PFOS is set at 2.3 ng/L (ppt).

Cancer Health-Based Value (cHBV) = 0.0076 µg/L (7.6 ng/L or ppt)

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(\text{SF x ADAF<2 yr x IR<2yr x 2}) + (\text{SF x ADAF2-<16 yr x IR2-<16yr x 14}) + (\text{SF x ADAF16+ yr x IR16+yr x 54})] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(13 \times 10^{*} \times 0.155 \text{ L/kg-d}^{**} \times 2) + (13 \times 3^{*} \times 0.040 \text{ L/kg-d}^{**} \times 14) + (13 \times 1^{*} \times 0.042 \text{ L/kg-d}^{**} \times 54)] / 70}$$

= 0.0076 µg/L (same as 7.6 ng/L or ppt)

*Age-dependent adjustment factor (ADAF) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2. ADAFs were maintained because the animals from the critical cancer study did not have early-life exposures to PFOS.
**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 (US EPA 2023a,b) (MDH 2023); Presents a carcinogenic hazard (CalEPA Office of Environmental Health Hazard Assessment 2023); Group 2B (possibly carcinogenic to humans) (IARC 2023)
Slope factor (SF):	13 per mg/kg-day (combined hepatocellular adenomas and carcinomas in female rats) (US EPA 2023a,b); tumor data from (Butenhoff 2012)
Source of cancer slope factor (SF):	POD of 19.8 mg/L from (US EPA 2023a,b) converted to 13 per mg/kg-d using a clearance rate

of 0.39 mL/kg-d (CalEPA Office of Environmental Health Hazard Assessment 2023). *[Note: EPA calculated a slope factor of of 39.5 per mg/kg-d from this POD using a clearance rate of 0.128 mL/kg-d].*

Tumor site(s): Liver

Volatile: No

Summary of Guidance Value History:

A chronic nHBV of 1 µg/L was first derived in 2002. A revised chronic nHBV of 0.3 µg/L was derived in 2007 and promulgated as a noncancer HRL (nHRL) in 2009. In 2017, MDH derived a revised nHBV (applicable to all durations) of 0.027 µg/L. In 2018, MDH revised the nHBV (applicable to all durations) to 0.015 µg/L. In 2020 MDH incorporated updated water intake rates (US EPA 2019). Using the updated intake rates did not change the HBV value. The 2024 nHBV of 0.0023 µg/L (2.3 ng/L) is lower than previous values as the result of: 1) utilizing epidemiological data as the basis for the POD; and 2) updating the toxicokinetic model, including more recent data on placental and breastmilk transfer. The 2024 cancer HBV of 0.0076 µg/L (7.6 ng/L) is a new value and MDH has revised their cancer classification to "likely to be carcinogenic".

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

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

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

Comments on extent of testing or effects:

[Note: MDH conducted a re-evaluation that focused on epidemiological data and sensitive health endpoints.]

[1] Evidence for endocrine effects in humans following PFOS exposure is largely based on increased TSH (thyroid stimulating hormone) and T3 (triiodothyronine) in adults and T4 (thyroxine) in children. However, findings in epidemiology studies were inconsistent, likely due in part to diurnal variations, differential effects across genders and age groups, timing of sampling, and limited number of studies. (US EPA 2023a,b) considers the current level of evidence suggestive but not indicative of adverse endocrine effects due to PFOS exposure due to the uncertainty in results. A database uncertainty factor has been incorporated into the reference serum level to reflect the need for more data regarding thyroid effects.

Studies in laboratory animals have demonstrated clear and consistent alterations in serum thyroid hormone levels, increased thyroid gland weight, and increased follicular cell

hypertrophy in the thyroid gland. Previous MDH guidance was based, in part, on thyroid effects in animals.

[2] In humans, it is widely accepted that PFOS exposure is likely associated with reduced antibody response, especially in infants and children. Immune effects are listed as a co-critical additivity endpoint based on a vaccine response study in young children. Additionally, there is some evidence for increases in asthma and respiratory infections.

