MINNESOTA MDH DEPARTMENT OF HEALTH

Protecting, maintaining and improving the health of all Minnesotans

March 1, 2013

Legislative Reference Library
645 State Office Building
100 Constitution Avenue
St. Paul, Minnesota 55155

Re: In The Matter of the Proposed Rules of the Minnesota Department of Health Relating to the Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Part 7860 and Part 7500: Revisor's Tracking Number: RD4130; Governor's Tracking Number: AD1084

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 March 11, 2013 *Minnesota State Register*.

MDH has prepared a Statement of Need and Reasonableness concerning the proposed rules. 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, M.P.H.
Health Risk Assessment Unit
Division of Environmental Health
Minnesota Department of Health
P.O. Box 64975
St. Paul, MN 55164

Enclosure: Statement of Need and Reasonableness

STATE OF MINNESOTA

Minnesota Department of Health

In the Matter of the Proposed Rules
Of the Minnesota Department of Health
Relating to Health Risk Limits for Groundwater,
Minnesota Rules, Chapter 4717, Part 7860 and Part 7500

STATEMENT OF NEED AND REASONABLENESS

February 2013

2/26/13
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/rulerelated.html

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

The proposed rules will be published 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 adoption of administrative rules, see *Minnesota Statutes*, section 14.001 et seq., and in particular, section 14.22.

Upon request, this SONAR can be made available in an alternative format, such as large print, Braille, or cassette tape. To make a request, contact Nancy Rice 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, email: nancy.rice@state.mn.us. TTY users may call the Minnesota Department of Health at (651) 201-5797.

MINNESOTA DEPARTMENT OF HEALTH

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

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

Groundwater Protection Act, 1989, Chapter 103H

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 degradation has occurred, the *Groundwater Protection Act* authorizes the Minnesota Department of Health (MDH) to develop and establish into rule health-protective limits, known as Health Risk Limits (HRLs), for contaminants found in groundwater that might be used for drinking purposes (*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. It is expressed as micrograms of a chemical per liter of water (µg/L). MDH calculates HRL values for specific durations of exposure.

MDH proposes to amend the existing rules on Health Risk Limits for Groundwater (HRL rules) found in *Minnesota Rules*, Chapter 4717. The proposed amendments will add new or updated HRL values for 12 groundwater contaminants to part 4717.7860 (see Section III.B.) and repeal the outdated HRL values in current rule in part 4717.7500 (see Section III.C.) for six of these 12 contaminants. No other parts of the HRL rules are being amended in 2012. The proposed amendments build on MDH's 2009 rule revision, which significantly revised the HRL rules (*Minnesota Rules*, parts 4717.7810 to 4717.7900).[1] Details on the 2009 HRL rule revision are presented in Section I.

In keeping with the *Minnesota Administrative Procedure Act* (APA) (*Minnesota Statutes*, section 14.131), MDH is required 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 four sections. Section I includes MDH's statutory authority to adopt HRL rules and past MDH rule revisions. MDH defines the concept of HRL values and summarizes the methods MDH used to derive the HRL values. Section II includes the scope of the amendments MDH proposes in 2012. Section III includes an

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[1] The current rules on the Health Risk Limits for Groundwater (*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 for Groundwater (*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

explanation of each provision in the proposed 2012 rules. Section IV includes a discussion of the regulatory factors and presents information on the performance-based rules, the additional notice plan and the impact of the proposed rules as required per *Minnesota Statutes*, section 14.131.

I. Background

This section presents background information on MDH's guidance on groundwater contaminants. It 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, and following).[2]

A. Statutory Authority

1. THE GROUNDWATER PROTECTION ACT, 1989

MDH derives its statutory authority to adopt HRL values from the *Groundwater Protection Act* of 1989 (the 1989 Act) (*Minnesota Statutes*, section 103H.201, subd. (1)(a)). 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 a HRL as (*Minnesota Statutes*, section 103H.005, subd. (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."

The authority to adopt HRL values is stated in *Minnesota Statutes*, section 103H.201, subd. (2)(a):

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

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

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

"(c) For systemic toxicants that are not carcinogens, the adopted health risk limits shall be derived using United States Environmental Protection Agency risk assessment methods using a reference dose, a drinking water equivalent, and a relative source contribution factor.

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

MDH's authority to review and revise HRL values is stated in *Minnesota Statutes*, section 103H.201, subd. (3)(a) and (b):

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

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

2. HEALTH STANDARDS STATUTE, 2001

Additional authority is implicit under the 2001 *Health Standards Statute* (*Minnesota Statutes*, section 144.0751) applicable 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 groundwater degradation, MDH has the necessary statutory authority to review, develop, and adopt HRL values for groundwater contaminants based on scientific methods to protect sensitive populations. This rulemaking amends rules based on statutory authority that the Legislature has not since amended, so Minnesota Statutes, section 14.125 does not apply. Thus, MDH has the authority to adopt the proposed rules.

B. Past MDH Rule Revisions

The MDH 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 use by risk assessors and risk managers 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 contaminants in drinking water called the Maximum Contaminant Levels (MCLs). These levels are legally enforceable under the National Primary Drinking Water Regulations. They apply only to public water systems. More information about MCLs is available in Section IV, subpoint 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, additional HRL values were adopted based on 1993 methods (henceforth, referred to as 1993-1994 HRL values).

In 2001, MDH toxicologists and risk assessors evaluated the adequacy of the 1993 methods to calculate the HRL values. The method review was designed 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 an updated risk 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 I.D.). In 2009,

MDH adopted the new methods and the HRL values for 21 groundwater contaminants that were 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).

Also during this time, in 2007, the Minnesota Legislature enacted a law concerning Water Levels Standards: Minnesota Laws, chapter 147, article 17, section 2. This law required that MDH set a Health Risk Limit 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 these HRLs were adopted into rule in 2009 along with the MCL for nitrate. These values might be replaced in the future if MDH derives new HRL values. To date, nine of the chemical MCL values remain in rule.

In 2011, MDH added HRL values for 14 contaminants to Minnesota Rules, Chapter 4717, part 7860 and repealed outdated HRL values for 26 contaminants from part 7500. For these 26, MDH had already updated HRL values for 15 and adopted them into rule in part 7860 in 2009, and values for eight contaminants with guidance eligible for adoption into rule were updated in 2011. MDH issued new alterative guidance that is not eligible for adoption into rule for the remaining three of the 26 guidance values repealed in 2011.

C. Defining Health Risk Limits (HRLs)

HRL values are a type of health-protective guidance developed by MDH for groundwater contaminants that pose a potential threat to human health if used for drinking water. The 1989 Act (*Minnesota Statutes*, section 103H.005, subd. (3)) defines a 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."

As previously stated, MDH defines a HRL as a 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. MDH calculates HRL values for specific durations of exposure. An HRL is expressed as micrograms of a chemical per liter of water (µg/L).

MDH develops and adopts HRL values for substances or chemicals that contaminate groundwater as a result of human activities (*Minnesota Statutes*, sections 103H.201 and 103H.005, subd. (6)). In deriving HRL values, MDH evaluates contaminant levels as

though the groundwater were used for drinking water. This is consistent with the declaration in *Minnesota Statutes*, section 115.063, subd. (2) that the "actual or potential use of the waters of the state for potable water supply is the highest priority use." Further, the stated statutory intent is to prevent degradation (*Minnesota Statutes*, section 103H.001) and to protect groundwater (*Minnesota Statutes*, section 115.063, subd. (1)).

Risk managers in partner state agencies such as the Minnesota Department of Agriculture (MDA) and the Minnesota Pollution Control Agency (MPCA) request and apply HRL values in 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, subd. (1)(c)(2)), neither the 1989 Act nor the current HRL rules (*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 in which HRL values might provide meaningful guidance. Nor can MDH anticipate all the factors that might determine whether the applying a 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 a 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 a 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.

The MDH 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., non-linear threshold carcinogens). The algorithms and explanation of concepts used to derive HRL values is presented in Appendix C of this SONAR. Additional information is available in MDH's 2008/2009 SONAR (MDH, 2008. See Part IV).

II. 2012 Proposed Rules

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

A. Scope

The 2012 proposed rules build on the 2009 HRL rule revision. The proposed revisions are limited to *Minnesota Rules*, part 4717.7860 and part 4717.7500 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 12 groundwater contaminants based on the 2009 methodology. The proposed HRL values will be appended to *Minnesota Rules*, part 4717.7860 (see Section III.B. for details); and
- Repeal outdated guidance in *Minnesota Rules*, part 4717.7500 for six contaminants adopted in 1993 or 1994 for which a new updated HRL value has been derived (see Section III.C. for details). (Note: the repealed values will be replaced with values added in *Minnesota Rules*, part 4717.7860, as noted above.)

B. Selection of Contaminants for Review

MDH selected the contaminants for the 2012 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 past interagency meetings between 2007 and 2010, 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 Contaminants of Emerging Concern (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). Twelve of the 21 chemicals with guidance

developed since the most recent rules amendments in 2010/2011 have been detected in groundwater and are eligible for adoption into rule (see Section III below).

As MDH reviewed each chemical, it posted the following information on MDH's Chemicals Under Review[3] 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 Human Health Based Water Guidance[4] webpage. MDH also notified subscribers to the MDH Groundwater Rules, Guidance and Chemical Review email notification account 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 2012 proposed amendments.

Applying the 2009 methods to HRL values from 1993 and 1994 yields new HRL values that might increase or decrease, 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.

Six of the 12 chemicals included in this 2012/2013 rulemaking currently have HRL values for cancer or chronic exposure. In all six cases, the new, proposed HRL values decreased from the 1993 or 1994 values. This differs from previous rulemaking years, when chemicals for some HRL values increased and others decreased, reflecting the potential for values to be altered based on the underlying data and algorithms. For more information about the algorithms used in calculating guidance, please see Appendix C.

MDH methods can be used to derive HRL values for both carcinogens and non-carcinogens. The scientific community now recognizes that cancer-causing chemicals can be assessed in two ways, depending on the way that the chemical causes cancer. Many carcinogens exhibit a non-linear threshold dose-response relationship in studies of

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

[4] 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.

toxicity, and a dose can be identified above which cancer will not develop (i.e., a threshold). For these contaminants, HRL values are based on the methodology for systemic toxicants. The way to evaluate linear (non-threshold) carcinogens involves methodology using carcinogenic potency described in the 2008/2009 SONAR (MDH, 2008). Among the 12 contaminants for which HRL values are proposed during this 2012/2013 rulemaking, there are no non-linear carcinogens.

III. 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, a 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, 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.
CAS number: XXX-XX-X
Year Adopted: 2013
Volatility: XX

	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					

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 (non-volatile, 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;
- **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 $[mg/kg\text{-}day]^{-1}$).
- **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:** Endpoints refer to the organ systems that are most susceptible to harm and that should be grouped together for evaluation when more than one chemical is present (additivity endpoint).

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% 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% 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:

- If the calculated HRL value is greater than the acute value, the HRL is set to equal the acute HRL value;
- If the calculated HRL value is greater than the short-term HRL value, the HRL is set equal to the short-term HRL value; and
- If 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 12 substances with new or updated guidance values:

Subp. 3d. 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN)

CAS number: 21145-77-7 or 1506-02-1
Year Adopted: 2013
Volatility: Moderate

Acute duration.
Not derived due to insufficient data.

Short-term duration.
The short-term non-cancer proposed HRL is 100 μg/L. The RfD is 0.070 mg/kg-day, the RSC is 0.5 and the intake rate is 0.289 L/kg-day. The No Observed Adverse Effect Level (NOAEL) Human Equivalent Dose (HED) is 7 mg/kg-day. The total uncertainty adjustment is 100 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; and 3 for database uncertainty {lack of multi-generational reproductive study}). Critical effects include increased severity of hepatocyte fine vacuolation observed in animal studies. There are no co-critical effects. The additivity endpoint is hepatic liver system.

Subchronic duration.
The subchronic non-cancer HRL is 30 μg/L. The RfD is 0.011 mg/kg-day, the RSC is 0.2 and the intake rate is 0.077 L/kg-day. The NOAEL HED is 1.1 mg/kg-day. The total uncertainty adjustment is 100 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; and 3 for database uncertainty {lack of multi-generational reproductive study}). Critical effects are changes in various biochemical liver parameters including increased albumin/ globulin ratio (A/G ratio) measured in blood serum, reductions in plasma glucose, cholesterol, and plasma triglyceride observed in animal studies. There are no co-critical effects. The additivity endpoint is liver (hepatic) system.

Chronic duration.
The chronic non-cancer HRL is 20 μg/L. The RfD is 0.0037 mg/kg-day, the RSC is 0.2 and the intake rate is 0.043 L/kg-day. The NOAEL HED is 1.1 mg/kg-day. The total uncertainty adjustment is 300 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; 3 for subchronic to chronic extrapolation {comparison of 7 and 13-week assessments suggested minimal changes; however, limited duration specific information precludes complete removal of uncertainty factor}; and 3 for database uncertainty {lack of multi-generational reproductive study}). Critical effects are various biochemical liver parameters including increased A/G ratio, reductions in plasma glucose, cholesterol, and plasma triglyceride observed in animal studies. There are no co-critical effects. The additivity endpoint is the liver (hepatic) system.

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

6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN)

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (μg/L)	ND	100	30	20	NA
RFD (mg/kg-day)	--	0.070	0.011	0.0037	--
RSC	--	0.5	0.2	0.2	--

	Acute	Short-term	Subchronic	Chronic	Cancer
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	0.289	0.077	0.043	--
Endpoints	--	hepatic (liver) system	hepatic (liver) system	hepatic (liver) system	--

Subp. 6a. Carbamazepine (5H-Dibenz (b,f) azepine-5-carboxamide)

CAS number: 298-46-4
Year Adopted: 2013
Volatility: Nonvolatile

Acute duration.
The acute-term non-cancer proposed HRL is 40 μg/L. The RfD is 0.013 mg/kg-day, the RSC is 0.8 and the intake rate is 0.289 L/kg-day. The critical Lowest Observed Adverse Effect Level (LOAEL) is 3.8 mg/kg-day based on the human minimum therapeutic dose for children at 200 mg/day. Because the LOAEL is based on a dose to humans it is not necessary to derive an HED. The total uncertainty factor is 300 (10 for intraspecies variability; 3 for database insufficiencies {neurobehavioral developmental endpoints have not been adequately evaluated in available studies}; and 10 LOAEL-to-NOAEL extrapolation). Critical effects include nervous system effects reported in various human studies (drowsiness, vision disturbances, and equilibrium disturbances). Co-critical effects are reduced body weight gain in offspring in laboratory animals during lactation. Developmental effects in humans including spina bifida, head and facial deformities and heart defects. The additivity endpoints are developmental and nervous system.

Short-term duration.
The short-term non-cancer proposed HRL value is 40 μg/L. The RfD is 0.013 mg/kg-day, the RSC is 0.8 and the intake rate is 0.289 L/kg-day. The critical LOAEL is 3.8 mg/kg-day based on human minimum therapeutic dose for children at 200 mg/day. The total uncertainty factor is 300 (10 for intraspecies variability; 3 for database insufficiencies {neurobehavioral developmental and immunotoxicity endpoints have not been adequately evaluated in available studies}; and 10 for LOAEL-to-NOAEL extrapolation). Critical effects reported in various human studies include hematological effects (porphyria, aplastic anemia); liver effects (liver enzyme induction, increased serum liver enzymes, jaundice, hepatitis); immune reactions (hypersensitivity); nervous system effects (central nervous system depression, double-vision, blurred vision, disturbance of

equilibrium, paresthesae, and suicide ideation); reproductive endocrine effects (male/female sex hormone disturbances); and thyroid hormone disturbances. Co-critical effects include reduced body weight gain in offspring during lactation reported in laboratory animals; and developmental effects in humans (spina bifida, head and facial deformities and heart defects). The additivity endpoints are developmental, hematological (blood) system, hepatic (liver) system, immune system, nervous system, male reproductive system (E), female reproductive system (E), and thyroid (E).

Subchronic duration.
The subchronic non-cancer HRL value must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the subchronic proposed non-cancer HRL value is set equal to the short-term proposed non-cancer HRL value of 40 μg/L. Additivity endpoints are the same as for the short-term duration.

Chronic duration.
The chronic non-cancer HRL value must be protective of the acute, short-term and subchronic exposures that occur within the chronic period and therefore, the chronic proposed non-cancer HRL value is set equal to the short-term proposed non-cancer HRL value of 40 μg/L. Additivity endpoints are the same for the short-term duration.

Cancer.
Not applicable. Carbamazepine has limited evidence for carcinogenicity based on a single rodent bioassay. The approved FDA drug labels contain mandatory cancer statements. MDH staff evaluated the available information and concluded that the non-cancer proposed HRL values are adequately protective of potential carcinogenicity.

Carbamazepine

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (μg/L)	40	40	40 (2)	40 (2)	NA
RFD (mg/kg-day)	0.013	0.013	(2)	(2)	--
RSC	0.8	0.8	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.289	0.289	(2)	(2)	--

	Acute	Short-term	Subchronic	Chronic	Cancer
Endpoints	developmental; nervous system	developmental; hematological (blood) system; hepatic (liver) system; immune system; nervous system; male reproductive system (E); female reproductive system (E); thyroid (E)	developmental, hematological (blood) system, hepatic (liver) system, immune system, nervous system, male reproductive system (E), female reproductive system (E), thyroid (E))	developmental, hematological (blood) system, hepatic (liver) system, immune system, nervous system, male reproductive system (E), female reproductive system (E), thyroid (E)	--

Subp. 6b. Carbon tetrachloride

CAS number: 56-23-5
Year Adopted: 2013
Volatility: High

Acute duration.
The acute non-cancer proposed HRL value is 100 µg/L. The RfD is 0.18 mg/kg-day, the RSC is 0.2 and the intake rate is 0.289 L/kg-day. The NOAEL HED is 5.3 mg/kg-day. The uncertainty adjustment is 30 (3 for intraspecies variability {toxicodynamics} and 10 for interspecies variability). The critical effect is increased litter resorptions. The co-critical effect is regenerative hepatocyte proliferation observed in animal studies. The additivity endpoints are developmental and hepatic (liver) system.

Short-term duration.
The short-term non-cancer proposed HRL value is 3 µg/L. The RfD is 0.0037 mg/kg-day, the RSC is 0.2 and the intake rate is 0.289 L/kg-day. The LOAEL HED is 1.1 mg/kg-day. The total uncertainty factor is 300 (3 for intraspecies variability {toxicodynamics}; 10 for interspecies variability; 3 for database uncertainty {no multi-generation study to adequately assess reproductive effects}; and 3 for minimal LOAEL-to-NOAEL extrapolation). The critical effect is minimal vacuolar degeneration in the liver observed in animal studies. There are no co-critical effects. The additivity endpoint is hepatic (liver) system.

