MINNESOTA MDH DEPARTMENT OF HEALTH

Protecting, maintaining and improving the health of all Minnesotans

August 24, 2015

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St. Paul, Minnesota 55155

Re: In The Matter of the Proposed Rules of the Department of Health Relating to the Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Part 7500, Part 7850, Part 7860, and Part 7865: Revisor's Tracking Number: RD04257

Dear Librarian:

The Minnesota Department of Health (MDH) intends to adopt rules relating to Health Risk Limits for Groundwater. We plan to publish a Dual Notice of Intent to Adopt Rules in the August 31, 2015 issue of the *Minnesota State Register*.

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

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

Sincerely,

Nancy Rice

Nancy Rice
Health Risk Assessment Unit
Division of Environmental Health
Minnesota Department of Health
P.O. Box 64795
St. Paul, MN 55164

Enclosure: Statement of Need and Reasonableness

STATE OF MINNESOTA

Minnesota Department of Health

In the Matter of the Proposed Rules
of the Minnesota Department of Health
Relating to Health Risk Limits for Groundwater,
Minnesota Rules, Chapter 4717, Part 7500, Part 7850, Part 7860 and Part 7865.
Revisor's ID Number: 04257

STATEMENT OF NEED AND REASONABLENESS

July 2015

8/4/15
Date

Edward Ehlinger, M.D., M.S.P.H.
Commissioner
Minnesota Department of Health
P.O. Box 64975
St. Paul, MN 55164

ABOUT THIS DOCUMENT

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

http://www.health.state.mn.us/divs/eh/risk/rules/water/proposedrules.html

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

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

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

ABBREVIATIONS AND ACRONYMS

ADAF	Age-Dependent Adjustment Factor
BBP	Butyl Benzyl Phthalate
BMDL	Benchmark dose lower-confidence limit
BPA	Bisphenol A
CEC	Contaminant of emerging concern
DBP	Dibutyl Phthalate
DEHP	Di(2-ethylhexyl) Phthalate
(E)	Endocrine[1]
EPA	U.S. Environmental Protection Agency
HBV	Health-Based Value
HED	Human Equivalent Dose
HRA	Health Risk Assessment
HRL	Health Risk Limit
LOAEL	Lowest Observed Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
MCL	Maximum Contaminant Limit (created by the U.S. Environmental Protection Agency)
MDH	Minnesota Department of Health
MMB	Minnesota Management and Budget
NTP	National Toxicology Program
PCP	Pentachlorophenol
RfD	Reference Dose
RSC	Relative Source Contribution
SF	Slope Factor
SONAR	Statement of Need and Reasonableness
TCE	1,1,2-trichloroethylene

[1] See Glossary for further detail

MINNESOTA DEPARTMENT OF HEALTH

STATEMENT OF NEED AND REASONABLENESS
Proposed Amendments to the Rules on Health Risk Limits for Groundwater
(Minnesota Rules, Chapter 4717, Parts 7500, 7850, and 7860)

TABLE OF CONTENTS

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

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

I. Introduction

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

This project proposes to amend Minnesota Rules, Chapter 4717, by revising or adding HRLs for 14 groundwater contaminants. In addition, MDH proposes an HRL for the surface water contaminant triclosan. Historically, MDH has adopted HRLs into rule only for groundwater contaminants. In 2013, the Minnesota Legislature directed MDH to accelerate its HRLs development for water contaminants, including triclosan (Laws 2013, chapter 137, article 2, section 8, subpart a). While Minnesota derives about 75 percent of the drinking water from groundwater, the other 25 percent of the population's drinking water comes from surface water, such as the Mississippi River or lakes. MDH therefore also has an important role in protecting the state's surface waters. Triclosan has been found in surface water in Minnesota, but it has not yet been detected in groundwater.

Specifically, the proposed amendments add new or updated HRL values for 14 contaminants to part 4717.7860 (see Section IV.B.). The proposal will repeal the outdated HRL values in parts 4717.7500, and 4717.7860 (see Section IV.C.) for six of these 14 contaminants. In addition, MDH proposes new values for di(2-ethylhexyl) phthalate, pentachlorophenol, and 1,1,2-trichloroethylene, which will make the Maximum Contaminant Limits (MCLs) in Minnesota Rules part 4717.7850, subpart (2), items C., E., and H., obsolete (required by Laws 2007, chapter 147, article 17, section 2). The amendments will therefore remove these chemicals from the list when the new values are added to part 4717.7860.

These proposed amendments build on MDH's 2009 rule revision and subsequent rulemaking.[2] Details on the 2009 HRL rule revision and subsequent rule adoption are

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

presented in Section II. MDH will not be amending any other parts of the HRLs rules in 2014/2015.

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

This SONAR is divided into five sections. Section I is this introduction. Section II identifies MDH's statutory authority to adopt HRL rules and describes past HRL rule revisions. It explains the concept of HRL values and summarizes the methods MDH used to derive the HRL values. Section III includes the scope of the amendments MDH proposes in 2014/2015. Section IV analyzes each provision in the proposed rules. Section V discusses statutory requirements: the regulatory factors, the performance-based nature of the rules, the additional notice plan, and the impact of the proposed rules, all as required per Minnesota Statutes, section 14.131.

II. Background

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

- describes the statutory authority to review, derive, adopt, and revise HRL values;
- provides historical information about MDH's past rule revisions;
- defines HRL values; and
- discusses the methods MDH used to derive HRL values.

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

A. Statutory Authority

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

1. THE GROUNDWATER PROTECTION ACT, 1989

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

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

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

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

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

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

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

> "(c) For systemic toxicants that are not carcinogens, the adopted health risk limits shall be derived using United States Environmental Protection

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

Agency risk assessment methods using a reference dose, a drinking water equivalent, and a relative source contribution factor.

"(d) For toxicants that are known or probable carcinogens, the adopted health risk limits shall be derived from a quantitative estimate of the chemical's carcinogenic potency published by the United States Environmental Protection Agency and determined by the commissioner to have undergone thorough scientific review."

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

"(a) The commissioner shall review each adopted health risk limit at least every four years.

"(b) The commissioner may revise health risk limits under subdivision 2."

2. COMMISSIONER OF HEALTH'S AUTHORITIES, MINNESOTA STATUTES, SECTION 144.12

Historically, MDH has focused on *groundwater* contaminants when adopting water guidance rules. Under statute, however, MDH has oversight over *surface water*, too. MDH has specific authority to control, by rule, pollution of streams and other waters and the distribution of water by persons for drinking or domestic use (Minnesota Statutes, section 144.12 subdivision 1(5)).

This authority, along with the Laws 2013 described below, provides MDH with the ability to propose HRL rules for triclosan, a contaminant that has been detected in the state's surface waters, but not yet in groundwater.

3. LAWS OF MINNESOTA, 2013

The Legislature granted MDH specific rulemaking authority for a particular chemical, triclosan, during the 2013 Legislative Session. In Laws 2013, chapter 137, article 2 (Clean Water Fund), section 8, MDH is directed, among other tasks, to accelerate development of health risk limits, including triclosan.

MDH developed health-based water guidance for triclosan in 2010, but has not proposed adopting this guidance into rule. For this HRL MDH re-evaluated triclosan to determine if updates were needed. MDH announced the results of the re-evaluation via MDH's subscription email service and on its website in August 2014. To meet the requirements of Laws 2013, MDH will include these updated health-based guidance values for triclosan in the rules proposed for adoption as HRLs.

4. HEALTH STANDARDS STATUTE, 2001

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

> "(1) be based on scientifically acceptable, peer-reviewed information; and
>
> (2) include a reasonable margin of safety to adequately protect the health of infants, children, and adults by taking into consideration risks to each of the following health outcomes: reproductive development and function, respiratory function, immunologic suppression or hyper-sensitization, development of the brain and nervous system, endocrine (hormonal) function, cancer, general infant and child development, and any other important health outcomes identified by the commissioner."

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

B. Past MDH Rule Revisions

MDH's Division of Environmental Health has been providing health-based guidance on drinking water contaminants for several decades. The earliest guidance that MDH developed was the Drinking Water Recommended Allowable Limits (RALs). A RAL was defined as a concentration of a contaminant in water that is protective of human health. RALs were primarily developed for private water supplies, but were also used for public water supplies in the absence of applicable federal standards.

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

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

Over time, MDH has been calculating updated guidance values for the chemicals in this list using the guidance calculation methods adopted into rule in 2009. When the updated

values are adopted into rule, the outdated 1993-1994 values in 4717.7500 are deleted and the updated values are added to Minnesota Rule 4717.7860.

In 2001, MDH toxicologists and risk assessors evaluated the adequacy of the 1993 methods to calculate the HRL values. MDH designed the method review to:

- Provide guidance on new contaminants found in Minnesota groundwater;
- Update existing HRL values with new toxicological research and exposure data;
- Incorporate advances in risk-assessment methods;
- Reflect changes in values and policies regarding children's environmental health; and
- Respond to the directive in the 2001 *Health Standards Statute* (Minnesota Statutes, section 144.0751) to protect sensitive subpopulations such as pregnant women and infants.

The review spanned seven years during which MDH hosted public meetings and invited stakeholder participation. MDH also convened subject-matter expert reviews of the methods to establish a scientifically accepted calculation for determining these values for risk. This evaluation yielded an updated risk equation, or algorithm, to derive HRL values and corresponding policies. MDH began formal rulemaking in 2008 by proposing an updated methodology to derive HRL values based on the United States Environmental Protection Agency's (U.S. EPA) risk-assessment guidelines (see Section II.D.). In 2009, MDH adopted the new methods and the HRL values for 21 groundwater contaminants that it had derived using the updated methodology. Minnesota Rules, Chapter 4717, parts 4717.7100 through 4717.7800 were repealed (except part 4717.7500) and revised rules as parts 4717.7810 through 4717.7900 were adopted. Additional details on the nature and scope of MDH's 2009 HRL rule revision are documented in the 2008/2009 SONAR (MDH, 2008).

In 2007, the Minnesota Legislature enacted two laws which place HRL values into rule. One law, Minnesota Session Laws 2007, chapter 37, section 1, directed MDH to adopt HRLs for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). MDH did this in August 2007 using the legislation's good cause exemption authority for rulemaking. The second law concerned the Water Levels Standards: Minnesota Laws, chapter 147, article 17, section 2. This law required MDH to set an HRL equal to the U.S. EPA Maximum Contaminant Level (MCL) value when the MCL value was more stringent (i.e., lower) than a Minnesota-derived HRL value. In response in 2007, MDH established 11 MCL values as HRLs, and adopted these HRLs into rule in 2009 along with the MCL for nitrate. MDH is now bringing these values up to date and replacing them as MDH derives new HRL values. To date, nine of the MCL values remain in rule. MDH has recently derived updated guidance values for four of them. Three of these, di(2-ehtylhexyl) phthalate (DEHP), pentachlorophenol (PCP) and 1,1,2-trichloroethylene (TCE), are eligible to be included in the 2014/2015 proposed rules amendments.

In 2011, MDH added HRL values for 22 contaminants to Minnesota Rules, Chapter 4717, part 7860, and updated part 7500 to reflect all changes.

In 2013, MDH added HRL values to Minnesota Rules, part 4717.7860 for six chemicals not previously in the HRL rules. In addition, MDH repealed outdated HRL values (adopted in 1993 and 1994) for six chemicals (from Minnesota Rules part 4717.7500) and replaced them (in part 4717.7860) with new HRL values. In total, MDH adopted new or updated HRL values for 12 chemicals in 2013.

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

Year	Number of new HRLs	Number of updated HRLs	Total Number of Chemicals with new or updated HRLs
2007	2	12	14
2009	6	15	21
2011	14	8	22
2013	6	6	12
2015 (proposed)	8	6	14
Total	36	47	73

C. Defining Health Risk Limits (HRLs)

HRL values are a type of health-protective guidance developed by MDH for water contaminants that pose a potential threat to human health if consumed in drinking water. The 1989 Act (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 drinking water contaminant, or a mixture of contaminants, that is likely to pose little or no health risk to humans, including vulnerable subpopulations, and has been adopted into rule. MDH calculates health-based water guidance values, a precursor to HRLs, for specific durations of exposure. An HRL is expressed as micrograms of a chemical per liter of water (µg/L).

In 2013, the Minnesota Legislature directed MDH to create an HRL for triclosan, a contaminant that has been detected in Minnesota surface waters. MDH has been calculating health-based water guidance for surface water contaminants for several years under the Drinking Water Contaminants of Emerging Concern (CEC) program, though MDH has not yet proposed adding them as rules. MDH is now proposing to adopt a triclosan HRL under its authority for protecting surface waters, as described in Section II A (above).

MDH develops health-based water guidance values for substances or chemicals that contaminate surface water or groundwater, or both, as a result of human activities (Minnesota Statutes, sections 103H.201 and 103H.005, subdivision (6)). MDH derives both surface water and groundwater guidance values using identical methodology. In calculating water guidance values, MDH evaluates contaminant levels as though the water were used for drinking water. This is consistent with the declaration in Minnesota Statutes, section 115.063, subdivision 2, that "the actual or potential use of the waters of the state for potable water supply is the highest priority use of that water and deserves maximum protection by the state…" Further, the stated statutory intent is to prevent degradation (Minnesota Statutes, section 103H.001) and to protect the waters of the state (Minnesota Statutes, section 115.063, subdivision (1)).

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

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

- specify a water quality level acceptable for human consumption;
- should not be interpreted as acceptable degradation levels;
- do not address non-ingestion pathways of exposure to contaminants in water (e.g., dermal or inhalation), except in apportioning exposure through the use of a Relative Source Contribution (RSC) factor (for more information on RSC, see MDH, 2008 [Part IV.E.1, page 51] and Minnesota Rules, part 4717.7820, subpart 22);
- do not account for economic or technological factors such as the cost or feasibility of treatment; and
- do not account for the potential impact on the environment outside the realm of drinking water, or the health of non-human species.

MDH cannot anticipate all the situations for which HRL values might provide meaningful guidance. Nor can MDH anticipate all the factors that might determine whether applying an HRL value is appropriate. As mentioned before, HRL values are but

one of several sets of criteria that state groundwater, drinking water, and environmental protection programs may use to evaluate water contamination. Each program must determine whether to apply an HRL or whether site-specific characteristics justify deviation from HRL values.

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

As stated previously, MDH derives HRL values using the methods MDH adopted in 2009 (Minnesota Rules, parts 4717.7810 through 4717.7900). The calculation used to develop an HRL value is a function of how toxic a chemical is (that is, the minimum quantity that will cause health effects), the duration of exposure, and the amount of water individuals drink (intake rates) during the exposure period.

MDH's approach for developing non-cancer HRL values (nHRL) for effects other than cancer is specified in rule (Minnesota Rules, part 4717.7830, subpart 2). MDH also uses this approach for chemicals that cause cancer only after a known dose level is exceeded (e.g., threshold carcinogens). The algorithms and explanation of concepts used to derive HRL values are presented in Appendix C of this SONAR. Additional information is available in MDH's 2008/2009 SONAR (MDH, 2008. See Part IV).

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III. 2014/2015 Proposed Rules

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

A. Scope

The 2014/2015 proposed rules build on the 2009 HRL rule revision. The proposed revisions are limited to Minnesota Rules, parts 4717.7500, 4717.7850, and 4717.7860 as noted below. MDH is not amending other parts of the HRL rules. Through the proposed rules, MDH intends to:

- adopt into rule HRL values for 14 groundwater contaminants with guidance developed using the 2009 methodology. The proposed HRL values will be appended to Minnesota Rules, part 4717.7860 (see Section IV.B. for details); and
- repeal outdated guidance in Minnesota Rules, parts 4717.7500 and 4717.7850 for six contaminants adopted in 1993 or 2007 for which a new updated HRL value has been derived (see Section IV.C. for details). (Note: the repealed values will be replaced with values added in Minnesota Rules, parts 4717.7860, as noted above.)

B. Selection of Contaminants for Review

MDH selected the contaminants for the 2014/2015 amendments based on recommendations from partner agencies such as the MPCA and the MDA, as well as nominations from other stakeholders and the general public. The agencies and nominators expressed a need for guidance on contaminants that might be of emerging concern and those that are commonly detected by the agencies in their monitoring and remediation efforts.

At interagency meetings between 2007 and 2014, representatives from MDA, MPCA, and MDH nominated chemicals for review, discussed their concerns about specific contaminants, and ranked a list of chemicals according to each agency's need for guidance. A final list of priority chemicals was generated from this process. In addition, chemicals nominated through the MDH CEC program (created in 2010) were ranked for priority in guidance development. MDH drew from these two processes to create work plans to assess chemicals for health risks and issue guidance (see Appendix D).

As MDH reviewed each chemical, it posted the following information on MDH's Chemicals Under Review[4] webpage: the chemical's name, its Chemical Abstracts Service (CAS) number, and the date it was posted. Upon completion of each review, MDH posted the guidance values and the chemical-specific summary sheets on the

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

Human Health Based Water Guidance[5] webpage. MDH also notified subscribers to MDH HRL Rules, Guidance and Chemical Review email notification account[6] about the updated guidance's availability.

C. Applying MDH-derived Methods

MDH derived the proposed HRL values using the methods it adopted in 2009. The 2009 methods reflect current scientific risk-assessment principles; therefore, MDH is not proposing any changes to these methods in the 2014/2015 proposed amendments.

Applying the 2009 methods to HRL values from 1993 and 1994 or the 2007 MCL-based HRLs yields new HRL values that might increase or decrease the previous values, based on cancer or chronic exposure endpoints. These fluctuations are related to several factors, such as:

- extent and quality of toxicity data for a chemical;
- changes in intake rates within the guidance algorithms to account for sensitive subpopulations (e.g., infants and children); and
- age-dependent adjustment factors used within the algorithms.

Among the 14 chemicals included in this 2014/2015 proposed rule, six currently have HRL values for cancer or chronic exposure. Of these, three are based on 1993 HRLs and three are 2009 MCL-based HRLs. Some of the new, proposed values will increase, some will decrease and one will stay the same, as shown below:

Chemical Abstract Service number	Chemical Name	Current HRL (µg/L)	Proposed HRL (µg/L) (Lowest value of all durations)	Change
85-68-7	**Butyl benzyl phthalate**	100 (1993 HRL)	100	No change
7440-43-9	**Cadmium**	4 (1993 HRL)	0.5	Lower
84-72-2	**Dibutyl phthalate (DBP)**	700 (1993 HRL)	20	Lower
117-81-7	**Di (2-ethylhexyl) phthalate (DEHP)**	6 (2009 MCL-based HRL)	7	Higher
87-65-5	**Pentachlorophenol (PCP)**	1 (2009 MCL-based HRL)	0.3	Lower

[5] The Groundwater Values Table is available at: http://www.health.state.mn.us/divs/eh/risk/guidance/gw/table.html All health-based guidance values for water are summarized in this table, including those that have not been adopted into rule.

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

Chemical Abstract Service number	Chemical Name	Current HRL (µg/L)	Proposed HRL (µg/L) (Lowest value of all durations)	Change
79-01-6	**1,1,2-trichloroethylene (TCE)**	5 (2009 MDL-based HRL)	0.4	Lower

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

MDH has two methods to derive HRL values depending on whether or not a dose or exposure can be found that causes no harm in studies of animals or people. Historically, these methods were applied according to the type of health effect that the chemical exposure caused and were termed 'non-cancer' and 'cancer' methods. However, the scientific community now recognizes that chemicals are better assessed according to what is known about finding a dose that causes no harm, regardless of the health effect.

Most toxicity studies find that at some low dose or exposure the chemical does no harm or has no effect on the animal tested. The concept of a dose considered to be without harm (with all higher doses causing harm) is called the threshold. Many carcinogens cause cancer only after exposure to high doses but also exhibit a threshold dose for effects other than cancer. That is, this lower threshold dose will not cause cancer or other health effects. MDH's threshold method, historically called a non-cancer method, has been used by MDH for any chemical that exhibits a threshold, including many carcinogens.

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

Among the 14 contaminants for which HRL values are proposed during this 2014/2015 rulemaking, there are three threshold carcinogens (butyl benzyl phthalate, dimethenamid, and dimethenamid-p) and four non-threshold carcinogens (acrylamide, di (2-ethylhexyl) phthalate, pentachlorophenol, and 1,1,2-trichloroethylene). For the three threshold carcinogens, the non-cancer HBV values are protective. For the four non-threshold carcinogens, cancer HBVs were calculated based on a 1/100,000 additional lifetime cancer risk. See also Appendix C for more information.

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IV. Rule-by-Rule Analysis

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

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

The Health Risk Limits table in Minnesota Rules, part 4717 7860 lists the HRL values derived for chemicals found in Minnesota's groundwater. As noted before, an HRL value represents the health-protective limit of the concentration of a contaminant in groundwater that poses little or no risk to human health, including vulnerable subpopulations, based on current scientific knowledge. HRL values are derived using the methodology specified in Minnesota Rules, parts 4717.7830 and 4717.7840 of existing HRL rules (see Appendix C for detailed explanations and definitions of the technical terms that follow).