In animal models, there is consistent evidence of decreased antibody response, decreased spleen and thymus weight, and alterations in immune cell function after PFOS exposure.

[3] In humans, it is widely accepted that decreased birth weight is likely associated with maternal PFOS serum levels. This likely association is supported by additional epidemiological evidence of related effects such as decreased birth length and postnatal growth. Low birth weight is the basis of the reference serum concentration.

Among the animal studies, decreased postnatal growth leading to developmental effects (e.g., lower pup body weight, delayed eye opening) have been observed.

[4] The evidence for male reproductive effects in humans is limited and largely based on suggestive associations between PFOS exposure and testosterone levels in male children and adults and decreased anogenital distance in children. Considerable uncertainties in these associations exist due to inconsistencies across studies and the limited number of studies available.

The evidence for female reproductive effects in humans is limited and largely based on suggestive associations between PFOS exposure and increased odds of preeclampsia. Considerable uncertainties in these associations exist due to inconsistencies across studies and the limited number of available studies.

Among the animal studies, there is evidence for decreased testicular and epididymal weight, for decreased sperm count, and for hormonal changes in pups, and for increased neonatal mortality.

[5] There is inconsistent evidence for PFOS exposure and neurotoxicity in humans. Most studies focused on neurodevelopment of infants and toddlers; across studies, both negative and positive associations on various developmental assessments were reported.

In a small number of available animal studies, there is limited evidence suggesting neurobehavioral alterations from PFOS exposure.

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

Web Publication Date: January 2024

Toxicological Summary for: Perfluorooctanoate

CAS: **45285-51-6 (anion)**
335-67-1 (free acid)
3825-26-1 (ammonium salt, APFO)
2395-00-8 (potassium salt)
335-95-5 (sodium salt)
335-93-3 (silver salt)

DTXSID: DTXSID40892486

Synonyms: PFOA; 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoic acid (IUPAC name); Perfluorooctanoic acid (free acid)

In 2024, the Minnesota Department of Health (MDH) completed a re-evaluation of PFOA that focused on epidemiological data. Recent reviews from the European Food Safety Authority, California Environmental Protection Agency, US Environmental Protection Agency, and National Academies of Sciences, Engineering, and Medicine were utilized as resources. Many toxicity studies in laboratory animals also exist; however, the points of departure are significantly higher than those identified in epidemiology studies. MDH also conducted a literature search for epidemiological studies published between 2021 and December 2022, which focused on potential sensitive endpoints (e.g., development, immune, thyroid), to capture information that postdated the reviews by the agencies listed above.

Short-term, Subchronic, and Chronic Noncancer Health-Based Value (nHBV) = 0.00024 µg/L (equivalent to 0.24 ng/L or ppt)*

*Due to the highly bioaccumulative nature of PFOA, serum concentrations are the most appropriate dose metric. PFOA has a half-life of approximately 2.5 years, and the bioaccumulated levels within women of reproductive age can be passed on to fetuses and infants through placental and breastmilk transfer. The standard equation used to derive health-based values (HBVs) is not adequate to address the bioaccumulative nature nor the maternal transfer of PFOA. Since 2017, a single PFOA HBV for all durations has been derived using a toxicokinetic (TK) model developed by MDH (Goeden 2019), which assesses a formula-fed infant scenario as well as a breastfed infant scenario. The TK model accounts for the bioaccumulation and maternal transfer of PFOA and more accurately represents real-world exposure scenarios. MDH typically calculates HBVs at the part per billion level with the final concentration rounded to one significant digit. However, serum concentrations are impacted by changes in water concentrations at the part per trillion (ppt) level. As a result, the PFOA HBV is expressed with two significant digits.

