

9-2-2008



Protecting, maintaining and improving the health of all Minnesotans

August 28, 2008

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Re: In The Matter of the Proposed Rules of the State Department of Health Governing the Establishment of Health Risk Limits for Groundwater, Minnesota Rules, Chapter 4717, Parts 7100 Through 7400, and parts 7600 through 7800 and Insertion of Revised Rules as Parts 7810 Through 7900; Governor's Tracking #AR 070

Dear Librarian:

The Minnesota Department of Health intends to adopt rules Governing the Establishment of Health Risk Limits for Groundwater. We plan to publish a Notice Of Hearing in the September 2, 2008 State Register.

The Department has prepared a Statement of Need and Reasonableness. As required by Minnesota Statutes, sections 14.131 and 14.23, the Department is sending the Library a 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 651-201-4925.

Yours very truly,

A handwritten signature in black ink that reads "Pam Shubat". The signature is written in a cursive, flowing style.

Pamela Shubat, Supervisor
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Enclosure: Statement of Need and Reasonableness

State of Minnesota

Minnesota Department of Health

In the Matter of Proposed Rules
Of the Minnesota Department of Health
Relating to Health Risk Limits for Groundwater,
Minnesota Rules, Parts 4717.7100 to 4717.7800 (to be repealed)
And Parts 7810 to 7900 (to be added)

Statement of Need and Reasonableness

July 11, 2008



Sanne Magnan, M.D., Ph.D.
Commissioner
P.O. Box 64975
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About This Document

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

<http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/revrule.html> .

Please feel free to contact MDH with any questions or concerns: email paul.moyer@health.state.mn.us, or call (651) 201-4912.

The proposed Rules will be published in Minnesota's *State Register* at a later time. Individuals who are on the HRL Revision subscription list will receive notice of publication. For Minnesota's statutory procedure for promulgation 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 Paul Moyer at the Minnesota Department of Health, Environmental Surveillance and Assessment Section, 625 North Robert Street, PO Box 64975, St. Paul, MN 55164-0975, ph. 651-201-4912, fax 651-201-4606, email paul.moyer@health.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 Amendment to Rules Governing Health Risk Limits for Groundwater, *Minnesota Rules, 4717.7810 et seq.*

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LIST OF ACRONYMS

Note: Many of these terms are described more thoroughly in the Glossary.

3-MC	3-Methylchloanthrene
3-MU	3-Methylcholanthrene
ACGIH	American Conference of Government Industrial Hygienists
ADAF	Age-dependent adjustment factor
AF	Adjustment Factor
AFO	Ammonium Perfluorooctanoate
AIHA	American Industrial Hygiene Association
APFO	Ammonium Perfluorooctanoic Acid
ASF	Age Sensitivity Factor
ATSDR	Agency for Toxic Substances and Disease Registry
AZT	3'azido-3'-Deoxythymidine
BaP	Benzo(a)pyrene
BMC	Benchmark Concentration
BMCL	Benchmark Concentration Level
BMD10	Benchmark Dose at 10% response
BMDL10	Benchmark Dose Level at 10% response
BW	Body Weight
C8	<i>see</i> PFOA
C _a	Concentration in Air
CAS	Chemical Abstracts Service
CATT	C8 Assessment of Toxicity Team
CFR	Code of Federal Regulations
CHRL	Cancer Health Risk Limit
CMA	Chemical Manufacturers Association
COT	Committee on Toxicity
CV	Comparison Values
C _w	Concentration in Water
d	Day
D _{<2} , D _{2 to <16} , D ₁₆₊	Duration (for each age group)
DBA	Dibenzanthracene
DDD	p,p'-Dichlorodiphenyldichloroethane
DDE	p,p'-Dichlorodiphenyldichloroethylene
DDT	p,p'-Dichlorodiphenyltrichloroethane
DEN	Diethylnitrosamine
DEP	Department of Environmental Protection (West Virginia)
DES	Diethylstilbestrol
DI	Daily water intake rate
DMBA	Dimethylbenz(a)anthracene
DMN	Dimethylnitrosamine
DNT	Developmental Neurotoxicity
DPH	5,5'-diphenylhydantoin
DWEL	Drinking Water Equivalent Level
E	Endocrine