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

Figure 1.
Example of table showing proposed rule

Subp. XX Chemical name. ← Heading Section
CAS number[7]: XXX-XX-X (identifies the chemical)
Year Adopted: 2015
Volatility: XX

Column Headings

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

Row headings

[7] Chemical Abstract Service number for assigning a unique number to chemicals. (*See glossary page 58)*

Heading section:

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

Row headings:

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

Column headings:

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

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

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

- "-" means not relevant
- "NA" means not applicable. "NA" in the cancer column means that the chemical has not been classified as a linear (non-threshold) carcinogen
- "ND" means not derived due to absence or paucity of toxicity information
- "None" means that the HRL value is based on a general adverse effect (e.g., reduced adult body weight) not attributable to a specific organ system and therefore it is not applicable for inclusion in the additivity calculations for the health risk index.

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

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

More information about each parameter can be found in Appendix C and in the 2008/2009 SONAR (MDH, 2008).

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

1. Proposed HRL Rules Amendments for New or Updated Guidance

The following pages describe HRL Rules amendments proposed for 14 substances with new or updated guidance values:

Subp. 2a. Acetaminophen

CAS number: 103-90-2
Year Adopted: 2015
Volatility: Nonvolatile

Acute duration.
The proposed acute nHRL is 200 µg/L. The RfD is 0.25 mg/kg-d and the intake rate is 0.289 L/kg-d. The Relative Source Contribution (RSC) is 0.2. MDH uses the EPA Exposure Decision Tree (EPA 2000c) to select appropriate RSCs. Given the significant potential non-water sources of exposure from multiple products available for infants and children, an RSC of 0.2 is selected rather than the default value of 0.5 used for

nonvolatile chemicals. The No Observed Adverse Effect Level (NOAEL) is 7.4 mg/kg-d, based on the human minimum therapeutic dose for infants at 40 mg/dose for up to 5.4 kg infant. Because the NOAEL was based on human data, no Human Equivalent Dose (HED) was calculated. The total uncertainty factor is 30 (10 for intraspecies variability, and 3 for database uncertainty [additional studies to evaluate gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted]). The critical effect is hepatotoxicity, or liver damage, in humans. The co-critical effects are liver effects in animals (increased serum liver enzymes, reduced hepatic glutathione, and liver histopathological changes) and acute liver failure in humans. The additivity endpoint (the way scientists evaluate the risk from exposure to multiple chemicals) is hepatic (liver) system.

Short-term duration.
The proposed short-term nHRL is 200 µg/L. The RfD is 0.25 mg/kg-d and the intake rate is 0.289 L/kg-d. The RSC is 0.2. MDH uses the EPA Exposure Decision Tree (EPA 2000c) to select appropriate RSCs. Given the significant potential non-water sources of exposure from multiple products available for infants and children, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals. The NOAEL is 7.4 mg/kg-d. The HED is not applicable. The total uncertainty factor is 30 (10 for intraspecies variability, 3 for database uncertainty [additional studies to evaluate gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted]). Critical effects are hepatoxicity and increased serum liver enzymes (ALT) in humans and animals. Co-critical effects are acute liver failure, hepatotoxicity, increased serum liver enzymes (ALT, AST) in humans and animals, decreased hepatic glutathione (GSH), and liver histopathological changes in animals. The additivity endpoint is hepatic (liver) system.

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

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

Cancer.
Not applicable. Acetaminophen is not classified as a carcinogen by International Agency for Research on Cancer, U.S. Food and Drug Administration, National Toxicology Program, U.S. EPA or California Office of Environmental Health Hazard Assessment.

Acetaminophen

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	200	200	200 (2)	200 (2)	NA
RFD (mg/kg-day)	0.25	0.25	(2)	(2)	--
RSC	0.2	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.289	0.289	(2)	(2)	--
Endpoints	hepatic (liver) system	hepatic (liver) system	hepatic (liver) system	hepatic (liver) system	--

Subp. 3e. Acrylamide

CAS number: 79-06-1
Year Adopted: 2015
Volatility: Nonvolatile

Acute duration.
Not derived due to insufficient data.

Short-term duration.
The proposed short-term nHRL is 7 µg/L. The RfD is 0.010 mg/kg-d and the intake rate is 0.289 L/kg-d. The Relative Source Contribution (RSC) is 0.2. MDH uses the EPA Exposure Decision Tree (EPA, 2000) to select appropriate RSCs. Due to evidence of acrylamide in breast milk (Sorgel, 2002) and baby food (FDA, 2006), along with evidence that dietary exposures for some people exceed 50 percent of the short-term RfD, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals. The point of departure selected was the benchmark dose lower-confidence limit ($BMDL_{10}$) of 1.33 mg/kg-d and the Human Equivalent Dose (HED) is 0.31 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [toxicodynamics][8] and 10 for intraspecies variability). Critical effects are reproductive toxicity in male rodents causing germ cell damage that results in fetal resorptions and implantation loss. Co-critical effects are neurotoxicity such as loss of hind-limb use and altered head tilt, male-mediated reproductive toxicity resulting in impaired mating and

[8] One of the Uncertainty Factors *See Glossary, page 61 and Appendix C, page 75)*

decreased number and vitality of fetuses, increased resorptions/implantation losses, developmental toxicity including neurobehavioral effects in young animals, decreased pup body weight, and increased resorptions/implantation losses. The additivity endpoints are developmental, male reproductive system, and nervous system.

Subchronic duration.
The subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 7 µg/L. The additivity endpoints are developmental, male reproductive system, and nervous system.

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

Cancer.
The proposed cancer HRL is 0.2 µg/L. The U.S. EPA cancer classification is "likely to be carcinogenic to humans." The cancer slope factor from EPA is 0.5 $(mg/kg\text{-}d)^{-1}$. Tumors were in the testes and thyroid in males.

Acrylamide

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	7	7 (2)	7 (2)	0.2
RFD (mg/kg-day)	--	0.010	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	0.5
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	--	0.289	(2)	(2)	$0.137_{(<2)}$ $0.047_{(2\ to\ <16)}$ $0.039_{(16+)}$
Endpoints	--	developmental, male reproductive system, nervous system	developmental, male reproductive system, nervous system	developmental, male reproductive system, nervous system	cancer

Subp. 5a. Bentazon

CAS number: 25057-89-0
Year Adopted: 2015
Volatility: Nonvolatile

Acute duration.
The proposed acute nHRL is 400 µg/L. The RfD is 0.22 mg/kg-d and the intake rate is 0.289 L/kg-d. The Relative Source Contribution (RSC) is 0.5. The NOAEL is 100 mg/kg-d and the HED is 22 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty to address the need for additional studies regarding thyroid effects). Critical effects are increased post-implantation loss and fetal resorptions. Co-critical effects are increased embryonic and fetal resorptions. The additivity endpoints are developmental and female reproductive system.

Short-term duration.
The proposed short-term nHRL is 60 µg/L. The RfD is 0.033 mg/kg-d and the intake rate is 0.289 L/kg-d. The RSC is 0.5. The NOAEL is 15 mg/kg-d and the HED is 3.3 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty to address the need for additional studies regarding thyroid effects that have been observed at other durations). Critical effects are reduced pup body weight gain. There are no applicable co-critical effects. The additivity endpoint is developmental.

Subchronic duration.
The proposed subchronic nHRL is 50 µg/L. The RfD is 0.020 mg/kg-d and the intake rate is 0.077 L/kg-d. The RSC is 0.2. The NOAEL is 3.2 mg/kg-d and the HED is 2 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty to address the need for additional studies regarding thyroid effects). Critical effects are bloody stools, anemia, and decreased body weight gain. There are no applicable co-critical effects. The additivity endpoint is hematological (blood) system.

Chronic duration.
The proposed chronic nHRL is 30 µg/L. The RfD is 0.0060 mg/kg-d and the intake rate is 0.043 L/kg-d. The RSC is 0.2. The Lowest Observed Adverse Effect Level (LOAEL) is 12 mg/kg-d and the HED is 1.8 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 10 for extrapolation from a LOAEL to a NOAEL). The critical effect is increased thyroid weight. There are no applicable co-critical effects. The additivity endpoint is thyroid.

Cancer.
Not applicable. No cancer classification is available for bentazon.

Bentazon

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	400	60	50	30	NA
RFD (mg/kg-day)	0.22	0.033	0.02	0.0060	--
RSC	0.5	0.5	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.289	0.289	0.077	0.043	--
Endpoints	developmental, female reproductive system	developmental	hematological (blood) system	thyroid	--

Subp. 6c. Bisphenol A (BPA)

CAS number: 80-05-7
Year Adopted: 2015
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL is 100 µg/L. The RfD is 0.16 mg/kg-d and the intake rate is 0.289 L/kg-d. MDH uses the EPA Exposure Decision Tree (EPA 2000c) to select appropriate RSCs. Given the significant potential non-drinking water sources of exposure from multiple sources available for infants, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals. The NOAEL is 2.7 mg/kg-d and the HED is 16 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty [additional studies to evaluate latent effects of early life exposure, neurobehavioral, immune system, and metabolic disease are warranted]). Critical effects are developmental (decreased pup body weight) and increased total T3 in male pups. Co-critical effects are developmental (decreased number and viability of offspring, pup and fetal body weight effects, delayed puberty in male and females, decreased weanling spleen and testes weights, undescended testes, and seminiferous tubule hypoplasia), female reproductive (decreased number and viability of offspring and changes in hormone ratios), liver (changes serum liver parameters, organ weight, morphology, and histology), male

reproductive effects (changes in hormone ratios, reduced spermatogenesis, organ weights, and morphology), renal (changes in kidney weights, morphology, and histology), thyroid (increased organ weight), and decreased maternal body weight during gestation. The additivity endpoints are developmental, female reproductive system (E), hepatic (liver) system, male reproductive system (E), renal (kidney) system, and thyroid (E).

Subchronic duration.
The proposed subchronic nHRL is 20 µg/L. The RfD is 0.0065 mg/kg-d and the intake rate is 0.077 L/kg-d. The RSC is 0.2. The NOAEL is 5 mg/kg-d and the HED is 0.65 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty [additional studies to evaluate latent effects of early life exposure, neurobehavioral, immune system, and metabolic disease are warranted]). Critical effects are centrilobular hepatocyte hypertrophy and increased kidney weight. Co-critical effects are increased centrilobular hepatocyte hypertrophy and liver weight effects. The additivity endpoints are hepatic (liver) system and renal (kidney) system.

Chronic duration.
The chronic nHRL value must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the proposed chronic nHRL is set equal to the proposed subchronic nHRL of 20 µg/L. Additivity endpoints are the same as the subchronic duration (hepatic [liver] system and renal [kidney] system).

Cancer.
Not applicable. No cancer classification is available for Bisphenol A.

Bisphenol A

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	100	20	20 (3)	NA
RFD (mg/kg-day)	--	0.16	0.0065	(3)	--
RSC	--	0.2	0.2	(3)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.289	0.077	(3)	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Endpoints	--	developmental, female reproductive system (E), hepatic (liver) system, male reproductive system (E), renal (kidney) system, thyroid (E)	hepatic (liver) system, renal (kidney) system	hepatic (liver) system, renal (kidney) system	--

Subp. 6d. Butyl Benzyl Phthalate

CAS number: 85-68-7
Year Adopted: 2015
Volatility: Low

Acute duration.
The proposed acute duration nHRL is 100 µg/L. The RfD is 0.15 mg/kg-d and the intake rate is 0.289 L/kg-d. The RSC is 0.2. MDH uses the EPA Exposure Decision Tree (EPA, 2000c) to select appropriate RSCs (MDH, 2008). Typically an RSC of 0.5 is used for nonvolatile contaminants. However, there is evidence that there are significant known or potential sources other than ingestion of water. An RSC of 0.2 was selected rather than the default value of 0.5 for nonvolatile contaminants. The NOAEL is 20 mg/kg-d and the HED is 4.6 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [toxicodynamics] and 10 for intraspecies variability). Critical effects are decreased pup body weight and decreased serum thyroid hormone levels in preweaning pups. There were no co-critical effects. The additivity endpoint is developmental (E).

Short-term duration.
The proposed short-term nHRL value is 100 µg/L. The RfD is 0.15 mg/kg-d and the intake rate is 0.289 L/kg-d. The RSC was set at 0.2 because there is evidence that there are significant known or potential pathways of exposure other than ingestion of water. The NOAEL is 20 mg/kg-d and the HED is 4.6 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [toxicodynamics] and 10 for intraspecies variability). Critical effects were decreased pup body weight and decreased serum thyroid hormone levels in preweaning pups. There were no co-critical effects. The additivity endpoint is developmental (E).

Subchronic duration.
The subchronic nHRL value must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL

value is set equal to the proposed short-term nHRL value of 100 µg/L. The additivity endpoint is the same as for the short-term duration (developmental [E]).

Chronic duration.
The chronic nHRL value must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the proposed chronic nHRL value is set equal to the proposed short-term nHRL value of 100 µg/L. The additivity endpoint is the same for the short-term duration (developmental [E]).

Cancer.
Not applicable. BBP was classified as a Group C carcinogen by EPA IRIS in 1993. In 2002, using the revised EPA cancer classification, the EPA Provisional Peer Reviewed Toxicity Values (PPRTV) program has classified BBP as "likely to be carcinogenic" (EPA, 2002b). PPRTV derived a cancer slope factor, however, MDH has chosen to not use the EPA PPRTV cancer slope factor to generate a cancer HBV. MDH considers BBP to be a nonlinear (threshold) carcinogen based on lack of positive genotoxicity data and evidence of clear morphological continuum from focal pancreatic acinar cell hyperplasia (preneoplastic lesion) to adenoma to carcinoma in male rats (NTP, 1997). Carcinogenicity was equivocal in female rats despite 2-fold higher dose levels and negative in mice (NTP, 1997). The RfD (0.15 mg/kg-d) is 162-fold lower than the NTP study NOAEL HED and is therefore considered to be protective against cancer.

Butyl Benzyl Phthalate

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	100	100	100 (2)	100 (2)	NA
RFD (mg/kg-day)	0.15	0.15	(2)	(2)	--
RSC	0.2	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.289	0.289	(2)	(2)	--
Endpoints	developmental (E)	developmental (E)	developmental (E)	developmental (E)	--

Subp. 6e. Cadmium

CAS number: 7440-43-9
Year Adopted: 2015
Volatility: Nonvolatile

Acute duration.
The proposed acute nHRL value is 5 µg/L. The RfD is 0.0077 mg/kg-d. The point of departure NOAEL is 1 mg/kg-d. The HED is 0.23 mg/kg-d and the RSC is 0.2. Typically, an RSC of 0.5 is used for moderately volatile contaminants for the acute and short-term durations. Given the significant potential for non-drinking water sources of dietary exposure to infants and children, an RSC of 0.2 was selected rather than applying the default RSC value of 0.5. The intake rate is 0.289 L/kg-d. The uncertainty adjustment is 30 (3 for interspecies differences [toxicodynamics] and 10 for intraspecies variability). The critical effects are decreased fetal body weight and body length and increased fetal skeletal malformations. The co-critical effects are decreased fetal body weight, body weight gain, and body length. The additivity endpoint is developmental.

Short-term duration.
The proposed short-term nHRL value is 1 µg/L. The RfD is 0.0016 mg/kg-d and the intake rate is 0.289 L/kg-d. The point of departure LOAEL is 0.71 mg/kg-d. The HED is 0.16 mg/kg-d and the RSC is 0.2 (for the same reason as described in the acute duration, above). The total uncertainty factor is 100 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 3 for extrapolation from a LOAEL to a NOAEL [the neurological effects observed at the LOAEL were subtle and a factor of 3 is expected to be sufficiently protective]). The critical effects are alteration in the development of cliff avoidance behavior and spontaneous locomotor activity in offspring exposed during the developmental period. The co-critical effects are decreased plasma essential ions and decreased glomerular filtration rate. The additivity endpoints are developmental, nervous system, and renal (kidney) system.

Subchronic duration.
The proposed subchronic nHRL value is 1 µg/L. The RfD is 0.00044 mg/kg-d, and the intake rate is 0.077 L/kg-d. The point of departure LOAEL is 0.2 mg/kg-d. The HED is 0.044 mg/kg-d and the RSC is 0.2. The total uncertainty factor is 100 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 3 for extrapolation from a LOAEL to a NOAEL [the bone effects observed at the LOAEL were subtle and a factor of 3 is expected to be sufficiently protective]). The critical effects are decreased femoral bone resistance to fracture, increased fragility of the femoral bone, increased markers for bone resorption, and decreased markers for bone formation in rapidly growing young animals. There are no co-critical effects. The additivity endpoints are developmental and skeletal.

Chronic duration.
The proposed chronic nHRL value is 0.5 µg/L. The RfD is 0.00011 mg/kg-d, and the intake rate is 0.043 L/kg-d. The point of departure urinary cadmium dose level$_{10}$ ($UCDL_{10}$) is 0.00033 mg/kg-d, where the $UCDL_{10}$ is the 95 percent lower confidence limit on the estimated internal cadmium dose (urinary cadmium expressed as µg/g creatinine) corresponding to the probability of 10 percent excess risk of low molecular weight proteinuria. Because a human study was used, an HED was not applicable. The RSC is 0.2. The total uncertainty factor is 3 (3 for intraspecies variability to account for sensitive subpopulations). The critical effect is low molecular weight proteinuria. The co-

critical effect is increased risk for osteoporosis. The additivity endpoints are renal (kidney) system and skeletal.

Cancer:
Not derived/not applicable.

Cadmium

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	5	1	1	0.5	NA
RFD (mg/kg-day)	0.0077	0.0016	0.00044	0.00011	--
RSC	0.2	0.2	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.289	0.289	0.077	0.043	--
Endpoints	developmental	developmental, nervous system, renal (kidney) system	developmental, skeletal	renal (kidney) system, skeletal	--

Subp. 8e. Dibutyl phthalate (DBP)

CAS number: 84-74-2
Year Adopted: 2015
Volatility: Low

Acute duration.
The proposed acute nHRL is 20 µg/L. The RfD is 0.023 mg/kg-d and the intake rate is 0.289 L/kg-d. The RSC is 0.2. Typically an RSC of 0.5 is used for nonvolatile contaminants. However, there is evidence that there are significant known or potential sources other than ingestion of water. Therefore, an RSC of 0.2 was selected rather than the default value of 0.5 for nonvolatile contaminants. The NOAEL is 10 mg/kg-d and the HED is 2.3 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database uncertainties [additional study is warranted for potential thyroid and immunological effects]). Critical effects are decreased fetal testosterone and decreased fetal testicular cell number and fetal testes size. Co-critical effects are decreased fetal testosterone and Sertoli cell atrophy and decreased total cell number and number of seminiferous tubules in fetal testes. The additivity endpoint is developmental (E).

Short-term duration.
The proposed short-term nHRL value is 20 µg/L. The RfD is 0.023 mg/kg-d, the RSC is 0.2 and the intake rate is 0.289 L/kg-d. The RSC selected was 0.2, for the same reason as noted in the acute duration description above. The NOAEL is 10 mg/kg-d and the HED is 2.3 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database uncertainties [additional study is warranted for potential thyroid and immunological effects]). The critical effect is decreased fetal testosterone and decreased fetal testicular cell number and fetal testes size. The co-critical effect is decreased fetal testosterone and Sertoli cell atrophy and decreased total cell number and number of seminiferous tubules in fetal testes. The additivity endpoint is development (E).

Subchronic duration.
The subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 20 µg/L. The additivity endpoint is the same as the short-term duration (developmental [E]).

Chronic duration.
The chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the proposed chronic nHRL is set equal to the proposed short-term nHRL of 20 µg/L. The additivity endpoint is the same as the short-term duration (developmental [E]).

Cancer.
Not applicable. U.S. EPA IRIS concluded that the cancer classification is Group D "not classifiable as to human carcinogenicity."

Dibutyl phthalate

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	20	20	20 (2)	20 (2)	NA
RFD (mg/kg-day)	0.023	0.023	(2)	(2)	--
RSC	0.2	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.289	0.289	(2)	(2)	--
Endpoints	developmental (E)	developmental (E)	developmental (E)	developmental (E)	--

Subp. 11c. Di(2-ethylhexyl) phthalate (DEHP)

CAS number: 117-81-7
Year Adopted: 2015
Volatility: Nonvolatile

Acute duration.
The proposed acute nHRL value is 20 µg/L. The RfD is 0.029 mg/kg-d. The RSC is 0.2. MDH uses the EPA Exposure Decision Tree (EPA 2000c) to select appropriate Relative Source Contributions (RSCs) (MDH 2008). Typically an RSC of 0.5 is used for nonvolatile contaminants for the acute and short-term durations and an RSC of 0.2 is used for subchronic and chronic durations. However, there is evidence that there are significant known or potential sources other than ingestion of drinking water. Therefore, an RSC of 0.2 was selected rather than applying the default RSC value. The intake rate is 0.289 L/kg-d. The BMDL is 3.8 mg/kg-d and the HED is 0.874 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [toxicodynamics] and 10 for intraspecies variability). The critical effect is male reproductive tract malformations (small testes, small epididymis, small cauda epididymis, and small seminal vesicles). The co-critical effects are increased fetal testicular testosterone, male reproductive tract lesions, and retained nipples in pre-weanling males. The additivity endpoints are developmental (E) and male reproductive system (E).