Subchronic duration.

The subchronic non-cancer HRL value must be protective of the short-term exposures that occur within the short-term period and therefore, the subchronic non-cancer proposed HRL value is set equal to the short-term non-cancer proposed HRL of 3 μg/L. The additivity endpoint is the same as for the short-term duration.

Chronic duration.
The chronic non-cancer HRL value must be protective of the short-term exposures that occur within the short-term period and therefore, the chronic non-cancer proposed HRL value is set equal to the short-term non-cancer proposed HRL value of 3 μg/L. The additivity endpoint is the same as for the short term duration.

Cancer:
The proposed HRL value for cancer is 1 μg/L. This chemical has been classified as "likely to be carcinogenic to humans" by the U.S. EPA. The slope factor is 0.07 (mg/kg-day)$^{-1}$. The source of the slope factor is U.S. EPA Integrated Risk Information System (IRIS) (EPA, 2010a). The tumor site and basis of the slope factor calculation is liver and adrenal glands.

Carbon tetrachloride

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (μg/L)	100	3	3 (2)	3 (2)	1
RFD (mg/kg-day)	0.18	0.0037	(2)	(2)	--
RSC	0.2	0.2	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	0.07
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2-<16}$) 1($ADAF_{16+}$)
Intake Rate (L/kg-day)	0.289	0.289	(2)	(2)	0.137$_{(<2)}$ 0.047$_{(2 to <16)}$ 0.039 $_{(16+)}$
Endpoints	developmental, hepatic (liver) system	hepatic (liver) system	hepatic (liver) system	hepatic (liver) system	cancer

Subp. 8b. 1,2-Dichloroethane

CAS number: 107-06-2
Year Adopted: 2013
Volatility: High

Acute duration.
Not derived due to insufficient data.

Short-term duration.
The short-term non-cancer proposed HRL value is 200 µg/L. The RfD is 0.23 mg/kg-day, the RSC is 0.2 and the intake rate is 0.289 L/kg-day. The NOAEL HED is 6.9 mg/kg-day and the total uncertainty factor is 30 (3 for interspecies extrapolation {toxicodynamics} and 10 for intraspecies variability). The critical effect is increased liver weight accompanied by increased serum cholesterol levels observed in animal studies. There are no co-critical effects. The additivity endpoint is hepatic (liver) system.

Subchronic duration.
The subchronic non-cancer HRL value must be protective of the short-term exposures that occur within the subchronic period and therefore, the subchronic non-cancer proposed HRL is set equal to the short-term non-cancer proposed HRL of 200 µg/L. The additivity endpoint is the same as for the short-term duration.

Chronic duration.
The chronic non-cancer proposed HRL value is 60 µg/L. The RfD is 0.012 mg/kg-day, the RSC is 0.2 and the intake rate is 0.043 L/kg-day. The LOAEL HED is 12.2 mg/kg-day. The total uncertainty adjustment is 1,000 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; 3 minimal LOAEL-to-NOAEL extrapolation; and 10 applied for using a less than chronic study {evidence that a longer duration may cause more severe adverse effects}). The critical effects are increased kidney weights (supported as adverse by tubular regeneration lesions seen at higher doses in the same study) observed in animal studies. Co-critical effects include increased liver weight with changes in liver enzymes at next highest dose level, and decreased body weight. The additivity endpoints are renal (kidney) system and hepatic (liver) system.

Cancer.
The proposed HRL value for cancer (cHRL) is 1 µg/L. This chemical has been classified as B2, a probable human carcinogen by the U.S. EPA. The slope factor is 0.091 $(mg/kg\text{-}day)^{-1}$. The source of the slope factor is U.S. EPA IRIS (EPA, 1991a). The tumor site and basis of the slope factor calculation is hemangiosarcoma.

1,2-Dichloroethane

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	200	200 (2)	60	1
RFD (mg/kg-day)	--	0.23	(2)	0.012	--
RSC	--	0.2	(2)	0.2	--
SF (per mg/kg-day)	--	--	--	--	0.091

ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	--	0.289	(2)	0.043	$0.137_{(<2)}$ $0.047_{(2\ to\ <16)}$ $0.039_{(16+)}$
Endpoints	--	hepatic (liver) system	hepatic (liver) system	renal (kidney) system, hepatic (liver) system	cancer

Subp. 8c. trans-1,2-Dichloroethene

CAS number: 156-60-5
Year Adopted: 2013
Volatility: High

Acute duration.
Not derived due to insufficient data.

Short-term duration.
Not derived due to insufficient data.

Subchronic duration.
The subchronic non-cancer proposed HRL value is 200 μg/L. The RfD is 0.091 mg/kg-day, the RSC is 0.2 and the intake rate is 0.077 L/kg-day. The Benchmark Dose Limit (BMDL) HED is 9.1 mg/kg-day. The total uncertainty factor is 100 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; and 3 for database insufficiency {lack of multigenerational study, data from inhalation studies did supplement dataset}). The point of departure BMDL is based on U.S. EPA modeling of immunotoxicity data. The critical effect is a decreased ability to produce antibodies against sheep red blood cells (RBCs) in male spleen cells, which was observed in animal studies. Co-critical effects include decreased thymus weight and clinical chemistry effects. The additivity endpoint is immune system.

Chronic duration.
The chronic non-cancer proposed HRL value is 40 μg/L. The RfD is 0.0091 mg/kg-day, the RSC is 0.2 and the intake rate is 0.043 L/kg-day. The BMDL HED is 9.1 mg/kg-day. The total uncertainty adjustment is 1,000 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; 10 for subchronic to chronic extrapolation; and 3 for database insufficiency {lack of multigenerational study, data

from inhalation studies did supplement dataset}). The BMDL is based on U.S. EPA modeling of immunotoxicity and the critical effect is decreased ability to produce antibodies against sheep RBCs in male spleen cells observed in animal studies. Co-critical effects for this duration include decreased thymus weight and clinical chemistry effects. The additivity endpoint is immune system.

Cancer.
Not applicable. "*Inadequate information to assess the carcinogenic potential*" of trans-1,2-dichloroethene, as noted by U.S. EPA IRIS in 2010.

trans-1,2-Dichloroethene

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (μg/L)	ND	ND	200	40	NA
RFD (mg/kg-day)	--	--	0.091	0.0091	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	--	--	0.077	0.043	--
Endpoints	--	--	immune system	immune system	--

Subp. 11a. N,N-Diethyl-meta-toluamide (DEET)

CAS number: 134-62-3
Year Adopted: 2013
Volatility: Low

Acute duration.
Not derived due to insufficient data.

Short-term duration.
The short-term non-cancer proposed HRL value is 200 μg/L. The RfD is 0.23 mg/kg-day, the RSC is 0.2 and the intake rate is 0.289 L/kg-day. The NOAEL HED is 23 mg/kg-day. The total uncertainty adjustment is 100 (3 for interspecies extrapolation {toxicodynamics}, 10 for intraspecies variability, and 3 for database insufficiencies {additional characterization of neurotoxicity and immunotoxicity is warranted}). Critical effects include decreased pup body weight observed in animal studies. Co-critical effects

include changes in activity level, increased response time. The additivity endpoints are developmental and nervous system.

Subchronic duration.
The subchronic non-cancer HRL value must be protective of the short-term exposures that occur within the subchronic period and therefore, the subchronic non-cancer proposed HRL value is set equal to the short-term non-cancer proposed HRL value of 200 μg/L. The additivity endpoints are the same as the short term duration.

Chronic duration.
The chronic non-cancer HRL value must be protective of the short-term exposures that occur within the chronic period and therefore, the chronic non-cancer proposed HRL value is set equal to the short-term non-cancer proposed HRL of 200 μg/L. Additivity endpoints are the same as the short-term duration.

Cancer.
Not applicable. The U.S. EPA 1998 Reregistration Eligibility Decision noted that the RfD Peer Review Committee recommended DEET be classified as Group D, "not classifiable as a human carcinogen."

N,N-Diethyl-meta-toluamide (DEET)

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (μg/L)	ND	200	200 (2)	200 (2)	NA
RFD (mg/kg-day)	--	0.23	(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, nervous system	developmental, nervous system	developmental, nervous system	--

Subp. 11b. 1,4-Dioxane

CAS number: 123-91-1
Year Adopted: 2013
Volatility: Low

Acute duration.

Not derived due to insufficient data.

Short-term duration.
Not derived due to insufficient data.

Subchronic duration.
The subchronic non-cancer proposed HRL value is 300 μg/L. The RfD is 0.12 mg/kg-day, the RSC is 0.2 and the intake rate is 0.077 L/kg-day. The NOAEL HED is 12 mg/kg-day. The total uncertainty adjustment is 100 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; and 3 for database insufficiencies {lack of a multigeneration reproductive/developmental study}). The critical effects are increased relative liver and kidney weight (with histological and clinical chemistry changes at a higher dose level); hepatocyte swelling; and nuclear enlargement of the nasal respiratory epithelium, all of which were observed in animal studies. Co-critical effects include increased nuclear enlargement of the bronchial epithelium. Additivity endpoints are hepatic (liver) system, renal (kidney) system, and respiratory system.

Chronic duration.
The chronic non-cancer proposed HRL value is 100 μg/L. The RfD is 0.025 mg/kg-day. The RSC is 0.2 and the intake rate is 0.043 L/kg-day. It has the same basis as the U.S. EPA IRIS 2010 value that was rounded to 0.03 mg/kg-day. The NOAEL HED is 2.5 mg/kg-day. The total uncertainty adjustment is 100 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; and 3 for database insufficiencies (lack of a multigeneration reproductive/developmental study). The critical effects are histopathological lesions in the liver and kidney (hepatic and renal degeneration and necrosis as well as regenerative hyperplasia in hepatocytes and renal tubule epithelial cells), which were observed in animal studies. Co-critical effects include increased relative liver weight; non-neoplastic lesions in the nasal cavity, liver and kidney; nuclear enlargement of nasal, tracheal and bronchial epithelium; decreased body weight and growth; and neoplastic lesions in the liver. (Note: Neoplastic lesions (liver adenomas) are addressed by the cancer proposed HRL value.) Additivity endpoints are hepatic (liver) system, renal (kidney) system, and respiratory system.

Cancer.
The proposed cancer HRL value is 1 μg/L. The U.S. EPA IRIS cancer classification is "likely to be carcinogenic to humans." The slope factor is 0.1 $(mg/kg\text{-}day)^{-1}$ from U.S. EPA IRIS based on hepatocellular adenomas and carcinomas in female mice. Additional tumor sites included: nasal squamous cell carcinomas; peritoneal mesotheliomas; and mammary gland adenomas.

1,4-Dioxane

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (μg/L)	ND	ND	300	100	1

	Acute	Short-term	Subchronic	Chronic	Cancer
RFD (mg/kg-day)	--	--	0.12	0.025	--
RSC	--	--	0.2	0.2	--
SF (per mg/kg-day)	--	--	--	--	0.1
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	--	--	0.077	0.043	$0.137_{(<2)}$ $0.047_{(2\ to\ <16)}$ $0.039_{(16+)}$
Endpoints	--		hepatic (liver) system; renal (kidney) system; respiratory system	hepatic (liver) system; renal (kidney) system; respiratory system	cancer

Subp. 12f. Metribuzin

CAS number: 21087-64-9
Year Adopted: 2013
Volatility: Low

Acute duration.
The acute non-cancer proposed HRL value is 30 µg/L. The RfD is 0.016 mg/kg-day, the RSC is 0.5, and the intake rate is 0.289 L/kg-day. The NOAEL HED is 0.48 mg/kg-day. The total uncertainty factor is 30 (3 for interspecies extrapolation {toxicodynamics} and 10 for intraspecies variability). The critical effects are higher pup mortality and decreased body weight gain (maternal), which were observed in animal studies. Co-critical effects include decreased motor and locomotor activity, drooping eyelids (ptosis), oral staining, and decreased body temperature. The additivity endpoint is developmental and nervous system.

Short-term duration.
The short term non-cancer proposed HRL value is 10 µg/L. The RfD is 0.006 mg/kg-day, the RSC is 0.5 and the intake rate is 0.289 L/kg-day. The NOAEL HED is 0.58 mg/kg-day. The total uncertainty factor is 100 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; 3 for LOAEL-to-NOAEL extrapolation). The critical effects include changes in thyroid hormone levels (thyroxine (T4) and triiodothyronine (T3) and

histopathological changes to the thyroid gland, all of which were observed in animal studies. There were no co-critical effects. The additivity endpoint is thyroid (E).

Subchronic duration.
The subchronic non-cancer HRL value must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the subchronic non-cancer HRL value is set equal to the short-term non-cancer proposed HRL value of 10 µg/L. The additivity endpoint is the same as the short-term duration.

Chronic duration.
The chronic non-cancer HRL value must be protective of the acute, short-term or subchronic exposures that occur within the chronic period and therefore, the chronic non-cancer proposed HRL value is set equal to the short-term non-cancer proposed HRL value of 10 µg/L. The additivity endpoint is the same as the short-term duration.

Cancer.
Not applicable. U.S. EPA IRIS concluded in 1996 that the cancer classification is Group D "not classifiable as to human carcinogenicity."

Metribuzin

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	30	10	10 (2)	10 (2)	NA
RFD (mg/kg-day)	0.016	0.006	(2)	(2)	--
RSC	0.5	0.5	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.289	0.289	(2)	(2)	--
Endpoints	developmental, nervous system	thyroid (E)	thyroid (E)	thyroid (E)	--

Subp. 12g. Naphthalene

CAS number: 91-20-3
Year Adopted: 2013
Volatility: Moderate

Acute duration.

The acute non-cancer proposed HRL value is 70 μg/L. The RfD is 0.038 mg/kg-day, the RSC is 0.5 and the intake rate is 0.289 L/kg-day. The LOAEL HED is 11.5 mg/kg-day. The total uncertainty factor is 300 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variation; 3 for database gaps {lack of 2-generation reproductive toxicity studies and lack of dose-response data for hemolytic anemia and cataract formation which have been observed in human epidemiological studies for naphthalene}; 3 for minimal LOAEL-to-NOAEL extrapolation. The critical effects are based on maternal nervous system effects including lethargy, shallow breathing and impaired posture observed in animal studies. There are no co-critical effects. The additivity endpoint is nervous system.

Short-term duration.
The short-term non-cancer proposed HRL value is 70 μg/L. The RfD is 0.038 mg/kg-day, the RSC is 0.5 and the intake rate is 0.289 L/kg-day. LOAEL HED is 11.5 mg/kg-day. The total uncertainty factor is 300 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variation; 3 for database insufficiencies {lack of 2-generation reproductive toxicity studies and lack of dose-response data for hemolytic anemia and cataract formation which have been observed in human epidemiological studies}; 3 for minimal LOAEL-to-NOAEL extrapolation). Critical effects are maternal nervous system effects which include lethargy, shallow breathing and impaired posture observed in animal studies. There are no co-critical effects. The additivity endpoint is nervous system.

Subchronic duration.
The subchronic non-cancer HRL value must be protective of the short-term exposures that occur within the short-term period and therefore, the subchronic non-cancer proposed HRL value is set equal to the acute/short-term non-cancer proposed HRL value of 70 μg/L. The additivity endpoint is the same as for the short-term duration.

Chronic duration.
The chronic non-cancer proposed HRL value is 70 μg/L. The RfD is 0.016 mg/kg-day, the RSC is 0.2 and the intake rate is 0.043 L/kg-day. The NOAEL HED is 15.6 mg/kg-day. The total uncertainty adjustment is 1,000 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variation; 10 for database insufficiencies {lack of 2-generation reproductive toxicity studies, lack of dose-response data for hemolytic anemia and cataract formation which have been observed in human epidemiological studies, and a lack of neurotoxicity studies in the subchronic and chronic durations}; 3 for subchronic-to-chronic extrapolation because effects did not increase in severity with increasing exposure duration and most effects were observed within a shorter duration). The critical effects are a decrease in terminal body weight observed in animal studies. Co-critical effects include decreased spleen weight, lethargy, slow breathing, prone body posture, increased rooting behavior, decreased body weight associated with decreased food and water consumption. The additivity endpoints are nervous system and spleen.

Cancer.
Not applicable. U.S. EPA IRIS classified this chemical in 1998 as Group C, "possible human carcinogen." There is evidence of carcinogenicity following inhalation exposure.

Naphthalene

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	70	70	70 (2)	70	NA
RFD (mg/kg-day)	0.038	0.038	(2)	0.016	--
RSC	0.5	0.5	(2)	0.2	--
SF (per mg/kg-day)	--	--	--	--	--
ADAF or $AF_{lifetime}$	--	--	--	--	--
Intake Rate (L/kg-day)	0.289	0.289	(2)	0.043	--
Endpoints	nervous system	nervous system	nervous system	nervous system, spleen	--

Subp. 18b. 1,2,4-Trichlorobenzene

CAS number: 120-82-1
Year Adopted: 2013
Volatility: High

Acute duration.
Not derived because of insufficient data.

Short-term duration.
The short term non-cancer proposed HRL value is 100 µg/L. The RfD is 0.17 mg/kg-day, the RSC is 0.2 and the intake rate is 0.289 L/kg-day. The NOAEL HED is 17 mg/kg-day. The total uncertainty factor is 100 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; and 3 for database insufficiencies {limited data suggests that the adrenal gland may be a more sensitive endpoint than the liver – additional short-term studies are warranted}). The critical effects are mild hepatic lesions, increase in mixed function oxidase, and decreased hematocrit and hemoglobin, all of which were observed in animal studies. Co-critical effects include adrenal weight gain and vacuolization of the middle zone of the adrenal cortex, decreased corticosterone levels, liver enzyme induction and sight hepatocellular hypertrophy. The additivity endpoints are hepatic (liver) system, adrenal (E), and hematological (blood) system.

Subchronic duration.

The subchronic non-cancer HRL value must be protective of the shorter-term exposures that occur within the subchronic periods and therefore, the subchronic non-cancer proposed HRL value is set equal to the short-term non-cancer proposed HRL value of 100 μg/L. The additivity endpoints are hepatic (liver) system, adrenal (E), and hematological (blood) system.