Reference Serum Concentration:	POD/Total UF = 2.8/3 = 0.93 ng/mL (human) *This serum level was developed using population-based data and should not be used for clinical assessment or interpreting serum levels in individuals.*
Source of toxicity value:	Determined by MDH in 2024
Point of Departure (POD):	2.8 ng/mL (equivalent to µg/L) serum concentration (California EPA Office of Environmental Health Hazard Assessment 2023), $BMDL_{5\%}$ for decreased haemophilus influenzae Type B (Hib) antibodies from (Abraham K 2020)
Dose Adjustment Factor (DAF):	Not applicable (POD is based on human serum level)
Human Equivalent Dose (HED):	Not applicable (POD is based on human serum level)
Total uncertainty factor (UF):	3
Uncertainty factor allocation:	A database UF of 3 was applied to account for remaining database uncertainties regarding potential adverse effects at or near the serum POD concentration (e.g., low birth weight, liver effects, thyroid effects). An UF for human toxicodynamic (TD) variability was not applied because the POD is based on a sensitive lifestage (i.e., young infants). Differences in human TK were determined to be adequately addressed through the exposure scenario and parameter values selected for use in the TK model.[#]
Critical effect(s):	Decreased antibody titers in infants
Co-critical effect(s):	Decreased antibody titers in children, decreased birthweight, increased cholesterol, increased ALT (liver enzyme)
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Immune system

[#]The POD is based on serum levels in one-year old infants, of whom nearly 80% were exclusively breastfed for at least 4 months. Very little information is available regarding PFOA half-life in infants. To evaluate the potential impact of TK variability, an upper-bounding scenario, in which all model parameters were set to upper percentile values, was evaluated. The maternal, peak infant, and lifetime steady-state serum levels produced by the upper-bounding scenario were ≤3-fold higher than MDH's selected Reasonable Maximum Exposure (RME) scenario. Since the upper-bounding scenario is considered worst-case and is very unlikely to represent a realistic scenario, the incorporation of an UF to address human TK variability was considered unnecessary. MDH's RME model parameter values used to derive the noncancer water guidance is considered adequately protective of the general population.

Toxicokinetic Model Description (Goeden 2019):

Serum concentrations can be calculated from the dose and clearance rate using the following equation:

$$Serum\ Concentration\left(\frac{\mu g}{L}\right) = \frac{Fluid\ IntakeRate\left(\frac{L}{kg \cdot day}\right) x\ Fluid\ Concentration\left(\frac{\mu g}{L}\right)}{Clearance\ Rate\left(\frac{L}{kg \cdot day}\right)}$$

Where:

Clearance Rate = Volume of Distribution (L/kg body weight) x (Ln2/half-life in days)

Two exposure scenarios were examined: 1) an infant fed with formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water throughout life; and 2) an infant exclusively breastfed 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. The serum concentration of the mother was calculated to be at steady state at the time of delivery, using the equation presented above and a time-weighted average (TWA) 95th percentile intake rate from birth to 30 years of age (sufficient time to attain steady-state).

Consistent with MDH methodology, a 95th percentile water and upper percentile (2 standard deviations above mean) breastmilk intake rates were used along with central tendency estimates for half-life, placental transfer, and breastmilk transfer. Breastmilk concentrations are calculated by multiplying the maternal serum concentration by a PFOA breastmilk transfer factor. For the breast-fed exposure scenario, a one-year period of breastfeeding is used as representative of an RME scenario.

Daily post-elimination serum concentrations were calculated as:

$$Serum\ Concentration\left(\frac{\mu g}{L}\right) = \left[\frac{Previous\ day + Today's\ Intake(\mu g)}{V_d\left(\frac{L}{kg}\right) \times BW(kg)}\right] \times e^{-k}$$

Where:

V_d = volume of distribution
BW = body weight
e^{-k} = represents clearance

Note: MDH has made several improvements to the TK model published in 2019 (Goeden 2019), including the following:

- The PFOA mass transferred to the infant is now subtracted from the maternal steady-state concentration on day 0 (the day of delivery).
- The daily calculation of the infant's serum concentration is now fully mass-based by adjusting both the current day as well as the previous day's intake by the current day's body weight.
- Maternal lactation was phased in over the first four days of lactation based on data from Neville *et al.* (1991).
- Water intakes, breastmilk intakes, and body weights were updated with more current information.
- Chemical-specific parameter values (i.e., clearance, half-life, placental transfer, breastmilk transfer, and volume of distribution) were updated to include literature information up to December 2022.