Short-term duration.
The proposed short-term nHRL value is 20 µg/L. The RfD is 0.029 mg/kg-d. The BMDL is 3.8 mg/kg-d and the HED is 0.874 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [toxicodynamics] and 10 for intraspecies variability). The critical effects are male reproductive tract malformations (small testes, small epididymis, small cauda epididymis, small seminal vesicles). The co-critical effects are increased fetal testicular testosterone, male reproductive tract lesions, retained nipples in pre-weanling males, and hormonal effects in pubertal males (changes in serum testosterone, increased luteinizing hormone, increased serum estradiol, increased testicular interstitial fluid testosterone, and decreased androgen synthesis). The additivity endpoints are developmental (E) and male reproductive system (E).

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

Chronic duration.
The chronic nHRL must be protective of exposures that occur within the acute, short-term, and subchronic periods and therefore, the proposed chronic nHRL is set equal to the

short-term nHRL of 20 µg/L. The additivity endpoints are developmental (E) and male reproductive system (E).

Cancer.
The proposed cancer HRL value is 7 µg /L. The cancer classification is Group B2, probable human carcinogen. The cancer slope factor is 0.014 $(mg/kg\text{-}d)^{-1}$ based on a 1982 study by the National Toxicology Program. The tumor site is the liver.

Di(2-ethylhexyl) phthalate (DEHP)

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	20	20	20 (2)	20 (2)	7
RFD (mg/kg-day)	0.029	0.029	(2)	(2)	--
RSC	0.2	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	0.014
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	0.289	0.286	(2)	(2)	$0.137_{(<2)}$ $0.047_{(2\ to\ <16)}$ $0.039_{(16+)}$
Endpoints	developmental (E); male reproductive system (E)	developmental (E); male reproductive system (E)	developmental (E); male reproductive system (E)	developmental (E); male reproductive system (E)	cancer

Subp. 11d. Dimethenamid and Dimethenamid-p

CAS number: 87674-68-8 and 163515-14-8
Year Adopted: 2015
Volatility: Moderate

Acute duration.
Not derived due to insufficient data.

Short-term duration.
The proposed short-term nHRL value is 600 µg/L. The RfD is 0.34 mg/kg-d, the RSC is 0.5 and the intake rate is 0.289 L/kg-d. The NOAEL is 149 mg/kg-d and the HED is

34 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 3 for database uncertainty to ensure that the short-term RfD is protective of potential developmental effects). Critical effects are liver effects (increased absolute and relative liver weights and change in increased liver enzyme levels). Co-critical effects are decreased pup body weights, decreased adult body weight gain, neurological effects (lacrimation, piloerection, excess salivation, and decreased motor activity), post implantation loss, and liver effects (increase in relative and absolute liver weight and changes in liver enzymes). The additivity endpoints are developmental, female reproductive system, hepatic (liver) system, and nervous system.

Subchronic duration.
The subchronic nHRL must be protective of the acute and short-term exposures that occur within the subchronic period. Therefore, the proposed subchronic nHRL is set equal to the proposed short-term nHRL of 600 µg/L. The additivity endpoints are the same as the short-term duration (developmental, female reproductive system, hepatic (liver) system, and nervous system).

Chronic duration.
The proposed chronic nHRL value is 300 µg/L. The RfD is 0.060 mg/kg-d, the RSC is 0.2 and the intake rate is 0.043 L/kg-d. The NOAEL is 7 mg/kg-d and the HED is 1.8 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability). Critical effects are decrease in body weight gain, and liver effects (increased relative liver weight and bile duct hyperplasia). There are no co-critical effects. The additivity endpoint is hepatic (liver) system.

Cancer.
Not applicable. The U.S. EPA classification for this chemical is Class C "possible human carcinogen" nonlinear approach recommended (EPA 1992c). Tumor sites are ovaries and liver (benign liver tumors). The chronic RfD (0.060 mg/kg-d) is protective for cancer risk.

Dimethenamid and Dimethenamid-p

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	600	600 (2)	300	NA
RFD (mg/kg-day)	--	0.34	(2)	0.060	--
RSC	--	0.5	(2)	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.289	(2)	0.043	--
Endpoints	--	developmental, female	developmental, female	hepatic (liver) system	--

	Acute	Short-term	Subchronic	Chronic	Cancer
		reproductive system, hepatic (liver) system, nervous system	reproductive system, hepatic (liver) system, nervous system		

Subp. 14. Pentachlorophenol (PCP)

CAS number: 87-86-5
Year Adopted: 2015
Volatility: Low

Acute duration.
The proposed acute nHRL value is 7 µg/L. The RfD is 0.0040 mg/kg-d, the RSC is 0.5, and the intake rate is 0.289 L/kg-d. The LOAEL is 5 mg/kg-d and the HED is 1.2 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, 3 for extrapolation from a minimal LOAEL to a NOAEL, and 3 for database uncertainty to address need for additional studies regarding potential thyroid effects on neurodevelopment). The critical effect is delayed skull ossification. The co-critical effect is reduction in serum levels of T_4 in pregnant animals. The additivity endpoints are developmental and thyroid (E).

Short-term duration.
The proposed short-term nHRL value is 7 µg/L. The RfD is 0.0040 mg/kg-d, the RSC is 0.5 and the intake rate is 0.289 L/kg-d. The LOAEL is 5 mg/kg-d and the HED is 1.2 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, 3 for extrapolation from a LOAEL to a NOAEL, and 3 for database uncertainty to address need for additional studies regarding potential thyroid effects on neurodevelopment). The critical effect is delayed skull ossification. The co-critical effects are decreased serum T_4 in pregnant, adult, preweanling, pre-pubertal, and pubertal animals and decreased serum T_3/T_4 ratio. The additivity endpoints are developmental (E) and thyroid (E).

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

Chronic duration.
The chronic nHRL must be protective of the acute , short-term and subchronic exposures that occur within the chronic period and therefore, the proposed non-cancer chronic HRL is set equal to the short-term nHRL of 7 µg/L. The additivity endpoints are

developmental (E), hepatic [liver] system, immune system, male reproductive system, and thyroid (E).

Cancer.
The proposed cancer HRL is 0.3 µg/L. The U.S. EPA cancer classification is "likely to be carcinogenic to humans." The cancer slope factor from EPA is 0.4 $(mg/kg\text{-}d)^{-1}$ based on a 1989 study by the National Toxicology Program. The tumor sites are liver and adrenal gland (pheochromocytomomas).

Pentachlorophenol

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	7	7	7 (2)	7 (2)	0.3
RFD (mg/kg-day)	0.0040	0.0040	(2)	(2)	--
RSC	0.5	0.5	(2)	(2)	
SF (per mg/kg-day)	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
ADAF or $AF_{lifetime}$	--	--	--	--	$0.137_{(<2)}$ $0.047_{(2\ to\ <16)}$ $0.039_{(16+)}$
Intake Rate (L/kg-day)	0.289	0.289	(2)	(2)	--
Endpoints	developmental, thyroid (E)	developmental (E), thyroid (E)	developmental (E), hepatic (liver) system, immune system, male reproductive system, thyroid (E)	developmental (E), hepatic (liver) system, immune system, male reproductive system, thyroid (E)	cancer

Subp. 17a. Sulfamethazine (includes sodium salt form)

CAS number: 57-68-1 (and 1981-58-4)
Year Adopted: 2015
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL value is 100 µg/L. The RfD is 0.040 mg/kg-d, and the intake rate is 0.289 L/kg-d. Typically an RSC of 0.5 is used for nonvolatile contaminants for the acute and short-term durations and an RSC of 0.2 is used for subchronic and chronic durations. Given the limited potential for exposure from other sources, an RSC of 0.8 was selected rather than applying the default RSC value. For individuals who take sulfonamide antibiotics by prescription, the additional exposure from drinking water will be negligible. The NOAEL is 5 mg/kg-d and the HED is 1.2 mg/kg-d. The total uncertainty factor is 30 (3 for interspecies differences [toxicodynamics] and 10 for intraspecies variation). The critical effect is thyroid follicular cell hypertrophy. There are no co-critical effects. The additivity endpoint is thyroid.

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

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

Cancer.
Not applicable.

Sulfamethazine

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	100	100 (2)	100 (2)	NA
RFD (mg/kg-day)	--	0.040	(2)	(2)	--
RSC	--	0.8	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.289	(2)	(2)	--
Endpoints	--	thyroid	thyroid	thyroid	--

Subp. 20. 1,1,2-Trichloroethylene (TCE)

CAS number: 79-01-6
Year Adopted: 2015
Volatility: High

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL value is 0.4 µg/L. The RfD is 0.00052 mg/kg-d, the RSC is 0.2 and the intake rate is 0.289 L/kg-d. A NOAEL was not identified. The LOAEL is 0.37 mg/kg-d and the HED is 0.052 mg/kg-d. The total uncertainty factor is 100 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 3 for use of a minimal LOAEL instead of a NOAEL). The critical effect is immune effects (impacts on humoral function and splenic T-cells observed in a developmental immune study). The co-critical effect is fetal heart malformations. The additivity endpoints are developmental and immune system.

Subchronic duration.
The proposed subchronic nHRL value is 0.4 µg/L. The RfD is 0.00017 mg/kg-d, the RSC is 0.2 and the intake rate is 0.077 L/kg-d. A NOAEL was not identified. The LOAEL is 0.37 mg/kg-d and the HED is 0.052 mg/kg-d. The total uncertainty factor is 300 (3 for interspecies differences [toxicodynamics], 10 for intraspecies variability, and 10 for use of a LOAEL instead of a NOAEL). The critical effect is immune effects (impacts on thymic T-cells, suppression of plaque forming cell response, and delayed hypersensitivity response observed in a developmental immune study). The co-critical effect is fetal heart malformations. The additivity endpoints are developmental and immune system.

Chronic duration.
The chronic nHRL value must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the proposed chronic nHRL is set equal to the proposed short-term and proposed subchronic nHRLs of 0.4 µg/L. The additivity endpoints are the same as the short-term and subchronic durations (developmental and immune system).

Cancer.
The proposed cancer HRL value is 2 µg/L. TCE is carcinogenic to humans by all routes of exposure, based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer and some human evidence of TCE carcinogenicity in the liver and lymphoid tissues. This conclusion is further supported by rodent bioassay data indicating carcinogenicity of TCE in rats and mice at tumor sites that include those identified in human epidemiologic studies (EPA, 2011c). The EPA 2011 slope factor is

0.05 (mg/kg-d)$^{-1}$ based on liver, kidney, and non-Hodgkin's lymphoma tumors in humans reported by Charbotel, et. al 2006.

1,1,2-Trichloroethylene

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	0.4	0.4	0.4 (3)	2
RFD (mg/kg-day)	--	0.00052	0.00017	(3)	--
RSC	--	0.2	0.2	(3)	--
SF (per mg/kg-day)	--	--	--	--	0.05
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$)
					3 ($ADAF_{2-<16}$)
					1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	--	0.289	0.077	(3)	0.137($_{<2}$)
					0.047($_{2\ to\ <16}$)
					0.039 ($_{16+}$)
Endpoints	--	developmental, immune system	developmental, immune system	developmental, immune system	cancer

4717.7865 Subp. 2. Triclosan

CAS number: 3380-34-5
Year Adopted: 2015
Volatility: Nonvolatile

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The proposed short-term nHRL value is 50 µg/L. The RfD is 0.067 mg/kg-d. Given the significant potential non-water sources of exposure an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals. The intake rate is 0.289. The BMDL is 7.23 mg/kg-d and the HED is 2.0 mg/kg-d. The total uncertainty adjustment is 30 (3 interspecies differences [for toxicodynamics] and 10 for intraspecies variability). The critical effect is decreased serum levels of total thyroxine. The co-critical effect is decreased serum estradiol. The additivity endpoints are developmental, female reproductive system (E), hepatic (liver) system, and thyroid (E).

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

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

Cancer.
Not applicable. The carcinogenicity classification of triclosan is "not likely to be carcinogenic in Human" (EPA, 2008a).

Triclosan

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	50	50 (2)	50 (2)	NA
RFD (mg/kg-day)	--	0.067	(2)	(2)	--
RSC	--	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.289	(2)	(2)	--
Endpoints	--	developmental, female reproductive system (E), hepatic (liver) system, thyroid (E)	developmental, female reproductive system (E), hepatic (liver) system, thyroid (E)	developmental, female reproductive system (E), hepatic (liver) system, thyroid (E)	--

C. PROPOSED DELETIONS: HEALTH RISK LIMITS (Minnesota Rules, parts 4717.7500, 4717.7850, and 4717.7860*)*

Based on MDH's recent review of health-based guidance values listed in Minnesota Rules, parts 717.7500, 4717.7850, and 4717.7860, MDH intends to repeal outdated guidance values for three of the contaminants adopted into rule in 2009 and three adopted into rule in 1993-1994. The 2014/2015 proposed rules include updated HRL values for each of the six contaminants. The specific subparts to be repealed are noted below:

Subparts to be repealed from part 4717.7500:

Subp. 19. Benzyl butyl phthalate (updated values for this chemical, shown in Section IV. B. of this SONAR, will be added to part 4717.7860)

Subp. 21. Cadmium (updated values for this chemical, shown in Section IV. B. of this SONAR, will be added to part 4717.7860)

Subp. 32. Dibutyl phthalate (updated values for this chemical, shown in Section IV. B of this SONAR, will be added to part 4717.7860)

Subparts to be repealed from part 4717.7850:

Subp. 2. (C.) Di(2-ethylhexyl) phthalate

Subp. 2. (E.) Pentachlorophenol

Subp. 2. (H.) 1,1,2-Trichloroethylene

Subparts to be repealed from part 4717.7860. Repealed guidance values will be replaced with updated guidance values:

Subp. 12. Di (2-ethylhexyl) phthalate (replaced with values shown above in Section IV. B.)

Subp. 14. Pentachlorophenol (replaced with values shown above in Section IV. B.)

Subp. 20. 1,1,2-trichloroethylene (TCE) (replaced with values shown above in Section IV. B.)

V. REGULATORY ANALYSIS

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

A. REGULATORY FACTORS

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

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

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

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

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

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

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

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

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

3. A determination of whether there are less costly or less intrusive

methods for achieving the purpose of the proposed rule

AND

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

Minnesota Rules, Chapter 4717, parts 7500, 7850, and 7860 establish HRL values, which are uniform, science-based values that protect the health of people who drink groundwater or surface water.

Unlike other rules that regulate citizen or industry activities, this HRL rules revision applies the specific methodology previously adopted to identified contaminants and calculates and adopts the calculated values themselves. As described in Section II. A. above, Minnesota Statutes, section 103H.201, subdivision 1, prescribes the methods that the Commissioner must use in deriving HRL values. In paragraph (c) the statute requires that the Commissioner establish HRLs for contaminants that are not carcinogens, "using United States Environmental Protection Agency risk assessment methods using a reference dose, a drinking water equivalent, and a relative source contribution factor."

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

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

Thus the statutes limit MDH's discretion about how it may determine allowable amounts of water contaminants. In 2009, the Commissioner adopted the methodology for carrying these directives out, which is now contained in Minnesota Rules, parts 4717.7820 and 4717.7830. This rulemaking project merely adds new values and repeals old values by applying the methodology adopted in 2009, which is not under review at present. MDH adopts the specific HRL values through a process designed to inform and engage the public.

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

HRL values, before being adopted into rule, are initially an alternative type of quantitative guidance on water contaminants, often derived at the request of other agencies. This guidance, known as a Health-Based Value (HBV), is derived using the same methodology as an HRL. While all HRL values were initially HBV values, not all HBV values are proposed for adoption into rule as HRLs.

The HBV values may be less costly in that the agency has not used resources needed to complete rulemaking. 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 consider them to be transient in nature when compared to the HRL values. HRLs values are more useful in long-term planning because they are considered more permanent. The promulgation of the guidance into rule standardizes the use of guidance statewide, and provides the authority and uniformity of rule.

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

5. The probable costs of complying with the proposed rule

Because the HRL rules do not specify how the health-protective numbers are to be applied, the probable cost of complying with the proposed amendments cannot be estimated. HRL values are only one set of criteria used to evaluate whether a contaminant's concentration in groundwater is associated with 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 be expected to present minimal, if any, risk to human health. Similarly, a contaminant concentration above an HRL value, without consideration of other information, might not necessarily indicate a public health problem. However, because the proposed HRL values for four chemicals are lower than the 1993/1994 or 2009 HRL values (cadmium, dibutyl phthalate, pentachlorophenol, and 1,1,2-trichloroethylene), the cost of remediating or preventing water contamination might increase. The proposed HRL values for the eight chemicals without 1993/1994 or 2009 HRL values represent new HRL values. Any costs associated with these are indeterminate.

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

The probable costs or consequences of not adopting the proposed amendments are immeasurable in terms of effects on water. As stated above, Minnesota's groundwater and some surface waters are primary sources of drinking water for 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 protections to segments of the population.

Though the state's goal is to prevent degradation of water, degradation prevention is the ideal and thus cannot always be achieved. Some water resources have already been contaminated by unintentional releases—by activities that occurred before the vulnerability of source waters to contamination was known; by activities that occurred before certain chemicals were identified as toxic; or before regulations prohibiting releases had been implemented. HRL values allow authorities to evaluate drinking water sources to ensure that there is minimal risk to human health from using them for drinking. A reliable source of water that is safe for human consumption is essential to a state's ability to safeguard a high standard of living for its citizens.

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

U.S. EPA's Office of Water publishes several sets of drinking water-related standards and health advisories such as Maximum Contaminant Level Goals (MCLGs), MCLs, Drinking Water Equivalent Levels (DWELs), 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, all, several, one, or none of these standards and advisories may have been developed by the U.S. EPA.

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

- HRL values are based strictly on human health;
- The derivation of HRL values explicitly includes a reasonable margin of safety for vulnerable sub-populations such as infants and children, who are considered to potentially be at higher risk than adults;
- MDH has more exposure time durations than U.S. EPA;
- MDH derives guidance for chemicals that are of high importance specifically to Minnesota; and
- In general, MDH can sometimes 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 it might not be possible to restore contaminated groundwater to a pristine condition, MCLGs do not provide meaningful values for practical application to groundwater contaminated by carcinogens.

EPA-derived MCLs are federal standards adopted for the regulation of *public* drinking water in Minnesota. However, MCLs incorporate a consideration of 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 impacted by contamination. The U.S. EPA has developed MCLs for 91

chemicals, with the most recent value developed in 2001. As a result, most MCLs were developed using outdated methods based only on adult intakes and body weight.

EPA-derived 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 to assist 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 RSC). HAs might also 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.

MDH also currently has health-based guidance for more chemicals important to Minnesota. While U.S. EPA has MCLs for 91 chemicals, there are currently Minnesota values for 136 chemicals. If all of the proposed HRL values are adopted in this rulemaking, there will be HRL values for a total of 150 chemicals in Minnesota.

Furthermore, EPA currently derives guidance values primarily for subchronic and chronic duration while MDH derives guidance for acute and short-term durations in addition to subchronic and chronic durations. Providing guidance for less than chronic durations helps ensure that risk management decisions are protective for all exposed individuals, including infants and children and not only adults.

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 priorities throughout the nation. At times, because of varying geographic and historical factors, including usage of chemicals, chemicals important nationally may not be as high in priority for Minnesota, and chemicals important to Minnesotans may not be ranked as high nationally. Guidance developed by MDH, however, is often based on requests from Minnesota risk managers who have detected a chemical at locations within the state, or from members of the public who have concerns about specific known or potential contaminants in Minnesota waters.

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

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

The proposed rules represent the only regulatory results, since as stated in item 7 above, there are no other state and federal rules related to the same specific purpose of setting

allowable water contaminant values for groundwater. MDH is not proposing enforceable standards but adopting guidance for risk managers and our partners to use in their evaluations and mitigation work. For these reasons the cumulative effect comes only from the applications of these rules.

The proposed amendments to the HRL rules 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 might determine whether the applying an HRL value is appropriate. Each program must determine whether to apply an HRL value or whether site-specific characteristics justify deviation from HRL values.

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

Overall, the incremental cumulative effect of these rules 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. The numerous scenarios under which HRL values might be applied by other agencies prohibit a more full analysis of incremental impact that is within the scope of this SONAR.

B. PERFORMANCE-BASED RULES

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

C. ADDITIONAL NOTICE

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

- Before the official beginning of rulemaking, on February 12, 2014, MDH sent a notice via its GovDelivery Water Rules, Guidance and Chemical Review Account to notify subscribers that it was contemplating rulemaking. A link to a Web page with a list of chemicals with eligible guidance, in addition to the guidance values, was included in the message. Comments were encouraged. This email was sent to 2,684 subscribers.

- One business day before to the Request for Comments publication, on April 11, 2014, MDH made phone calls or sent emails to seven individuals or environmental advocacy or trade organizations who in the past had requested notice about MDH rulemaking activity related to HRL values. MDH also sent emails to two staff of other State agencies. The notices provided information about pending publication of the Request for Comments, and links to MDH's Rules Web page with information about each chemical under consideration.