ECA	Enforceable Consent Agreement
ECAO	Environmental Criteria and Assessment Office
ED1, ED5, ED10	Effective Dose for a % increase in tumor response
EDT	Exposure Decision Tree
ENU	EthylNitrosourea
EPA	U.S. Environmental Protection Agency
EPTC	Ethyl Dipropylthiocarbamate
ERG	Eastern Research Group
ESA	Ethanesulfonic Acid
ETU	Ethylene Thiourea
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
FTOH	Fluorotelomer Alcohol
HA	Health Advisory
HBV	Health-Based Value
HEAST	Health Effects Assessment Summary Tables
HED	Human Equivalent Dose
HEOD	1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo,exo-5,8-dimethanonaphthalene, or Dieldrin
HMX	High-Molecular weight rdX
HPV	High Production Volume
HRA	Health Risk Assessment
HRL	Health Risk Limit
IARC	International Agency for Research on Cancer
IIT	Illinois Institute of Technology
IP	Intraperitoneal
IR	Intake Rate
IRIS	Integrated Risk Information System
JOEM	Journal of Occupational and Environmental Medicine
kg	Kilogram
L	Liter
LADD	Lifetime Average Daily Dose
LED1, LED5, LED10	Lowest Estimated Dose for a % increase in tumor response
LOAEL	Lowest Observed Adverse Effect Level
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MCPP	2-(2-Methyl-4-chlorophenoxy) propionic acid
MDA	Minnesota Department of Agriculture
MDH	Minnesota Department of Health
mg	Milligrams
µg	Micrograms
MN	Minnesota
MNU	MethylNitrosourea
MOA	Mode of Action
MPCA	Minnesota Pollution Control Agency
MRL	Minimum Risk Level
N	Nitrogen
NA	Not Applicable

NCHS	National Center for Health Statistics
NCPHG	North Carolina Public Health Goal
ND	No Data
NHANES	National Health and Nutrition Examination Survey
nHRL	Noncancer Health Risk Limit
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OA	Oxanilic Acid
OEHHA	Office of Environmental Health Hazard Assessment (California EPA)
OW	Office of Water
OXA	Oxanilic Acid
PAH	Polycyclic Aromatic Hydrocarbon
PBB	Polybrominated Biphenyls
PBDE	Polybrominated Diphenyl Ethers
PBPK	Physiologically Based Pharmacokinetic
PCB	Polychlorinated Biphenyl
PFHS	Perfluorohexanesulfonate
PFNA	Perfluorononanoic Acid
PFOA, or C8	Perfluorooctanoic Acid
PFOS	Perfluorooctanesulfonate
PO	Post Office
POD	Point of Departure
PPAR	Peroxisome Proliferator Activated Receptor
ppb	Parts per Billion
ppm	Parts per Million
RDX	Research Department eXplosive
RfC	Reference Concentration
RfD	Reference Dose
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (Netherlands)
RPF	Relative Potency Factor
RSC	Relative Source Contribution
SAB	Science Advisory Board
SAR	Structure-Activity Relationship
SETAC	Society of Environmental Toxicology and Chemistry
SF	Slope Factor
SIDS	Screening Information Data Set
SONAR	Statement of Need and Reasonableness
$t_{1/2}$	Half-Life
T3	Triiodothyronine (hormone)
TAC	Target Indoor Air Concentrations
TCDD	Tetrachloro-dibenzo-p-dioxin
TCE	Trichloroethane
TLV	Threshold Limit Value
TPH	Total Petroleum Hydrocarbons
TSCA	Toxic Substances Control Act
TT4	Total Thyroxine (hormone)
TTY	Teletypewriter
TWA	Time-Weighted Average

U.S.C.
UF
ug
VTA
WDHFS
WHO

United States Code
Uncertainty Factor
Micrograms (*see also* μg)
Voluntary Testing Agreement
Wisconsin Department of Health and Family Services
World Health Organization