Summary of TK Model Parameter Values Used to Derive Non-Cancer HBV for PFOA

Model Parameter	Value Used
Half-life ($t_{½}$)	Central Tendency = 902 days (2.47 years) Mean value from (Li 2022) The TK model estimates serum levels from birth to approximately 50 years of age. Critical lifestage is <4 years of age for which serum half-life information is not available. The overall mean was used for the RME scenario. A 95th percentile half-life value of 5.4 years was used in the upper-bounding scenario evaluation.
Placental transfer	Central Tendency = 0.83 (mean of mean values from 25 studies) The mean upper percentile value (1.39) was selected as an upper-end value for the upper-bounding scenario evaluation.
	Central Tendency = 0.068 (95th upper confidence limit (UCL) of the mean from 7 studies). Validation testing of model infant serum predictions indicated that use of the overall mean of

<table>
<tr><th>Model Parameter</th><th>Value Used</th></tr>
<tr><td>Breastmilk transfer</td><td>the 7 studies (0.046) resulted in underestimating breastfed infant serum levels whereas the 95th UCL did not. A value of 0.12 was used as representative of an upper-end value for the upper-bounding scenario evaluation.</td></tr>
<tr><td>Breastmilk Intake Rate (mL/kg-day) and corresponding Body Weight (kg)</td><td>Upper Percentile intake for exclusively[1] breastfed infants ((US EPA 2011), Table 15-1). Body weight at birth was set at 3.38 kg (Donahue 2010). Remaining body weights (kg) were calculated from data presented in US EPA's Table 15-1 for each age group (i.e., mL/day ÷ mL/kg-day):

Age Group — Intake Rate (mL/kg-d) — Body Weight (kg)
>Birth to <1 month — 220 — 4.3
1 to < 3 months — 190 — 5.2
3 to < 6 months — 150 — 6.7
6 to < 12 months — 130 — 7.7</td></tr>
<tr><td>Duration (months) of Breastfeeding</td><td>Upper percentile = 12 months (Breastfeeding Report Card for 2022 (CDC 2022)) reporting that nearly 70 percent of mothers in Minnesota report breastfeeding at six months, with 36.5 percent still exclusively breastfeeding at six months.</td></tr>
<tr><td>Water Intake Rate (mL/kg-day)</td><td>Upper Percentile Intake = Formula-fed infants (up to 2 years old, Table 3-5); for >2 years of age values (Table 3-1); and for lactating women (Table 3-3) (US EPA 2019) were used. Body weights (kg) were calculated from data presented in the aforementioned EPA tables (i.e., mL/day ÷ mL/kg-day):

<table>
<tr><th>Age Group</th><th>Intake Rate (mL/kg-d)</th><th>Body Weight (kg)</th></tr>
<tr><td><1 month</td><td>240</td><td>3.6</td></tr>
<tr><td>1 to < 3 months</td><td>290</td><td>3.8</td></tr>
<tr><td>3 to < 6 months</td><td>186</td><td>7.0</td></tr>
<tr><td>6 to < 12 months</td><td>151</td><td>8.9</td></tr>
<tr><td>1 to < 2 years</td><td>119</td><td>10.5</td></tr>
<tr><td>2 to < 3 years</td><td>67</td><td>13.4</td></tr>
<tr><td>3 to < 6 years</td><td>45</td><td>18.6</td></tr>
<tr><td>6 to < 11 years</td><td>41</td><td>30.7</td></tr>
<tr><td>11 to < 16 years</td><td>31</td><td>56.8</td></tr>
<tr><td>16 to < 21 years</td><td>31</td><td>71.4</td></tr>
<tr><td>21 to < 30 years</td><td>47</td><td>72.5</td></tr>
<tr><td>30 to < 40 years</td><td>44</td><td>74.5</td></tr>
<tr><td>40 to < 50 years</td><td>43</td><td>78.5</td></tr>
<tr><td>50 to < 60 years</td><td>42</td><td>80.7</td></tr>
</table>
For calculation of maternal serum concentration at time of delivery, a time-weighted average water intake rate was calculated from birth to 30 years of age, resulting in a 95th percentile water intake rate of 48 mL/kg-day.</td></tr>
</table>