- Request for Comments: MDH published the "Request for Comments" notice in the *Minnesota State Register* on April 14, 2014. The notice provided an overview of possible amendments to the current HRL rules and invited public comment. The notice is available from the *Minnesota State Register* website at: http://www.comm.media.state.mn.us/bookstore/stateregister/38_42.pdf#page=8. The day of the publication, MDH sent out a GovDelivery notice to the 2,750 subscribers of the Water Rules, Guidance and Chemical Review account to provide notice of the Request for Comments publication. A list of the contaminants with guidance under consideration was included in the email, along with links to MDH HRL Rules Web page and to the Request for Comments in the *State Register*.

- MDH HRL rule amendment public meeting: MDH hosted a public meeting on Thursday, August 7, 2014, at the Orville Freeman Building in St. Paul, MN. MDH sent notification about the public meeting via its GovDelivery account for Water Rules, Guidance and Chemical Review before the meeting on July 2, 2014, (2,809 subscribers) and maintained materials on its website.

  At this meeting, MDH staff gave an overview of the chemical selection and review process, and presented information on the proposed amendments and the types of guidance MDH develops for groundwater contaminants. MDH encouraged attendees to ask questions, engage in discussion with staff and submit written comments. Questions centered on 1) how to choose and apply guidance for a duration (Application of rules is outside of the scope of the rules.); 2)

whether surface water contaminants in addition to triclosan are being considered for rulemaking (MDH is not proposing other surface water guidance for adoption into rule now.); and 3) rulemaking timing and process (MDH offered more detailed information about rulemaking, including options for commenting on the rules.). MDH offered to meet with stakeholders upon request. MDH made all meeting materials, including answers to the questions asked at the meeting, available on MDH's HRL rule amendments Web pages after the public meeting.[9] Including MDH staff, about 11 persons attended the public meeting.

As of March 2, 2015, MDH has received no written or oral comments in response to the Request for Comments. More than 60 days have elapsed since its publication.

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

MDH's Notice Plan did not include notifying the Commissioner of Agriculture or the state Council on Affairs of Chicano/Latino People because the rules do not affect farming operations per Minnesota statutes, section 14.111, or the Chicano/Latino people per Minnesota statutes, section 3.9223, subdivision 4.

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

- MDH HRL rule amendment website: MDH created new Web pages for the 2014/2015 HRL rule amendment.[10] MDH periodically updates these Web pages and includes, or will include, information such as: drafts of the proposed amendments to the rules (made available online before MDH's HRL public meeting-see details below), the SONAR, notices requesting public comments,

[9] Materials and handouts for MDH's meeting on the amendments to the rules on Health Risk Limits for Groundwater are available at:
http://www.health.state.mn.us/divs/eh/risk/rules/water/rules2015/publicmeeting/index.html
[10] MDH's amendments to the rules on Health Risk Limits for Groundwater are available at:
http://www.health.state.mn.us/divs/eh/risk/rules/water/overview.html

public meeting announcements and related handouts, the rule amendment schedule, and brief explanations of the rulemaking process.

- MDH email subscription service: MDH maintains a free email subscription list for sending updates on water rules and guidance on the chemicals reviewed. Anyone may subscribe through links on the MDH HRL rules amendment Web pages. MDH routinely sends updates on the HRL rule amendment to the email subscribers. The updates include information such as: information on new or updated guidance values for specific chemicals, the publication of notices requesting comments, announcements regarding the public meeting, and the availability of drafts of the proposed rules and the SONAR. As of April 14, 2014, MDH's Groundwater Rules, Guidance and Chemical Review email subscription account had 2,750 subscribers. As of March 2, 2015, the number of subscribers had grown to 2,938 subscribers.

D. IMPACT OF PROPOSED RULES

1. Consultation with MMB on Local Government Impact

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

2. Determination about rules requiring local implementation

As required by Minnesota Statutes, section 14.128, subdivision 1, MDH has considered whether the proposed rules will require a local government to adopt or amend any ordinance or other regulation in order to comply with these rules. MDH has determined that they *do not* because no local government develops or enforces groundwater quality standards through ordinances or regulations. Local units of government have consulted with MDH on the use of HRL values for interpreting the results of well monitoring.

3. Cost of complying for small business or city

MDH *cannot* determine small business or city costs incurred in complying with the proposed amendments because the rules do not have any implementation, regulation or enforcement requirements. The amendments simply provide health-based guidance for water contaminants; the rules do not address application or use. The guidance is one set of criteria for risk managers to evaluate potential health risks from contaminated groundwater. Risk managers have the flexibility in determining if and when to apply the HRL values and how costs should be considered. MDH is unaware of any small business or city that applies the health-based guidance. Therefore, there is no evidence that complying with the rules will exceed $25,000 for any small business or city.

E. LIST OF WITNESSES

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

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

VI. CONCLUSION

As stated in Minnesota statute, "the actual or potential use of the waters of the state for potable water supply is the highest priority use of that water and deserves maximum protection by the state." (Minnesota Statutes, section 115.063(2). Roughly 75 percent of Minnesota's drinking water is from groundwater and 25 percent is from surface water, leading to a need to protect both sources of water. The proposed amendments update MDH's human health-based guidance as requested and needed by risk managers to protect water and public health. This work is part of MDH's long-term plan to continue to review, develop, update, and add to the HRL rules on water contaminants.

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

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APPENDIX A: GLOSSARY OF TERMS USED IN RISK ASSSESSMENT

Acute duration: A period of 24 hours or less.

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

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

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

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

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

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

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

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

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

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

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

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

Cancer Slope Factor: See *Slope Factor*.

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

OR,

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

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

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

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

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

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

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

Database Factor: see Uncertainty Factor.

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

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

Dosimetric Adjustment Factor (DAF): A multiplicative factor used to adjust observed experimental or epidemiological data to human equivalent concentration for assumed ambient scenario.

Duration: Duration refers to the length of the exposure period under consideration. The default durations evaluated for non-cancer health effects are acute, short-term, subchronic, and chronic. See individual definitions for more information. These definitions are from "A Review of the Reference Dose and Reference Concentration Processes," U.S. EPA, Risk Assessment Forum (December 2002, http://www.epa.gov/raf/publications/pdfs/rfd-final).
The default durations evaluated for cancer health effects correspond to the age groups upon which the age dependent adjustment factors (ADAF) are based. These age groups were identified in the "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens," U.S. EPA, Risk Assessment Forum (March 2005, http://www.epa.gov/cancerguidelines/guidelines-carcinogen-supplement.htm). The age groups are: from birth up to 2 years of age; from 2 up to 16 years of age; and 16 years of age and older.

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

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

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

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

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 human dose (for other than the inhalation routes of exposure) 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 95^{th} 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 2.2046226 pounds.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Relative Source Contribution (RSC): The portion of the RfD that is "allocated" to ingestion of water. Applying this factor acknowledges that non-ingestion exposure pathways (e.g., dermal contact with water, inhalation of volatilized chemicals in water) as well as exposure to other media, such as air, food, and soil may occur. The *Minnesota Groundwater Protection Act*, in Minnesota Statutes, section 103H.201, subdivision 1(d), requires that MDH use a relative source contribution in deriving health risk limits for systemic toxicants. MDH relied upon U.S. EPA's Exposure Decision Tree approach contained in Chapter 4 of the Ambient Water Quality Criteria document (http://water.epa.gov/scitech/swguidance/standards/upload/2005_05_06_criteria_humanhealth_method_complete.pdf) 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 contains greater uncertainty than HRL values and HBVs due to limited availability of information. 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 in order 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: 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 deleterious effect is expected to occur.

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

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

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

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

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

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

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

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

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

Weight of Evidence (WOE): An approach requiring a critical evaluation of the entire body of available data for consistency and biological plausibility. Potentially relevant

studies should be judged for quality and studies of high quality given much more weight than those of lower quality.

APPENDIX B: BIBLIOGRAPHY

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APPENDIX C: CONCEPTS USED IN MDH-DERIVED HRLs

Described below are the basic principles that underlie MDH's risk algorithm adopted in 2009 (Minnesota Rules, part 4717.7830, subpart 2) as stated in Section II.D. MDH used these methods to derive the HRL values that are included in the 2014/2015 proposed amendments. Detailed descriptions of these concepts are also available in MDH's 2008/2009 SONAR (MDH, 2008. See Part IV).

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

Toxicity

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

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

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

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

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

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

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

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

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

- U.S. Environmental Protection Agency (EPA)
    - Reregistration Eligibility Decisions (REDs) from the Office of Pesticide Programs

    - The Health Effects Support Documents for Contaminant Candidate List Regulatory Determination from the Office of Ground Water and Drinking Water
    - The Integrated Risk Information System (IRIS)
    - The National Center for Environmental Assessment (NCEA) risk assessments
- California EPA
    - The Public Health Goal technical support documents from the Office of Environmental Health Hazard Assessment (OEHHA)
- Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles;
- National Toxicology Program (NTP) study report and toxicity studies;
- Health Canada's Priority Substances Assessment Program and Screening Assessment Reports
- European Commission chemical reviews
    - European Commission Enterprise and Industry Chemicals
    - European Food Safety Authority
    - European Union Pesticide Database
- The World Health Organization's (WHO) Concise International Chemical Assessment Documents; 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).

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

- Acute: 0.289 L/kg-day
- Short-term: 0.289 L/kg-day
- Subchronic: 0.077 L/kg-day
- Chronic: 0.043 L/kg-day

These default values are time-weighted averages based on the data reported in U.S. EPA's Per Capita Report (EPA, 2004c) and a revised assessment for the Child-Specific Exposure Factors Handbook (EPA, 2007b).

For linear carcinogens HRLs, as noted in the 2008/2009 SONAR, "MDH has adopted EPA's approach for integrating age-dependent sensitivity adjustment factors and exposure information. The default intake rates corresponding to the age-dependent adjustment factor (ADAF) age groups used in deriving cancer HRLs are based on the TWA of the 95th percentile intake rate for each age range. The values are 0.137 L/kg-day

(up to 2 years of age), 0.047 L/kg-day (2 to up to 16 years of age), and 0.039 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). For additional information, please see the 2008/2009 MDH SONAR.

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

Based on qualitative evaluation and the U.S. EPA's Exposure Decision Tree (EPA, 2000c), MDH used the following default RSC values: for nonvolatile, low and moderately volatile chemicals, an RSC of 50 percent (0.5) is used for the acute and short-term durations that use the intake rate for young infants; for subchronic and chronic durations, 20 percent (0.2) is used. In contrast, for all durations for highly volatile chemicals, an RSC of 20 percent (0.2) is used because inhalation exposure would be 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 – toxicokinetics (absorption, distribution, metabolism and elimination of the chemical) and toxicodynamics (the body's response to the chemical). 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 available, a default uncertainty factor of 3 is applied for the toxicodynamics. Chemical-specific information for either or both subparts may lead to a combined factor of greater than 10. If human data is the source of the POD then a factor of 1 may be used.

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

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

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

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

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

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

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

MDH Health Risk Limit Algorithms

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

Non Cancer HRLs (nHRLs)

The algorithm for nHRLs is:

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

Where:

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

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

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

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

$IR_{duration}$ = the intake rate (IR) of ingestion of water, or simply the amount of water, on a per body weight basis, ingested on a daily basis (liters per kg body weight per day or L/kg-day). The default IR corresponds to the time-weighted average (TWA) of the 95th percentile intake rate during the relevant duration: acute and short-term - 0.289 L/kg-day, based on intake for 1 up to 3 months of age; subchronic - 0.077 L/kg-day, based on a TWA up to 8 years of age; and chronic - 0.043 L/kg-day, based on a TWA over a lifetime of approximately 70 years (Minnesota Rules, part 4717.7820, subpart 14).

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

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

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

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

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

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

$$\text{Short-term nHRL} = \frac{(0.0037\ mg/kg/d) \times (0.2) \times (1000\ \mu g/mg)}{(0.289\ L/kg\text{-}d)}$$

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

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

$$\text{Subchronic NHRL} = \frac{(0.0098 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ µg/mg})}{(0.077 \text{ L/kg-d})}$$

$$= 25 \text{ rounded to } 30 \text{ µg/L}$$

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

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = $nHRL_{short\text{-}term}$ = 3 µg/L

Notes

- RfDs and uncertainty adjustments are derived by MDH, unless otherwise noted. The RfDs and the endpoints are usually based on animal studies but may be based on human studies.
- RfDs are based on human equivalent dose (HED) calculated from the point of departure in the selected animal studies. HED is the human dose (for other than the inhalation routes of exposure) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species dose (MDH, 2011).
- A health endpoint designation of "none" is used when a general adverse effect (e.g., decreased adult body weight) cannot be attributed to a specific organ system.
- The duration-specific nHRL value is derived using the following equation as previously stated in Section II.D. and specified in Minnesota Rules, part 4717.7830, subp 2:
- The terms used in this section are explained in the Glossary (see Appendix A).

Cancer HRLs:

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

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

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: 0.137 L/kg-day, for up to 2 years of age ($IR_{<2}$); 0.047 L/kg-day, for 2 up to 16 years of age ($IR_{2<16}$); and 0.039 L/kg-day, for 16 years of age and older (IR_{16+}).

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

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

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

$$cHRL = \frac{(1\times10^{-5})\times1{,}000\,\frac{\mu g}{mg}}{SF\times AF_{lifetime}\times0.043\,\frac{L}{kg\text{-}day}}$$

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.

0.043 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 2014/2015 CONTAMINANTS

MDH selected the contaminants for the 2014/2015 amendments based on input from programs within MDH, such as the Site Assessment and Consultation Unit (SAC), Drinking Water Protection Section, and Contaminants of Emerging Concern (CEC) programs. It also relied on advice from partner state agencies, such as the Minnesota Pollution Control Agency (MPCA) and the Minnesota Department of Agriculture (MDA). At periodic interagency meetings, representatives from these agencies nominated chemicals for review and discussed their concerns and priorities. Listed below are the 2014/2015 chemicals with proposed HRLs and the origin of the guidance requests.

Request for Guidance on Groundwater Contaminants

Origin of Guidance Request	**Chemical**	**Origin of Guidance Request**	**Chemical**
CEC nomination	Acetaminophen	CEC nomination	Di (2-ethylhexyl) phthalate (DEHP)
CEC nomination	Acrylamide	Interagency priority	Dimethenamid
Interagency priority	Bentazon	Interagency priority	Dimethenamid-p
CEC nomination	Bisphenol A	Interagency priority	Pentachlorophenol
CEC nomination	Butyl benzyl phthalate	CEC nomination	Sulfamethazine
Interagency priority	Cadmium	Interagency priority	1,1,2-Tricloroethylene
CEC nomination	Dibutyl phthalate	CEC nomination	Triclosan

APPENDIX E: CHEMICAL SUMMARY SHEETS

Note: The following documents represent the Health Based Values (HBVs) for chemicals included in the 2014/2015 proposed amendments. These chemical summary sheets are also available on MDH's Human Health-Based Water Guidance Table[5] and the HRL rule amendment webpages.[10] Upon adoption of the 2014/2015 amendments, these HBV summary sheets will be updated as HRL summary sheets, and posted online.

Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: August 2014
Expiration Date: August 2019

Toxicological Summary for Acetaminophen:

CAS: 103-90-2
Synonyms: N-(4-hydroxyphenyl) acetamide, Tylenol, Paracetamol, Paracetol, Acetamide, N-(4-hydroxyphenyl)-, 4'-Hydroxyacetanilide, 4-(acetylamino)phenol, 4-acetamidophenol, Acetanilide, 4'-hydroxy-, p-Acetamidophenol, p-Acetaminophenol, p-Acetylaminophenol, p-Hydroxyacetanilide, APAP

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

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

$$= \frac{\text{(0.25 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 173 rounded to **200 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-water sources of exposure from multiple products available for infants and children an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.

Reference Dose/Concentration:	0.25 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	7.4 mg/kg-d (NOAEL, based on the human minimum therapeutic dose for infants at 40 mg/dose for up to 5.4 kg infant (McNeil Consumer Healthcare 2010)
Human Equivalent Dose (MDH, 2011):	Not applicable
Total uncertainty factor:	30

Uncertainty factor allocation:	10 for intraspecies variability; 3 for database uncertainty (additional studies to evaluate gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted)
Critical effect(s):	Hepatotoxicity in humans
Co-critical effect(s):	Liver effects in animals (increased serum liver enzymes, reduced hepatic glutathione, liver histopathological changes); acute liver failure in humans.
Additivity endpoint(s):	Hepatic (liver) system

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

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

$$= \frac{\text{(0.25 mg/kg-d) x (0.2*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 173 rounded to **200 µg/L**

*See footnote for acute section for RSC rationale

Reference Dose/Concentration:	0.25 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	7.4 mg/kg-d (NOAEL, based on the human minimum therapeutic dose for infants at 40 mg/dose for up to 5.4 kg infant (McNeil Consumer Healthcare 2010)
Human Equivalent Dose (MDH, 2011):	Not applicable
Total uncertainty factor:	30
Uncertainty factor allocation:	10 for intraspecies variability; 3 for database uncertainty (additional studies to evaluate gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted)
Critical effect(s):	Hepatoxicity and increased serum liver enzymes (ALT) in humans and animals
Co-critical effect(s):	Acute liver failure, hepatotoxicity, increased serum liver enzymes (ALT, AST) in humans and animals; decreased hepatic glutathione (GSH), and liver histopathological changes in animals
Additivity endpoint(s):	Hepatic (liver) system

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

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

$$= \frac{\text{(0.28 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 727 rounded to 700 µg/L

Reference Dose/Concentration:	0.28 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	27.8 mg/kg-d (LOAEL based on dosing of 1950 mg/day, McNeil Consumer Healthcare 2010)
Human Equivalent Dose (MDH, 2011):	Not applicable
Total uncertainty factor:	100
Uncertainty factor allocation:	10 for intraspecies variability; 3 for use of minimal LOAEL instead of NOAEL; 3 for database uncertainty (additional studies evaluating gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted)
Critical effect(s):	Increased serum liver enzymes (ALT) in humans and animals
Co-critical effect(s):	Liver effects in animals (hepatotoxicity, increased bilirubin, reduced hepatic glutathione, liver histopathological changes); and humans (acute liver failure)
Additivity endpoint(s):	Hepatic (liver) system

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

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

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

$$= \frac{\text{(0.093 mg/kg-d) x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

= 433 rounded to 400 µg/L

Reference Dose/Concentration:	0.093 mg/kg-d (human)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	27.8 mg/kg-d (LOAEL based on dosing of 1950 mg/day, McNeil Consumer Healthcare 2010)
Human Equivalent Dose (MDH, 2011):	Not applicable
Total uncertainty factor:	300

Uncertainty factor allocation:	10 for intraspecies variability; 3 for use of minimal LOAEL; 3 use of subchronic human data for chronic duration; 3 for database uncertainty (additional studies evaluating gestational and early life exposures and to adequately characterize the dose-response and adversity of cyclooxygenase (COX) enzyme inhibition are warranted)
Critical effect(s):	Increased serum liver enzymes (ALT) in humans.
Co-critical effect(s):	Liver effects in animals (increased serum liver enzymes ALT, reduced glutathione, liver histopathological changes); Kidney effects in animals (increased severity of nephropathy); Thyroid effects in animals (thyroid follicular cell hyperplasia)
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system, Thyroid

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

Cancer Health Based Value (cHBV) = Not Applicable. Not classified as a carcinogen by IARC, U.S. FDA, NTP, U.S. EPA or California OEHHA

Volatile: No

Summary of Guidance Value History:
Health-based guidance values for acetaminophen were published in 2011. Acetaminophen was re-evaluated in 2014 to incorporate more recent toxicity information. The re-evaluation did not result in quantitative changes; therefore, the 2014 HBVs are identical to the 2011 guidance values. The re-evaluation did provide some additional information regarding health effects identified in the Health Standards Statute (see below).

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

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

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

Comments on extent of testing or effects:
[1] Thyroid hyperplasia was reported in a 2-yr dietary study in mice at human equivalent doses approximately 150 times higher than the chronic RfD of 0.093 mg/kg-day. No effects on thyroid

hormones were found in a small short-term study in humans at a dose over 170 times higher than the short-term RfD or in mice at a dose 26 times higher than the short-term RfD. One epidemiology study reported a weak association between increased risk of cryptorchidism in offspring of mothers who used acetaminophen during pregnancy. Thyroid was identified as a co-critical endpoint for the chronic duration; however, the chronic HBV was set to the short-term value and, therefore, is considered protective for possible thyroid effects.

In vitro studies reported decreased testosterone production in fetal rat and adult human testes exposed to acetaminophen but no effects on fetal testosterone production by human fetal testes *in vitro*. In human fetal testes explants, decreased insulin-like factor 3 (INSL3) levels were reported. The biological relevance of *in vitro* testes studies is unknown and testosterone effects for acetaminophen have not been evaluated *in vivo*.