PART I. INTRODUCTION

With Session Laws 2007 (Chapter 147, Article 17, section 2), the Legislature created timelines for the Minnesota Department of Health (MDH) to conclude its longstanding rules revision project for health-based groundwater quality standards. To that end, MDH proposes to delete *Minnesota Rules*, ch. 4717, parts 7100 through 7800 and insert revised rules as parts 7810 through 7900. The revised rules establish methods for calculating health-protective limits, called "Health Risk Limits" (HRLs), for contaminants in groundwater; use that formula to calculate HRLs for individual chemicals; address new legal requirements; and establish a procedure for assessing risk from multiple chemicals. The *Minnesota Administrative Procedures Act* requires that MDH justify and explain the need for revisions to an existing rule in a Statement of Need and Reasonableness (SONAR). This document fulfills that requirement.

The *Minnesota Groundwater Protection Act* (Act) authorizes promulgation of HRLs. The goal of the Act is to maintain groundwater "free from degradation caused by human activities." The Act, however, also recognizes that this goal is aspirational and therefore not always possible (*Minnesota Statutes*, section 103H.001). The Act authorizes HRLs for those situations where this goal has not been achieved; that is, where groundwater quality monitoring results show that there is a "degradation of groundwater" (*Minnesota Statutes*, section 103H.201, subd. (1)). HRLs are applicable to the use of groundwater as drinking water (*Minnesota Statutes*, section 103H.005, subd. (3)). The Legislature has declared elsewhere that the "actual or potential use of the waters of the state for potable water supply is the highest priority use" for the state's waters (*Minnesota Statutes*, section 115.063(2)). Thus, HRLs are not intended to be used as standards appropriate for the environment generally, but as conservative, health-protective upper limits for contaminants in groundwater that may serve as drinking water.

Because groundwater is a potential source of drinking water for all Minnesotans, MDH has worked continually towards the imperative of deriving HRLs that protect all members of the population. Personal and demographic characteristics and behaviors may make some individuals or groups more vulnerable to harm from contaminants in drinking water. People may be more vulnerable because they drink more water; that is, they are more exposed. People may also be more vulnerable because of genetic factors, pre-existing health conditions, age, diet, and a host of other factors. Infants and children are more highly exposed than adults because for their body weight, they drink more than adults. There are also reasons to believe that at certain life stages, such as organ development, people may be more sensitive to toxic effects than at other life stages.

The most significant changes in this revision represent a concerted effort to ensure that the process used for deriving HRLs incorporates provisions necessary to protect sensitive or highly exposed populations. This reflects not only MDH's mission to protect the health of all Minnesotans, but also the mandate in the 2001 Health Standards Statute that safe drinking water standards include "a reasonable margin of safety to adequately protect the health of infants, children, and adults" (*Minnesota Statutes*, section 144.0751).

Many of the changes resulting from this effort are based on scientific data; for example, toxicity testing indicating that development is a particularly sensitive period for a specific chemical, and data indicating that, for their body weight, infants and children drink more than do adults. Other changes may reflect

societal values; data that, while not conclusive, are cause for concern based on physiological and biological reasons; or the mandate of MDH to protect the health of all Minnesotans.

The remainder of this document provides background information necessary to understand the recommended rules revision and responds to questions about effects of implementation. Part II provides an Executive Summary. Part III explains what HRLs are, reviews the statutory authority for and the history of HRLs, and explains the need to revise the HRLs at this time. Part IV summarizes the basic steps for assessment of human health risk from environmental contaminants and explains MDH's derivation of HRLs in this context. Part V responds to statutorily mandated questions regarding the impact of implementing the rules. Part VI describes the derivation of individual HRLs. A glossary, references, and appendices provide technical information appropriate for readers interested in more detail.

For information that *Minnesota Statutes*, section 14.131 requires be included in each Statement of Need and Reasonableness (SONAR), see Part V.