Chronic duration.
The chronic non-cancer proposed HRL value is 100 μg/L. The RfD is 0.021 mg/kg-day. The RSC is 0.2 and the intake rate is 0.043 L/kg-day. The NOAEL HED is 2.1 mg/kg-day. The total uncertainty adjustment is 100 (3 for interspecies extrapolation {toxicodynamics}; 10 for intraspecies variability; and 3 for use of a subchronic study for the chronic duration - effects and points of departure across duration indicates limited increase in severity of effects). The critical effect is increased adrenal weight observed in animal studies. Co-critical effects include increased liver weight and increased liver enzyme levels; adrenal weight gain and vacuolization of the middle zone of the adrenal cortex, decreased corticosterone levels; increased kidney weights and renal mineralization. The additivity endpoints are hepatic (liver) system, adrenal (E), and renal (kidney) system.

Cancer.
The proposed cancer HRL value is 4 μg/L. The cancer classification is "likely to be carcinogenic to humans." The slope factor is 0.029 $(mg/kg\text{-}day)^{-1}$ based on liver tumors in male mice from U.S. EPA National Center for Environmental Assessment (NCEA), 2009.

1,2,4-Trichlorobenzene

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (μg/L)	ND	100	100 (2)	100	4
RFD (mg/kg-day)	--	0.17	(2)	0.021	--
RSC	--	0.2	(2)	0.2	--
SF (per mg/kg-day)	--	--	--	--	0.029
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2-<16}$) 1($ADAF_{16+}$)
Intake Rate (L/kg-day)	--	0.289	(2)	0.043	$0.137_{(<2)}$ $0.047_{(2 \text{ to } <16)}$ $0.039_{(16+)}$

	Acute	Short-term	Subchronic	Chronic	Cancer
Endpoints	--	hepatic (liver) system; adrenal (E); hematological (blood) system	hepatic (liver) system; adrenal (E); hematological (blood) system	hepatic (liver) system; adrenal (E); renal (kidney) system	cancer

Subp. 21a. 1,2,3-Trichloropropane

CAS number: 96-18-4
Year Adopted: 2013
Volatility: Moderate

Acute duration.
The short-term non-cancer proposed HRL value is 7 μg/L. The RfD is 0.0042 mg/kg-day, the RSC is 0.5, and the intake rate is 0.289 L/kg-day. The BMDL HED is 0.42 mg/kg-day. The total uncertainty adjustment is 100 (3 for interspecies variability {toxicodynamics}; 10 for intraspecies variability; and 3 for database insufficiencies {lack of additional information related to developmental toxicity}). The critical effect is decreased fetal survival observed in animal studies. There are no co-critical effects. The additivity endpoint is developmental.

Short-term duration.
The short-term non-cancer proposed HRL value is 7 μg/L. The RfD is 0.0042 mg/kg-day, the RSC is 0.5, and the intake rate is 0.289 L/kg-day. The BMDL HED is 0.42 mg/kg-day. The total uncertainty adjustment is 100 (3 for interspecies variability {toxicodynamics}; 10 for intraspecies variability; and 3 for database insufficiencies {lack of additional information related to developmental toxicity}). The critical effect is decreased fetal survival observed in animal studies. There are no co-critical effects. The additivity endpoint is developmental.

Subchronic duration.
The subchronic non-cancer HRL value must be protective of the shorter-term exposures that occur within the subchronic periods and therefore, the subchronic non-cancer proposed HRL value is set equal to the short-term non-cancer proposed HRL value of 7 μg/L. The additivity endpoint is the same as for the short-term duration.

Chronic duration.
The chronic non-cancer HRL value must be protective of the shorter-term exposures that occur within the chronic periods and therefore, the chronic non-cancer proposed HRL

value is set equal to the short-term non-cancer proposed HRL value of 7 µg/L. The additivity endpoint is the same as for the short-term duration.

Cancer.
The cancer proposed HRL value is 0.003 µg/L. The U.S. EPA cancer classification is "likely to be carcinogenic to humans." The slope factor is 30 $(mg/mg\text{-}day)^{-1}$. The source of the slope factor is a EPA IRIS (2009). The tumor sites are the forestomach, liver, Harderian gland, oral cavity and uterus.

1,2,3- Trichloropropane

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	7	7	7 (2)	7 (2)	0.003
RFD (mg/kg-day)	0.0042	0.0042	(2)	(2)	--
RSC	0.5	0.5	(2)	(2)	--
SF (per mg/kg-day)	--	--	--	--	30
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	0.289	0.289	(2)	(2)	$0.137_{(<2)}$ $0.047_{(2\ to\ <16)}$ $0.039_{(16+)}$
Endpoints	developmental	developmental	developmental	developmental	cancer

Subp. 22a. Tris(2-chloroethyl) phosphate

CAS number: 115-96-8
Year Adopted: 2013
Volatility: Low

Acute duration.
Not derived due to insufficient data.

Short-term duration.
The short-term non-cancer proposed HRL value is 300 µg/L. The RfD is 0.15 mg/kg-day, the RSC is 0.5, and the intake rate is 0.289 L/kg-day. The NOAEL HED is 14.5 mg/kg-day. The total uncertainty factor is 100 (3 for interspecies extrapolation {toxicodynamics}, 10 for intraspecies variability, 3 for database insufficiencies {absence of adequate multigenerational developmental study}). The critical effects are increased absolute and

relative kidney weights and decreased serum cholinesterase observed in animal studies. Co-critical effects include decreased number of male pups per litter. The additivity endpoints are renal (kidney) system, nervous system, developmental system.

Subchronic duration.
The subchronic non-cancer proposed HRL value is 200 µg/L. The RfD is 0.068 mg/kg-day, the RSC is 0.2 and the intake rate is 0.077 L/kg-day. The NOAEL HED is 6.8 mg/kg-day. The total uncertainty factor is 100 (3 for interspecies extrapolation {toxicodynamics}, 10 for intraspecies variability, and 3 for database insufficiencies {absence of adequate multigenerational developmental study}). The critical effect is increased kidney weights, observed in animal studies. There are no co-critical effects. The additivity endpoint is renal (kidney) system.

Chronic duration.
The chronic non-cancer proposed HRL value must be protective of shorter term exposures that occur within the chronic period and therefore, the chronic non-cancer proposed HRL value is set equal to the subchronic non-cancer proposed HRL value of 200 µg/L. The additivity endpoint is the same as for the subchronic duration.

Cancer.
The cancer proposed HRL value is 5 µg/L. The U.S. EPA cancer classification is "likely to be carcinogenic to humans." The International Agency for Research on Cancer classification is Group 3, "not classifiable as to its carcinogenicity to humans." The slope factor is 0.02 $(mg/kg\text{-}day)^{-1}$. The source of the slope factor is U.S. EPA Provisional Peer Reviewed Toxicity Values in 2009. The tumor site is the kidney.

Tris(2-chloroethyl) phosphate

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	300	200	200 (3)	5
RFD (mg/kg-day)	--	0.15	0.068	(3)	--
RSC	--	0.5	0.2	(3)	--
SF (per mg/kg-day)	--	--	--	--	0.02
ADAF or $AF_{lifetime}$	--	--	--	--	10 ($ADAF_{<2}$) 3 ($ADAF_{2\ to\ <16}$) 1 ($ADAF_{16+}$)
Intake Rate (L/kg-day)	--	0.289	0.077	(3)	$0.137_{(<2)}$ $0.047_{(2\ to\ <16)}$ $0.039_{(16+)}$

	Acute	Short-term	Subchronic	Chronic	Cancer
Endpoints	--	developmental, nervous system, renal (kidney) system	renal (kidney) system	renal (kidney) system	cancer

2. Rule Wording Change and Renumbering

Current HRL rules state either "Year Effective:" or "Year Proposed:" to indicate when the rule was adopted or proposed. To clarify and make these tables consistent, MDH proposes updating current HRL rule wording to "Year Adopted:" followed by the year of adoption. New, proposed HRL rules will also use this wording. Also, in order to continue listing the substances alphabetically within the HRL Rules, MDH is proposing renumbering of the rules.

The proposed wording and renumbering changes to current HRL rules are shown below. None of these changes affect guidance values currently in rule. (See section III.B.1. for proposed rule amendments that involve guidance values.)

Subp. 3. Acetochlor.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 3a. Acetochlor ESA.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 3b. Acetochlor OXA.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 3c. Acetone.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 4. Alachlor.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 5. Atrazine.

Year ~~Established: 2008~~ Adopted: 2009

Supb. 6. Benzene.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 7. Chloroform.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 8. Cyanazine.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 8a. Dichlorodifluoromethane.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. ~~8b~~ 8d. 1,1-Dichloroethylene.

Year ~~Proposed: 2010~~ Adopted: 2011

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

Year ~~Established: 2008~~ Adopted: 2009

Subp. 10. Dichloromethane.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 11. Dieldrin.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 12. Di–(2-ethylhexyl) phthalate.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 12a. Ethylbenzene.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 12b. Ethylene glycol.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 12c. Metolachlor and S-Metolachlor.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 12d. Metolachlor ESA.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 12e. Metolachlor OXA.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 13. Nitrate (as N).

Year ~~Established: 2008~~ Adopted: 2009

Subp. 14. Pentachlorophenol.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 14a. Perfluorobutane sulfonate (PFBS).

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 14b. Perfluorobutyrate (PFBA).

Year ~~Proposed: 2010~~ Adopted: 2011

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

Year ~~Established: 2008~~ Adopted: 2009

Subp. 16. Perfluorooctanoic acid (PFOA) and salts.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 17. Simazine.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 18. 1,1,2,2-Tetrachloroethylene.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 18a. Toluene.

Year ~~Proposed: 2010~~ Adopted: 2011

Subp. 19. 1,1,1-Trichloroethane.

Year ~~Established: 2008~~ Adopted: 2009

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

Year ~~Established: 2008~~ Adopted: 2009

Subp. 21. 2(2,4,5-Trichlorophenoxy)propionic acid (2,4,5-TP or Silvex).

Year ~~Established: 2008~~ Adopted: 2009

Subp. 22. 1,3,5-Trimethylbenzene.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 23. Vinyl Chloride.

Year ~~Established: 2008~~ Adopted: 2009

Subp. 23a. Xylenes.

Year ~~Proposed: 2010~~ Adopted: 2011

C. PROPOSED DELETIONS: HEALTH RISK LIMITS TABLE (Minnesota Rules, part 4717.7500*)*

Based on MDH's recent review of health-based guidance values listed in *Minnesota Rules*, part 4717.7500, MDH intends to repeal outdated guidance values for six of the contaminants adopted into rule in 1993-1994. The 2012/2013 proposed rules include updated proposed HRL values for each of the six contaminants. The specific subparts to be repealed are noted below:

Subparts and chemicals to be repealed from part 4717.7500:

23 Carbon Tetrachloride	66 Metribuzin
40 1,2-Dichloroethane	66a Naphthalene
42 trans-1,2-Dichloroethene	86 1,2,3-Trichloropropane

Updated proposed HRL values for each of these chemicals will be added to *Minnesota Rules*, part 4717.7860, as described above in Section III.B.

IV. REGULATORY ANALYSIS

This section discusses the regulatory factors and presents information on 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 rule, including classes that will bear the costs and classes that will benefit

Because these rules address the groundwater Minnesotans rely on for drinking, 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 groundwater monitoring and contamination response programs intended to protect the health of all Minnesotans. Additionally, 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 conveys advice on eliminating or reducing risks to the consumer, the responsible governmental unit, or the water operator.

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

The proposed amendments provide protection to 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 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 groundwater 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 7860 and 7500 establish HRL values, which are uniform, science-based values that protect the health of people who drink water that comes from groundwater.

Unlike other rules revision that regulate activities of citizens or industry, this HRLs rules revision applies the specific methodology previously adopted for calculating HRLs values to identified contaminants and adopts the calculated values themselves. As described on page 2 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 HRLs 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 groundwater contaminants. In 2009, the Commissioner adopted the methodology for carrying these directives out, which is now contained in Minnesota Rules, part 4717.7860. This rulemaking project merely adds new values and repeals old values by applying this 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.

In addition to the HRLs, MDH derives another, alternative type of quantitative guidance on groundwater contaminants, sometimes at the request of other agencies. This guidance, known as Health-Based Values (HBVs), is derived using the same methodology as the 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 are unpromulgated, State agencies and the regulated community consider them to be transient in nature as compared to the HRLs. HRLs 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.

All health-based guidance values that are adopted into HRL rules are called Health-Based Values (HBVs) before adoption. HBVs for groundwater contaminants that MDH has derived through the HRL standard methodology are eligible for rule adoption. Thus,

MDH rejected 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 a HRL value would be expected to present minimal, if any, risk to human health. Similarly, a contaminant concentration above a HRL value, without consideration of other information, might not necessarily indicate a public health problem. However, because the proposed HRL values for six chemicals are lower than the 1993/1994 values (carbon tetrachloride, 1,2-dichloroethane, trans-1,2-dichloroethene, metribuzin, naphthalene, and 1,2,3-trichloropropane), the cost of remediating or preventing water contamination might increase. The proposed HRL values for the six chemicals without 1993/1994 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 groundwater. As stated above, groundwater is a primary source of drinking water for Minnesota, making the need to protect it 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 protections to segments of the population.

Though the state's goal is to prevent degradation of groundwater, degradation prevention is the ideal and thus cannot always be achieved. Some groundwater resources have already been contaminated by unintentional releases—by activities that occurred before the vulnerability of groundwater 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 groundwater to ensure that there is minimal risk to human health from using the groundwater for drinking. A reliable source of groundwater that is safe for human consumption is essential to the ability of a state 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 a RSC.

MDH currently has health-based guidance for more chemicals important to Minnesota. For example, while U.S. EPA has MCLs for 91 chemicals, there are currently Minnesota HRL values for 130 chemicals. If all of the proposed HRL values are adopted in this rulemaking, there will be HRL values for a total of 136 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 location 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 a 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 groundwater contaminant values. 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 a HRL is appropriate. Each program must determine whether to apply a HRL or whether site-specific characteristics justify deviation from HRL values.

Health-based guidance is only one set of criteria that state groundwater 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 a 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 a HRL value is exceeded might invoke an agency's 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:

- Request for Comments: MDH published the "Request for Comments" notice in the *Minnesota State Register*) on July 9, 2012. 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/37_02.pdf#page=9.

  MDH made phone calls to six people representing organizations that in the past requested notification about MDH rulemaking activity related to HRL values. Emails were also sent to these requestors in addition to two staff within other State agencies. The email notices contained a link to the MDH Rules Web page that provides information about each chemical under consideration.

  Rules contacts

Name	Organization	Date contacted	Method of contact
Bonnie Brooks	Minnesota Pollution Control Agency	7/6/12	Email
Carol Ley	3M	7/10/2012	Phone and email
Michael Neuman	Environmental Justice Advocates of Minnesota	7/5/2012	Phone and web contact form
Michael Robertson	Minnesota Chamber of Commerce	7/5/2012	Phone message and email
Kathleen Schuler	Institute for Agriculture and Trade Policy	7/5/2012	Phone message and email
Kris Sigford	Minnesota Center for Environmental Advocacy	7/5/2012	Phone message and email
Deanna White	Clean Water Action	7/5/2012	Phone message and email

Name	Organization	Date contacted	Method of contact
Joe Zachmann	Minnesota Department of Agriculture	7/6/12	Email

After MDH published the Request for Comments on July 9, 2012, it sent a GovDelivery notice to 2,319 subscribers to the Groundwater Rules, Guidance and Chemical Review account about the availability of the notice and how to access it. In addition, MDH held a public meeting concerning the chemicals under consideration for rule-making on August 28, 2012 (see below.).

As of December 17, 2012, MDH has received no written comments in response to the Request for Comments . More than 60 days have elapsed since its publication.

- Notice of Intent to Adopt: 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* 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 – Dual Notice* and a copy of the SONAR to the Legislature and the Legislative Reference Library. Copies of the proposed rules and the SONAR will be made available at no charge, upon request.

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 3.922.

In addition to the APA requirements, MDH also engaged in outreach efforts to inform stakeholders and the public about the 2012/2013 HRL rule amendments. MDH hosted a public meeting on August 28, 2012 and routinely posted updates on its Web pages, as well as sent electronic announcements through its email subscription list. Details of MDH's outreach efforts are described below.

- MDH HRL rule amendment website: MDH created new Web pages for the 2012/2013 HRL rule amendment.[5] 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,

[5] 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/amendment.html

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

- MDH email subscription service: MDH maintains an email subscription list to send updates on groundwater rules and guidance on the chemicals reviewed. MDH routinely sends updates on the HRL rule amendment to the email subscribers. The updates include information such as: 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 July 9, 2012, MDH's Groundwater Rules, Guidance and Chemical Review email subscription account had 2,319 subscribers.

- Other: On April 17, 2012, MDH emailed 2,246 persons subscribing to the HRA GovDelivery Groundwater Rules, Guidance and Chemical Review account information about the intent to amend the existing HRL rules in 2012/2013. The email described the nature and scope of the possible amendments.

- MDH HRL rule amendment public meeting: MDH hosted a public meeting on August 28, 2012. 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) the rulemaking process and timelines; 2) methods used to derive guidance in Minnesota and other states and the U.S. Environmental Protection Agency Office of Water; and 3) questions about the values of specific chemicals. 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.[6] Including MDH staff, about 15 persons attended the public meeting. In November, MDH received one oral follow-up comment and request for a meeting. MDH agreed to meet with the requestor. However, as of December 17, 2012, the requestor has not proposed meeting times.

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

D. IMPACT OF PROPOSED RULES

1. CONSULTATION WITH MMB ON LOCAL GOVERNMENT IMPACT

As required by *Minnesota Statutes*, section 14.131, MDH consulted with the Minnesota Management and Budget (MMB) on the impact the proposed rules might have on local governments. MDH did so by sending to the MMB Commissioner, copies of the documents sent to the Governor's Office for review and approval before MDH published the *Notice of Intent to Adopt*. The documents sent to MMB included: the Governor's Office Proposed Rule and SONAR Form; the proposed rules; and the SONAR. MDH sent these documents to MMB on January 4, 2013.

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 (through ordinances or regulations) groundwater quality standards. Local government has 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 groundwater contaminants; the rules do not address any 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 the "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
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V. CONCLUSION

Groundwater is a primary source of drinking water for Minnesotans. The actual or potential use of this resource for drinking purposes is the "highest priority use" of groundwater and is afforded maximum protection by the state (*Minnesota Statutes*, 115.063). The proposed amendments update MDH's human health-based guidance requested and needed by risk managers to protect groundwater and public health. This effort is part of MDH's long-term plan to continue to review, develop, update and add to the HRL rules on groundwater contaminants.