In humans taking oral contraceptives, acetaminophen may increase circulating ethinylestradiol after ingestion of a single acetaminophen dose (approximately 14 mg/kg-day or approximately 50 times higher than the acute, short-term and subchronic RfDs and 150 times higher than the chronic RfD). Acetaminophen was negative in mouse and rat uterotrophic assays at human equivalent doses greater than 600 times higher than the acute/short-term RfDs.

[2] A limited number of animal studies have reported that acetaminophen suppressed humoral and cellular immunity at doses that were either toxic to the liver or over 150 times higher than the RfDs. Acetaminophen was associated with suppression of serum neutralizing antibody response, increased nasal symptoms, and a rise in circulating monocytes in human volunteers infected with intranasal rhinovirus type 2 in a small double-blind, placebo-controlled human clinical trial at doses over 200 times higher than the RfDs. Acetaminophen may cause bronchoconstriction in individuals with aspirin-induced asthma at doses more than 50 times higher than the RfDs. There are conflicting epidemiology data regarding a possible association with prenatal or early life exposure to acetaminophen and childhood asthma. The most common limitation in these epidemiology studies was the lack of control for "indication for use" (i.e. infection, fever, or illness may have been important confounders that were not considered and data was not adjusted accordingly) and doses were not adequately characterized.

[3]Multiple human studies have reported no increase in developmental effects from acetaminophen use during pregnancy and the overall weight-of-evidence suggests that acetaminophen is not a developmental toxicant in humans. There are conflicting human data regarding associations between acetaminophen use during pregnancy and risk of gastroschisis in offspring. No other malformation has been shown to be causally associated with single-ingredient acetaminophen. Recent human studies reported possible weak associations between acetaminophen use during pregnancy and increased risk of asthma, increased risk of autistic disorder from acetaminophen use after measles-mumps-rubella vaccination; and increased risk of cryptorchidism (undescended testes) in offspring. At the present time there is insufficient evidence for a casual association and further studies are needed before these recent findings can be linked to acetaminophen.

Experimental animal studies do not suggest increased malformations from therapeutic use of acetaminophen during pregnancy. One laboratory animal study reported decreased body weight gain in offspring and decreased survival of offspring at a human equivalent dose over 500 times higher than the acute RfD. In another study, effects on survival and body weight gain in offspring, persisting to adulthood, and sperm abnormalities occurred at human equivalent doses approximately 200 times higher than the acute and short-term RfDs.

[4] No effects on pregnancy or offspring were reported in several laboratory animal studies at human equivalent doses up to over 500 times higher than the acute and short-term RfDs. In a continuous breeding animal study, effects on reduced fertility and reproduction were observed at human equivalent dose 800 times higher than the acute and short-term RfDs.

[5]Acetaminophen is not considered to be a neurotoxicant based on lack of secondary observations in animal studies. In laboratory animals, clinical neurotoxicity symptoms were reported only at very high doses over 1,700 times higher than the RfDs. No effects were reported at doses 1,000 times higher than the RfDs. An acute subcutaneous injection study in neonatal animals reported altered locomotor activity and failure to acquire spatial learning in adulthood; however, the relevance of injection studies for oral exposure is questionable. A few epidemiology studies reported associations between acetaminophen during pregnancy and higher risk of hyperkinetic disorders, ADHD medication use, and ADHD-like behaviors, decreased motor skill development, communication skills, and externalizing or internalizing behaviors in children. One epidemiology study reported no association between exposures during pregnancy and IQ or attention deficits in children. However, these epidemiology studies have several limitations, including lack of dose characterization, and cannot be used to establish a causal relationship between acetaminophen use and neurotoxicity in humans.

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Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: August 2014
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Toxicological Summary for Acrylamide:

CAS**: 79-06-1**
Synonyms: Acrylamide monomer, 2-Propenamide, Propenamide, Vinyl Amide, Acrylic Amide

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 7 µg/L

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

$$= \frac{\text{(0.010 mg/kg/d) x (0.2*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 6.9 rounded to **7 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA, 2000) to select appropriate RSCs. Due to evidence of acrylamide in breast milk (Sorgel, 2002) and baby food (FDA, 2006), along with evidence that dietary exposures for some people exceed 50% of the short-term RfD, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.

Reference Dose/Concentration:	0.010 mg/kg-d (Long-Evans Rats)
Source of toxicity value:	MDH, 2014 (same as ATSDR, 2012)
Point of Departure (POD):	1.33 mg/kg-d ($BMDL_{10}$, Sublet, 1989)
Human Equivalent Dose (MDH, 2011):	0.31 mg/kg-d (PBPK basis, ATSDR, 2012)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Reproductive toxicity in male rodents causing germ cell damage that results in fetal resorptions and implantation loss
Co-critical effect(s):	Neurotoxicity such as loss of hindlimb use and altered head tilt; Male-mediated reproductive toxicity resulting in impaired mating and decreased number and vitality of fetuses, increased resorptions/implantation losses; Developmental toxicity including neurobehavioral effects

	in young animals, decreased pup body weight, and increased resorptions/implantation losses
Additivity endpoint(s):	Developmental, Male Reproductive system, Nervous system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 7 µg/L

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

$$= \frac{\text{(0.0070 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 18 rounded to 20 µg/L

Reference Dose/Concentration:	0.0070 mg/kg-d (F344 rats)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	1 mg/kg-d (NOAEL, Burek, 1980)
Human Equivalent Dose (MDH, 2011):	1 x 0.21 = 0.21 mg/kg-d
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Peripheral nerve degeneration
Co-critical effect(s):	Neurological effects (decreased ability to learn, nerve damage/degeneration, altered head tilting), reproductive toxicity causing implantation losses and direct damage to male germ cells, developmental effects (decreased pup body weights, implantation loss), decreased adult body weight gain
Additivity endpoint(s):	Developmental, Male Reproductive system, Nervous system

The Subchronic nHBV must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 7 µg/L. Additivity endpoints: Developmental, Male reproductive system, Nervous system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 7 µg/L

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

$$= \frac{\text{(0.0037 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 17 rounded to 20 µg/L

Reference Dose/Concentration:	0.0037 mg/kg-d (F344 rats)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.44 mg/kg-d ($BMDL_{05}$, ATSDR, 2012)
Human Equivalent Dose (MDH, 2011):	0.11 mg/kg-d (PBPK basis, ATSDR, 2012)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Nerve degeneration
Co-critical effect(s):	Nerve degeneration
Additivity endpoint(s):	Nervous system

The Chronic nHBV must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 7 µg/L. Additivity endpoints: Developmental, Male reproductive system, Nervous system

Cancer Health Based Value (cHBV) = 0.2 µg/L

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

$$= \frac{(1E\text{-}5) \times (1000\ \mu g/mg)}{[(0.5 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.5 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.5 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 0.205 rounded to **0.2 µg/L**

Cancer classification:	Likely to be carcinogenic to humans (USEPA, 2010)
Slope factor:	0.5 (F344 rats, Johnson, 1986)
Source of slope factor:	USEPA, 2010
Tumor site(s):	Tunica vaginalis mesotheliomas in testes and male thyroid tumors

Volatile: No (Nonvolatile)

Summary of Guidance Value History: No previous MDH guidance.

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

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

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

Comments on extent of testing or effects:

[1] Endocrine effects have been seen only at very high doses. Decreased testosterone and serum prolactin level and alterations in thyroid hormone levels in have been reported in laboratory animals at doses 2,000 times higher than the current short-term reference dose. Alterations in the adrenal gland have also been reported in a chronic drinking water study in rats at doses over 1,000 times higher than the chronic reference dose.

[2] Immunotoxicity of acrylamide has been directly tested in two recent short-term studies. For acrylamide exposure to compromise immune system function, a very high dose of approximately 1,000 times higher than the current short-term reference dose was needed. At 100 times the current short-term reference dose, subtle changes in lymphocyte populations in the serum were detected. Immunotoxicity has also been indirectly tested during the chronic 2-year cancer studies, and no secondary observations have been noted on immune function in these three high quality long-term studies.

[3] Developmental effects include increased resorptions/implantation losses, reduced pup body weight, altered behavior activities and decreased learning ability, and changes in the brains of young rodents. Neurotoxicity is among the more sensitive developmental effects and has been reported at doses 100-500 times greater than the short-term reference dose.

[4] The short-term reference dose is based on reproductive toxicity in males (increased pre- and post-implantation losses, decreased live pups per litter, increased resorptions, decreased sperm count, abnormal sperm and decreased breeding success). Two-fold higher doses cause reproductive effects in females (body weight gain decreases and loss of hind limb use during gestation).

[5] Neurotoxicity, in the form of nerve degeneration and damage, is the critical effect for subchronic and chronic water guidance. Two to three-fold higher doses also caused other types of neurotoxicity in rodents such as altered hind limb use, head tilting, and difficulty learning. Developmental neurotoxicity has also been shown to occur at doses 100-500 times greater than the short-term reference dose (discussed above).

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Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Web Publication Date: June 2014
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Toxicological Summary for Bentazon:

CAS**: 25057-89-0**
Synonyms: Bentazone, Basagran, Herbatox, Leader, Laddock, 3-Isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide

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

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

$$= \frac{\text{(0.22 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 381 rounded to **400 µg/L**

Reference Dose/Concentration:	0.22 mg/kg-d (Wistar/HAN rats)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	100 mg/kg-d (NOAEL, Becker et al., 1986a in U.S. Environmental Protection Agency, 1998)
Human Equivalent Dose (MDH, 2011):	100 mg/kg-d x 0.22 = 22 mg/kg-day
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty to address the need for additional studies regarding thyroid effects.
Critical effect(s):	Increased post-implantation loss and fetal resorptions
Co-critical effect(s):	Increased embryonic and fetal resorptions
Additivity endpoint(s):	Developmental; Female Reproductive System

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 60 µg/L

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

$$= \frac{\text{(0.033 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 57 rounded to **60 µg/L**

Reference Dose/Concentration:	0.033 mg/kg-d (Wistar/HAN rats)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	15 mg/kg-d (NOAEL, Suter et al.,1989 in U.S. Environmental Protection Agency, 1998)
Human Equivalent Dose (MDH, 2011):	15 mg/kg-d x 0.22 = 3.3 mg/kg-d
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty to address the need for additional studies regarding thyroid effects that have been observed at other durations.
Critical effect(s):	Reduced pup body weight gains
Co-critical effect(s):	N/A
Additivity endpoint(s):	Developmental

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

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

$$= \frac{\text{(0.02 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 52 rounded to **50 µg/L**

Reference Dose/Concentration:	0.02 mg/kg-d (Beagle dogs)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	3.2 mg/kg-d (NOAEL, Allen et al., 1989 in U.S. Environmental Protection Agency, 1998)
Human Equivalent Dose (MDH, 2011):	3.2 mg/kg-d x 0.63 = 2 mg/kg-d
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty to address the need for additional studies regarding thyroid effects.
Critical effect(s):	Bloody stools, anemia, and decreased body weight gain.
Co-critical effect(s):	N/A
Additivity endpoint(s):	Hematological (blood) system

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

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

$$= \frac{(0.006 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ µg/mg})}{(0.043\text{L/kg-d})}$$

= 28 rounded to **30 µg/L**

Reference Dose/Concentration:	0.006 mg/kg-d (B6C3F1 mice)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	12 mg/kg-d (LOAEL,Tajima et al.,1984 in U.S. Environmental Protection Agency, 1998)
Human Equivalent Dose (MDH, 2011):	12 mg/kg-d x 0.15 = 1.8 mg/kg-d
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for extrapolation from a LOAEL to a NOAEL
Critical effect(s):	Increased thyroid weight
Co-critical effect(s):	N/A
Additivity endpoint(s):	Thyroid

Cancer Health Based Value (cHBV) = "Not Applicable"

Volatile: No

Summary of Guidance Value History:
A noncancer Chronic HBV of 200 µg/L was derived in 1998. In 2014 Acute, Short-term, Subchronic, and Chronic HBVs of 400, 60, 50 and 30 µg/L were derived. The Acute, Short-term and Subchronic HBVs are new values. The 2014 Chronic HBV is approximately 7 times lower than the previous HBV as a result of incorporating: 1) HED adjustments, 2) more recent intake rate data that include higher intakes early in life, and 3) rounding to one significant digit.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	No	Yes	Yes	No
Effects?	Yes[1]	No	Yes[2]	Yes[3]	Yes[4]

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

Comments on extent of testing or effects:

[1] Endocrine activity of bentazon per se has not been evaluated. However, alterations in thyroid organ weights have been noted and serve as the basis for the chronic RfD. A database uncertainty factor was incorporated into the acute, short-term and subchronic RfDs to address the need for additional studies regarding thyroid function.

[2] The acute and short-term RfDs are based on developmental effects such as post-implantation losses, fetal resorptions, and decreased pup body weights. Delays in ossification of multiple areas of the skeleton have also been described. Decreased pup body weight and body weight gains were also reported in animals dosed with up to 1500 times the short term RfD. One study reported animals experiencing partial abortions, embryonic resorptions, and no living fetuses at doses more than 5000 times the short term RfD.

[3] One male reproductive study in mice found no effects on spermatogenesis. The short-term RfD is based on incidence of postimplantation loss and fetal resorptions in animals dosed with bentazon. At 400 times the short-term RfD, animals had 100% postimplantation loses. There was a higher incidence of embryonic and fetal resorptions in animals treated with 300 times the short-term RfD.

[4] Neurotoxicity has not directly been studied for bentazon. Secondary observations in an animal study included sedation, ataxia and tremors at a dose more than 1500 times the subchronic RfD.

Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for Bisphenol A:

CAS**: 80-05-7**

Synonyms: BPA; 4'-(1-Methylethylidene)bisphenol 4,4'-Bisphenol A; 4,4'-Isopropylidenediphenol; Phenol, 4,4'-(1-methylethylidene)bis- *p,p'*-isopropylidenebisphenol; 2,2-bis(4-hydroxyphenyl)propane

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

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

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

$$= \frac{\text{(0.16 mg/kg/d) x (0.2*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 111 rounded to 100 µg/L

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-drinking water sources of exposure from multiple sources available for infants, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.

Reference Dose/Concentration:	0.16 mg/kg-d (rat)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	2.7 mg/kg-d (NOAEL, Delclos et al. 2014)
Human Equivalent Dose (MDH, 2011):	2.7 x 5.8 = 16 mg/kg-d [chemical-specific DAF for neonatal rats]
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (additional studies to evaluate latent effects of early life exposure, neurobehavioral, immune system, and metabolic disease are warranted)

Critical effect(s):	Developmental (decreased pup body weight), increased total T3 in male pups
Co-critical effect(s):	Developmental (decreased number and viability of offspring, pup and fetal body weight effects, delayed puberty in male and females; decreased weanling spleen and testes weights, undescended testes, seminiferous tubule hypoplasia), Female reproductive (decreased number and viability of offspring; changes in hormone ratios), Liver (changes serum liver parameters, organ weight, morphology and histology), Male reproductive effects (changes in hormone ratios, reduced spermatogenesis, organ weights and morphology), Renal (changes in kidney weights, morphology and histology), Thyroid (increased organ weight), Decreased maternal body weight during gestation
Additivity endpoint(s):	Developmental, Female reproductive system (E), Hepatic (liver) system, Male reproductive system (E), Renal (kidney) system, Thyroid (E)

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

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

$$= \frac{\text{(0.0065 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 16.9 rounded to 20 µg/L

Reference Dose/Concentration:	0.0065 mg/kg-d (mouse)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	5.0 mg/kg-d (NOAEL,Tyl et al. 2008)
Human Equivalent Dose (MDH, 2011):	5 x 0.13 = 0.65 mg/kg-d
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (additional studies to evaluate latent effects of early life exposure, neurobehavioral, immune system, and metabolic disease are warranted)
Critical effect(s):	Centrilobular hepatocyte hypertrophy; increased kidney weight
Co-critical effect(s):	Increased centrilobular hepatocyte hypertrophy, liver weight effects)
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

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

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

$$= \frac{\text{(0.0065 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 30.2 rounded to 30 µg/L

Reference Dose/Concentration:	0.0065 mg/kg-d (mouse)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	5.0 mg/kg-d (NOAEL,Tyl et al., 2008)
Human Equivalent Dose (MDH, 2011):	5 x 0.13 = 0.65
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (additional studies to evaluate latent effects of early life exposure, neurobehavioral, immune system, and metabolic disease are warranted)
Critical effect(s):	Centrilobular hepatocyte hypertrophy, increased kidney weight
Co-critical effect(s):	Increased centrilobular hepatocyte hypertrophy, liver weight effects
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

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

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	No cancer classification is available for bisphenol A
Slope factor:	Not applicable
Source of slope factor:	Not applicable
Tumor site(s):	Not applicable

Volatile: No

Summary of Guidance Value History:
No previous 1993/1994 HRLs exist for Bisphenol A. In 1998, a chronic nHBV of 300 µg/L was derived. In 2012, new nHBVs were developed for acute (300 µg/L), short-term (300 µg/L) and subchronic (100 µg/L) durations and the chronic nHBV was lowered to (100 µg/L). In 2014, BPA was re-evaluated. The acute HBV was removed, the short-term value decreased to 100 µg/L and the subchronic/chronic nHBVs

decreased to 20 µg/L based upon 1) a re-evaluation of the toxicity data with inclusion of more recent information, and (2) new life-stage toxicokinetic information that resulted in revised dose-adjustment factors (DAFs).

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

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

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

Comments on extent of testing or effects:

[1]Unconjugated (free) BPA is a well-known endocrine-active substance and has been extensively studied. BPA is metabolized quickly in the liver to an endocrine-inactive form (i.e., glucuronide conjugate) that is rapidly excreted in human urine. The estrogenic potency of free BPA is more than 1,000-fold lower than estrogens and BPA has a weaker binding affinity to classical hormone receptors than endogenous hormones. Estrogen, testosterone and thyroid hormone levels and hormone receptor results from laboratory animal studies at doses below 5 mg/kg-d have been inconsistent and contradictory. However, study design limitations, dose-response interpretation issues, inconsistencies in results and conflicting data in the low dose region exists. The RfDs are considered protective for endocrine effects in humans, in part, because humans and non-human primates efficiently metabolize BPA to its endocrine-inactive conjugate which is rapidly excreted in the urine. In a rodent study assessing effects resulting from early life (*in utero* and direct dosing for 3 months after birth) changes in estradiol, thyroid hormone, progesterone and prolactin levels were reported only at doses more than 3,000-fold higher than the RfDs presented above. No effects were reported on FSH or LH at doses 30,000 times higher than the subchronic RfD. Effects on serum levels of sex hormone ratios are considered as co-critical effects for the short-term duration.

[2] Immunotoxicity of BPA has not been thoroughly evaluated, but a limited number of studies evaluating either direct or *in utero* exposure to BPA using non-standard test methods suggest that BPA may interfere with immune homeostasis (cytokine activity, macrophage activity, tumor necrosis factor secretion, and T-cell activity). Several studies found no effect on adult spleen or thymus weights or histopathology of adult immune organs but one study reported spleen and thymus atrophy at a dose 4,500 times higher than the short-term RfD. BPA is a skin sensitizer in humans exposed dermally but there is no clear evidence that BPA interferes with overall immune system function. In general, doses more than 90 times higher than the short-term RfD and more than 2,000 times higher than the subchronic/chronic RfDs are required to elicit a significant immune response. A few studies reported immune-related cellular effects at lower doses, including increased IgG1, IL-4, and various splenocyte T-cell populations at doses more than 6 times higher than the subchronic RfD. Inconsistent results have been reported for IgG2a, interferon-ɣ, and splenic cell numbers. These low dose cellular-level effects have not been associated with adverse functional immune outcomes related to enhancement or suppression of response to pathogens and the biological significance is uncertain. Database limitations and uncertainties regarding available immune system data were considered in the derivation of the RfDs. The spleen, an immune system organ, was

identified as a co-critical developmental additivity endpoint based on transient organ weight effects in weanling animals.

[3]The National Toxicology Program (NTP) has identified the brain, behavior, and prostate as developmental endpoints of "some concern" for fetuses, infants, and children. In other words, NTP considers there are insufficient data from human studies to support possible effects on the brain, behavior and the prostate; however, limited evidence in some animal studies cannot be dismissed. NTP concluded that the significance of the limited data from animal studies to humans is unknown at this time. See footnote #5 below for information about neurodevelopmental effects for brain and behavior. A few reports suggest that BPA exposure during gestation and infancy may increase susceptibility to prostate cancer, mammary cancer, impact mammary gland development, or contribute to metabolic diseases (e.g., obesity, diabetes) later in life; however, current data are inadequate to determine whether BPA exposure in early life leads to cancer or metabolic disease in adulthood. A statistically significant increase in mammary gland ductal hyperplasia, a potential indicator of mammary gland development, was reported in rats at a dose over 30,000 times higher than the chronic RfD. The biological significance of this finding will not be known until results from an ongoing chronic study become available. Delayed puberty in male and female animals has been reported, although a recent large-scale study in rats found no effects on pubertal onset, except for delayed testes descent reported at a dose over 1,000 times higher than the short-term RfD. Developmental effects are considered as critical and co-critical effects for the short-term duration RfD and uncertainties related to neurobehavioral effects and metabolic disease are addressed in the derivation of the RfDs using a database uncertainty factor.