PART II. EXECUTIVE SUMMARY

Health Risk Limits (HRLs) are health-protective limits for concentrations of contaminants in groundwater. The Minnesota Department of Health (MDH) derives its authority and promulgates HRLs for groundwater contaminants under the *Groundwater Protection Act of 1989* (*Minnesota Statutes*, sections 103H.001 *et seq.*). MDH first promulgated HRLs in 1993 and 1994. MDH is now proposing a major revision of the HRL rules. MDH needs to make these changes because of the detection of additional contaminants in Minnesota's groundwater; new toxicological research on environmental contaminants; evolving priorities for evaluating chemical exposure in children; advances in risk assessment methods and guidelines; mandates in Minnesota's 2001 Health Standards Statute (*Minnesota Statutes*, section 144.0751) and Minnesota Session Laws 2007 (Chapter 147, Article 17, section 2); and needs expressed by Minnesota risk managers.

The term "revision," when used in reference to the existing HRL rules, shall, in the remainder of this document, refer to the repeal of the existing rules and the adoption of new rules conforming to the procedures and practices outlined herein.

II.A. MDH-DERIVED HEALTH RISK LIMITS

MDH derives HRLs using Environmental Protection Agency (EPA) risk assessment methods and guidelines. Risk assessment methods require that MDH determine the health effects associated with a chemical and the lowest dose at which an adverse effect may arise; an evaluation of human exposure; and an integration of these and other considerations that may contribute to human health risk. The following section briefly describes the approach MDH's scientists used to employ new developments to calculate the values it proposes in this rule change.

An MDH-derived HRL is the concentration of a chemical in drinking water that, based on the current level of scientific understanding, is likely to pose little or no health risk to humans, including vulnerable subpopulations. This concentration 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 during the exposure period. In addition, a HRL value incorporates several adjustment factors to account for uncertainty in our understanding of a chemical's health risks; chemicals with fewer studies will tend to have a higher degree of conservatism built into the HRL value to compensate for the higher degree of uncertainty.

II.A.1. Toxicity

The accepted method for assessing potential toxicity to humans is through controlled laboratory studies using mammals. Therefore, throughout this SONAR, the term "animal" shall be used to describe mammalian species. In toxicity testing, animals are divided into groups and each group is administered one of several doses of a chemical, usually daily, over a set period of time. Testing has two goals: first, to identify the hazard or toxic effects caused by the chemical; and second, to evaluate the relationship between the dose and the animal's response. The dose-response relationship may vary depending on when (e.g., the life stage) and for how long (duration) the exposure occurred.

In evaluating the dose and the response, researchers seek to determine the lowest dose at which adverse effects related to dosing are observed (the "lowest observed adverse effect level," or LOAEL) and the highest dose at which no adverse effects related to dosing 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 pre-determined percent of the dosed animals (e.g., the benchmark dose). The dose resulting from dose-response evaluation (also referred to as a point of departure (POD) dose) serves as the starting point for deriving health-protective concentrations for environmental media.

For noncancer effects, the dose selected from the dose-response evaluation is reduced by variability and uncertainty factors (UFs) to account for what is not known about a chemical's toxicity to a human population. The factors account for: (i) uncertainty in extrapolating from animal data to humans; (ii) variation in sensitivity among human individuals; (iii) uncertainty in extrapolating from effects observed in a short-term study to potential effects from a longer exposure; (iv) uncertainty associated with using a study in which health effects were found at all doses tested; and (v) deficiencies in available data. In the absence of chemical-specific information, each of the five factors is typically assigned a value between 1 and 10. Values of 1 and 10 are most common, but other values, such as $10^{0.5}$ (half of 10 on a logarithmic scale, or approximately 3) are sometimes used. Values assigned to all factors are multiplied to determine the overall uncertainty factor. Half-power values (e.g., $10^{0.5}$) are factored as whole numbers when they occur singly but as powers or logs when they occur in tandem (EPA 2002c). Therefore, individual UFs of 3 and 10 would be expressed as 30 (3×10^1), whereas individual UFs of 3 and 3 would be expressed as 10 ($10^{0.5} \times 10^{0.5} = 10^1$). The product of multiplying uncertainty and variability factors is usually at least 100. If the uncertainty associated with a chemical's toxicity warranted application of uncertainty and variability factors whose product exceeded 3,000, MDH deemed that it had insufficient chemical information to derive an RfD (and therefore a HRL). The dose level selected from the dose-response evaluation (i.e., the point of departure dose, POD) is divided by the product of the uncertainty and variability factors to calculate a reference dose (RfD). An RfD is expressed in milligrams of chemical per kilogram of body weight per day (mg/kg-day) and is defined as an estimate of a dose level that is likely to be without an appreciable risk of adverse effects.