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

APPENDIX A: GLOSSARY OF TERMS USED IN RISK ASSSESSMENT

Acute duration: A period of 24 hours or less.

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

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

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

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

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

Animal Study: A controlled experiment in which a cohort of test animals, usually mice, rats, or dogs, is exposed to a range of doses of a chemical and assessed for health effects. For the purposes of the MDH HRL rules, only studies of mammalian species were considered; studies relating to fish, amphibians, plants, etc. were 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).

Biologically Based Dose-Response (BBDR) Model: A predictive model that describes biological processes at the cellular and molecular level linking the target organ dose to the adverse effect.

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 Concentration (HEC): The human concentration (for inhalation exposure) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species concentration. This adjustment may incorporate toxicokinetic information on the particular agent, if available, or use a default procedure.

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 95th percentile intake rate for the relevant duration was used.

Interspecies Factor: see *Uncertainty Factor.*

Intraspecies Factor: see *Uncertainty Factor.*

Kilogram (kg): One kilogram is equivalent to 2.2046226 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. 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): 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: Neurotoxicity is 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.

Precursor Event: An early condition or state preceding the pathological onset of a disease.

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, subd. (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_human health_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: For the purpose of the HRL revision, 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 HRLvalues 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 2002b). 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 ($10^{0.5} \times 10^{0.5} = 10^1$).

Uncertainty and variability factors are typically values of three or ten and are multiplied together. In keeping with the U.S. EPA RfC/RfD Technical Panel (EPA, 2002b) recommendation and the rationale supporting it, MDH has not derived a 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

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

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APPENDIX C: CONCEPTS USED IN MDH-DERIVED HRLs

Described below are the basic principles that underlie MDH's risk algorithm adopted in 2009 (*Minnesota Rules*, part 4717.7830, subpart 2) as stated in Section I.D. MDH used these methods to derive the HRL values that are included in the 2012/2013 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.

1. 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, 2002b). In cases where sufficient toxicological information is available, MDH derives RfDs for the various time periods as defined by EPA.

In evaluating the proposed non-cancer HRL 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 the 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.

2. 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, subd. (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

3. 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 2011) 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, 2002b). 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, 2002b) recommendation and the rationale supporting it, MDH has not derived a 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.

4. MDH Health Risk Limit Algorithms

As noted in Section I.D., MDH uses 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 III.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 non-cancer HRL value for carbon tetrachloride, using the algorithm for nHRLs:

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

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

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

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

$$\text{Subchronic Non-cancer HRL} = \frac{(0.0098\ mg/kg/d) \times (0.2) \times (1000\ \mu g/mg)}{(0.077\ L/kg\text{-}d)}$$

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

The calculated subchronic non-cancer HRL (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 non-cancer HRL is set equal to the short-term non-cancer HRL value. Hence, the subchronic non-cancer HRL value for carbon tetrachloride is set equal to 3 µg/L. The health endpoints include the hepatic and immune system. In this case:

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

Notes

- RfDs and uncertainty adjustments are derived by MDH, unless otherwise noted. The RfDs and the endpoints are usually based on animal studies but may be based on human studies.
- RfDs are based on human equivalent dose (HED) calculated from the point of departure in the selected animal studies. HED is the human dose (for 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 non-cancer HRL value is derived using the following equation as previously stated in Section I.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:

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

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:

$$cHRL = \frac{(1 \times 10^{-5}) \times 1{,}000 \frac{\mu g}{mg}}{SF \times AF_{lifetime} \times 0.043 \frac{L}{kg-day}}$$

Where:

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

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

SF = adult-exposure based cancer slope factor.

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

0.043 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 2012/2013 CONTAMINANTS

Note: MDH selected the contaminants for the 2012/2013 amendments based on input from programs within MDH, such as the Site Assessment and Consultation Unit (SAC), Drinking Water 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 2012/2013 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	6-Acetyl-1,1,2,4,4,7-hexamethyltetraline (AHTN)	CEC nomination and Interagency priority	1,4-Dioxane
CEC nomination	Carbamazepine	Interagency priority	Metribuzin
Interagency priority	Carbon Tetrachloride	Interagency priority	Naphthalene
Interagency priority	1,2-Dichloroethane	Interagency priority	1,2,4-Trichlorobenzene
Interagency priority	*trans*-1,2-Dichloroethene	CEC nomination	1,2,3-Trichloropropane
CEC nomination	N,N-Diethyl-meta-toluamide (DEET)	CEC nomination	Tris(2-chloroethyl) phosphate

APPENDIX E: CHEMICAL SUMMARY SHEETS

Note: The following documents represent the Health Based Values (HBVs) for chemicals included in the 2010 proposed amendments. These chemical summary sheets are also available on MDH's Groundwater Values Table[4] and the HRL rule amendment webpages.[5] Upon adoption of the 2012/2013 amendments, these HBV summary sheets will be updated as HRL summary sheets, and posted online.

2012 Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Web Publication Date: June 2012
Expiration Date: June 2017

Chemical Name: 6-Acetyl-1,1,2,4,4,7 hexamethyltetraline

CAS: 21145-77-7 or 1506-02-1

Synonyms: AHTN; Tonalide; Musk tetralin; Polycyclic musks; 7-Acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene;Acetyl-hexamethyl-tetrahydronaphthalene; 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one

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

While developmental studies in animals are available, the quantity and quality of the information is not sufficient to derive an acute guidance value. Based on the available information, the short-term HBV for AHTN is protective of developmental effects.

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

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Short-term intake rate, L/kg/d)

= (0.070 mg/kg/d) x (0.5) x (1000 ug/mg)
(0.289 L/kg-d)

= 121 rounded to **100 ug/L**

Reference Dose / Concentration:	0.070 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	32 mg/kg-d (NOAEL); 14-day dietary range-finder study (Api et al. 2004)
Human Equivalent Dose Adjustment:	7 mg/kg-day [32 mg/kg-day x 0.22] (MDH, 2011)

Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty (lack of multi-generational reproductive study)
Critical effect(s):	Increased severity of hepatocyte fine vacuolation
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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

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

$$= \frac{\text{(0.011 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 28 rounded to **30 ug/L**

Reference Dose / Concentration:	0.011 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	5 mg/kg-d (NOAEL), Subchronic dietary study (Api et al. 2004)
Human Equivalent Dose Adjustment:	1.1 mg/kg-day [5 mg/kg-day x 0.22] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty (lack of multi-generational reproductive study).
Critical effect(s):	Effects on various biochemical liver parameters including increased A/G ratio, reductions in plasma glucose, cholesterol, and plasma triglyceride
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

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

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

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

= 17 rounded to **20 ug/L**

Reference Dose / Concentration:	0.0037 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	5 mg/kg-d (NOAEL), Subchronic dietary study (Api et al. 2004)
Human Equivalent Dose Adjustment:	1.1 mg/kg-day [5 mg/kg-day x 0.22] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability; 3 for subchronic to chronic extrapolation (comparison of 7 and 13-week assessments suggested minimal changes; however, limited duration specific information precludes complete removal of uncertainty factor); 3 for database uncertainty (lack of multi-generational reproductive study).
Critical effect(s):	Effects on various biochemical liver parameters including increased A/G ratio, reductions in plasma glucose, cholesterol, and plasma triglyceride
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Based Value (cHBV) = Not Applicable

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

Volatile: Yes (moderate)

Summary of changes since 1993/1994 HRL promulgation:
In 2011 Short-term, Subchronic and Chronic HBVs of 200, 40, and 20 ug/L were derived. MDH reevaluated the HBVs in 2012 to incorporate HED methodology. Of the resulting Short-term, Subchronic and Chronic HBVs (100, 30 and 20 ug/L), the Short-term and Subchronic values are lower (2-fold and 1.3-fold) than the values derived in 2011 and the Chronic value remained the same.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Secondary observation[5]
Effects?	No[1]	Yes[2]	Yes[3]	No[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. AHTN has been reported to have very weak estrogenic and anti-estrogenic potency *in vitro* and an antagonist effect on estradiol in zebrafish. AHTN also had marginal repressing *in vitro* effects on androgen and progesterone receptors. However, no estrogenic effects were seen in an *in vivo* mouse uterotrophic assay; therefore, AHTN is not currently considered to be a mammalian endocrine disruptor *in vivo*. However, the mouse uterotrophic assay may not have been sufficient to detect subtle estrogenic effects because the mice were not fully immature at the end of the 2-week exposure period. Possible dose-related effects on uterine distension and pro-estrous cyclicity were reported in rats exposed to AHTN in the diet for 13 weeks; however, these effects are not well-characterized and the RfDs for liver effects are considered protective of potential endocrine effects because uterine and pro-estrous effects were noted at doses approximately 15, 100 and 300-fold higher than the short-term, subchronic, and chronic RfDs, respectively.

2. AHTN has not been tested directly for systemic immunotoxicity. AHTN was non-sensitizing via dermal contact in animals or humans. AHTN is considered to be a potential photosensitizer after irradiation with u.v. light. No secondary effects on immune system organs were observed in a 13-week dietary study.

3. AHTN is not generally considered a developmental toxicant even when tested at doses that were maternally toxic. However, at high doses in a range-finder study (over 300 times greater than the short-term RfD and about 6,000 times greater than the chronic RfD), some fetuses had

whole-body edema, although statistical significance was not presented. Therefore, the short-term, subchronic and chronic values are protective of potential developmental effects.

4. No effects on reproductive organs were found in a 13-week oral study examining male and female reproductive and accessory organs. AHTN was not a reproductive toxicant in a peri/postnatal study that evaluated neurobehavioral effects; however, dosing was limited to the period during pregnancy after organogenesis (missing the most sensitive exposure period for most developmental effects) through lactation and the study was not a standard multi-generational reproductive study where exposures would continue for a prolonged period of time before pregnancy and post-lactation.

5. Neurotoxicity was evaluated by the dermal route of exposure. AHTN was determined to be non-neurotoxic in dermal subchronic studies. In an animal study with oral exposure during pregnancy (after organogenesis) through lactation, the offspring did not exhibit neuro-behavioral effects. The study exposure period, however, was limited and did not cover a broader period before mating and during the lifetime of the offspring that is typical of standard multigenerational reproductive studies. AHTN given by gavage during gestation caused maternal nervous system toxicity in rats as exhibited by decreased motor activity and excessive salivation at a dose approximately 300 times greater than the short-term RfD and about 6,000 times greater than the chronic RfD.

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EPA Office of Drinking Water
http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf

EPA Office of Pesticide Programs http://www.epa.gov/pesticides/reregistration/status.htm

EPA Toxicity and Exposure Assessment for Children's Health (TEACH)
http://www.epa.gov/teach/

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http://www.epa.gov/oppt/vccep/pubs/chemmain.html

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2011 Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
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Chemical Name: Carbamazepine (5H-Dibenz(b,f)azepine-5-carboxamide)

CAS: 298-46-4

Synonyms: Tegretol®; Equetro®; Carbatrol®, Mazepine, CBZ

Acute Non-Cancer Health-Based Value ($nHBV_{acute}$) = 40 ug/L

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

$$= \frac{\text{(0.013 mg/kg/d) x (0.8*) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 36 rounded to **40**

* MDH utilizes the U.S. EPA Exposure Decision Tree (U.S. EPA 2000) to select appropriate RSCs, ranging from 0.2 to 0.8. An RSC greater than 0.8 may be warranted for those who have no other route of exposure besides drinking water because of the unlikelihood of exposure from any other sources. However, without additional information a specific value cannot be determined at this time. Therefore, the recommended upper limit default of 0.8 was utilized. For those who take carbamazepine according to prescription, the additional drinking water exposure will be negligible.

Reference Dose / Concentration:	0.013 mg/kg-d (human)
Source of toxicity value:	MDH, 2011
Point of Departure:	3.8 mg/kg-d [LOAEL based on the human minimum therapeutic dose for children at 200 mg/day (100 mg - 2x/day)(Novartis 2011), equivalent to 3.8 mg/kg bw-d based on an average 53 kg 12-yr old child (McDowell and National Center for Health Statistics (U.S.) 2008)].
Human Equivalent Dose Adjustment:	Not applicable
Total uncertainty factor:	300

UF allocation:	10 intraspecies variability, 3 database insufficiencies (neurobehavioral developmental endpoints have not been adequately evaluated in available studies), 10 for use of a LOAEL instead of a NOAEL.
Critical effect(s):	Nervous system effects reported in various human studies (drowsiness, vision disturbances, and equilibrium disturbances).
Co-critical effect(s):	Reduced body weight gain in offspring in laboratory animals during lactation. Developmental effects in humans including spinal bifida, head and facial deformities and heart defects;
Additivity endpoint(s):	Developmental, Nervous system

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

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

$$= \frac{\text{(0.013 mg/kg/d) x (0.8*) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 36, rounded to **40 ug/L**

*Refer to RSC explanation provided for the acute non-cancer health-based value.

Reference Dose / Concentration:	0.013 mg/kg-d (human)
Source of toxicity value:	MDH, 2011
Point of Departure:	3.8 mg/kg-d [LOAEL based on human minimum therapeutic dose for children at 200 mg/day (100 mg - 2x/day)(Novartis 2011), equivalent to 3.8 mg/kg bw-d based on an average 53 kg 12-yr old child (McDowell and National Center for Health Statistics (U.S.) 2008)]
.Human Equivalent Dose Adjustment:	Not applicable
Total uncertainty factor:	300
UF allocation:	10 intraspecies variability, 3 database insufficiencies (neurobehavioral developmental and immunotoxicity endpoints have not been adequately evaluated in

	available studies), 10 for use of a LOAEL instead of a NOAEL.
Critical effect(s):	Critical effects reported in various human studies include hematological effects (porphyria, aplastic anemia); liver effects (liver enzyme induction, increased serum liver enzymes, jaundice, hepatitis); immune reactions (hypersensitivity); nervous system effects (central nervous system depression, double-vision, blurred vision, disturbance of equilibrium, paresthesae, and suicide ideation); reproductive endocrine effects (male/female sex hormone disturbances) and thyroid hormone disturbances.
Co-critical effect(s):	Reduced body weight gain in offspring during lactation reported in laboratory animals; and developmental effects in humans (spinal bifida, head and facial deformities and heart defects).
Additivity endpoint(s):	Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Male reproductive system (E), Female reproductive system (E), Thyroid (E).

Subchronic Non-Cancer Health-Based Value ($nHBV_{subchronic}$) = Short-term nHBV = 40 ug/L

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

$$= \frac{\text{(0.013 mg/kg/d) x (0.8*) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

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

* Refer to RSC explanation provided for the acute non-cancer health-based value.

Reference Dose / Concentration:	0.013 mg/kg-d (human)
Source of toxicity value:	MDH, 2011
Point of Departure:	3.8 mg/kg-d [LOAEL based on human minimum therapeutic dose for children at 200 mg/day (100 mg - 2x/day)(Novartis 2011),

	equivalent to 3.8 mg/kg bw-d based on an average 53 kg 12-yr old child (McDowell and National Center for Health Statistics (U.S.) 2008)].
Human Equivalent Dose Adjustment:	Not applicable
Total uncertainty factor:	300
UF allocation:	10 intraspecies variability, 3 database insufficiencies (neurobehavioral developmental and immunotoxicity endpoints have not been adequately evaluated in available studies), 10 for use of a LOAEL instead of a NOAEL.
Critical effect(s):	Critical effects reported in various human studies include hematological effects (porphyria, decreased white blood cell counts, eosinophilia, thrombocytopenia, aplastic anemia); liver effects (liver enzyme induction, increased serum liver enzymes, jaundice, hepatitis); immune reactions (hypersensitivity); nervous system effects (suicide ideation); kidney effects (antidiuresis or hyponatremia, elevated BUN); reproductive endocrine effects (male/female sex hormone disturbances); skeletal effects (elevated serum markers for bone resorption, decreased bone density in children, decreased vitamin D levels); and thyroid hormone disturbances.
Co-critical effect(s):	Reduced body weight gain in offspring during lactation observed in laboratory animals. Developmental effects in humans including spinal bifida, head and facial deformities and heart defects.
Additivity endpoint(s):	Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Renal (kidney) system, Male reproductive system (E), Female reproductive system (E), Skeletal system, Thyroid (E).

The Subchronic nHBV must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 40 ug/L. Additivity endpoints: Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Male reproductive system (E), Female reproductive system (E),Thyroid (E).

Chronic Non-Cancer Health-Based Value ($nHBV_{chronic}$) = Short-term nHBV = 40 ug/L

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

$$= \frac{\text{(0.0057 mg/kg/d) x (0.8*) x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

= 106, rounded to 100 ug/L

* Refer to RSC explanation provided for the acute non-cancer health-based value.

Reference Dose / Concentration:	0.0057 (human)
Source of toxicity value:	MDH, 2011
Point of Departure:	5.7 mg/kg-d [LOAEL based on human minimum therapeutic dose for adults at 400 mg/day (200 mg - 2x/day)(Novartis 2011), equivalent to 5.7 mg/kg bw-d based on an average 70 kg adult].
Human Equivalent Dose Adjustment:	Not applicable
Total uncertainty factor:	1,000
UF allocation:	10 for intraspecies extrapolation; 3 for database insufficiencies (neurobehavioral developmental, immunotoxicity, and endocrine endpoints have not been adequately evaluated in available studies), and 10 for use of a LOAEL, 3 for subchronic to chronic duration (because most of the human studies were conducted based on subchronic human exposure durations and a chronic animal study found progression of liver, kidney, spleen and testes effects from the 1-yr interim sacrifice period to the end of the 2-yr study.
Critical effect(s):	In various human studies, effects include hematological effects (porphyria, decreased white blood cell counts, eosinophilia, thrombocytopenia, aplastic anemia); liver effects (liver enzyme induction, increased serum liver enzymes, jaundice, hepatitis);

	kidney effects (antidiuresis or hyponatremia, elevated BUN); reproductive endocrine effects (male/female sex hormone disturbances); skeletal effects (decreased blood calcium and altered vitamin D leading to effects on bone density, and increased risk of bone fractures); and thyroid hormone disturbances.
Co-critical effect(s):	Developmental effects in humans including spinal bifida, head and facial deformities and heart defects. In animal studies, co-critical effects including development effects such as reduced body weight gain in offspring during lactation, increased number of unossified phalangeal nuclei of forelimbs in fetuses, considered indicative of slight fetal growth retardation and enlarged cerebral ventricles and cleft palate. Liver effects in animals including liver tumors, hepatic macules, hepatocytic vacuolar degeneration and hyperplasia and centrilobular liver hypertrophy. Kidney histopathologic lesions in animals including crater/granular/rough, cysts and ischemic lesions. In animal studies: Benign interstitial cell adenomas in testes, dose-related incidence of testicular atrophy and decreases sperm production.
Additivity endpoint(s):	Developmental system, Hematological (blood) system, Hepatic (liver) system, Renal (kidney) system, Male reproductive system (E), Female reproductive system (E), Skeletal (bone) system, Thyroid (E).