Model Parameter	Value Used
Volume of Distribution (L/kg)	Central Tendency = 0.36 (calculated from human clearance rate of 0.28 mL/kg-d (California EPA Office of Environmental Health Hazard Assessment 2023)) and the mean half-life of 902 days (Li 2022): $CR \div (Ln2/half\text{-}life) = V_d$ 0.28 mL/kg-d ÷ (Ln2/902 d) = 364 mL/kg or rounded to 0.36 L/kg

[1]Note: Exclusively breastfed as defined by (US EPA 2011) refers to infants whose sole source of milk is breastmilk and not formula. Exclusively breastfed infants in the studies underlying these USEPA estimates were not excluded from other foods, typically after six months. This definition differs from other sources, which may define exclusive breastfeeding as breastmilk being the only source of nourishment (solid or liquid).

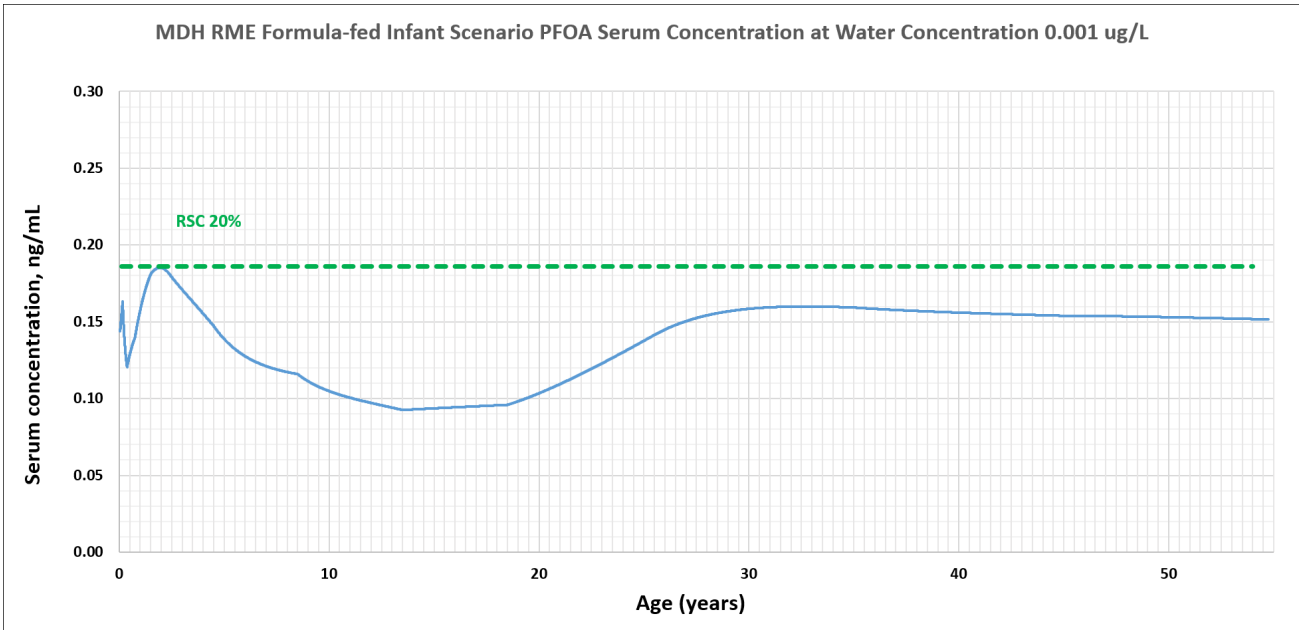
A relative source contribution factor (RSC) is incorporated into the derivation of HBV values to account for exposure sources other than drinking water. MDH utilizes the US EPA 2000 Exposure Decision Tree process to derive appropriate RSCs. The default duration-specific RSCs (0.5, 0.2, and 0.2 for short-term, subchronic and chronic, respectively) are based on the magnitude of contribution of non-drinking water exposures that occur during the relevant exposure duration (Minnesota Department of Health (MDH) 2008). However, in the case of PFOA, application of an RSC needs to account for the long elimination half-life, such that a person's serum concentration at any given age/duration is not only the result of current or recent exposures but also from years past and/or maternal transfer.