Understanding the relationship between 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) and short periods of high exposure (e.g., infancy). EPA (EPA 2002c) has recommended the derivation of

acute, short-term, subchronic, and chronic RfDs. If sufficient toxicological information was available, MDH derived RfDs for the various duration periods defined by EPA. The RfD values derived would be protective of all types of adverse effects for a given duration of exposure.

In the HRL revision, MDH has listed not just the noncancer effects occurring at the lowest effect dose, but also effects that occur at similar doses. This provides more information to risk managers and can affect the results of an assessment when multiple chemicals are present. 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. In documentation supporting the rules, MDH has noted whether the information that it reviewed for each chemical includes assessments of developmental, reproductive, immunological, endocrine, or neurological effects.

HRLs for most carcinogens employ the default assumption for linear carcinogens, i.e., 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.

In standard cancer assays, animals are dosed only during their adult lives; early life is not included in the dosing and assessment period. Differences among infants, children, adolescents, and adults in absorption, distribution, biotransformation, excretion, target organ sensitivity, cell-protective mechanisms, and homeostatic control suggest that cancer may develop and progress differently among these age groups. MDH evaluated recent data analyses by EPA and other researchers that examine whether the timing and duration of an animal's exposure to a carcinogen make a difference in the development of cancer. Generally, results indicate that cancer incidence from short-term early-life exposure can be similar to that from chronic adult-only exposure, and can be disproportionate to the duration of the exposure. In the 1993/1994 promulgations these analyses were not available.

The *Groundwater Protection Act* requires that MDH use cancer potency slopes published by EPA when deriving cancer HRLs. In calculating cancer HRLs in this revision, MDH used methodology contained in the recent EPA Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (EPA 2005a) to account for the potential for increased cancer potency when exposure occurs early in life. 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.

EPA has recommended that risk assessors apply this supplemental approach only to carcinogens with a mutagenic mode of action. In contrast, and based on comments from the Science Advisory Board (EPA 2004b) and the external Expert Advisory Panel (ERG 2005) MDH adopted the EPA approach as a default approach for all linear carcinogens, regardless of whether the mode of action was known to be mutagenic. Chemical-specific information regarding life-stage sensitivity was used in place of the default approach whenever possible. Non-linear carcinogens, i.e., those for which cancer risk is not directly proportional to dose at low dose levels, were evaluated using an RfD approach as recommended in the recent EPA Final Guidelines for Carcinogenic Risk Assessment (EPA 2005b).

In the 1993/1994 HRL promulgations, MDH evaluated chemicals considered possible human carcinogens (EPA Group C classification) for noncancer effects and assigned an additional 10-fold uncertainty factor (a "Group C factor") for possible carcinogenicity. In this revision, as recommended by the external Expert Advisory Panel (ERG 2005), MDH conducted a case-by-case evaluation for such chemicals and used scientific judgment to determine whether or not the data supported a finding of carcinogenicity. If adequate evidence of carcinogenicity existed and an EPA cancer potency slope was available, a cancer HRL was derived. In the absence of an EPA cancer potency slope factor, application of a Group C factor was considered. If the evidence of carcinogenicity was inadequate, MDH derived a noncancer chronic HRL using a chronic RfD. In this case the noncancer HRL did not incorporate a Group C factor.

For HRL chemicals with both cancer and noncancer endpoints, MDH derived cancer and noncancer HRLs if toxicity data were sufficient.

II.A.2. Intake rate

In deriving HRLs, the RfD (for noncancer) or dose associated with additional cancer risk equal to or less than 1/100,000 (for cancer) is converted from mg/kg-day to a water concentration in micrograms per liter ($\mu\text{g/L}$) by dividing by an intake rate. Intake rate is expressed as the quantity of water consumed per kilogram of body weight per day (L/kg-day).