The Chronic nHBV must be protective of the acute, short-term and subchronic exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 40 ug/L. Additivity endpoints: Developmental, Hematological (blood) system, Hepatic (liver) system, Immune system, Nervous system, Male reproductive system (E), Female reproductive system (E),Thyroid (E).

Cancer Health-Based Value (cHBV) = Not Applicable

Carbamazepine has limited evidence for carcinogenicity based on a single rodent bioassay. The approved FDA drug labels contain mandatory cancer statements. MDH staff evaluated the available information and concluded that the noncancer nHBVs are adequately protective of potential carcinogenicity. MDH staff considered: 1) the limited amount of information available to be insufficient for quantitative dose-response assessment; 2) carbamazepine is generally considered to be non-genotoxic; 3) the absence of human epidemiology studies supporting carcinogenicity potential; and 4) the chronic RfD is 1100-fold lower than the lowest dose evaluated in the single rodent bioassay.

Cancer classification:	Not classified by U.S. EPA or IARC. Classified by FDA as carcinogenic in rats with unknown significance to humans.
Slope factor:	Not available
Source of slope factor:	Not applicable
Tumor site(s):	Hepatocellular tumors in females; Benign interstitial adenomas in testes in males.

Volatile: No

Summary of Guidance Value History:
No previous guidance values have been derived for carbamazepine. The above HBVs 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	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, including decreased thyroid hormones, in the absence of clinical hypothyroidism, have occurred in multiple human studies and in only a few animal studies. Thyroid effects in animal studies were noted at human equivalent doses over 10 times higher than the human LOAEL. Reduced serum sex hormone binding globulin (SHBG) which results in decreased serum free estrogen and testosterone has occurred in men and women receiving carbamazepine therapy for epilepsy. Sex hormone studies in mammalian animal studies were not available, but reported effects on testes and spermatogenesis in animals occurred at human equivalent doses from 7.3 to 23 mg/kg-d (within the human therapeutic maintenance dose

range) and decreased fertility was reported in animals at human equivalent doses of over 8 times higher than the human LOAEL and above the "not to exceed" dose level of approximately 17 mg/kg-d for human adults. The human equivalent doses for thyroid effects in animals are over 3,000 times higher than the RfD and the human equivalent dose for reproductive effects are over 400 times higher than the RfD. Carbamazepine may also affect the pituitary gland because adverse effects in humans include edema and hyponatremia which is believed to be related to a syndrome of inappropriate antidiuretic hormone secretion. MDH based the RfD, in part, on endocrine effects observed in humans at therapeutic dose levels.

2. Human immunotoxicity effects have been reported at therapeutic doses. Serious hypersensitivity reactions, including life-threatening Stevens-Johnson syndrome and toxic epidermal necrosis (SJS/TEN) have occurred in sensitive individuals and there has been some association with development of drug-induced autoimmune disorders. Populations sensitive to SJS/TEN include those who are genetically susceptible due to the presence of an inherited HLA-B*1502 gene allele. The SJS/TEN effects generally occur within the first several weeks after starting treatment. Sensitive populations with genetic sensitivity include many Asians. Caucasian, African-Americans, Native Americans and Hispanics largely do not have this allele.

Some clinical studies have shown immunosuppression including inhibition of lymphocytic protein synthesis, decreased CD4+/CD8+ ratio, decreased IgA, and induced changes in IgG and IgM plasma levels with unknown clinical significance (Basta-Kaim, Budziszewska et al. 2008). A single 7-day mouse study with some reporting and study design deficiencies found some indicators of potential immunosuppression related to CBZ at 5, 10, or 15 mg/kg-d [HED 0.65, 1.3 and 2.0]. Although these effects are at human equivalent doses that are 2-8 times lower than the human LOAEL, the study limitations and lack of replication to-date prevent using this data quantitatively. However, a database uncertainty factor of 3 is used to account, in part, for limitations in availability of adequate immunotoxicity data and an uncertainty factor of 10 is used to account of sensitive populations. The RfD based on the human LOAEL is 36 times lower than the lowest dose causing slight immunosuppression effects in mice and is considered to be protective for immunotoxicity.

3. Human developmental effects have been reported at therapeutic doses in many prospective studies of epileptic women who have taken carbamazepine while pregnant. Most developmental effects in animal studies have occurred at doses near or above 200 mg/kg-d, with a human equivalent dose > 44 mg/kg-d which is over 8 times higher than the human LOAEL and over 2,000 times higher than the RfD. A smaller number of animal studies reported slight effects on skeletal and brain development and slight fetal and pup growth retardation of uncertain biological or statistical significance at human equivalent doses at or near the human LOAEL (HED ranging from 4.4 to 9.75 mg/kg-d) but are over 200 times higher than the RfD. Study limitations prevented use of the animal studies for quantitative evaluation. MDH based the RfD, in part, on developmental effects observed in humans at therapeutic dose levels.

[4.] Carbamazepine has produced decreased fertility in animal studies at human equivalent doses of 52 mg/kg-day or more (over 10 times higher than the human LOAEL and over 2500 times higher than the RfD). Effects on testes and spermatogenesis in animals occurred at human equivalent doses from 7.3 to 23 mg/kg-d (within the human therapeutic maintenance dose range) and decreased fertility was reported in animals at human equivalent doses of over 8 times higher than the human LOAEL and above the "not to exceed" dose level of approximately 17 mg/kg-d for human adults. MDH based the RfD, in part, on reproductive effects observed in humans at therapeutic dose levels.

[5.] The neurotoxicity dataset is limited by the absence of a multigenerational rodent study to evaluate neurobehavioral developmental toxicity and/or pending completion of ongoing human clinical trials to measure various neurobehavioral developmental parameters in children who were exposed during gestation. A small number of animal studies reported slight effects on brain development at HEDs at or near the human LOAEL. Temporary, reversible neurotoxicity occurs in human during the first few weeks of therapeutic doses. Neurotoxicity can occur in 5-14% of patients and persons with prior brain injury and elderly may be more sensitive. Typical neurotoxicity symptoms include diplopia, drowsiness, blurred vision, disturbed equilibrium and paresthesae. Long-term or irreversible neurotoxic effects are not known to occur with carbamazepine therapy. Neurotoxicity reactions can be reduced or prevented by gradually building up the therapeutic dose from initial, smaller starting doses.

The FDA-approved drug labeling indicates a risk for suicidal behavior and ideation for persons taking antiepileptic drugs, in general. Pooled analyses of 199 clinical trials of 11 different antiepileptic drugs with a median treatment period of 12 weeks showed an estimated incidence of 0.43% compared to 0.24% among controls. The increase was observed as early as one week after starting treatment and the trials did not go longer than 24 weeks, so the risk beyond 24 weeks is uncertain (Novartis Pharmaceuticals Corporation 2011).

One limited mouse study of neurobehavioral effects of carbamazepine in adult offspring whose mothers were exposed during gestation reported effects on locomotor activity and startle response at a human equivalent dose of approximately 14 times higher than the human LOAEL and over 4,000 times higher than the RfD. Enlarged cerebral ventricles were reported in fetuses of mice exposed at a human equivalent dose of 5.2 mg/kg-day, similar to the human LOAEL, but this effect is of questionable biological and statistical significance and the study design is limited.

Carbamazepine may also be a neurodevelopmental toxicant in humans, causing effects in children (aged 9 mo to 5 yrs) exposed to carbamazepine *in utero* as measured by the Bayley Scales of Infant Development or the Griffiths Mental Development Scales (OR 7.7, 95% CI 1.4 to 43.1; $p<0.01$) (Cummings, Stewart et al. 2011). Newborn infants exposed *in utero* had no alterations in brainstem auditory evoked potentials. However, significant effects on latencies of brainwaves III and V and brainwaves I-V interwave intervals were correlated with third trimester exposure (Poblano, Belmont et al. 2002). Neurodevelopmental outcomes in 6-yr old

children exposed *in utero* to carbamazepine are currently being studied a large multicenter study in the US and UK and the mean IQ in an interim study of 3-yr olds was not impacted (Meador, Baker et al. 2009). MDH based the RfD, in part, on neurotoxicity effects observed in humans at therapeutic dose levels.

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2012 Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Web Publication Date: June 2012
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Chemical Name: Carbon Tetrachloride

CAS: 56-23-5

Synonyms: Tetrachloromethane, Carbona, Carbon chloride, Carbon tet, Methane tetrachloride, Perchloromethane, benzinoform, 1,1,1,1-Tetrachloromethane, Benzinoform, Freon 10, Halon 104, Tetraform, Tetrasol

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

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Acute intake rate, L/kg/d)

= (0.18 mg/kg/d) x (0.2) x (1000 ug/mg)
(0.289 L/kg-d)

= 124 rounded to **100 ug/L**

Reference Dose / Concentration:	0.18 mg/kg-d (F344N rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	25 mg/kg-d (NOAEL), Developmental study (Narotsky, et al., 1997b)
Human Equivalent Dose Adjustment:	5.3 mg/kg-d [25 x 0.21] (MDH, 2011)
Total uncertainty factor:	30
UF allocation:	3 for intraspecies variability (toxicodynamics); 10 for interspecies variability
Critical effect(s):	Increased litter resorptions
Co-critical effect(s):	Regenerative hepatocyte proliferation
Additivity endpoint(s):	Developmental system; Hepatic (liver) system

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

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Short-term intake rate, L/kg/d)

$$= \frac{(0.0037 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.289 \text{ L/kg-d})}$$

= 2.6 rounded to **3 ug/L**

Reference Dose / Concentration:	0.0037 mg/kg-d (F344N rats)
Source of toxicity value:	MDH 2012
Point of Departure:	5 mg/kg-d (minimal LOAEL), 10-day immunotoxicity gavage study (Smialowicz et al, 1991)
Human Equivalent Dose Adjustment:	1.1 mg/kg-d [5 x 0.21] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 for intraspecies variability (toxicodynamics); 10 for interspecies variability; 3 for database uncertainty – no multi-generation study to adequately assess reproductive effects; 3 for minimal LOAEL to NOAEL extrapolation
Critical effect(s):	Minimal vacuolar degeneration in the liver
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Subchronic Non-Cancer Health Based Value ($nHBV_{subchronic}$) = $nHBV_{short\text{-}term}$ = 3 ug/L

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

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

= 25 rounded to 30 ug/L

Reference Dose / Concentration:	0.0098 mg/kg-d (SD rats)
Source of toxicity value:	MDH 2012
Point of Departure:	3.9 mg/kg-d ($BMDL_{adj}$); 12-week gavage study (Bruckner, et al., 1986)
Human Equivalent Dose Adjustment:	0.98 mg/kg-d [3.9 x 0.25] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for intraspecies variability (toxicodynamics); 10 for interspecies variability; 3 for database uncertainty – no multi-generation study to adequately assess reproductive effects
Critical effect(s):	Increased serum liver enzyme levels, liver lesions

Co-critical effect(s):	Increased liver enzyme levels, liver lesions, increased liver weight, alterations of liver histopathology, increased bilirubin, decreased serum glucose, increased spleen and thymus weights
Additivity endpoint(s):	Hepatic (liver) system, Immune system

The Subchronic nHBV must be protective of the short-term exposures that occur within the short-term period and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 3 ug/L. Additivity Endpoints: Hepatic (liver) system.

Chronic Non-Cancer Health Based Value ($nHBV_{chronic}$) = $nHBV_{short\text{-}term}$ = 3ug/L

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

$$= \frac{\text{(0.0033 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

= 15.3 rounded to 20 ug/L

Reference Dose / Concentration:	0.0033 mg/kg-d (laboratory animal)
Source of toxicity value:	MDH 2012 (same as U.S. EPA 2010)
Point of Departure:	3.9 mg/kg-d ($BMDL_{adj}$); 12-week gavage study (Bruckner, et al., 1986)
Human Equivalent Dose Adjustment:	0.98 mg/kg-d [3.9 x 0.25] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 for intraspecies variability (toxicodynamics); 10 for interspecies variability; 3 for database uncertainty – no multi-generation study to adequately assess reproductive effects; 3 for extrapolation from subchronic to chronic duration
Critical effect(s):	Increased serum liver enzyme levels, liver lesions
Co-critical effect(s):	Increased liver enzyme levels, liver lesions, increased liver weight, alterations of liver histopathology, increased bilirubin, decreased serum glucose, increased spleen and thymus weights
Additivity endpoint(s):	Hepatic (liver) system, Immune system

The chronic nHBV must be protective of the short-term exposures that occur within the short-term period and therefore, the chronic nHBV is set equal to the short-term nHBV of 3 ug/L. Additivity Endpoints: Hepatic (liver) system.

Cancer Health Based Value (HBV) = 1 ug/L

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

$$= \frac{\text{(1E-5) x (1000 ug/mg)}}{[(0.07 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.07 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.07 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 1.46 rounded to **1 ug/L**

Cancer classification:	"Likely to be carcinogenic to humans" (U.S. EPA IRIS 2010)
Slope factor:	0.07 (laboratory animal; 2-year cancer inhalation study (Nagano et al 2007b as cited by U.S. EPA ISIS 2010)
Source of slope factor:	(U.S. EPA IRIS 2010)
Tumor site(s):	Liver, Adrenal Glands

Volatile: Yes (high)

Summary of changes since 1993/1994 HRL promulgation:
A cancer HRL of 3 ug/L was promulgated in 1993. In 2010, a revised cancer HBV of 1 ug/L was derived. This value is 3 times lower than the 1993 cancer HRL (3 ug/L) as the result of: 1) utilizing more recent intake rates which incorporate higher intake rates during early life; 2) application of age-dependent early-life cancer sensitivity adjustment factors; 3) the use of a new slope factor derived by U.S. EPA IRIS 2010; and 4) rounding to one significant digit. In 2010, Acute, Short-term, Subchronic and Chronic HBVs of 200, 3, 3, and 3 ug/L were derived. MDH reevaluated the non-cancer HBVs in 2012 to incorporate HED methodology. The resulting Acute HBV (100 ug/L) is 2-fold lower than the 2010 value. The Short-term, Subchronic and Chronic (non-cancer) HBVs (3 ug/L) are unchanged.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	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] In a developmental study in rats, the researchers suggested that the all-or-none nature of the observed full-litter resorptions point to a maternally mediated response and produced evidence that the response is associated with reduced levels of progesterone and luteinizing hormone (LH) in the dams during dosing with carbon tetrachloride. (Narotsky et al., 1997a, 1995 cited in U.S. EPA 2010).

Greim et al. (2009) hypothesized modes of action (MOA) for the induction of mouse pheochromocytomas that included endocrine disturbance, impairment of mitochondrial function, uncoupling of oxidative phosphorylation, hepatoxicity, and nephrotoxicity leading to impaired calcium homeostasis, but provided no support for any of these hypothesized MOAs.(cited in U.S. EPA 2010)

[2]Results of available studies indicate that carbon tetrachloride produces adverse effects on T-cell-dependent immunity at administered doses (beginning at 50 mg/kg-day) that are hepatotoxic. However, it is important to note that immunological effects were, at least in part, secondary to hepatotoxicity and the process of hepatic repair.

[3,4]The critical study selected for the acute HBV is a developmental study that reported increased litter resorptions beginning at a Human Equivalent Dose of 10.5 mg/kg-day. No adequate oral reproductive toxicity studies were conducted for carbon tetrachloride. Developmental effects (decreased fetal body weight and delayed ossification) and reproductive effects (testicular atrophy, testicular degeneration, and reduced fertility) were reported in inhalation studies at doses higher than those that produced liver and kidney toxicity.

[5]No oral animal toxicity studies reported neurotoxicity following exposure to carbon tetrachloride. Human reports of exposure to high doses of carbon tetrachloride by inhalation or ingestion mentioned headaches, drowsiness, comas, or seizures. In acute inhalation studies, animals exposed to high doses (4600-1200 ppm) of carbon tetrachloride experienced stupor, incoordination, and unconsciousness.

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2012 Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Web Publication Date: June 2012
Expiration Date: June 2017

Chemical Name: 1,2-Dichloroethane

CAS: 107-06-2

Synonyms: ethylene dichloride, 1,2-DCA

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

Due to limited information, no acute guidance value is derived. Based on the available information, the short-term HBV for 1,2-DCA is also protective of developmental effects.

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

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Short-term intake rate, L/kg/d)

= (0.23 mg/kg/d) x (0.2) x (1000 ug/mg)
(0.289 L/kg-d)

= 159 rounded to **200 ug/L**

Reference Dose / Concentration:	0.23 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	30 mg/kg-d (NOAEL based on Daniel et al., 1994)
Human Equivalent Dose Adjustment:	6.9 mg/kg-d [30 x 0.23] (MDH, 2011)
Total uncertainty factor:	30
UF allocation:	3 for interspecies extrapolation (toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased liver weight accompanied by increased serum cholesterol levels.
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Subchronic Non-Cancer Health Based Value ($nHBV_{subchronic}$) = $HBV_{short-term}$ = 200 ug/L

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

$$= \frac{\text{(0.12 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 311 rounded to 300 ug/L

Reference Dose / Concentration:	0.12 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	58 mg/kg-d (LOAEL based on NTP, 1991)
Human Equivalent Dose Adjustment:	12.2 mg/kg-d date58 x 0.21] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (toxicodynamics), 10 for intraspecies variability, 3 for use of a minimal LOAEL-to-NOAEL
Critical effect(s):	Increased kidney weights (supported as adverse by tubular regeneration lesions seen at higher doses in the same study)
Co-critical effect(s):	Increased liver weight with changes in liver enzymes at next dose level, decreased body weight
Additivity endpoint(s):	Renal (kidney) system, hepatic (liver) system

The subchronic HBV must be protective of the short-term exposures that occur within the subchronic period and therefore, the subchronic HBV is set equal to the Short-term HBV of 200 ug/L. Health Endpoint(s): Hepatic (liver) system.