Serum concentrations are the best measure of cumulative exposure for PFOA and can be used in place of the reference dose in the Exposure Decision Tree process. Biomonitoring results for the general public reported in the most recent National Report on Human Exposure to Environmental Chemicals (CDC 2021) can be used to represent non-water exposures for older children and adults. The reference serum concentration is 0.93 ng/mL. Both the geometric mean (1.42 ng/mL) and the 95th percentile (3.77 ng/mL) PFOA serum concentration from the most recently available National Report exceed the reference serum concentration. Based on placental transfer data, newborn infants would have PFOA body burdens similar to their mothers. Even at low levels of exposure, PFOA would accumulate in women of reproductive age. Studies assessing young infants (e.g., <6 months of age) who are exclusively breastfed exhibit serum levels that are approximately 3-fold higher than their mothers (e.g., (Fromme 2010), (Gyllenhammar 2018)). It is likely that infants will have similar or, in the case of breastfed infants, higher serum concentrations than their mothers. Consequently, the RSC is set at the floor value of 20% for all life stages.

As mentioned above, two RME scenarios were examined: 1) an infant fed formula reconstituted with contaminated water starting at birth and continuing consumption of contaminated water throughout life; and 2) an infant exclusively breastfed for 12 months by a chronically-exposed mother, followed by consumption of contaminated water throughout life.

For the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water below an RSC of 20% throughout life is 0.0010 µg/L (equivalent to 1.0 ng/L or ppt) (Figure 1).

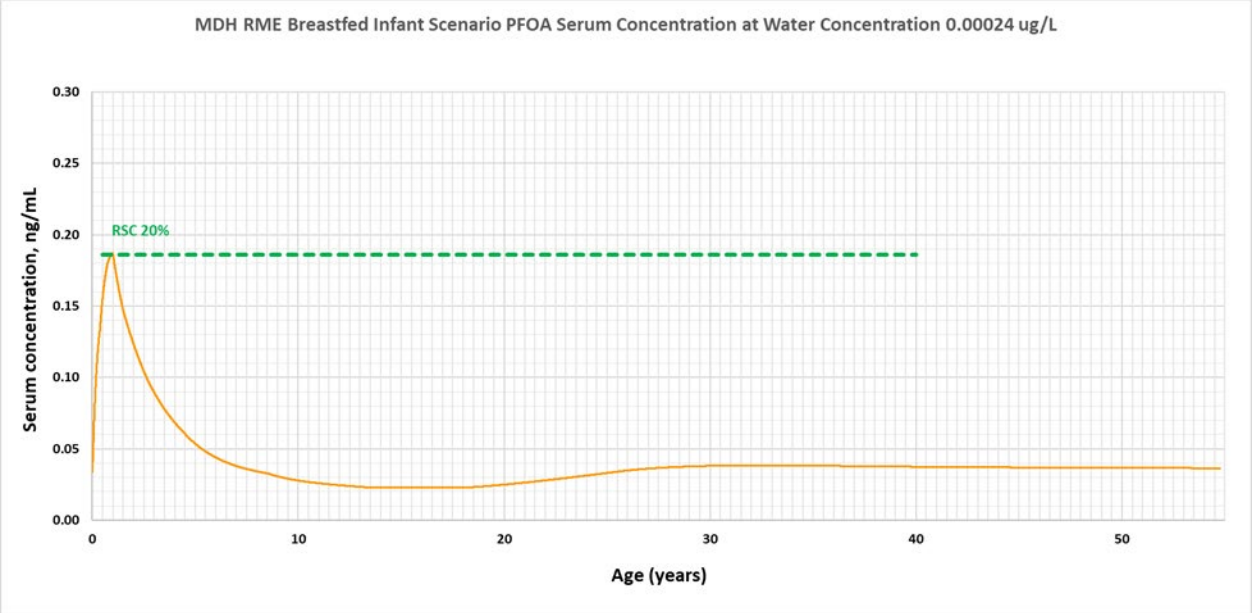
Figure 1. MDH RME Formula-fed Infant Scenario PFOA Serum Concentration at Water Concentration 0.001 ug/L