Studies of water consumption indicate that infants and young children drink more water for their body weight than do adults. The algorithm used for the 1993/1994 HRLs followed standard risk assessment practice at the time and used a default adult daily intake rate of two liters and a default adult body weight of 70 kilograms (equivalent to approximately 0.029 L/kg-day). Based on current intake information, 0.029 L/kg-day corresponds to the 86th percentile of adult consumers of water from community supplies.

Newborns derive all, or nearly all, their nutrition from liquid. Intake rates fall rapidly with age; by age seven, intake rates are nearly the same as those of adults. Generally, HRLs are thought of as protecting against adverse health effects from long-term exposures to contaminants in drinking water. However, they must protect against adverse effects from shorter exposures as well. MDH considered sensitive life stages and subpopulations as well as the magnitude and duration of exposure necessary to elicit a toxic effect.

In Section II.A.1. it was noted that EPA has recommended the evaluation of multiple exposure durations, including: acute – dosing up to 24 hours; short-term– repeated dosing for more than 1 day, up to approximately 30 days; subchronic– repeated dosing for more than 30 days, up to approximately ten percent of a lifespan in humans (more than 30 days up to approximately 90 days in typical laboratory rodent studies); and chronic– repeated dosing for more than approximately ten percent of a life span. The external Expert Advisory Panel (ERG 2005) also recommended that MDH evaluate less-than-chronic exposure durations to ensure that shorter periods of exposure were adequately protected. In this rules revision MDH has used a life expectancy of 78 years (NCHS 2006).

The relevant duration is defined from the time point in the assessment at which the adverse effect was first observed. Protocols for toxicity testing do not necessarily evaluate or report effects observed at interim time points (i.e., before the end of the study). The effects reported at the end of the study

could have arisen earlier and thus may have resulted from a shorter duration. MDH acknowledges this limitation and the potential to overestimate the effective duration. However, in the absence of interim time point assessment information, MDH has opted to use the duration of the study as the relevant dosing duration.

MDH has used data reported in EPA's Per Capita Report (EPA 2004c) and a revised assessment for the draft Child-Specific Exposure Factors Handbook (EPA, 2007b) (see Table 2 in Section IV.D.1) to calculate default water intake rates for the various durations specified above. For the derivation of noncancer HRLs, MDH selected the following default duration-specific intake rates: acute or short-term—0.289 L/kg-day, based on the 95th percentile intake from 1 up to 3 months of age; subchronic—0.077 L/kg-day, based on a time-weighted average (TWA) of the 95th percentile intake from birth up to 8 years of age; and chronic—0.043 L/kg-day, based on TWA of the 95th percentile intake over a lifetime of approximately 70 years of age.

In addition to duration considerations MDH considered life-stage sensitivity. When the developmental period was identified as the most susceptible life stage, MDH selected the acute and short-term default intake rate for infants aged 1 up to 3 months (i.e., 0.289 L/kg-day) as the default intake for deriving HRLs based on developmental effects.

MDH has adopted EPA's approach for integrating age-dependent sensitivity adjustment factors and exposure information for the derivation of HRLs for linear carcinogens. The default intake rates corresponding to the age-dependent adjustment factor 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 lifetime duration used by EPA to characterize lifetime cancer risk is 70 years. Although this is no longer the life expectancy of the U.S. population, a value of 70 years corresponds to the equivalent duration over which health effects are typically assessed in chronic studies of laboratory animals. Therefore, 70 years has remained the standard definition of "lifetime" even as human life expectancy has increased.

MDH will depart from the above default intake rates if sufficient chemical-specific information indicates that a different duration or intake rate is more appropriate. In these cases MDH will use the data presented in Table 2 (Section IV.D.1) to calculate an appropriate TWA intake rate for the duration specified by the chemical-specific information.

II.A.3. Risk Characterization

An RfD or a cancer potency slope incorporates information about the toxicity of a single chemical associated with a given oral dose. Neither of these values, however, provides information about multiple exposures, whether from other routes of exposure (e.g., inhalation) or from multiple chemicals. Issues such as these are addressed in a risk assessment process called "risk characterization."