Chronic Non-Cancer Health Based Value ($nHBV_{chronic}$) = 60 ug/L

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

$$= \frac{\text{(0.012 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

= 56 rounded to **60 ug/L**

Reference Dose / Concentration:	0.012 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	58 mg/kg-d (LOAEL based on NTP, 1991)
Human Equivalent Dose Adjustment:	12.2 mg/kg-d [58 x 0.21] (MDH, 2011)
Total uncertainty factor:	1000
UF allocation:	3 for interspecies extrapolation (toxicodynamics), 10 for intraspecies variability, 3 for use of a minimal LOAEL-to-NOAEL, 10 applied for using a less than chronic study (evidence that a longer duration may cause more severe adverse effects)
Critical effect(s):	Increase kidney weights (supported as adverse by tubular regeneration lesions seen at higher doses in the same study)
Co-critical effect(s):	Increased liver weight with changes in liver enzymes at next highest dose level, decreased body weight
Additivity endpoint(s):	Renal (kidney) system, hepatic (liver) system

Cancer Health Based Value (cHBV) = 1 ug/L

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

$$= \frac{\text{(1E-5) x (1000 ug/mg)}}{[(9.1E\text{-}2\ (mg/kg\text{-}d)^{-1})(10)(0.137\ L/kg\text{-}d)(2) + (9.1E\text{-}2\ (mg/kg\text{-}d)^{-1})(3)(0.047\ L/kg\text{-}d)(14) + (9.1E\text{-}2\ (mg/kg\text{-}d)^{-1})(1)(0.039\ L/kg\text{-}d)(54)]/70}$$

= 1.13 rounded to **1 ug/L**

Cancer classification:	B2 probable human carcinogen
Slope factor:	9.1E-2 (laboratory animal) (NCI, 1978)
Source of slope factor:	IRIS, 1991
Tumor site(s):	Hemangiosarcoma – basis of slope factor calculation (additional tumor types also observed include squamous-cell carcinomas, mammary adenocarcinoma alveolar/bronchiolar adenomas, endometrial stromal polyps and sarcomas, and hepatocellular carcinomas

Volatile: Yes, Highly

Summary of Guidance Value History:
A cancer HRL of 4 ug/L was promulgated 1993. In 2011, MDH derived a cancer HBV (1 ug/L) that is 4-fold lower than the 1993 HRL as the result of: 1) application of the early-life age-dependent default potency adjustment factors; 2) utilizing higher intake rates; and 3) rounding to one significant figure. In 2011, Short-term, Subchronic and Chronic HBVs of 200, 200, and 90 ug/L were derived. MDH reevaluated the non-cancer HBVs in 2012 to incorporate HED methodology. The resulting Short-term and Subchronic HBVs (200 ug/L) are unchanged. The updated Chronic HBV (60 ug/L) is 1.5-fold lower than the 2011 value.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	Yes	Yes	Yes	Secondary Observation
Effects?	No	Yes[1]	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] Conflicting data exists for 1,2-DCA regarding immunologic effects. In a 14-day gavage study in mice by Munson et al., a dose related reduction in IgM, and a significant but not dose related reduction in cell-mediated immunity were reported. In the high dose group (49 mg/kg-d administered dose, 6.9 mg/kg-d Human Equivalent Dose), a 30% decrease in total leukocyte number was observed. However, in a 90-day drinking water study in mice by the same authors, no immune related effects were reported. The authors commented that the conflicting data may be the result of differences in dosing protocol (gavage vs. drinking water) and duration of exposure. Similar effects were not reported in the 1991 NTP 90-day drinking water and gavage study in rats that included interim measurement of some immunological parameters (e.g., leukocyte numbers) on days 3, 7, 14, and 45.

[2] 2 Developmental toxicity studies in animals have not shown 1,2-dichloroethane to be fetotoxic or teratogenic following oral exposure, although indications of embryo-lethality at maternally toxic doses have been reported by Payan et al., 1995 and are the basis of the acute HBV value described above.

[3] Studies in animals suggest that reproductive effects of 1,2-dichloroethane may be induced at oral doses that are maternally toxic. In a study using higher doses of 1,2-dichloroethane, rats

that were treated with an administered dose 198 mg/kg-d (45.5 mg/kg-d Human Equivalent Dose) for 14 days during gestation showed 30% reduced body weight gain and dose-related increased percentages of non-surviving implants per litter (resorptions plus dead fetuses) and resorption sites per litter (Payan et al. 1995).

[4] In a 13 week gavage study in rats (NTP, 1991), clinical signs included tremors, salivation, ruffed fur, and dyspnea at administered doses 240 mg/kg-d (55.2 mg/kg-d Human Equivalent Dose) and higher. Mild necrotic lesions of the cerebellum were also observed at these doses which are several times higher than the critical Human Equivalent Dose (12.2 mg/kg-d) selected for the subchronic and chronic HBVs. Acute inhalation studies have shown that high concentration of 1,2-DCA can cause central nervous system depression that included tremors, uncertain gait, and narcosis were seen in rats, guinea pigs, and rabbits.

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2012 Health Based Guidance Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Web Publication Date: June 2012
Expiration Date: June 2017

Chemical Name: trans-1,2-Dichloroethene

CAS#: 156-60-5

Synonyms: trans-1,2-Dichloroethylene

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

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

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

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Subchronic intake rate, L/kg/d)

= (0.091 mg/kg/d) x (0.2) x (1000 ug/mg)
(0.077 L/kg-d)

= 236 rounded to **200 ug/L**

Reference Dose / Concentration:	0.091 mg/kg-d (mice)
Source of toxicity value:	MDH 2012
Point of Departure:	65 mg/kg-d (BMDL based on U.S. EPA modeling of immunotoxicity data from Shopp et al. (1985))
Human Equivalent Dose Adjustment:	9.1 mg/kg-d [65 mg/kg-d x 0.14] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics), 10 for intraspecies variability, 3 for database insufficiency (e.g., for lack of multigenerational study, data from inhalation studies did supplement dataset)
Critical effect(s):	Decreased ability to produce antibodies against sheep RBCs in male spleen cells
Co-critical effect(s):	Decreased thymus weight, clinical chemistry

	effects
Additivity endpoint(s):	Immune system

Chronic Non-Cancer Health based Value ($nHBV_{chronic}$) = 40 ug/L

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

$$= \frac{\text{(0.0091mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

= 42 rounded to **40 ug/L**

Reference Dose / Concentration:	0.0091 mg/kg-d (mice)
Source of toxicity value:	MDH 2012
Point of Departure:	65 mg/kg-d (BMDL based on U.S. EPA modeling of immunotoxicity data from Shopp et al. (1985))
Human Equivalent Dose Adjustment:	9.1 mg/kg-d [65 mg/kg-d x 0.14] (MDH, 2011)
Total uncertainty factor:	1000
UF allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics), 10 for intraspecies variability, 10 for subchronic to chronic extrapolation, 3 for database insufficiency (for lack of multigenerational study, data from inhalation studies did supplement dataset)
Critical effect(s):	Decreased ability to produce antibodies against sheep RBCs in male spleen cells
Co-critical effect(s):	Decreased thymus weight, clinical chemistry effects
Additivity endpoint(s):	Immune system

Cancer Health Based Value (cHBV) = Not applicable

Cancer classification:	"*Inadequate information to assess the carcinogenic potential*" of trans-1,2-DCE.
Slope factor:	None
Source of slope factor:	EPA IRIS 2010
Tumor site(s):	None

Volatile: Yes (high)

Summary of changes since 1993/1994 HRL promulgation:
A Chronic HRL of 100 ug/L was promulgated in 1993. In 2011, Subchronic and Chronic HBVs of 600 and 100 ug/L were derived. The Subchronic HBV value represented a new guidance value and the Chronic value did not change. MDH reevaluated the HBVs in 2012 to incorporate HED methodology. The resulting Subchronic and Chronic HBVs (200 and 40 ug/L) are lower (3-fold and 2.5-fold) than the values derived in 2011.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	Yes	Yes	No	No
Effects?	No	Yes[1]	Yes[2]	No[3]	Secondary observations[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] Shopp et al. (1985) measured depression in humoral immune status following 90 days of exposure via drinking water. These effects form the basis of the subchronic and chronic HBVs.
[2]A single inhalation developmental study exists. Decreased fetal body weight was observed at doses estimated to be over 400-fold higher than the minimal short-term critical Human Equivalent Dose. A database uncertainty factor has been applied, in part, due to the lack of oral developmental/reproductive studies.
[3]Examination of the reproductive organs of animals in the 90-day study did not report any histological changes. A database uncertainty factor has been applied, in part, due to the absence of a multigenerational study.
[4]Neurological effects have not been adequately studied. Acute exposures (e.g., single, high dose) have reported effects.

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2012 Health Based Guidance Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Web Publication Date: June 2012
Expiration Date: June 2017

Chemical Name: N, N-Diethyl-3-methylbenzamide (DEET)
CAS: 134-62-3

Synonyms: N,N-Diethyl-m-toluamide; Diethyltoluamide
Trade Names: DEET; OFF; Cutter; Repel

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

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

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

$$= \frac{\text{(0.23 mg/kg/d) x (0.2*) x (1000 ug/mg)}}{\text{(0.289L/kg-d)}}$$

= 159 rounded to **200 μg/L**

* MDH utilizes the U.S. EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the potential exposure to DEET through sources other than water (e.g., use of products containing DEET) an RSC of < 0.2 may be warranted. However, without additional information a specific value cannot be determined. Therefore, the lower limit default of 0.2 recommended in the U.S. EPA Exposure Decision Tree (EPA 2000) was utilized.

Reference Dose / Concentration:	0.23 mg/kg-d (rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	100 mg/kg-d (NOAEL, 2 generation study, MRID 41368401 as cited in EPA 1989 & EPA 1998a. LOAEL = 250 mg/kg-d)
Human Equivalent Dose Adjustment:	23 mg/kg-d (100 mg/kg-d x 0.23) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 database insufficiencies (additional characterization of neurotoxicity and immunotoxicity is warranted)
Critical effect(s):	Decreased pup body weight

Co-critical effect(s):	Changes in activity level, increased response time
Additivity endpoint(s):	Developmental, Nervous system

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

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

$$= \frac{\text{(0.12 mg/kg/d) x (0.2*) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 312 rounded to 300 μg/L

* MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential exposure to DEET through sources other than water (e.g., use of products containing DEET) an RSC of < 0.2 may be warranted. However, without additional information a specific value cannot be determined. Therefore, the lower limit default of 0.2 recommended in the EPA Exposure Decision Tree (EPA 2000) was utilized.

Reference Dose / Concentration:	0.12 mg/kg-d (hamsters)
Source of toxicity value:	MDH, 2012
Point of Departure:	61 mg/kg-d (NOAEL, 90-day study in hamsters (MRID 41344101 1989 as cited by U.S. EPA 1998a and 1990a).
Human Equivalent Dose Adjustment:	11.6 mg/kg-d (61 mg/kg-d x 0.19) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 database insufficiencies (additional characterization of neurotoxicity and immunotoxicity is warranted)
Critical effect(s):	Decreased body weight and food consumption
Co-critical effect(s):	Decreased pup body weight, increased response time, decreased vertical activity, increased liver weight
Additivity endpoint(s):	Developmental, Hepatic (liver) 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 200 ug/L. Additivity endpoints: Development, Nervous system

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

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

$$= \frac{\text{(0.23 mg/kg/d) x (0.2*) x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

$$= 1070 \text{ rounded to } 1000 \text{ } \mu g/L$$

* MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential exposure to DEET through sources other than water (e.g., use of products containing DEET) an RSC of < 0.2 may be warranted. However, without additional information a specific value cannot be determined. Therefore, the lower limit default of 0.2 recommended in the EPA Exposure Decision Tree (EPA 2000) was utilized.

Reference Dose / Concentration:	0.23 mg/kg-d (rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	90 mg/kg-d (NOAEL, chronic neurological assessment of F2 offspring from the 2 generation study, Schoenig et al 1993. LOAEL = 225 mg/kg-d as cited by EPA 1998)
Human Equivalent Dose Adjustment:	23 mg/kg-d (90 mg/kg-d X 0.26) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies extrapolation, 10 intraspecies variability, 3 database insufficiencies (additional characterization of neurotoxicity and immunotoxicity is warranted)
Critical effect(s):	Increased motor activity
Co-critical effect(s):	Increased response time, decreased vertical activity, decreased pup weight, increased liver weight, decreased adult body weight
Additivity endpoint(s):	Developmental, Hepatic (liver) system, 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 200 μg/L. Additivity endpoints: Development, Nervous system.

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification: Group D (EPA 1998a)

Volatile: No

Summary of health-based guidance history:
Short-term, Subchronic and Chronic HBVs were issued in February 2011. MDH reevaluated the HBVs in 2012 to incorporate HED methodology. The resulting HBVs did not change.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No	Yes	Yes	Yes	Yes
Effects?	Secondary Observations[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] No studies directly assessing endocrine effects have been conducted. Male and female reproductive tract effects (see footnote 4) have been reported; however, it is not clear whether these effects are the result of endocrine activity.

[2] A single 14-day subcutaneous injection study has been conducted. A decrease in the antibody plaque-forming (PFC) response was reported. It should be noted that oral exposure would result in first pass metabolism of DEET in the liver to a greater extent than subcutaneous injection. The subcutaneous dose level at which decreased PFC response was noted is slightly lower than the oral exposure points of departure used for the short-term, subchronic and chronic duration RfDs. However they are ~30-60-fold higher than the RfD values. A database UF was incorporated in to the short-term, subchronic and chronic duration RfDs, in part, to address the need for additional characterization of immunological effects.

[3] Three developmental studies and a 2 generation reproductive/developmental study have been conducted. The developmental studies did not report developmental effects except at doses that resulted in severe toxicity (e.g., increased mortality) in the pregnant animals. The 2-generation study reported decreased pup body weight during lactation at the highest dose tested. Decreased pup body weight forms the basis of the short-term RfD. Decreased pup body weight occurred at a dose level similar to the subchronic and chronic point of departures. This effect is included as a health endpoint for these durations.

[4] An 8-week study in dogs and a 90 day study in hamsters reported decreased organ weight or histological changes in the testes/epididymis weights. However, these effects were not reported in the 1 year dog study at similar dose levels. Macroscopic and histologic evaluation of females exposed in the 1 year dog study reported an increased incidence of mild hyperplasia of the epithelia of the uterus and uteruses distended with fluid. The male and female reproductive tract effects above were reported at dose levels more than 7-fold higher than the short-term, subchronic or chronic duration point of departures. The doses at

which the effects were observed are more than 700-fold higher than the short-term, subchronic and chronic RfDs. No effects on reproductive parameters (e.g., fertility, organ weights) were reported in the 2 generation reproductive study conducted in rats.

[5] Two neurotoxicity studies in rats have been conducted. One was an acute (single exposure) study and one was a chronic (~9 month) study. Changes in reaction time and activity levels were observed. The results of the acute study were insufficient to determine a point of departure with confidence. The results of this study, however, were used as part of the justification for incorporating a database uncertainty factor in to the derivation of the RfD. The results of the chronic study were utilized as the basis of the chronic duration RfD. General toxicity studies, particularly in dogs, have also observed neurological effects (e.g., tremors, excessive salivation). A database UF was incorporated into the short-term, subchronic and chronic duration RfD derivation to address concerns that additional characterization of neurotoxicity is warranted.

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2011 Health Based Guidance Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Web Publication Date: June 2011
Expiration Date: June 2016

Chemical Name: 1,4-Dioxane

CAS: 123-91-1

Synonyms: diethylene ether; 1,4-diethylene dioxide; diethylene oxide; dioxyethylene ether; and dioxane

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

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

Subchronic Non-Cancer Health Based Value ($nHBV_{subchronic}$) = 300 ug/L

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

$$= \frac{\text{(0.12 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 312 rounded to **300 ug/L**

Reference Dose / Concentration:	0.12 mg/kg-d (F344/DuCrj rats)
Source of toxicity value:	MDH 2011
Point of Departure:	52 mg/kg-d (NOAEL from 13 week drinking water study in rats by Kano et al 2008)
Human Equivalent Dose Adjustment:	52 mg/kg-d x DAF = 52 x 0.23 = 12 mg/kg-d (MDH 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are address by the HED adjustment); 10 for intraspecies variability; and 3 for database insufficiencies

	(lack of a multigeneration reproductive/developmental study)
Critical effect(s):	Increased relative liver and kidney weight (with histological and clinical chemistry changes at higher dose level); hepatocyte swelling; and nuclear enlargement of the nasal respiratory epithelium
Co-critical effect(s):	Increased nuclear enlargement of the bronchial epithelium
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system, Respiratory system

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

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

$$= \frac{\text{(0.025 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

= 116 rounded to **100 ug/L**

Reference Dose / Concentration:	0.025 mg/kg-d (Sherman rats)
Source of toxicity value:	MDH 2011 (Note: same basis as EPA IRIS 2010 value that was rounded to 0.03 mg/kg-d)
Point of Departure:	9.6 mg/kg-d (NOAEL from 2 year drinking water study in rats by Kociba et al 1974)
Human Equivalent Dose Adjustment:	9.6 mg/kg-d x DAF = 9.6 x 0.26 = 2.5 mg/kg-d (EPA IRIS 2010, Table 5-7)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are address by the HED adjustment); 10 for intraspecies variability; and 3 for database insufficiencies (lack of a multigeneration reproductive/developmental study)
Critical effect(s):	Histopathological lesions in the liver and kidney (hepatic and renal degeneration and necrosis as well as regenerative hyperplasia in hepatocytes and renal tubule epithelial cells)
Co-critical effect(s):	Increased relative liver weight; nonneoplastic

	lesions in the nasal cavity, liver and kidney; nuclear enlargement of nasal, tracheal and bronchial epithelium; decreased body weight and growth; and neoplastic lesions in the liver**
Additivity endpoint(s):	Hepatic (liver) system; Renal (kidney) system; Respiratory system

**neoplastic lesions (liver adenomas) are addressed by the Cancer HBV

Cancer Health Based Value (cHBV) = 1 ug/L

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

$$= \frac{\text{(1E-5) x (1000 ug/mg)}}{[(0.10 \times 10 \times 0.137\ \text{L/kg-d} \times 2) + (0.10 \times 3 \times 0.047\ \text{L/kg-d} \times 14) + (0.10 \times 1 \times 0.039\ \text{L/kg-d} \times 54)] / 70}$$

= 1.03 rounded to **1 ug/L**

Cancer classification:	"Likely to be carcinogenic to humans"
Slope factor:	0.10 per mg/kg-d (laboratory animal) (hepatocellular adenomas and carcinomas in female mice, Kano et al 2009)
Source of slope factor:	U.S. EPA, IRIS 2010 (United States Environmental Protection Agency 2010)
Tumor site(s):	Slope factor based on liver adenomas and carcinomas. Additional tumor sites included: nasal squamous cell carcinomas; peritoneal mesotheliomas; and mammary gland adenomas

Volatile: Yes (low volatile)

Summary of Guidance Value History:
The cancer (1 μg/L) HBV is 30-fold lower than the 2002 cancer HBV of 30 μg/L as the result of: 1) use of a more recent cancer risk assessment; 2) application of age-dependent early-life cancer sensitivity adjustment factors; 3) utilizing more recent intake rates which incorporate higher intake rates during early life, and 4) rounding to one significant figure.