[4] Female reproductive effects, including decreased numbers of litters per breeding pair and changes in hormone ratios, are considered co-critical effects in the derivation of the short-term RfD. Estrous cycle effects were reported at doses 450 times higher than the short-term RfD and over 11,000 times higher than the subchronic/chronic RfDs. Male reproductive effects were reported in adult animals and included multinucleated giant cells in seminiferous tubules, reduced spermatogenesis in pubertal animals and various reproductive organ weight effects (testes, prostate, seminal vesicles, and epididymis). Reports of BPA effects on sperm parameters and testosterone are inconsistent. Male and female reproductive effects are considered as co-critical effects for the derivation of the short-term RfD.

[5] NTP has identified the brain and behavior as endpoints of "some concern" for fetuses, infants and children. This means that there are insufficient data from human studies, but limited evidence of potential neurotoxicity in some animal studies cannot be dismissed, although significance to humans is unknown. Experimental evidence in a well-conducted developmental neurotoxicity study in rats does not support brain developmental neuropathological changes in offspring exposed via maternal dietary doses up to 700 times higher than the short-term RfD. Low dose (defined as doses < 5 mg/kg-d) gestational and/or neonatal exposures have been reported to cause various neurodevelopmental effects in offspring in a variety of studies. Some studies suggest possible effects of early life exposure on various sexually dimorphic behaviors, changes in maternal behaviors nursing and nesting behaviors, anxiety, aggression and learning performance resulting from doses below the short-term RfD; however, there has been a lack of consistency, reproducibility and a variety of study design or reporting limitations in existing data. Several brain morphology studies with various methodological flaws and/or using routes of exposure that are not relevant for evaluating the oral route (e.g., injection studies) have reported effects on various biochemical and neurotransmitter gene expression changes in brain tissues. Developmental neurobehavioral endpoints were identified as areas of data uncertainty in the derivation of acute and short-term RfDs/HBVs.

Acute or short-term exposure to adult animals has resulted in nervous system effects in some studies including piloerection, decreased locomotor activity, sedation, lethargy, arched back, and vocalization. These effects occurred at high gavage doses that were over 700 times higher than the short-term RfD. One study reported decreased serum cholinesterase in female rats exposed to a dose that was about 900 times higher than the short-term RfD, but this effect has not been evaluated in other studies and the biological significance is unknown.

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Health Based Value for Groundwater
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Toxicological Summary for Butyl Benzyl Phthalate:

CAS: 85-68-7

Synonyms: BBP; Butylbenzyl phthalate; Butyl benzylphthalate; 1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester

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

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

$$= \frac{\text{(0.15 mg/kg/d) x (0.2)* x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 104 rounded to **100 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs (MDH 2008, Appendix K). Typically an RSC of 0.5 is utilized for nonvolatile contaminants. However, there is evidence that there are significant known or potential sources other than ingestion of water. An RSC of 0.2 was selected rather than the default value of 0.5 for nonvolatile contaminants.

Reference Dose/Concentration:	0.15 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	MDH 2012
Point of Departure (POD):	20 mg/kg-d (NOAEL from Nagao et al., 2000)
Human Equivalent Dose (HED):	20 x 0.23 = 4.6 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics and 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight and decreased serum thyroid hormone levels
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental (E) (body weight, thyroid hormone levels)

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

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

$$= \frac{\text{(0.15 mg/kg/d) x (0.2)* x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 104 rounded to **100 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs (MDH 2008, Appendix K). Typically an RSC of 0.5 is utilized for nonvolatile contaminants. However, there is evidence that there are significant known or potential sources other than ingestion of water. An RSC of 0.2 was selected rather than the default value of 0.5 for nonvolatile contaminants.

Reference Dose/Concentration:	0.15 mg/kg-d (Sprague Dawley rats)
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Human Equivalent Dose (HED):	20 x 0.23 = 4.6 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics and 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight and decreased serum thyroid hormone levels
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental (E) (body weight, thyroid hormone levels)

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

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

$$= \frac{\text{(0.15 mg/kg/d) x (0.2)* x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 390 rounded to 400 µg/L

Reference Dose/Concentration: Use the Short-term RfD**

**The calculated Subchronic RfD (0.83 mg/kg-d) is higher than the Short-term RfD (0.15 mg/kg-d), which is based on developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page

34). Therefore, the Subchronic RfD is set to the Short-term RfD.

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

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

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

$$= \frac{\text{(0.15 mg/kg/d) x (0.2)* x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

$$= 698 \text{ rounded to } 700 \text{ µg/L}$$

Reference Dose/Concentration: Use the Short-term RfD[**]

[**]The calculated Chronic RfD (1.1 mg/kg-d) is higher than the Short-term RfD (0.15 mg/kg-d), which is based on developmental effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Chronic RfD is set to the Short-term RfD.

The Chronic nHBV must be protective of the acute and short-term exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 100 µg/L. Additivity endpoints: Developmental (E) (body weight, thyroid hormone levels).

Cancer Health Based Value (cHBV) = "Not Applicable"[#]

	Group C (US EPA IRIS 1993)
Cancer classification:	"Likely to be carcinogenic" (US EPA PPRTV 2002)
Slope factor:	0.0019 per mg/kg-d[#]
Source of slope factor:	US EPA PPRTV 2002
Tumor site(s):	Pancreas

[#] MDH has chosen to not use the EPA PPRTV cancer slope factor to generate a cancer HBV. MDH considers BBP to be a nonlinear carcinogen based on lack of positive genotoxicity data and evidence of clear morphological continuum from focal pancreatic acinar cell hyperplasia (preneoplastic lesion) to adenoma to carcinoma in male rats (NTP 1997). Carcinogenicity was equivocal in female rats despite 2-fold higher dose levels and negative in mice (NTP 1997). The 2 year NTP 1997 cancer bioassay $NOAEL_{HED}$ was 32.4 mg/kg-d. The RfD (0.15 mg/kg-d) is 162-fold lower than the NTP study $NOAEL_{HED}$ and is therefore considered to be protective against cancer.

Volatile: No

Summary of Guidance Value History:

The 2012 HBVs (100 µg/L) are the same as the 1993 HRL chronic value (100 µg/L), however, the basis of the value has changed as the result of: 1) utilization of more recent toxicity information; 2) removal of the 10-fold Group C uncertainty factor; 3) utilization of more recent intake rates which incorporate higher intake rates during early life; and 4) rounding to one significant digit.

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

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

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

Comments on extent of testing or effects:

[1] Potential estrogen activity of BBP and the major BBP metabolites MBuP and MBeP has been investigated in both *in vitro* and *in vivo* studies. Only weak estrogen activity at high concentrations/doses of BBP was reported.

Some epidemiology studies have identified associations between phthalate exposure and changes in reproductive development in newborn boys. However, these effects were not consistently observed and studies were generally accompanied by multiple confounding factors such that it is not possible to draw conclusions.

Multiple studies in laboratory animals have demonstrated antiandrogen-like activity of BBP and its major metabolites. Indicators of antiandrogenic activity include reduced anogenital distance, areolas in neonatal males, reduced testicular weight, and disrupted testicular migration following *in utero* and lactational exposure.

Decreased pup body weight and serum levels of thyroid hormones in developing laboratory animals exposed to BBP *in utero* and via lactation have been reported at dose levels below those causing male reproductive developmental effects. Decreased body weight and changes in thyroid hormone levels are identified as critical effects and form the basis of the RfD.

[2] Several mechanistic toxicological studies and epidemiological studies have been conducted to evaluate immunotoxicity, mainly on other phthalates (e.g., DEHP). The mechanistic studies typically utilized topical or subcutaneous injection as the route of exposure. Epidemiological studies have suggested an association with PVC-related exposure and asthma.

Limited studies specifically evaluating immunologic effects have been conducted in laboratory animals. No significant immune suppression or enhancement was observed in rats treated with 0.6, 1.2 or 2.4% BBP for up to 12 months. Limited studies on a related phthalate, DEHP, suggest that immunological effects could occur at a similar order of magnitude dose as those causing male developmental effects. It is anticipated that the RfD for BBP will be protective of male developmental effects as well as immunological effects.

[3] Some epidemiology studies have identified an association between phthalate exposure and male reproductive and neurobehavioral development. However, effects were not consistently observed and further studies are needed before conclusions can be drawn.

Studies in laboratory animals have identified the male reproductive system, particularly in during the developmental stage, to be a target for the toxicity of BBP. Decreased pup body weight and serum levels of thyroid hormones in developing laboratory animals exposed to BBP *in utero* and via lactation have been reported at dose levels below those causing male reproductive developmental effects. Decreased body weight and changes in thyroid hormone levels are identified as critical effects and form the basis of the RfD.

The developmental effects of the major BBP metabolites (mono butyl phthalate (MBP) and mono benzyl phthalate (MBzP)) was similar to the effects observed after exposure to BBP, suggesting that MBP and MBzP may be responsible for the developmental effects of BBP.

[4] BBP and its major metabolites (MBP & MBzP) have been found to adversely affect the reproductive organs in experimental animal studies which may impact fertility. The developmental period is a sensitive life stage to the male reproductive effects of BBP. Main effects reported include a decrease reproductive organ weights, damage to the testis, epididymis, prostate, seminal vesicle and to reduced sperm concentrations, and at higher BBP doses reduced fertility, in addition to increases in relative liver and kidney weights. Decreases in pup body weight and changes in serum thyroid hormone levels, the basis of the RfD, occurred at dose level lower than those associated with male reproductive developmental effects.

[5] Some epidemiological studies have reported associations between maternal phthalates and metabolites and neurobehavioral changes in offspring. Two 2-generational studies conducted in laboratory animals have assessed neurological endpoints. Neither study reported evidence of neurological impairment. A related phthalate, DBP, has also been evaluated for neurodevelopmental effects and no neurobehavioral impairment was observed.

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Toxicological Summary for Cadmium:

CAS**: 7440-43-9**
Synonyms: None

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = 5 µg/L

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

$$= \frac{\text{(0.0077 mg/kg/d) x (0.2*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 5.3 rounded to **5 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-drinking water sources of dietary exposure to infants and children, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.

Reference Dose/Concentration:	0.0077 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	MDH 2014
Point of Departure (POD):	1 mg/kg-d (NOAEL, Sutou, Yamamoto et al. 1980a and Sutou, Yamamoto et al. 1980b)
Human Equivalent Dose (MDH, 2011):	1.0 x 0.23 = 0.23 mg/kg-day
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased fetal body weight and body length, increased fetal skeletal malformations
Co-critical effect(s):	Decreased fetal body weight, body weight gain and body length
Additivity endpoint(s):	Developmental

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 1 µg/L

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

$$= \frac{(0.0016 \text{ mg/kg/d}) \times (0.2^*) \times (1000 \text{ µg/mg})}{(0.289 \text{ L/kg-d})}$$

= 1.1 rounded to **1 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-drinking water sources of dietary exposure to infants and children, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.

Reference Dose/Concentration:	0.0016 mg/kg-d (Wistar rats)
Source of toxicity value:	MDH 2014
Point of Departure (POD):	0.71 mg/kg-d (LOAEL, Ali, Murthy et al. 1986)
Human Equivalent Dose (MDH, 2011):	0.71 x 0.22 = 0.16 mg/kg-day
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for extrapolation from a LOAEL to a NOAEL (the neurological effects observed at the LOAEL were subtle, a factor of 3 is expected to be sufficiently protective)
Critical effect(s):	Alteration in the development of cliff avoidance behavior and spontaneous locomotor activity in offspring exposed during the developmental period
Co-critical effect(s):	Decreased plasma essential ions, decreased glomerular filtration rate
Additivity endpoint(s):	Developmental; Nervous system; Renal (kidney) system

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

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

$$= \frac{(0.00044 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ µg/mg})}{(0.077 \text{ L/kg-d})}$$

= 1.1 rounded to **1 µg/L**

Reference Dose/Concentration:	0.00044 mg/kg-d (Wistar rats)
Source of toxicity value:	MDH 2014
Point of Departure (POD):	0.2 mg/kg-d (LOAEL, Brzoska, Majewska et al. 2005a and Brzoska and Maniuszko-Jakoniuk 2005a)
Human Equivalent Dose (MDH, 2011):	0.2 x 0.22 = 0.044 mg/kg-day
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for extrapolation from a LOAEL to a NOAEL (the bone effects observed at the LOAEL were subtle, a factor of 3 is expected to be sufficiently protective)

Critical effect(s):	Decreased femoral bone resistance to fracture, increased fragility of the femoral bone, increased markers for bone resorption, and decreased markers for bone formation in rapidly growing young animals
Co-critical effect(s):	None
Additivity endpoint(s):	Developmental; Skeletal

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

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

$$= \frac{\text{(0.00011 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

= 0.51 rounded to **0.5 µg/L**

Reference Dose/Concentration:	0.00011 mg/kg-d (human)
Source of toxicity value:	ATSDR 2012
Point of Departure (POD):	0.00033 mg/kg-d ($UCDL_{10}$*, ATSDR 2012)
Human Equivalent Dose (MDH, 2011):	Not applicable - human study used
Total uncertainty factor:	3
Uncertainty factor allocation:	3 for intraspecies variability to account for sensitive subpopulations
Critical effect(s):	Low molecular weight proteinuria
Co-critical effect(s):	Increased risk for osteoporosis
Additivity endpoint(s):	Renal (kidney) system; Skeletal

*$UCDL_{10}$ is the 95% lower confidence limit on the estimated internal cadmium dose (urinary cadmium expressed as ug/g creatinine) corresponding to the probability of 10% excess risk of low molecular weight proteinuria.

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	B1; probable human carcinogen (U.S. EPA 1994) through the inhalation route
Slope factor:	Not available. There are no positive studies of orally ingested cadmium suitable for quantitation.
Source of slope factor:	N/A
Tumor site(s):	N/A

Volatile: No

Summary of Guidance Value History: The 2014 acute HBV for cadmium (5 ug/L) is slightly higher than the 1993 Health Risk Limit (HRL) of 4 ug/L. The reasons it is higher are: 1) use of more recent toxicity information; and 2) rounding to one significant digit. The 2014 chronic HBV for cadmium (0.5

ug/L) is eight times lower than the 1993 Health Risk Limit (HRL) of 4 ug/L. The subchronic and short-term noncancer HBVs are 4 times lower. The reasons that the 2014 HBVs for the short-term, subchronic, and chronic durations are lower than the 1993 HRL are: 1) use of more recent toxicity information; 2) use of more recent intake rates that account for higher exposures during early life; and 3) rounding to one significant digit.

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

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

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

Comments on extent of testing or effects:

[1] In female animals treated with cadmium at levels at least 400 times the subchronic RfD, decreases of estradiol, FSH, LH, and progesterone were observed.

[2] Immune effects have been observed in some studies, but not in others. In mice exposed to cadmium at doses more than 100 times the short-term RfD immunosuppression has been noted, but the mechanism is unclear. In a second study, mice exposed to cadmium 125 times higher than the short-term RfD showed enhanced T-lymphocyte-independent responses and suppressed T-lymphocyte-dependent responses. These responses may be due to a compensatory mechanism that is part of humoral immunity. Although one study showed that cadmium at doses 250 times higher than the short term RfD increased mortality from an infectious agent, a second study with a dose 2,000 times the short term RfD failed to show altered resistance to an infectious agent. A primate study showed that cadmium stimulated cell-mediated immunity at a dose of more than 2,000 times the short term RfD.

[3] Developmental effects form the basis for the acute, short-term, and subchronic RfDs. While neurological effects in animals exposed *in utero* forms the basis of the short-term RfD, adverse skeletal effects in rapidly growing animals forms the basis of the acute and subchronic RfDs. Multiple studies reported reduced fetal body weight and size as well as an increase in skeletal malformations in pups exposed in utero to cadmium at levels at least 30 times higher than the acute RfD. Other developmental effects such as fetal resorptions and delayed ossification were noted from 300 to over 5000 times the acute RfD.

[4] Epidemiology studies have been conducted examining the effect of cadmium on male and female reproductive toxicity. The results have been inconsistent. Although two studies showed a relationship between male sex hormone levels and cadmium, others did not. The relationship between sperm quality and serum cadmium levels is also not clear. While one study reported a decrease in sperm quality with

increased blood cadmium level, two others did not. Data on reproductive toxicity in women is limited. Among infertile women, no association between cadmium body burden and the risk of endometriosis was observed. Elevated urine cadmium levels have been associated with an increased time to pregnancy. A number of animal studies have also demonstrated reproductive effects, but at very high dose levels greater than 3,000 times the acute RfD.

[5] Neurotoxicity following *in utero* exposure is the basis of the short-term RfD. In some animal studies, effects have been reported at doses 50 times the chronic RfD. Other studies have reported neurological effects in rats exposed to cadmium at doses thousands of times higher than the short-term RfD. The effects have included impacts on grooming, learning, movement, rearing, behavior, hearing, and vision.

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Health Based Value for Groundwater
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Toxicological Summary for Dibutyl Phthalate:

CAS: 84-74-2

Synonyms: DBP; Di-n-butyl phthalate; 1,2-Benzenedicarboxylic acid, dibutyl ester; Dibutyl 1,2-benzenedicarboxylate

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

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

$$= \frac{\text{(0.023 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 15.9 rounded to **20 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate Relative Source Contributions (RSCs) (MDH 2008, Appendix K). Typically an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations. However, there is evidence that there are significant known or potential sources other than ingestion of water. Therefore, a 0.2 RSC was selected rather than the default value of 0.5 for nonvolatile contaminants.

Reference Dose/Concentration:	0.023 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	MDH 2012
Point of Departure (POD):	10 mg/kg-d (NOAEL from Lehmann et al 2004 and Boekelheide et al., 2009)
Human Equivalent Dose (HED):	10 x 0.23 = 2.3 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database uncertainties (additional study is warranted for potential thyroid and immunological effects)
Critical effect(s):	Decreased fetal testosterone, decreased testicular cell number and testes size
Co-critical effect(s):	Decreased fetal testosterone, Sertoli cell atrophy, decreased total cell number and number of seminiferous tubules

Additivity endpoint(s): Development (E) (male reproductive system)

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

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

$$= \frac{\text{(0.023 mg/kg/d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 15.9 rounded to **20 µg/L**

* Rationale for selecting an RSC of 0.2 - same explanation as that provided for the acute duration (see above).

Reference Dose/Concentration:	0.023 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	MDH 2012
Point of Departure (POD):	10 mg/kg-d (NOAEL from Lehmann et al 2004 and Boekelheide et al., 2009)
Human Equivalent Dose (HED):	10 x 0.23 = 2.3 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database uncertainties (additional study is warranted for potential thyroid and immunological effects)
Critical effect(s):	Decreased fetal testosterone, decreased testicular cell number and testes size
Co-critical effect(s):	Decreased fetal testosterone, Sertoli cell atrophy, decreased total cell number and number of seminiferous tubules
Additivity endpoint(s):	Development (E) (male reproductive system)

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

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

$$= \frac{\text{(0.023 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 59.7 rounded to 60 µg/L

Reference Dose/Concentration: Use the Short-term RfD**

**The calculated Subchronic RfD (0.13 mg/kg-d) is higher than the Short-term RfD (0.023 mg/kg-d), which is based on male reproductive developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Subchronic RfD is set to the Short-term RfD.

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

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

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

$$= \frac{\text{(0.023 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

$$= 107 \text{ rounded to } 100 \text{ µg/L}$$

Reference Dose/Concentration: Use the Short-term RfD**

**The calculated Chronic RfD (0.043 mg/kg-d) is higher than the Short-term RfD (0.023 mg/kg-d), which is based on male reproductive developmental effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Chronic RfD is set to the Short-term RfD.

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

Cancer Health Based Value (cHBV) = "Not Applicable"

Cancer classification: Group D (not classifiable)
Source: US EPA IRIS 1993

Volatile: No

Summary of Guidance Value History:

The 2012 HBVs (20 µg/L) are 35-fold lower than the 1993 HRL value (700 µg/L) as the result of: 1) utilization of more recent toxicity information resulting in a 4-fold lower RfD; 2) utilization of more recent intake rates which incorporate higher intake rates during early life; and 3) rounding to one significant digit.

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

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

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

Comments on extent of testing or effects:

[1] Some epidemiology studies have identified associations between phthalate exposure and changes in thyroid and reproductive hormones. However, these effects were not consistently observed and studies were generally accompanied by multiple confounding factors such that it is not possible to draw conclusions.

In vitro studies evaluating pituitary cell proliferation and thyroid receptor interactions suggest that DBP may impact thyroid function. The relevance of the *in vitro* effects to *in vivo* is unclear. Potential DBP thyroid effects following *in vivo* exposure have not been evaluated. Changes in thyroid hormone serum levels were identified as sensitive effects following butyl benzyl phthalate exposure in laboratory animals. The lack of thyroid studies on DBP is part of the rationale for incorporating a database uncertainty factor into the derivation of the RfD.

In studies conducted in laboratory animals changes in FSH, LH and PRL have also been reported but effects were not consistent across doses or time points of evaluation. Disruption of fetal testes steroidogenesis was been identified as a sensitive effect and forms the basis for the RfD.