The *Groundwater Protection Act* requires that MDH use a "relative source contribution" (RSC) factor when deriving HRLs for noncancer effects. The RSC allocates only a portion of the RfD to exposure from ingestion of water, and reserves the remainder of the RfD for other water-related exposures (e.g., inhalation of volatilized chemicals, dermal absorption) as well as exposures via other contaminated

media such as food, air, and soil. MDH has relied upon EPA's Exposure Decision Tree approach (EPA 2000c) to determine appropriate default RSC values.

MDH derived HRLs for contaminants that are present in Minnesota's groundwater solely as the result of human activity, or for naturally occurring compounds present at elevated levels due to human activity. HRLs are often used to make decisions for cleaning up pollutants at contaminated sites where media other than groundwater may also be contaminated. The level of media contamination, the completed routes of exposure and the potentially exposed populations will vary from site to site and from chemical to chemical. Using the Exposure Decision Tree, MDH determined the following default RSC values. For acute and short-term exposure (based on infant intake rates), the RSC is 0.2 for highly volatile contaminants or 0.5 for other chemicals; for subchronic or chronic exposures, the RSC is 0.2 for all chemicals. MDH recognizes that departures from the outlined approach may be appropriate in the application of HRLs by MDH or other state agencies, and there may be situations where the Exposure Decision Tree could be used in conjunction with site-specific information to derive a site-specific RSC. Such site-specific RSCs are not appropriate for general use as a statewide or regional value.

In response to requests made by state risk managers, MDH provided additional information about the toxicity of HRL chemicals and about strategies for more complex risk evaluations. The types of information, such as a more extensive list of noncancer health endpoints and both cancer and noncancer HRLs for a single chemical, have been noted above.

Certain chemicals dissolved in drinking water have a tendency to volatilize, or escape, into the air. For volatile chemicals, inhalation exposure may be a special risk management concern. The revised rules include a volatility classification (e.g., high, moderate, low or non-volatile) for each chemical. MDH included this so that risk managers could more readily conduct a site-specific evaluation of inhalation exposure in situations where highly volatile chemicals have contaminated the groundwater and this groundwater is used for domestic purposes (e.g., bathing, showering, etc.).

While toxicity is usually evaluated for individual chemicals, real-life exposures involve multiple chemicals. In the rules, MDH includes methods that risk managers can use to sum up the risks from multiple chemicals that share a common health endpoint in order to assess the combined health risk at the site being evaluated. This common health risk index approach is a default approach; if specific data about a mixture are available, other approaches may be used and, in fact, are likely to be preferable.

II.B. MDH-DERIVED HRL ALGORITHMS

MDH applied the various duration-specific intake rates to the default HRL algorithm for noncancer effects (nHRL):

$$\text{nHRL}_{\text{duration}} = \frac{\text{RfD}_{\text{duration}} \times \text{RSC} \times 1,000}{\text{IR}_{\text{duration}}}$$

Where:

$\text{nHRL}_{\text{duration}}$ = the noncancer health risk limit, for a given duration, expressed in units of micrograms of chemical per liter of water ($\mu\text{g/L}$).

- RfD_{duration} = the reference dose, for a given duration, expressed in units of milligram 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.
- RSC = the relative source contribution factor which represents the percentage of total exposure to a substance or chemical that is allocated to ingestion of water. The default RSC is 0.2 for highly volatile chemicals. For other chemicals the default RSC is 0.5 for acute and short-term HRLs and 0.2 for subchronic or chronic HRLs.
- 1,000 = a factor used to convert milligrams (mg) to micrograms (μg).
- IR_{duration} = the intake rate 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.

MDH will depart from the above default HRL algorithm and parameter values if sufficient chemical-specific information indicates that a different duration or intake rate is more appropriate. In these cases a time-weighted intake rate would be calculated over the duration specified by the chemical-specific information. The RfD, RSC and IR values used for each chemical in deriving each nHRL are identified in the rules.