The noncancer subchronic and chronic HBVs are new values.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No[1]	No[2]	Yes	No[4]	Yes
Effects?	-	-	Yes[3]	-	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)] Relevant oral toxicity studies have not been conducted. However, based on available indirect information there is no evidence that 1,4-dioxane exhibits endocrine activity.

[2)] No oral immunotoxicity studies. Based on available indirect information there is no evidence that 1,4-dioxane alters immune function.

[3)] Only one oral study, a teratogenicity study in rats (Giavini et al 1985) is available. In this study, pregnant females and their fetuses exposed to a human equivalent dose of 230 mg/kg-d (≥ 2000-fold higher than the subchronic and chronic RfDs) weighed less than unexposed animals. A slightly but significantly higher incidence of reduced sternum ossification was also noticed in these exposed fetuses. No other significant differences between treated and control groups were observed, including number of implantations and of live fetuses, post-implantation loss, and incidence of malformations.

[4)] No oral reproductive studies have been conducted and therefore only ancillary information is available.

[5)] In laboratory animals, the neurological effects of acute high-dose exposure included staggered gait, narcosis, paralysis, coma, and death. A single oral dose at a human equivalent dose level of 252 mg/kg-d (≥2000-fold higher than the subchronic and chronic RfDs) resulted in reduced the dopamine and serotonin content of the hypothalamus, the neurochemical profile of all other brain regions were not affected.

No repeat oral dosing studies evaluating neurotoxicity per se have been conducted and therefore only ancillary information is available. No histopathologic alterations were observed in the brain, spinal cord, and sciatic nerve from rats receiving up to 2 year exposure via the drinking water at dose levels up to ~1600 mg/kg-d [HED ~ 416] (~3500-fold higher than the subchronic and chronic RfDs).

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2012 Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Web Publication Date: June 2012
Expiration Date: June 2017

Chemical Name: Metribuzin
CAS: 21087-64-9

Synonyms: 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one; Sencor, Lexone, Preview

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

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

$$= \frac{\text{(0.016 mg/kg/d) x (0.5) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 27.7 rounded to **30 µg/L**

Reference Dose / Concentration:	0.016 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	2.2 mg/kg-d (NOAEL, LOAEL = 7.9 mg/kg-day based on parental and developmental effects seen by Porter et al, 1988 as cited in the 1998 U.S. EPA RED and 2006 EU DAR.)
Human Equivalent Dose Adjustment:	0.48 mg/kg-d (2.2 x 0.22) (MDH, 2011)
Total uncertainty factor:	30
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability
Critical effect(s):	Higher pup mortality, decreased body weight gain (maternal).
Co-critical effect(s):	Decreased motor and locomotor activity, drooping eyelids (ptosis), oral staining, and decreased body temperature.
Additivity endpoint(s):	Developmental, Nervous system

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

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

$$= \frac{\text{(0.006 mg/kg/d) x (0.5) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 10.4 rounded to **10 µg/L**

Reference Dose / Concentration:	0.006 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	2.4 mg/kg-d (LOAEL, based on thyroid effects reported by Krotlinger and Vogel, 1982 as cited in the 2006 EU DAR.)
Human Equivalent Dose Adjustment:	0.58 mg/kg-d (2.4 x 0.24) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 for LOAEL-to-NOAEL (statistically significant thyroid hormone level changes along with thyroid histopathological changes reported at the lowest dose tested. A value of 3 rather than 10 was utilized because the changes to T4 and T3 levels were similar in magnitude and no histopathological thyroid changes were observed at 1.3 mg/kg-d following a 2-year exposure.
Critical effect(s):	Changes in thyroid hormone levels (thyroxine (T4) and triiodothyronine (T3), and histopathological changes to the thyroid gland.
Co-critical effect(s):	None.
Additivity endpoint(s):	Thyroid (E)

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

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

$$= \frac{\text{(0.006 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 16 rounded to 20 µg/L

Reference Dose / Concentration:	0.006 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	2.4 mg/kg-d (LOAEL, based on thyroid effects reported by Krotlinger and Vogel, 1982 as cited in the 2006 EU DAR.)
Human Equivalent Dose Adjustment:	0.58 mg/kg-d (2.4 x 0.24) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 for LOAEL-to-NOAEL (statistically significant thyroid hormone level changes along with thyroid histopathological changes reported at the lowest dose tested. A value of 3 rather than 10 was utilized because the changes to T4 and T3 levels were similar in magnitude and no histopathological thyroid

	changes were observed at 1.3 mg/kg-d following a 2-year exposure.
Critical effect(s):	Changes in thyroid hormone levels (thyroxine (T4) and triiodothyronine (T3), and histopatholigical changes to the thyroid gland.
Co-critical effect(s):	None.
Additivity endpoint(s):	Thyroid (E)

The Subchronic HBV must be protective of the acute and short-term exposures that occur within the subchronic period and therefore, the Subchronic HBV is set equal to the Short-term HBV of 10 µg/L. The Additivity endpoints are: Thyroid (E)

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

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

$$= \frac{\text{(0.0035 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

= 16 rounded to 20 µg/L

Reference Dose / Concentration:	0.0035 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	1.3 mg/kg-d (LOAEL based on decreased body weight gain and thyroid effects reported by Christenson & Wahle, 1993 as cited in the 1998 U.S. EPA RED and 2006 EU DAR.)
Human Equivalent Dose Adjustment:	0.35 mg/kg-d (1.3 x 0.27) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies extrapolation (toxicodynamics), 10 intraspecies variability, 3 LOAEL to NOAEL (statistically significant thyroid hormone level changes with histopathological changes at higher doses)
Critical effect(s):	Decreased body weight gain, changes in thyroid hormone levels (thyroxine (T4) and triiodothyronine (T3), (and histopathological changes to the thyroid gland at higher doses).
Co-critical effect(s):	None
Additivity endpoint(s):	Thyroid (E)

The Chronic HBV must be protective of the acute, short-term or subchronic exposures that occur within the chronic period and therefore, the Chronic HBV is set equal to the Short-term HBV of 10 µg/L. The Additivity endpoints are: Thyroid (E).

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

Cancer classification:	D, not classifiable as to human carcinogenicity. No human data and inadequate evidence from animal bioassays.
Slope factor:	Not applicable
Source of slope factor:	None.
Tumor site(s):	None.

Volatile: No (low volatility)

Summary of changes since 1993/1994 HRL promulgation:
A non-cancer Chronic HRL of 200 µg/L was promulgated in 1993. In 2010 Acute, Short-term, Subchronic, and Chronic HBVs of 40, 10, 10, and 10 were derived. These values were 5 to 20-fold lower than the 1993 HRL as a result of incorporating: 1) a more recent evaluation of the toxicity information, 2) updated intake rates that include higher intake rates in children, and 3) rounding to one significant digit. MDH reevaluated the HBVs in 2012 to incorporate HED methodology. The resulting Acute HBV (30 µg/L) is 1.5 fold lower than the 2010 value. The Short-term, Subchronic and Chronic HBVs (10 µg/L) are unchanged.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	No	Yes	Yes	Yes
Effects?	Yes[1]	--	No[2]	No[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]The critical study selected as the basis of the short-term HBV is a nine-week thyroid mechanism of toxicity study in rats. Additional repeated dose oral toxicity studies have also observed thyroid effects. (Note: the unpublished studies included here are cited in the European Union Draft Assessment Report, 2006.)

[2,3]Several animal studies are available on metribuzin treatment and developmental effects. In general, the maternal toxic effects are accompanied by toxic effects to the fetus. The effects include a reduction in maternal body weight gain and food consumption as well as fetal mortality. These effects formed the basis of the acute HBV and were observed at dose levels >10-fold higher than the short-term point of departure. (Note: all unpublished studies included here are cited in the European Union Draft Assessment Report, 2006.)

[4]Neurological effects were listed as co-critical effects and the additivity endpoint for the acute duration based on motor and locomotor activity in females given a single bolus dose at levels similar to the acute point of departure. In a 90-day dietary neurotoxicity study in Fisher F-344 rats, there were no reported treatment-related findings at 62.3 in the functional observational battery (FOB), motor and locomotor activity measures, or observed clinical signs. (Note: the unpublished studies included here are cited in the European Union Draft Assessment Report, 2006.)

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2011 Health Based Guidance Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Issue Date: May 2011
Expiration Date: May 2016

Chemical Name: Naphthalene
CAS: 91-20-3

Synonyms: Camphor tar; mighty 150; mighty rd1; Mothballs; Moth Flakes; Naphthalene; Naphthalene, crude; Naphthalene; Naphthalene, molten; Naphthene; tar camphor; white tar

Non-Cancer Acute Health Based Value ($nHBV_{acute}$) = 70 µg/L

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Short-term L/kg/d)

= (0.038 mg/kg/d) x (0.5) x (1000 ug/mg)
(0.289 L/kg-d)

= 66 rounded to **70 µg/L**

Reference Dose / Concentration:	0.038 mg/kg-day (Sprague Dawley rats)
Source of toxicity value:	MDH, 2011
Point of Departure:	50 mg/kg-day (LOAEL), (National Toxicology Program (NTP) 1991) developmental gavage study in SD rats (No NOAEL)
Human Equivalent Dose Adjustment:	11.5 [50 mg/kg-d x 0.23] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 interspecies extrapolation (toxicodynamics); 10 intraspecies variation; 3 database gaps – lack of 2-generation reproductive toxicity studies and lack of dose-response data for hemolytic anemia and cataract formation which have been observed in human epidemiological studies for naphthalene; 3 LOAEL-to-NOAEL – a default of 10 was not applied because the neurological effects observed did not persist at this dose for the entire length of the NTP study (however the neurological effects did persist at higher doses)
Critical effect(s):	Maternal nervous system effects which included lethargy, shallow breathing and impaired posture
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Non-Cancer Short-term Health Based Value ($nHBV_{short-term}$) = 70 µg/L

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Short-term L/kg/d)

= (0.038 mg/kg/d) x (0.5) x (1000 ug/mg)
(0.289 L/kg-d)

= 66 rounded to **70 µg/L**

Reference Dose / Concentration:	0.038 mg/kg-day (Sprague Dawley rats)
Source of toxicity value:	MDH, 2011
Point of Departure:	50 mg/kg-day (LOAEL), (National Toxicology Program (NTP) 1991) developmental gavage study in SD rats (No NOAEL)
Human Equivalent Dose Adjustment:	11.5 [50 mg/kg-d x 0.23] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 interspecies extrapolation (toxicodynamics); 10 intraspecies variation; 3 database gaps – lack of 2-generation reproductive toxicity studies and lack of dose-response data for hemolytic anemia and cataract formation which have been observed in human epidemiological studies for naphthalene; 3 LOAEL-to-NOAEL – a default of 10 was not applied because the neurological effects observed did not persist at this dose for the entire length of the NTP study (however the neurological effects did persist at higher doses)
Critical effect(s):	Maternal nervous system effects which included lethargy, shallow breathing and impaired posture
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Non-Cancer Subchronic Health Based Value ($nHBV_{subchronic}$) = $nHBV_{short\text{-}term}$ = 70 µg/L

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Subchronic L/kg/d)

= (0.052 mg/kg/d) x (0.2) x (1000 ug/mg)
(0.077 L/kg-d)

= 135 rounded to 100 µg/L

Reference Dose / Concentration:	0.052 mg/kg-day (Fischer 344 rats)
Source of toxicity value:	MDH, 2011
Point of Departure:	71 mg/kg-day (NOAEL), (Battelle's Columbus Laboratories (BCL) 1980a) gavage study in F344 rats
Human Equivalent Dose Adjustment:	15.6 [71 mg/kg-d x 0.22] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 interspecies extrapolation (toxicodynamics); 10 intraspecies variation; 10 database gaps – lack of 2-

	generation reproductive toxicity studies, lack of dose-response data for hemolytic anemia and cataract formation which have been observed in human epidemiological studies for naphthalene, and a lack of neurotoxicity studies in the subchronic and chronic durations
Critical effect(s):	Decrease in terminal body weight
Co-critical effect(s):	Decreased spleen weight, lethargy, slow breathing, prone body posture, increased rooting behavior, decreased body weight associated with decreased food and water consumption
Additivity endpoint(s):	Nervous system; spleen

The subchronic nHBV must be protective of the short-term exposures that occur within the short-term period and therefore, the subchronic nHBV is set equal to the acute / short-term nHBV of 70 µg/L. Additivity endpoints: Nervous system

Non-Cancer Chronic Health Based Value ($nHBV_{chronic}$) = 70 µg/L

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

$$= \frac{\text{(0.016 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

$$= 74 \text{ rounded to } 70 \text{ µg/L}$$

Reference Dose / Concentration:	0.016 mg/kg-day (Fischer 344 rats)
Source of toxicity value:	MDH 2011
Point of Departure:	71 mg/kg-day (NOAEL), (Battelle's Columbus Laboratories (BCL) 1980a) gavage study in F344 rats
Human Equivalent Dose Adjustment:	15.6 [71 mg/kg-d x 0.22] (MDH, 2011)
Total uncertainty factor:	1000
UF allocation:	3 interspecies extrapolation (toxicodynamics); 10 intraspecies variation; 10 database gaps – lack of 2-generation reproductive toxicity studies, lack of dose-response data for hemolytic anemia and cataract formation which have been observed in human epidemiological studies for naphthalene, and a lack of neurotoxicity studies in the subchronic and chronic durations; 3 subchronic-to-chronic extrapolation because effects did not increase in severity with increasing exposure duration and most effects were observed within a shorter duration
Critical effect(s):	Decrease in terminal body weight
Co-critical effect(s):	Decreased spleen weight, lethargy, slow breathing, prone body posture, increased rooting behavior, decreased body weight associated with decreased food and water consumption
Additivity endpoint(s):	Nervous system; spleen

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Group C – there is evidence of carcinogenicity following inhalation exposure
Slope factor:	NA
Source of slope factor:	NA
Tumor site(s):	NA

Volatile: Yes (moderate)

Summary of changes since 1993/1994 HRL promulgation:
The acute, short-term, subchronic, and chronic HBV (70 µg/L) is 4 times lower than the 1993/94 chronic HRL (300 µg/L) as the result of: 1) utilizing of more recent intake rate data that incorporates higher intakes early in life, 2) more recent lower RfD values, 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	Yes	Yes	No	Yes
Effects?	-	Yes[1]	Yes[2]	Secondary Observation	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:
Note: individuals, particularly, infants, deficient in G6PDH are thought to be especially sensitive to naphthalene-induced hemolytic anemia.

[1]Decreased spleen weights seen in mice exposed to naphthalene for 14-days and 90-day by gavage (Shopp et al 1984) and it is listed as a secondary effect for the short-term duration and a co-critical effect for the subchronic and chronic durations. Lymphoid depletion of the thymus was seen in 2/10 female rats exposed to naphthalene by gavage for 13 weeks at 2 times the critical subchronic and chronic $LOAEL_{HED}$.

[2] Developmental studies were conducted in three species (rats, mice, and rabbits). A reduction in number of live pups per litter were observed at levels approximately 4 times critical acute and short-term $LOAEL_{HED}$ of 11.5 mg/kg-day. Malformations in offspring were observed at an HED of 104 mg/kg-day which is 3 times greater than the critical subchronic and chronic $LOAEL_{HED}$. No developmental effects were seen in the absence of significant maternal toxicity. Malformations are listed as a secondary effect for the subchronic and chronic durations.

[3] Neurotoxicity (lethargy, slow breathing) was considered the critical acute and short-term effect. Tolerance to neurological effects developed in low dose groups but persisted at higher doses. Neurological effects are listed as co-critical effects for the subchronic and chronic durations.

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2012 Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Web Publication Date: June 2012
Expiration Date: June 2017

Chemical Name: 1,2,4-Trichlorobenzene
CAS: 120-82-1

Synonyms: None

Acute Non-Cancer Health Based Value ($nHBV_{acute}$) = Not derived (insufficient information)

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

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

$$= \frac{\text{(0.17 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 118 rounded to **100 µg/L**

Reference Dose / Concentration:	0.17 mg/kg-d (rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	75 mg/kg-d (NOAEL) – Developmental gavage study (Black et al. 1988). (LOAEL 150 mg/kg-d)
Human Equivalent Dose Adjustment:	17 mg/kg-d (75 x 0.23) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability; 3 for database insufficiencies (limited data suggests that the adrenal gland may be a more sensitive endpoint than the liver – additional short-term studies are warranted)
Critical effect(s):	Mild hepatic lesions, increase in mixed function oxidase, and decreased hematocrit and hemoglobin
Co-critical effect(s):	Adrenal weight gain and vacuolization of the middle zone of the adrenal cortex, decreased corticosterone levels, liver enzyme induction and sight hepatocellular hypertrophy
Additivity endpoint(s):	Hepatic (liver) system; Adrenal (E); Hematological (blood) system

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

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Subchronic intake rate, L/kg/d)

= (0.070 mg/kg/d) x (0.2) x (1000 ug/mg)
(0.077 L/kg-d)

= 182 rounded to 200 µg/L

Reference Dose / Concentration:	0.070 mg/kg-d (rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	8.9 mg/kg-d NOAEL - 2 generation drinking water study in rats (Robinson, et al., 1981). (LOAEL 33 mg/kg-d)
Human Equivalent Dose Adjustment:	2.1 mg/kg-d (8.9 x 0.24) (MDH, 2011)
Total uncertainty factor:	30
UF allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability
Critical effect(s):	Increased adrenal weight
Co-critical effect(s):	Increased liver weight and increased liver enzyme levels; adrenal weight gain and vacuolization of the middle zone of the adrenal cortex, decreased corticosterone levels; increased kidney weights
Additivity endpoint(s):	Hepatic (liver) system; Adrenal (E); Renal (kidney) system

The Subchronic nHBV must be protective of the shorter-term exposures that occur within the subchronic periods and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 100 µg/L (Additivity endpoints: Hepatic (liver) system; Adrenal (E); Hematological (blood) system.