[2] Several mechanistic toxicological studies and epidemiological studies have been conducted, mainly on other phthalates (e.g., DEHP). The mechanistic studies typically utilized topical or subcutaneous injection as the route of exposure. Epidemiological studies have suggested an association with PVC-related exposure and asthma.

Laboratory animal studies on DEHP suggest immunological effects at doses of similar magnitude to those causing male reproductive developmental effects. The need for immunological study of DBP is part of the rationale for incorporating a database uncertainty factor into the derivation of the RfD.

[3] Some epidemiology studies have identified an association between phthalate exposure and male reproductive and neurobehavioral development. However, effects were not consistently observed and results from these studies are generally accompanied by multiple confounding factors such that it is not possible to draw definite conclusions.

Studies in laboratory animals have identified a variety of developmental effects following exposure to DBP. Disruption of fetal testicular development has been identified as a sensitive effect. Increased malformations and decreased offspring viability were observed at higher doses, doses ~10 to 20-fold higher than those associated with fetal testicular development. The sensitive effects of fetal testicular development and steroidogenesis form the basis of the RfD.

[4] Some epidemiology studies have identified an association between phthalate exposure and male reproductive effects. However, effects were not consistently observed and these studies are generally accompanied by multiple confounding factors such that it is not possible to draw conclusions.

Studies in laboratory animals have identified a variety of male reproductive effects, including testicular effects and decreased fertility. The fetal male reproductive system is more sensitive than the mature male reproductive system following exposure to DBP. Fetal male reproductive effects form the basis of the RfD.

[5] Some epidemiological studies have identified an association between phthalate exposure and changes in neurobehavioral development. However, these studies are generally accompanied by multiple confounding factors such that it is not possible to draw definitive conclusions.

Neurodevelopmental studies have been conducted in laboratory animals. Neurobehavioral impairment was not observed.

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Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for Di(2-ethylhexyl) phthalate:

CAS: 117-81-7
Synonyms: DEHP; Bis(2-ethylhexyl)phthalate

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

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

$$= \frac{\text{(0.029 mg/kg/d) x (0.2)* x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

$$= 20.1 \text{ rounded to } 20 \text{ µg/L}$$

* MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate Relative Source Contributions (RSCs) (MDH 2008, Appendix K). Typically an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations and an RSC of 0.2 is used for subchronic and chronic durations. However, there is evidence that there are significant known or potential sources other than ingestion of drinking water. Therefore, an RSC of 0.2 was selected rather than applying the default RSC value.

Reference Dose/Concentration:	0.029 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	3.8 mg/kg-d (BMDL, Blystone et al. 2010)
Human Equivalent Dose (HED):	3.8 x 0.23 = 0.874 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are addressed by the HED adjustment), 10 for intraspecies variability
Critical effect(s):	Male reproductive tract malformations (small testes, small epididymis, small cauda epididymis, small seminal vesicles)

Co-critical effect(s):	Increased fetal testicular testosterone, male reproductive tract lesions, retained nipples in pre-weanling males
Additivity endpoint(s):	Developmental (E), Male reproductive system (E)

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

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

$$= \frac{\text{(0.029 mg/kg/d) x (0.2)* x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

$$= 20.1 \text{ rounded to } 20 \text{ µg/L}$$

* Rationale for selecting an RSC of 0.2 - same explanation as that provided for the acute duration (see above).

Reference Dose/Concentration:	0.029 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	3.8 mg/kg-d (BMDL, Blystone et al. 2010)
Human Equivalent Dose (HED):	3.8 x 0.23 = 0.874 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are addressed by the HED adjustment), 10 for intraspecies variability
Critical effect(s):	Male reproductive tract malformations (small testes, small epididymis, small cauda epididymis, small seminal vesicles)
Co-critical effect(s):	Increased fetal testicular testosterone, male reproductive tract lesions, retained nipples in pre-weanling males, hormonal effects in pubertal males (changes in serum testosterone, increased luteinizing hormone, increased serum estradiol, increased testicular interstitial fluid testosterone, and decreased androgen synthesis)
Additivity endpoint(s):	Developmental (E), Male reproductive system (E)

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

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

$$= \frac{(0.029 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.077 \text{ L/kg-d})}$$

$$= 75.3 \text{ rounded to } 80 \text{ µg/L}$$

Reference Dose/Concentration:	0.029 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	3.8 mg/kg-d (BMDL, Blystone et al. 2010)
Human Equivalent Dose (HED):	3.8 x 0.23 = 0.874 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are addressed by the HED adjustment), 10 for intraspecies varibiability
Critical effect(s):	Male reproductive tract malformations (small testes, small epididymis, small cauda epididymis, small seminal vesicles)
Co-critical effect(s):	Increased fetal testicular testosterone, male reproductive tract lesions, retained nipples in pre-weanling and adult males, hormonal effects in pubertal and young adult males (changes in serum testosterone, increased luteinizing hormone), increased serum estradiol and testicular interstitial fluid testosterone in pubertal males, decreased androgen synthesis in pubertal males
Additivity endpoint(s):	Developmental (E), Male reproductive system (E)

The Subchronic nHBV must be protective of exposures that occur within the acute and short-term periods and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 20 µg/L. Additivity endpoints: Developmental (E), Male reproductive system (E).

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

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

$$= \frac{(0.029 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.043 \text{L/kg-d})}$$

$$= 135 \text{ rounded to } 100 \text{ µg/L}$$

Reference Dose/Concentration: Same as subchronic RfD, see information above for details about the reference dose. Chronic exposure to adult animals resulted in decreased spermatogenesis and testes tubular atrophy.

The Chronic nHBV must be protective of exposures that occur within the acute, short-term, and subhchronic periods and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 20 µg/L. Additivity endpoints: Developmental (E), Male reproductive system (E).

Cancer Health Based Value (cHBV) = 7 µg/L

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

$$= \frac{\text{(1E-5) x (1000 ug/mg)}}{[(0.014 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.014 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.014 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 7.3 rounded to 7 µg/L

Cancer classification: Group B2, probable human carcinogen
Slope factor: 0.014 $(mg/kg\text{-}d)^{-1}$ (laboratory animal) (NTP, 1982)
Source of slope factor: EPA 1993
Tumor site(s): Liver

Volatile: No

Summary of Guidance Value History:
The 2013 noncancer HBVs (20 µg/L) for acute, short-term, and subchronic durations are new. There is a 2009 HRL_{MCL} of 6 µg/L based on the US EPA Maximum Contaminant Level (MCL). There was a previous 1993/94 cancer HRL of 20 µg/L (based on liver cancer and an oral slope factor of 0.014 from IRIS 1991).

The 2013 cancer HBV (7 µg/L) is slightly higher than the 2009 MCL-based chronic HBV (6 µg/L) due to: 1) utilization of more recent lifetime intake rates which incorporate higher intake rates during early life; 2) application of age-dependent early-life cancer sensitivity adjustment factors; and 3) rounding to one significant digit.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Yes

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Effects?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

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

Comments on extent of testing or effects:

[1] It is well documented in an extensive number of laboratory animal studies that DEHP is anti-androgenic, causing decreases in fetal testosterone at critical windows of male reproductive development *in utero*, leading to postnatal male reproductive organ malformations. The effect of DEHP and/or metabolites on testosterone and thyroid hormone levels in humans have been studied in several epidemiology studies with conflicting results. In animal studies, thyroid hormones have been affected at doses over 3,000 times higher than the RfD. DEHP does not appear to have estrogenic effects in animals or humans. Endocrine effects, based on anti-androgenic responses, are identified as co-critical effects.

[2]In humans, associations between inhalation of phthalate dust, including DEHP, and asthma-like symptoms have been reported in some epidemiology studies; however, there are no reported associations between oral exposure and asthma or allergy in humans. Low doses of phthalates have affected antibodies in animal studies only when given by subcutaneous or intraperitoneal injection, but not by oral ingestion. No developmental immune effects were found in offspring at doses over 2,000 times higher than the RfDs. Spleen and thymus weights were decreased in offspring exposed prenatally to doses over 800 times higher than the RfD.

[3]As an anti-androgen, DEHP inhibits the normal biological effects of androgens (male sex hormones). This interference results in alterations in normal male sexual development. Interference at different stages of life can alter fetal, neonatal, and adolescent (puberty) development, based on laboratory animal studies. In humans, the effects of DEHP and/or metabolites on neurobehavioral development, male reproductive and pubertal development have been reported in several epidemiology studies with conflicting results. Developmental effects on the male reproductive system are identified as critical effects and provide the basis for the RfDs.

[4]Reproductive system effects of DEHP and/or metabolites in humans, including effects on male fertility, have been reported in several epidemiology studies with conflicting results. Male reproductive system effects are identified as critical effects based on laboratory animal studies and provide the basis for the RfDs.

[5]Neurobehavioral developmental effects in humans, including effects on psychomotor development, IQ, internalizing and socializing behaviors, have been associated with phthalates in some epidemiology studies. In laboratory animals, DEHP caused some neurotoxicity including reduced grip strength, reduced hind-limb splay, and increased brain weight in offspring exposed prenatally at doses over 8,000 times higher than the RfD. No neurobehavioral effects were reported in a 14-day neurotoxicity study at doses over 10,000 times higher than the RfDs. Impaired spatial learning and memory in aged animals exposed prenatally were reported at a dose about 10 times higher than the RfD. No neurobehavioral

effects were reported in chronic studies although increased brain weights in rats and mice were reported at doses over 6,500 times higher than the RfD.

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Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for Dimethenamid and Dimethenamid-P:

CAS**: 87674-68-8 & 163515-14-8**
Synonyms: (*RS*)-2-Chloro-*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl)acetamide, Frontier Herbicide, Dimethenamid-P ((*S*)-isomer)

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

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 600 µg/L

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

$$= \frac{\text{(0.34 mg/kg/d) x (0.5) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 588 rounded to **600 µg/L**

Reference Dose/Concentration:	0.34 mg/kg-d(Sprague Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure:	149 mg/kg-d(NOAEL, Randall 1996)
Human Equivalent Dose:	149 x 0.23 = 34 mg/kg-d(MDH, 2011)
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty to ensure that the short-term RfD is protective of potential developmental effects
Critical effect(s):	Liver effects (increased absolute and relative liver weights and change in increased liver enzyme levels)
Co-critical effect(s):	Decreased pup body weights; decreased adult body weight gain; neurological effects (lacrimation, piloerection, excess salivation, decreased motor activity); post implantation loss; liver effects (increase

	in relative and absolute liver weight and changes in liver enzymes)
Additivity endpoint(s):	Developmental, Hepatic (liver) system, Nervous system, Reproductive system (female)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{short-term}$ = 600 µg/L

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

$$= \frac{\text{(0.27 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 701 rounded to 700 µg/L

Reference Dose/Concentration:	0.27 mg/kg-d(Sprague Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure:	33.5 mg/kg-d(NOAEL, Ruckman 1990)
Human Equivalent Dose:	33.5 x 0.25 = 8 mg/kg-d(MDH, 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased adult body weight and body weight gain; clinical chemistry changes (increased protein and cholesterol); liver effects (increase absolute and relative liver weight, changes in liver enzyme levels, histological changes)
Co-critical effect(s):	Decrease in body weight and body weight gain in pups and adults; liver effects (increased liver weight, hepatocellular hypertrophy, changes in liver enzyme levels)
Additivity endpoint(s):	Developmental, Hepatic (liver) system

The Subchronic nHBV must be protective of the acute and short-term exposures that occur within the acute and short-term periods and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 600 µg/L. Additivity endpoints: Developmental, Liver system, Nervous system, Reproductive system (female)

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

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

$$= \frac{\text{(0.06 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.043L/kg-d)}}$$

= 279 rounded to **300 µg/L**

Reference Dose/Concentration:	0.06 mg/kg-d(Sprague Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure:	7 mg/kg-d(NOAEL, Ruckman 1990)
Human Equivalent Dose:	7 x 0.26 = 1.8 mg/kg-d(MDH, 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decrease in body weight gain; liver effects (increased relative liver weight, bile duct hyperplasia)
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Class C "possible human carcinogen" nonlinear approach recommended (EPA 1992)
Slope factor:	None
Source of slope factor:	None
Tumor site(s):	Ovarian and liver (benign liver tumors)

The chronic RfD (0.06 mg/kg-d) is protective for cancer risk.

Volatile: Yes (moderate)

Summary of Guidance Value History:
The chronic HBV of 300 µg/L is 7.5 times higher than the 1999 chronic HBV of 40 µg/L as the result of: 1) the identification of dimethenamid as a nonlinear carcinogen and removal of the 10-fold Group C carcinogen uncertainty factor; 2) the derivation of human equivalent doses; and 3) rounding to one significant digit.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	No	Yes	Yes	Yes
Effects?	No	No	Yes[1]	Yes[2]	Yes[3]

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

Comments on extent of testing or effects:

[1]Developmental effects are listed as a co-critical effect for the short-term and subchronic durations. Decreased pup body weight was observed in reproductive and developmental animal studies at doses 100 times higher than the short-term RfD (0.34 mg/kg-d).

[2]Reproductive effects are listed as a co-critical effect for the short-term duration. A decrease in the number of implantations was observed in a 2-generation reproductive study at a dose 25 times higher than the short-term RfD (0.34 mg/kg-d) and an increase in post implantation loss was observed in the same study at a dose 100 times higher than the short-term RfD. Isolated instances of late abortions occurred in a rabbit developmental study at a dose 200 times higher than the short-term RfD.

[3]Nervous system effects are listed as a co-critical effect for the short-term duration. A range of neurological effects were reported in acute and developmental studies in rats. The effects included lethargy, excessive salivation, increased lacrimation (increased tear production), increase bristling of hair, and decreased motor activity. The effects occurred at doses starting at 130 times higher than the short-term RfD (0.34 mg/kg-d).

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Health Based Values for Groundwater
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Toxicological Summary for Pentachlorophenol (PCP):

CAS: 87-86-5

Synonyms: Santophen, Pentachlorol, Chlorophen, Chlon, Dowicide 7, Pentacon, Penwar, Sinituho, Penta

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = 7 µg/L

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

$$= \frac{\text{(0.0040 mg/kg/d) x (0.5) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 6.9 rounded to **7 µg/L**

Reference Dose/Concentration:	0.0040 mg/kg-d(Sprague Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	5 mg-kg-day (LOAEL) Schwetz et al. 1974
Human Equivalent Dose (HED):	5 x 0.23 = 1.2 mg/kg-d(Minnesota Department of Health (MDH), 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics ; 10 for intraspecies variability; 3 for extrapolation from a minimal LOAEL to a NOAEL; 3 for database uncertainty to address need for additional studies regarding potential thyroid effects on neurodevelopment
Critical effect(s):	Delayed skull ossification
Co-critical effect(s):	Reduction in serum levels of T_4 in pregnant animals
Additivity endpoint(s):	Developmental; Thyroid (E)

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 7 µg/L

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

$$= \frac{(0.0040 \text{ mg/kg/d}) \times (0.5) \times (1000 \text{ ug/mg})}{(0.289 \text{ L/kg-d})}$$

= 6.9 rounded to **7 µg/L**

Reference Dose/Concentration:	0.0040 mg/kg-d(Sprague Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	5 mg/kg-d (LOAEL) Schwetz et al. 1974
Human Equivalent Dose (HED):	5 x 0.23 = 1.2 mg/kg-d(Minnesota Department of Health (MDH), 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics; 10 for intraspecies variability; 3 for extrapolation from a LOAEL to a NOAEL; 3 for database uncertainty to address need for additional studies regarding potential thyroid effects on neurodevelopment
Critical effect(s):	Delayed skull ossification
Co-critical effect(s):	Decreased serum T_4 in pregnant and adult animals, pre-weanling, pre-pubertal and pubertal animals; decreased serum T_3/T_4 ratio
Additivity endpoint(s):	Developmental (E); Thyroid (E)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short\text{-}term}$ = 7 µg/L

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

$$= \frac{(0.0031) \times (0.2) \times (1000 \text{ ug/mg})}{(0.077 \text{ L/kg-d})}$$

= 8.05 rounded to 8 µg/L

Reference Dose/Concentration:	0.0031 mg/kg-d(Beagle dogs)
Source of toxicity value:	MDH 2013
Point of Departure (POD):	1.5 mg/kg-d (LOAEL) Mecler et al. 1996 aci (U.S. Environmental Protection Agency (EPA) - IRIS, 2010)
Human Equivalent Dose (HED):	1.5 x 0.62 = 0.93 mg/kg-d(Minnesota Department of Health (MDH), 2011)
Total uncertainty factor:	300

Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics; 10 for intraspecies variability; 10 for extrapolation from a LOAEL to a NOAEL
Critical effect(s):	Increased liver weight accompanied by histological changes; increased thyroid weights
Co-critical effect(s):	Decreased T_4 concentrations in pregnant and adult animals, pre-weanling, pre-pubertal and pubertal animals; decreased induction of T_4 upon stimulation with TSH in adult females; increased scrotal circumference during pubertal development; seminiferous tubule atrophy at puberty; decreased sperm density in the body of the epidydimides at puberty, suppression of serum antibody response to antigen
Additivity endpoint(s):	Developmental (E); Hepatic (liver) system; Immune system; Male Reproductive system; Thyroid (E)

The Subchronic nHBV must be protective of the acute and short-term exposures that occur within the acute and short-term, periods and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 7 µg/L. Health Endpoints: Developmental (E), Hepatic (liver) system, Immune system, Male Reproductive system, Thyroid (E).

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $nHBV_{Short\text{-}term}$ = 7 µg/L

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

$$= \frac{\text{(0.0031 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.043L/kg-d)}}$$

= 14.4 rounded to 10 µg/L

Reference Dose/Concentration:	0.0031 mg/kg-d(Beagle dogs)
Source of toxicity value:	MDH 2013
Point of Departure (POD):	1.5 mg/kg-d (LOAEL) Mecler et al. 1996 aci (U.S. Environmental Protection Agency (EPA) - IRIS, 2010)
Human Equivalent Dose (HED):	1.5 x 0.62 = 0.93 mg/kg-d(Minnesota Department of Health (MDH), 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics; 10 for intraspecies variability; 10 for extrapolation from a LOAEL-NOAEL

Critical effect(s):	Increased liver weight accompanied by histological changes; increased thyroid weights
Co-critical effect(s):	Decreased T_4 concentrations in pregnant and adult animals, pre-weanling, pre-pubertal and pubertal animals; decreased induction of T_4 upon stimulation with TSH in adult females; increased scrotal circumference during pubertal development; seminiferous tubule atrophy at puberty; decreased sperm density in the body of the epidydimides at puberty, suppression of serum antibody response to antigen
Additivity endpoint(s):	Developmental (E); Hepatic (liver) system; Immune system; Male Reproductive system; Thyroid (E)

The Chronic nHBV must be protective of the acute and short-term exposures that occur within the acute, short-term, and subchronic periods and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 7 µg/L. Health Endpoints: Developmental (E), Hepatic (liver) system, Immune system, Male Reproductive system, Thyroid (E).

Cancer Health Based Value (cHBV) = 0.3 µg/L

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

$$= \frac{(1E\text{-}5) \times (1000\ ug/mg)}{[(4E\text{-}1 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (4E\text{ -}1 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (4E\text{-}1 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 0.257 rounded to **0.3 µg/L**

Cancer classification:	Likely to be carcinogenic to humans (U.S. Environmental Protection Agency (EPA) - IRIS, 2010)
Slope factor:	0.4 $(mg/kg\text{-}d)^{-1}$ (laboratory animal) (NTP 1989)
Source of slope factor:	EPA IRIS 2010
Tumor site(s):	liver tumors; adrenal gland tumors (pheochromocytomas)

Volatile: No

Summary of Guidance Value History: The 2008 Health Risk Limit (HRL) for pentachlorophenol (1 µg/L) was set at the EPA Office of Water Maximum Contaminant Level (MCL). An earlier HRL (3 µg/L) promulgated in 1993 was based on cancer. The above noncancer HBVs represent new values. The revised cancer HBV above is approximately 3-fold lower than the 2008 HRL due to: 1) revised cancer slope factor, 2) application of age-dependent adjustment factors to address early life sensitivity, and 3) rounding to one significant digit.

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

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

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

Comments on extent of testing or effects:

1. Endocrine effects are listed as a co-critical for all durations. Reductions of thyroxine (T_4), decreased triiodothyronine/thyroxine (T_3/T_4) ratios, decreased response to stimulation with thyroid stimulating hormone (TSH), and increase in thyroid weights were reported in laboratory animals.

2. Immunological effects were reported in short-term and subchronic studies in both mice and rats. In one study, male rats showed lymphocyte effects and suppression of antibody responses when exposed to PCP at levels 16.5 times the short-term RfD. However, another study reported no effects on lymphocytes or leukocytes in male rats exposed to doses over 15,000 times higher than the RfD. One study in mice reported non-statistically significant decreases in lymphocytes at a HED 3,500 higher than the RfD. Immune effects of technical grade PCP (but not for analytical grade), including reduced host-resistance to viral infection, reduced T-cell activity and reduced macrophage activity were reported in adult male mice at approximately 325 times the short-term RfD; however, immune effects at this level were considered to be related to impurities. Analytical grade PCP (>99% purity) caused reduced thymus weight in female mice at doses over 700 times higher than the RfD. Suppression of antibody responses were observed at dose levels similar to the subchronic point of departure and have been identified as a co-critical effect.