A sharp decrease in the formula-fed infant serum levels between the 1 to < 3 month and 3 to <6 months is noted. The formula-fed infant water intake drops from 290 to 186 mL/kg-d as body weight increases from 3.8 to 7 kg across the same time period.

Applying this water concentration (1 ng/L) in the context of a breast-fed infant results in peak infant serum concentrations that significantly exceed the RSC of 20%. In order to maintain a serum concentration at or below an RSC of 20% for the breastfed infant scenario, the water concentration should not exceed 0.00024 µg/L (or 0.24 ng/L or ppt) (Figure 2).

Figure 2. MDH RME Breastfed Infant Scenario PFOA Serum Concentration at Water Concentration 0.00024 µg/L



Due to bioaccumulation in the mother and subsequent transfer to breastmilk, the breastfed infant exposure scenario produces the lower PFOA water concentration. To ensure protection of all segments of the population, the final noncancer HBV for PFOA is set at 0.00024 µg/L (0.24 ng/L).

Cancer Health-Based Value (cHBV) = 0.0000079 µg/L (0.0079 ng/L or ppt)

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

$$= \frac{(1E\text{-}5) \times (1\ \mu g/1000\ ng)}{[(0.0126 \times 10^{*} \times 0.155\ L/kg\text{-}d^{**} \times 2) + (0.0126 \times 3^{*} \times 0.040\ L/kg\text{-}d^{**} \times 14) + (0.0126 \times 1^{*} \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 0.0000079 µg/L (same as 0.0079 ng/L or ppt)

*Age-dependent adjustment factor (ADAF) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2. ADAFs were maintained because the cohort from the critical cancer study was unlikely to have early-life exposure to PFOA.

**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 (US EPA 2023a,b) (MDH 2023); Strong evidence of carcinogenicity (CalEPA Office of Environmental Health Hazard Assessment 2023); and Group 1 (carcinogenic to humans) (IARC 2023)
Slope factor (SF):	0.0126 per ng/kg-day (renal cell carcinoma in humans) (Shearer JJ 2021)
Source of cancer slope factor (SF):	Serum slope factor 0.00325 per ng/mL from (US EPA 2023a,b) converted to 0.0126 per ng/kg-d using a clearance rate of 0.28 mL/kg-d (CalEPA Office of Environmental Health Hazard Assessment 2023)
Tumor site(s):	Human: Kidney (basis of guidance), Testicle Animal: Liver, Pancreas

Volatile: No

Summary of Guidance Value History:

A chronic nHBV of 7 µg/L was first derived in 2002. A revised chronic nHBV of 0.3 µg/L was derived in 2007 and promulgated as a noncancer HRL (nHRL) in 2009. In 2016, EPA released a Health Advisory of 0.07 µg/L for PFOA, which MDH recommended on an interim basis while a re-evaluation was conducted. As a result of the re-evaluation, which incorporated the most recent toxicological information and included the application of the TK model, the 2017 nHBV decreased to 0.035 µg/L for all nonacute durations. The 2017 guidance was adopted as a HRL in 2018. In 2020, MDH classified PFOA as "likely to be carcinogenic at high doses" and added Thyroid (E) and Pancreas as Additivity Endpoints. The 2024 nHBV of 0.00024 µg/L (0.24 ng/L) is lower than previous values as the result of: 1) utilizing epidemiological data as the basis for the POD; and 2) updating the toxicokinetic model, including more recent data on placental and breastmilk transfer. The 2024

cancer HBV of 0.0000079 µg/L (0.0079 ng/L) is a new value, and MDH has revised their cancer classification to "likely to be carcinogenic".