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

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Chronic intake rate, L/kg/d)

= (0.021 mg/kg/d) x (0.2) x (1000 ug/mg)
(0.043 L/kg-d)

= 98 rounded to **100 µg/L**

Reference Dose / Concentration:	0.021 mg/kg-d (rats)
Source of toxicity value:	MDH, 2012
Point of Departure:	8.9 mg/kg-d NOAEL - 2 generation drinking water study in rats (Robinson, et al., 1981) (LOAEL 33 mg/kg-d)
Human Equivalent Dose Adjustment:	2.1 mg/kg-d (8.9 x 0.24) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (toxicodynamics); 10

	for intraspecies variability; 3 for use of a subchronic study for the chronic duration - effects and points of departure across duration indicates limited increase in severity of effects)
Critical effect(s):	Increased adrenal weight
Co-critical effect(s):	Increased liver weight and increased liver enzyme levels; adrenal weight gain and vacuolization of the middle zone of the adrenal cortex, decreased corticosterone levels; increased kidney weights and renal mineralization
Additivity endpoint(s):	Hepatic (liver) system; Adrenal (E); Renal (kidney) system

Cancer Health Based Value (cHBV) = 4 µg/L

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

$$= \frac{\text{(1E-5) x (1000 ug/mg)}}{[(0.029 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.029 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.029 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 3.54 rounded to **4 µg/L**

Cancer classification:	"Likely to be carcinogenic to Humans"
Slope factor:	0.029 $(mg/kg\text{-}day)^{-1}$ based on liver tumors in male mice
Source of slope factor:	EPA, NCEA 2009 (provisional peer reviewed slope factor based on the data from the CMA 1994b study)
Tumor site(s):	Liver in male and female mice

Volatile: Yes (highly volatile)

Summary of changes since 1993/1994 HRL promulgation:
Short-term, Subchronic and Chronic non-cancer HBVs of 200, 200, and 100 µg/L and a Cancer HBV of 4 µg/L were derived in 2011. MDH reevaluated the non-cancer HBVs in 2012 to incorporate HED methodology. The resulting Short-term and Subchronic HBVs (100 µg/L) are 2-fold lower than the values derived in 2011 and the Chronic HBV (100 µg/L) is unchanged.

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

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

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] Increased adrenal gland weight was identified as the critical effect for the subchronic and chronic durations. This effect was also a co-critical effect for the short-term duration and was seen at a dose (53 mg/kg-d) that was 30% lower than the short-term point of departure of 75 mg/kg-d. However, the adrenal effect was observed in a short-term study that utilized only one dose level, which precludes evaluation of a dose response or identification of a point of departure. A database uncertainty factor was incorporated into the derivation of the short-term RfD to address the lack of adequate short-term studies evaluating effects on the adrenal gland.

Mice dermally exposed to 30% and 60% solutions of 1,2,4-trichlorobenzene experienced increased adrenal gland weight and adrenal amyloidosis. A single intraperitoneal injection of 1,2,4-trichlorobenzene resulted in decreased in T4 levels in rats at a dose 4.5 to 7 times higher than the short-term critical NOAEL of 75 mg/kg-day.

[2] In an oral developmental study, offspring exposed to 1,2,4-trichlorobenzene (and evaluated as embryos) exhibited a decrease in head and crown rump lengths, a decrease in the number of somites, and a decrease in embryonic protein content at a dose approximately 5 times higher (360 mg/kg-d) than the short-term point of departure of 75 mg/kg-day and more than 10 times higher than the subchronic and chronic point of departure. Also, one 2 generation and 2 additional developmental oral studies have been conducted. No developmental effects were reported at dose levels up to ~54 mg/kg-d in the 2 generation study in rats. No developmental effects were reported in mice at dose levels up to 130 mg/kg-d or in rats exposed at dose levels up to 300 mg/kg-d.

[3] In a reproductive study there was an increased incidence of dead embryos and fewer implantations in offspring exposed to 1,2,4-TCB on gestation days 9 through 13 at a dose approximately 5 times higher than the short-term point of departure of 75 mg/kg-day and more than 10 times higher than the subchronic and chronic point of departure. Examination of reproductive organs was performed in oral subchronic toxicity studies and histopathological examination was performed in chronic carcinogenicity studies. Results from these studies do not indicate that the reproductive system is a sensitive endpoint.

[4] The 2 generation oral study included assessment of locomotor activity at various intervals up to 90 days in rats exposed to 1,2,4-TCB in drinking water at doses up to ~54 mg/kg-d - no effects were observed.

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2012 Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Web Publication Date: June 2012
Expiration Date: June 2017

Chemical Name: 1,2,3-Trichloropropane
CAS: 96-18-4

Synonyms: Glyceryl trichlorohydrin; glycerol trichlorhydrin; allyl trichloride; propane, 1,2,3-trichloro-; trichlorohydrin

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

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Acute intake rate, L/kg/d)

= (0.0042 mg/kg/d) x (0.5) x (1000 ug/mg)
(0.289 L/kg-d)

= 7.3 rounded to **7 µg/L**

Reference Dose / Concentration:	0.0042 mg/kg-d (mice)
Source of toxicity value:	MDH 2012
Point of Departure:	3.2 mg/kg-d (BMDL, EPA IRIS 2009 based on NTP 1990)
Human Equivalent Dose Adjustment:	0.42 mg/kg-d [3.2 x 0.13] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 interspecies variability (toxicodynamics); 10 intraspecies variability; 3 database uncertainty based on lack of additional information related to developmental toxicity.
Critical effect(s):	Decreased fetal survival
Co-critical effect(s):	None found
Additivity endpoint(s):	Developmental

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

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Short-term intake rate, L/kg/d)

= (0.0042 mg/kg/d) x (0.5) x (1000 ug/mg)
(0.289 L/kg-d)

= 7.3 rounded to **7 µg/L**

Reference Dose / Concentration:	0.0042 mg/kg-d (mice)
Source of toxicity value:	MDH 2012
Point of Departure:	3.2 mg/kg-d ((BMDL, EPA IRIS 2009 based on NTP 1990)
Human Equivalent Dose Adjustment:	0.42 mg/kg-d [3.2 x 0.13] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty based on lack of additional information related to developmental toxicity.
Critical effect(s):	Decreased fetal survival
Co-critical effect(s):	None found
Additivity endpoint(s):	Developmental

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

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

$$= \frac{\text{(0.004 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 10.4 rounded to 10 µg/L

Reference Dose / Concentration:	0.004 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	5.7 mg/kg-d (LOAEL, NTP 1993; 17-wk, gavage, rats)
Human Equivalent Dose Adjustment:	1.2 mg/kg-d [5.7 x 0.21] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty based on lack of additional information related to developmental toxicity; 3 for use of a minimal LOAEL instead of NOAEL.
Critical effect(s):	Significant, dose-related reduction in serum pseudocholinesterase in female rats; considered to be related to early indications of liver toxicity.
Co-critical effect(s):	Significant decrease in fertility, significant decrease in the number of live pups, significant increase in cumulative days to litter; significant decrease in the proportion of males
Additivity endpoint(s):	Hepatic (liver) system, Developmental (reproductive)

The Subchronic nHBV must be protective of the shorter-term exposures that occur within the subchronic periods and therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 7 µg/L (Additivity endpoint: Developmental).

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

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

$$= \frac{(0.003 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.043 \text{ L/kg-d})}$$

= 14 rounded to 10 µg/L

Reference Dose / Concentration:	0.003 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	1.1 mg/kg-d (BMDL, NTP 1993)
Human Equivalent Dose Adjustment:	0.26 mg/kg-d (1.1 x 2.4) (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies variability (toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty based on lack of additional information related to developmental toxicity.
Critical effect(s):	Increased absolute liver weight in male rats.
Co-critical effect(s):	Liver necrosis, renal tubule hyperplasia, pancreatic acinar hyperplasia
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system*, Pancreas*

The Chronic nHBV must be protective of the shorter-term exposures that occur within the chronic periods and therefore, the Chronic nHBV is set equal to the Short-term nHBV of 7 µg/L (Additivity endpoint: Developmental).

*Renal and pancreatic effects were listed as additivity endpoints for the chronic duration because they were identified as co-critical effects in chronic studies. The calculated subchronic and chronic water concentrations were very similar (10 µg/Lfor both subchronic and chronic) so renal effects were included as an additivity endpoint for the chronic duration even though the chronic HBV is set equal to the subchronic value.

Cancer Health Based Value (cHBV) = 0.003 µg/L

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

$$= \frac{(1E\text{-}5) \times (1000 \text{ ug/mg})}{[(30 \times 10 \times 0.137 \text{ L/kg-d} \times 2) + (30 \times 3 \times 0.047 \text{ L/kg-d} \times 14) + (30 \times 1 \times 0.039 \text{ L/kg-d} \times 54)] / 70}$$

= 0.0034 rounded to **0.003 µg/L**

Cancer classification:	"Likely to be carcinogenic to humans" (EPA IRIS 2009)
Slope factor:	30 $(mg/kg\text{-}d)^{-1}$ (laboratory animal) (NTP 1993)
Source of slope factor:	EPA IRIS 2009 (for female mice)
Tumor site(s):	Forestomach, liver, Harderian gland, oral cavity, uterus.

Volatile: Yes (moderate)

Summary of changes since 1993/1994 HRL promulgation:
A cancer HRL of 40 µg/L was promulgated in 1993. In 2010, a revised cancer HBV of 0.003 µg/L was derived. The 2010 cancer HBV is over 10,000 times lower than the 1993 HRL. Acute, Short-term, Subchronic and Chronic HBVs of 20, 20, 10, and 10 µg/L were derived in 2010. MDH reevaluated the non-cancer HBVs in 2012 to incorporate HED methodology. The resulting HBVs (7 µg/L for each duration) are 3-fold and 1.5-fold lower than the 2010 values.

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

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

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] Secondary observations from histological evaluation of endocrine organs in existing animal studies showed mild changes in thyroid, testes, ovaries and epididymis at doses at nearly 2000 times higher than the acute, short-term, subchronic or chronic RfDs. Effects on increased estrous cycle length were reported in mice at over 900-fold above the acute, short-term subchronic, and chronic RfDs. Rats had increased incidences of preputial and clitoral gland tumors, mammary tumors, and pancreatic tumors and mice had increased incidences of uterine/cervical tumors at doses 300-800 fold higher than the chronic RfD.

[2] Immunotoxicity and immune function were not directly studied. Secondary observations noted in other studies include dose-related plasma cell hyperplasia and mandibular lymph node hyperplasia in female rats at doses at nearly 2000 times higher than the acute, short-term subchronic or chronic RfDs. The immunological significance of these effects is not known because none of these studies evaluated immune function.
[3]A 2-generation reproductive study was conducted in mice which found decreased viability of embryo/fetus, reduced fertility in females, decreased proportion of viable male pups, and effects on estrous cycle. This study is considered the critical study for both the acute and short-term endpoints. The most sensitive effect was decreased fetal/embryo viability occurring at a benchmark dose which was 800-1100 times higher than the subchronic and chronic RfDs.

[4]Neurotoxicity was not tested directly and there is no evidence of effects on neurological function or behavior. However, relative brain weights were significantly increased at doses over 2000-fold higher than the LOAEL for subchronic and chronic RfDs. There were no changes in brain cells or function noted in rats or mice after chronic oral exposure.

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2011Health Based Value for Groundwater
Health Risk Assessment Unit, Environmental Health Division
651-201-4899
651-201-5797 TDD

Issue Date: May 2011
Expiration Date: May 2016

Chemical Name: Tris(2-chloroethyl)phosphate

CAS: 115-96-8

Synonyms: TCEP; Tris(chloroethyl)phosphate; 2-Chloroethanol phosphate; Phosphoric acid, tris(2-chloroethyl)ester; Tri(2-chloroethyl)phosphate; Trichloroethylene phosphate; Tris(2-chloroethyl)orthophosphate; Ethanol, 2-chloro-, phosphate (3:1)

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

Due to limited information, no acute guidance value is derived. Based on the available information, the short-term HBV for TCEP is also protective of potential developmental effects.

Short-Term Non-Cancer Health Based Value ($nHBV_{short\text{-}term}$) = 300 ug/L

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

$$= \frac{\text{(0.15 mg/kg/d) x (0.5) x (1000 ug/mg)}}{\text{(0.289 L/kg-d)}}$$

= 259 rounded to **300 ug/L**

Reference Dose / Concentration:	0.15 mg/kg-d (rat, Fischer 344/N)
Source of toxicity value:	(MDH, 2011)
Point of Departure:	66 mg/kg-d (time-adjusted NOAEL - Matthews et al. 1990; NTP 1991a) with a time-adjusted LOAEL of 125 mg/kg-d.
Human Equivalent Dose Adjustment:	66 x 0.22 = 14.5 mg/kg-d (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address uncertainty

	regarding toxicodynamics (toxicokinetic portion addressed by HED), 10 intraspecies variability, 3 database insufficiencies (absence of adequate multigenerational developmental study)
Critical effect(s):	Increased absolute and relative kidney weights in male rats
Co-critical effect(s):	Decreased number of male pups per litter
Additivity endpoint(s):	Renal (kidney) system, Nervous system, Developmental

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

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

$$= \frac{\text{(0.068 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.077 L/kg-d)}}$$

= 177 rounded to **200 ug/L**

Reference Dose / Concentration:	0.068 mg/kg-d (rat, Fischer 344/N)
Source of toxicity value:	(MDH, 2011)
Point of Departure:	31 mg/kg-d (time-adjusted NOAEL; NTP 1991a, EPA PPRTV 2009)
Human Equivalent Dose Adjustment:	31 x 0.22 = 6.8 mg/kg-d (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address uncertainty regarding toxicodynamics (toxicokinetic portion addressed by HED), 10 intraspecies variability, 3 database insufficiencies (absence of adequate multigenerational developmental study)
Critical effect(s):	Increased kidney weights
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

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

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

$$= \frac{\text{(0.067 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.043 L/kg-d)}}$$

= 311 rounded to 300 ug/L

Reference Dose / Concentration:	0.067 mg/kg-d (rat, Fischer 344/N)
Source of toxicity value:	(MDH, 2011)
Point of Departure:	25.8 mg/kg-d ($BMDL_{10}$adj; NTP 1991a and Matthews et al. 1993, BMD modeling by ATSDR 2009)
Human Equivalent Dose Adjustment:	25.8 x 0.26 = 6.7 mg/kg-d (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address uncertainty regarding toxicodynamics (toxicokinetic portion addressed by HED), 10 intraspecies variability, 10 for use of LOAEL instead of NOAEL; 3 database insufficiencies (absence of adequate multigenerational developmental study
Critical effect(s):	Renal tubule hyperplasia
Co-critical effect(s):	Regenerative renal cell proliferation including hyperplasia and hypertrophy of urinary tubule epithelium and nuclei enlargement.
Additivity endpoint(s):	Renal (kidney) system

The Chronic nHBV must be protective of shorter term exposures that occur within the chronic period and therefore, the Chronic nHBV is set equal to the Subchronic nHBV of 200 ug/L. Additivity endpoints: Renal (kidney) system

Cancer Health Based Value (cHBV) = 5 ug/L

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

$$= \frac{\text{(1E-5) x (1000 ug/mg)}}{[(0.02 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.02 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.02 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 5.1 rounded to **5 ug/L**

Cancer classification:	"Likely to be carcinogenic to humans" (EPA PPRTV 2009) IARC Group 3 – not classifiable as to its carcinogenicity to humans (IARC 1999)
Slope factor:	0.02 $(mg/kg\text{-}d)^{-1}$(laboratory animal) (NTP 1991a)
Source of slope factor:	EPA PPRTV 2009
Tumor site(s):	Kidney

Volatile: No (low volatile)

Summary of changes since 1993/1994 HRL promulgation:
There was no 1993/1994 HRL promulgated for TCEP. The above HBV represent new guidance values.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	No	Yes	Yes	Yes
Effects?	No[1]	No[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 parameters generally consisted of organ weights and gross and microscopic pathology of endocrine glands (thyroid, pituitary, adrenals). No alterations of these parameters were found in rats or mice for TCEP. No studies were available regarding effects on thyroid or sex hormones or endocrine function. In vitro studies were negative for estrogenic activity measured by reporter gene expression in yeast cells. TCEP also did not show estrogenic or anti-estrogenic activity in human endometrial cancer cells. TCEP was shown to decrease sperm concentration and motility and increase numbers of abnormal sperm in rats. Reproductive effects that may be related to sperm effects occurred at dose

levels > 600-fold higher than the short-term, subchronic, and chronic RfDs. TCEP had no effect on estrous cycle in rats.

2. TCEP has not been tested directly for immunotoxicity. Gross and microscopic evaluation of thymus, spleen and lymph nodes during toxicity studies did not reveal treatment-related alterations of immune system organs. TCEP was not a skin sensitizer in animal studies (EU 2009).
3. In general, exposure of rodents during gestation to TCEP did not result in adverse developmental effects to the fetuses or newborn animals; however, an adequate multigeneration study has not been performed. Malformations or behavioral effects in offspring were not found, even at overtly maternally-toxic doses. However, in a continuous breeding protocol reproductive study, there was a change in sex ratio in births occurring in the second generation of exposed mice and there was a reduction in the number of live pups per litter in the first generation. The effects on sex ratio occurred at dose levels >150-fold higher than the short-term, subchronic, and chronic RfDs.
4. Continuous exposure of two generations of mice to TCEP reduced fertility which was reported to be primarily related to alterations in sperm concentration, motility and abnormalities. There was a reduction in the number of litters, the number of live pups per litter and the number of pairs delivering a 5th litter. Reproductive effects related to reduced fertility occurred at dose levels >200-fold higher than the short-term, subchronic, and chronic RfDs.
5. TCEP affected the nervous system in acute, intermediate and chronic exposure studies. In rats, TCEP has produced adverse neurological effects including morphological and behavioral effects. Brain lesions in rat studies included degenerative lesions including necrosis with hemorrhage, necrosis with loss of neurons in hippocampus, thalamic necrosis, and benign granular cell tumors. Very high oral doses of TCEP caused inhibition of serum cholinesterase in rats and plasma cholinesterase and brain neuropathy target esterase in hens, but did not produce delayed neurotoxicity. In rats, a high dose of TCEP caused ataxia, convulsions, hyperactivity, brain lesions and impaired performance in a water maze. The nervous system was identified as a critical endpoint for the short-term durations. Nervous system effects occurred at doses approximately >400-fold higher than the subchronic and chronic RfDs.

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