3. Skeletal malformations are listed as critical effects for the acute and short-term durations. Delayed skull ossification was observed in rats. In addition, a range of skeletal malformations such as lumbar spurs, abnormal sternebrae, abnormal vertebrae, and decreased distance from crown to rump were observed starting at doses almost 900-fold higher than the RfD.

4. Male reproductive system effects are identified as co-critical. At a dose 1,700 times higher than the short-term Rfd, the incidence of fetal resorptions was 100% and at 3,300 times the short-term RfD, the sex ratio was skewed to 100% males. Distended lumina of the uterus, the presence of macrophages in the uterus, and increased uterine weight as well as increased time to vaginal patency were observed in the female rat offspring at doses 4,600 times higher than the short-term RfD.

[5.] Neurotoxicity testing was performed as part of a chronic study in mice. Although the mice showed dose-related increases in motor activity and startle response, they showed no treatment-related effects in pinna, corneal or righting reflexes, visual placement, grip strength or rota-rod testing. These effects were examined beginning at doses 1,900 times higher than the chronic RfD.

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Health Based Values for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

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Toxicological Summary for Sulfamethazine:

CAS**:** 57-68-1 and 1981-58-4 (sodium salt)
Synonyms: Sulfadimidine; 4-Amino-N-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide; Benzenesulfonamide, 4-amino-N-(4,6-dimethyl-2-pyrimidinyl)-; Sulfanilamide, N(sup 1)-(4,6-dimethyl-2-pyrimidinyl)-; Sulfanilamide, N1-(4,6-dimethyl-2-pyrimidinyl)-; sulphamethazine; sulphadimidine; sulfadine; 4-amino-N-4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide, monosodium salt, SMZ

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

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

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

$$= \frac{\text{(0.04 mg/kg/d) x (0.8)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

$$= 111 \text{ rounded to } 100 \text{ µg/L}$$

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

Reference Dose/Concentration:	0.04 mg/kg-d(Sprague-Dawley CR/CD rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	5 mg/kg-d(NOAEL, McClain 1993 and 1995)
Human Equivalent Dose (HED):	5 x 0.23 = 1.2 mg/kg-d(MDH 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability

Critical effect(s):	Thyroid follicular cell hypertrophy
Co-critical effect(s):	None
Additivity endpoint(s):	Thyroid

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

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

$$= \frac{\text{(0.017 mg/kg/d) x (0.8)}^{*} \text{ x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

$$= 177 \text{ rounded to } 200 \text{ µg/L}$$

* Rationale for selecting an RSC of 0.8 - same explanation as that provided for the short-term duration (see above).

Reference Dose/Concentration:	0.017 mg/kg-d(Fischer 344 rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	2.2 mg/kg-d(NOAEL, Littlefield et al. 1990)
Human Equivalent Dose (HED):	2.2 x 0.23 = 0.51 mg/kg-d(MDH 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Thyroid follicular cell hyperplasia
Co-critical effect(s):	Thyroid follicular cell hypertrophy, increased thyroid weight, increased serum thyroid stimulating hormone (TSH), decreased pup body weight at weaning
Additivity endpoint(s):	Developmental, Thyroid (E)

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

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

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

$$= \frac{\text{(0.019 mg/kg/d) x (0.8)}^{*} \text{ x (1000 ug/mg)}}{}$$

(0.043L/kg-d)

= 354 rounded to 400 µg/L

[*] Rationale for selecting an RSC of 0.8 - same explanation as that provided for the short-term duration (see above).

Reference Dose/Concentration:	0.019 mg/kg-d(Fischer 344 rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	2.4 mg/kg-d(NOAEL, Littlefield et al. 1990/Fullerton et al. 1987)
Human Equivalent Dose (HED):	2.4 x 0.24 = 0.58 mg/kg-d(MDH 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Thyroid follicular cell hyperplasia, decreased thyroid hormone (T4), decreased total thyroid:pituitary hormone ratio [(T3+T4)/TSH)]
Co-critical effect(s):	Thyroid (thyroid follicular cell hypertrophy, increased thyroid weight, increased serum TSH, histological effects in pituitary), decreased pup body weight at weaning, splenic red pulp pigmentation and hematopoietic proliferation
Additivity endpoint(s):	Developmental, Hematological (blood) system, Thyroid (E)

The Chronic HBV must be protective of the acute, short-term, and subchronic exposures that occur within the acute, short-term, and subchronic periods and therefore, the Chronic HBV is set equal to the Short-term HBV of 100 µg/L. Additivity endpoints: Thyroid.

Cancer Health Based Value (cHBV) = Not Applicable

Volatile: No

Summary of Guidance Value History:
No previous guidance values exist. The non-cancer health-based values presented above represent new values.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	No

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

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

Comments on extent of testing or effects:

[1] In laboratory animals, sulfamethazine (SMZ) increased thyroid stimulating hormone (TSH) and decreased thyroid hormone (T4). Thyroid hormones were not affected in non-human primates at administered doses over 17,000 times higher than the subchronic RfD. Thyroid and pituitary hormone effects were identified as critical and co-critical effects.

[2]Immunotoxicity studies for SMZ in animals or humans are not available; however, the sulfonamide antibiotic drug class is generally known to cause hypersensitivity immune reactions in humans and dogs based on clinical experience. SMZ forms the same types of reactive metabolites that have been related to sulfonamide hypersensitivity. Immunotoxic effects include skin rashes, hives, and serious life-threatening hypersensitivity reactions. Sulfonamide hypersensitivity is considered to be related to drug metabolism deficiencies and/or variability among sensitive individuals. Immunotoxicity is addressed through the use of an uncertainty factor of 10 to account for sensitive populations.

[3]Human infants exposed to sulfonamides *in utero* or during the first 2 months after birth have increased risk of kernicterus, a bilirubin-induced permanent brain dysfunction. Exposed infants have a greater risk for jaundice and hemolytic anemia. Malformations (i.e., cleft palate, hydroureter and hydronephrosis) occurred in laboratory animals exposed to SMZ *in utero* at doses over 2,900 times higher than the short-term RfD. Developmental effects were identified as co-critical for the subchronic and chronic durations.

[4]Reproductive performance and fertility were decreased in rats at HED doses over 4,000 times higher than the RfDs. No reproductive effects were reported in laboratory animals at doses over 1,900 times higher than the RfDs.

[5]Neurotoxicity has not been directly evaluated for SMZ. For a similar sulfonamide, SMX, no effects on neurological clinical signs were observed in chronic studies with non-human primates and rats at doses 4,000 times or more than the RfD. The thyroid plays and important role in normal neurodevelopment, so the RfDs based on thyroid effects are considered protective.

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Health Based Values for Groundwater
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Toxicological Summary for Trichloroethylene (TCE):

CAS: 79-01-6
Synonyms: 1,1,2-Trichloroethene, 1,1-Dichloro-2-Chloroethylene, 1-Chloro-2,2-Dichloroethylene, Acetylene Trichloride, TCE, Trethylene, Triclene, Tri, Trimar, Trilene

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

The study design of the key study evaluated for the acute duration was insufficient for derivation of an RfD. Based on the available information, there is confidence that short-term and subchronic HBVs are protective of acute developmental effects from exposure to TCE.

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 0.4 µg/L

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

$$= \frac{\text{(0.00052 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 0.36 rounded to **0.4 µg/L**

Reference Dose/Concentration:	0.00052 mg/kg-d(laboratory animal)
Source of toxicity value:	MDH 2012
Point of Departure (POD):	0.37 mg/kg-d(LOAEL, Peden-Adams et al. 2006)
Human Equivalent Dose (HED):	0.37 x 0.14 = 0.052 mg/kg-d(MDH 2011)
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics), 10 for intraspecies variability, 3 for use of a minimal LOAEL instead of a NOAEL
Critical effect(s):	Immune effects (impacts on humoral function and splenic T-cells observed in a developmental immune study)
Co-critical effect(s):	Fetal heart malformations

Additivity endpoint(s): Developmental, Immune system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 0.4 µg/L

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

$$= \frac{\text{(0.00017 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 0.44 rounded to **0.4 µg/L**

Reference Dose/Concentration:	0.00017 mg/kg-d(laboratory animal)
Source of toxicity value:	MDH 2012
Point of Departure (POD):	0.37 mg/kg-d(LOAEL, Peden-Adams et al. 2006)
Human Equivalent Dose (HED):	0.37 x 0.14 = 0.052 mg/kg-d(MDH 2011)
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics), 10 for intraspecies variability, 10 for use of a LOAEL instead of a NOAEL
Critical effect(s):	Immune effects (impacts on thymic T-cells, suppression of PFC response, delayed hypersensitivity response observed in a developmental immune study)
Co-critical effect(s):	Fetal heart malformations
Additivity endpoint(s):	Developmental, Immune system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = Subchronic $nHBV_{Subchronic}$ = 0.4 µg/L

Calculated Chronic nHBV

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

$$= \frac{\text{(0.00017 mg/kg/d)}^{**} \text{ x (0.2) x (1000 ug/mg)}}{\text{(0.043L/kg-d)}}$$

= 0.79 rounded to 0.8 µg/L

**See the subchronic information above for more details about the reference dose

The Chronic nHBV must be protective of the acute, short-term, and subchronic exposures that occur within the acute, short-term, and subchronic periods and therefore, the Chronic nHBV is set equal to the Short-term and Subchronic nHBV of 0.4 µg/L. The Additivity Endpoints are: Developmental, Immune system.

Cancer Health Based Value (cHBV) = 2 µg/L

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

$$= \frac{\text{(1E-5) x (1000 ug/mg)}}{[(0.05 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.05 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.05 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 2 µg/L

Cancer classification:	Carcinogenic to humans by all routes of exposure based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer and some human evidence of TCE carcinogenicity in the liver and lymphoid tissues. This conclusion is further supported by rodent bioassay data indicating carcinogenicity of TCE in rats and mice at tumor sites that include those identified in human epidemiologic studies."
Slope factor:	0.05 (human) (Charbotel et al. 2006)
Source of slope factor:	EPA 2011
Tumor site(s):	Kidney, Liver, Non-Hodgkin's Lymphoma

Volatile: Yes (high)

Summary of Guidance Value History:
The 2013 short-term, subchronic, and chronic HBV (0.4 µg/L) is approximately 12 times lower than Maximum Contaminant Level (MCL) based HRL of 5 µg/L as the result of: 1) use of more recent intake rates which incorporate higher intake rates during early life, 2) a 20 to 70-fold decrease in the RfD value, and 3) rounding to one significant digit.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes – Secondary Observations	Yes	Yes	Yes	Yes
Effects?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

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

Comments on extent of testing or effects:

[1] Studies explicitly evaluating endocrine effects of TCE have not been conducted. Secondary observations in studies designed to evaluate reproductive parameters provide limited evidence of endocrine effects. A limited number of epidemiological studies have reported effects such as decreased levels of testosterone and abnormal menstrual cycles.

Decreased testosterone and abnormal menstrual cycles have been evaluated in animals studies, and these effects, like those above reported in humans, occur at levels >1000-fold higher than the short-term, subchronic and chronic RfDs. Therefore, it is likely that the Short-term, Subchronic and Chronic HBVs are protective of these effects.

[2] Human and animal studies provide strong evidence that TCE plays a role in autoimmune disease and hypersensitivity. There is also some evidence that TCE may play a role in immunosuppressive effects although the evidence for these effects is weaker. Immune-related effects observed in human and animals studies are not limited to diseases but also involve organs and tissues within the immune system. Immune effects provide the basis of the RfDs (0.00017 – 0.00052 mg/kg-d) for the short-term, subchronic, and chronic durations.

[3] A number of developmental outcomes have been observed in animal and human studies following inhalation and oral exposure to TCE. Some of the adverse developmental effects that have been observed in these studies included: spontaneous abortion, perinatal death, pre- or post-implantation loss, increased resorptions, low birth weight and decreased postnatal growth, and congenital malformations and fetal cardiac defects in particular. Fetal cardiac malformations (Johnson et al. 2003) were identified as a sensitive effect in the recent EPA IRIS Toxicological Review (2011). The RfDs derived by MDH (0.00017 mg/kg-d– 0.00052 mg/kg-d) that are based on immune effects are 90-300 times lower than LOAEL reported in the Johnson et al. 2003 and are therefore considered to be protective of fetal cardiac malformations.

[4] There is consistent evidence in animal and human studies that exposure to TCE is associated with adverse reproductive effects in males and females. A limited number of epidemiological studies have reported effects such as decreased levels of testosterone and abnormal menstrual cycles at exposure levels >1000-fold higher than the short-term, subchronic and chronic RfDs.

Reproductive studies in laboratory animals have evaluated effects on sperm, fertility, reproductive organs, and parturition. These effects, like those above reported in humans also occurred at levels >1000-fold higher than the short-term, subchronic and chronic RfDs.

[5] TCE is associated with a variety of neurological effects in both animal and human studies. Most neurological effects associated with TCE were observed in inhalation studies but some neurological effects have also been observed following oral exposure to the TCE. The strongest evidence of neurological effects in human resulting from exposure to TCE is for changes in trigeminal nerve function or morphology and impairment of vestibular functions (includes symptoms such as headaches, dizziness, and nausea). There is more limited evidence that TCE may cause delayed motor function, changes in auditory, visual, and cognitive function or performance. The lowest HED_{99} dose levels for neurological effects range from 3.5 mg/kg-d(developmental neurotoxicity in mice) to 7.3 mg/kg-d(trigeminal nerve effects in humans). The RfDs derived by MDH (0.00017 – 0.00052 mg/kg-d) are >6700-fold lower and are therefore protective of neurological effects observed in inhalation and oral animal and human studies.

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Toxicological Summary for Triclosan:

CAS**: 3380-34-5**

Synonyms: 5-Chloro-2-(2, 4-dichlorophenoxy)phenol; 2,4,4'-trichloro-2'-hydroxydiphenyl ether; 5-chloro-(2,4-dichlorophenoxy)phenol; trichloro-2'-hydroxydiphenyl ether; CH-3565; Lexol 300; Irgasan DP 300

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

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

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

$$= \frac{\text{(0.067 mg/kg/d) x (0.2*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 46 rounded to **50 µg/L**

* MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-water sources of exposure (EPA 2008 b.e) an RSC of 0.2 is selected.

Reference Dose/Concentration:	0.067 mg/kg-d (male Wistar rats PND 23-54)
Source of toxicity value:	MDH 2014
Point of Departure (POD):	7.23 mg/kg-d (BMDL for decreased total thyroxine (tT4) from Zorrilla et al 2009 based on a benchmark response of 20%)
Human Equivalent Dose (MDH, 2011):	7.23 x 0.28 = 2.0 mg/kg-d
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Decreased serum total thyroxine (tT4)
Co-critical effect(s):	Increased liver weights in pregnant animals, decreased fetal body weight, decreased serum estradiol, decreased tT4
Additivity endpoint(s):	Developmental; Female reproductive system (E); Hepatic (liver) system; Thyroid (E)

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

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

$$= \frac{\text{(0.033 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

$$= 85.7 \text{ rounded to } 90 \text{ µg/L}$$

Reference Dose/Concentration:	0.033 mg/kg-d (CD-1 mice)
Source of toxicity value:	MDH 2014
Point of Departure (POD):	25 mg/kg-d (LOAEL,13 week study, MRID 43022605 aci EPA 2008a)
Human Equivalent Dose (MDH, 2011):	25 x 0.13 = 3.3 mg/kg-d
Total uncertainty factor:	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for extrapolating from a LOAEL to a NOAEL
Critical effect(s):	liver enzyme changes indicative of liver damage
Co-critical effect(s):	Decreased serum tT4 levels
Additivity endpoint(s):	Hepatic (liver) system; Thyroid (E)

The Subchronic nHBV must be protective of the shorter exposure durations that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term, nHBV of 50 µg/L. Addivity Endpoints: Developmental; Female reproductive system (E); Hepatic (liver) system; Thyroid (E).

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

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

$$= \frac{\text{(0.047 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

$$= 219 \text{ rounded to } 200 \text{ µg/L}$$

Reference Dose/Concentration:	0.047 mg/kg-d (CD-1 mice)
Source of toxicity value:	MDH 2014
Point of Departure (POD):	10 mg/kg-d (NOAEL,18 month dietary study, See 1996 aci EPA 2008a, SCCP 2009 and Rodricks et al 2010)
Human Equivalent Dose (MDH, 2011):	10 x 0.14 = 1.4 mg/kg-d
Total uncertainty factor:	30

Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Changes in hematological (blood) parameters (e.g., decreased hemoglobin, hematocrit); hepatocellular hypertrophy, increased liver weight
Co-critical effect(s):	Changes in hematological (blood) parameters; increased incidence or severity of histological changes in the liver;decreased serum tT4 levels
Additivity endpoint(s):	Hematological (blood) system; Hepatic (liver) system; Thyroid (E)

The Chronic nHBV must be protective of the short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 50 µg/L. Addivity Endpoints: Developmental; Female reproductive system (E); Hepatic (liver) system; Thyroid (E).

Cancer Health Based Value (cHBV) = "Not Applicable"

Cancer classification: "Not likely to be carcinogenic in Human" (EPA 2008a)

Slope factor: NA

Volatile: No

Summary of Guidance Value History:

An nHBV of 50 µg/L was derived in 2010 for short-term, subchronic and chronic exposure durations. An Acute nHBV of 200 µg/L was also derived in 2010. The re-evaluation in 2014 incorporated more recent toxicity information and the HED methodology. An Acute value was not derived because it could not be substantiated that the effects were due to acute (< 1 day) of exposure. The re-evaluation did not result in a change to the final short-term, subchronic and chronic nHBV values which remain at 50 µg/L.

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

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

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

Comments on extent of testing or effects:

[1] Dose-related decreases in serum levels of a variety of hormones (thyroxine (T4), estradiol, testosterone) have been reported. Alterations in thyroxine and estradiol levels have been identified as critical/co-critical effects and form the basis for the short-term HBV. Triclosan has also been evaluated for estrogenic activity using the sensitive utertrophic screening assay. When administered alone triclosan

did not exhibit activity. When co-administered with ethinyl estradiol (E2) triclosan potentiated the estrogenic response. Using a range of E2 doses the authors demonstrated that at lower E2 doses high doses of triclosan were needed to cause potentiation. The lowest dose of E2 tested was within the range of doses women on contraceptives or hormone therapy may be exposed to. However potentiation at this E2 dose required triclosan human equivalent doses that were >70 times higher than the short-term, subchronic and chronic RfDs.

Decreases in testes weight and testosterone levels have been observed but the dose levels at which these effects have occurred has been inconsistent. Decreases in male reproductive organ weights were reported at dose levels similar in magnitude to the short-term point of departure by Kumar et al (2009). However, these observations are not consistent with other studies and there are concerns regarding the purity of triclosan used in this study. Given these uncertainties MDH has chosen not to include the results from Kumar study in the derivation of the RfD.

Under *in vitro* conditions triclosan has exhibited antagonistic activity in both estrogen and androgen responsive bioassays.

[2] Skin sensitizing potential of triclosan has been extensively studied in multiple species, including humans, and resulted in no evidence of skin sensitization. A limited number of epidemiological studies have reported positive associations between exposure to triclosan (as measured by urinary triclosan levels) and increased allergic sensitization to inhalant and food allergens. These associations have not been consistent across studies. Study limitations include cross-sectional design, lack of clinical confirmation and exposure to multiple chemicals. In an animal model of asthma, dermal administration of triclosan did not result in airway reactivity. However, when dermally administered in conjunction with an injected allergen triclosan produced enhanced airway hyperreactivity; however this indicator of asthma in laboratory animals is inconsistent with the epidemiology studies that found no association between triclosan and asthma in humans.

The association between triclosan and allergic sensitization is difficult to explain since triclosan itself has been shown to have no sensitizing potential and little if any information is available regarding potential mechanism of triclosan in relation to allergic disease. More experimental studies are needed to determine triclosan's potential role in allergen sensitization.

[3] Decreased pup weight with accompanying developmental delays in ossification have been reported at human equivalent dose levels > 100 times higher than the short-term, subchronic or chronic RfDs.

[4] A 2 generation study has been conducted in rats. No effects on fertility indices were reported at human equivalent dose levels 500 times higher than the short-term, subchronic or chronic RfDs. The impact of triclosan exposure on puberty has been evaluated in both males and females. No effects on reproductive development were observed at human equivalent dose levels >500 times higher than the short-term, subchronic or chronic RfDs.

[5] A single 14 day neurotoxicity study has been performed. Inhibition of movement, decreased muscular tone, polydypsia and polyuria were observed at human equivalent dose levels nearly 1000 times higher than the short-term, subchronic or chronic RfDs. No change in brain weight, histological alterations or peripheral nerve changes were reported.

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