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

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

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

Comments on extent of testing or effects:

[Note: MDH conducted a re-evaluation that focused on epidemiological data and sensitive health endpoints.]

[1] Evidence for endocrine effects in humans following PFOA exposure is largely based on increased TSH (thyroid stimulating hormone) and T3 (triiodothyronine) in adults and T4 (thyroxine) in children. However, findings in epidemiology studies were inconsistent, likely due in part to diurnal variations, differential effects across genders and age groups, timing of sampling, and limited number of studies. US EPA (2023) considers the current level of evidence for thyroid effects to be suggestive due to the uncertainty in results. A database uncertainty factor has been incorporated into the reference serum level to reflect the need for more data regarding thyroid effects.

Studies in laboratory animals have demonstrated clear alterations in serum thyroid hormone levels, increased thyroid gland weight, and increased follicular cell hypertrophy in the thyroid gland. Previous MDH guidance was based, in part, on thyroid effects in animals.

[2] It is widely accepted that PFOA exposure is likely associated with reduced antibody response, especially in infants and children. An immune study in infants forms the basis of the PFOA reference serum concentration used to derive the 2024 nHBV. There is also limited supporting evidence of increased risk of asthma, eczema, and autoimmune disease.

In animal models, there is consistent evidence of decreased antibody response, decreased spleen and thymus weight, and alterations in immune cell function after PFOA exposure.

[3] It is widely accepted that decreased birth weight is likely associated with maternal PFOA serum levels. This likely association is supported by additional epidemiological evidence of related effects such as decreased birth length and postnatal growth. In general, these effects have been reported around similar serum levels as effects on the immune system, which is the basis of the reference serum concentration.

Among the animal studies, decreased postnatal growth leading to developmental effects (e.g., lower pup body weight, delayed eye opening, delayed vaginal opening, and accelerated preputial separation) have been observed. Delayed mammary gland development in female mice exposed in utero has also been reported at low dose levels.

[4] The evidence for male reproductive effects in humans is limited and largely based on suggestive associations between PFOA exposure and testosterone levels in male children and adults and decreased anogenital distance in children. Considerable uncertainties in these associations exist due to inconsistencies across the limited number of studies available.

The evidence for female reproductive effects in humans is limited and largely based on suggestive associations between PFOA exposure and increased odds of preeclampsia, and changes to female reproductive milestones and female reproductive hormonal outcomes. Considerable uncertainties in these associations exist due to inconsistencies across studies and the limited number of available studies. In general, these effects have been reported at doses somewhat higher than effects on the immune system, birth weight, and liver effects.

Among the animal studies, there was no effect of PFOA on reproductive or fertility parameters in female rats. However, it should be noted that female rats have a very high PFOA elimination rate compared to male rats or other species. Increased full litter resorptions and increased stillbirths were observed in pregnant mice exposed to doses resulting in very high serum concentrations. No evidence of altered testicular and sperm structure or function was reported in adult male rats exposed to doses producing high serum concentrations. Increased sperm abnormalities and decreased testosterone were reported at high serum concentrations.

[5] The evidence for effects on the nervous system in humans is limited and largely based on neurodevelopment, including neuropsychological and cognitive development, executive function, and behavioral problems. There are considerable uncertainties due to inconsistency in magnitude and direction of effects across the limited number of studies available.

Information from animal studies is also quite limited. The offspring of mice fed PFOA throughout gestation had detectable levels of PFOA in their brains at birth. Locomotor activity, anxiety-related or depression-like behavior, and muscle strength were not altered. Circadian activity tests revealed sex-related differences in exploratory behavior patterns.

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