The magnitude of the HRL value is a function of the reference dose (RfD) and the intake rate. In general, for a given chemical, the shorter-duration RfD values will be higher than 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. In most cases, therefore, the calculated HRL values decrease with increasing duration, e.g., acute HRLs are greater than short-term HRLs, short-term HRLs are greater than subchronic HRLs, and so on. It is possible, however, that the RfD for a shorter-duration is the same, or in rare cases lower, than the RfD for a longer-duration. This could result if a short-duration was sufficient to elicit an adverse effect, if a more sensitive endpoint was assessed in the shorter-duration study, or if a different species or life stage was assessed. The intake rate also impacts the magnitude of the HRL value. As shown above, the shorter-duration intake rates are higher than the longer-term intake rates. These factors may cause a calculated shorter-duration HRL to be less (lower) than a 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 any higher shorter-term exposure that occurs within its defined time span. For example, it would not be prudent to promulgate a short-term HRL of 20 $\mu\text{g}/\text{L}$ and a subchronic HRL of 80 $\mu\text{g}/\text{L}$ even if analysis of the available studies and intake rates yielded these values. The subchronic value implies that 80 $\mu\text{g}/\text{L}$ has no adverse effects for an exposure duration of 30 days up to 10% of a lifetime, but the short-term study has established that 20 $\mu\text{g}/\text{L}$ is the appropriate limit for shorter exposures (30 days). Adoption of 80 $\mu\text{g}/\text{L}$ for the subchronic HRL would allow exposures that exceed the 20 $\mu\text{g}/\text{L}$ short-term HRL. In this instance, logic dictates that the 80 $\mu\text{g}/\text{L}$ subchronic value be overridden by the short-term value of 20 $\mu\text{g}/\text{L}$. When a substitution occurs, the table of HRL values and endpoints may list endpoints for the longer-duration HRL that are not

applicable to the substituted value when it is used for shorter durations. This is done to assure that any potential relevant health endpoints are not discarded when the substitution is made.

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

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

Where:

cHRL = the cancer health risk limit expressed in units of micrograms of chemical per liter of water ($\mu\text{g}/\text{L}$).

(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 ($[\text{cancer incidence per mg/kg-day}]$ or $[\text{mg/kg-day}]^{-1}$).

ADAF = the age-dependent adjustment factor for each age group: 10, for up to 2 years of age ($\text{ADAF}_{<2}$); 3, for 2 up to 16 years of age ($\text{ADAF}_{2 \text{ to } <16}$); and 1, for 16 years of age and older (ADAF_{16+}).

IR = the intake rate for each age group: 0.137 L/kg-day, for up to 2 years of age ($\text{IR}_{<2}$); 0.047 L/kg-day, for 2 up to 16 years of age ($\text{IR}_{2 \text{ to } <16}$); 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 ($D_{2 \text{ to } <16}$); and 54, for 16 years of age and older (D_{16+}).

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

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

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

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.

$\text{AF}_{\text{lifetime}}$ = the lifetime adjustment factor based on chemical-specific data.

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

The SF, slope factor adjustment, and IR values used for each chemical in deriving each cHRL will be identified in the rules. Adjustments to the toxicity and intake rate components of the risk algorithm,

along with MDH's evaluation of less-than-chronic durations and developmental and reproductive testing, are the foundation of MDH's efforts to ensure that HRLs protect all life stages.

The RfD and the cancer slope factor use scientifically sound methods to analyze the most current available toxicological data while continuing to make use of preexisting data.

In accordance with the general rule for calculations involving multiplication or division, HRLs 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 were typically rounded to one significant figure. Rounding was performed as the final step in the calculation process.

The following rounding procedures were used: (1) if the digit 5, 6, 7, 8, or 9 is dropped, increase the preceding digit by one unit; (2) if the digit 0, 1, 2, 3, or 4 is dropped, do not alter the preceding digit.

II.C. SUMMARY

MDH devoted extensive effort to developing and evaluating the methods and techniques incorporated in these algorithms. Locating, evaluating, and integrating new toxicological information about HRL chemicals was basic to this effort. Recent concerns about susceptible subpopulations such as children and Minnesota's Health Standards statute, however, required that MDH go beyond toxicological review and reconsider the methods and assumptions it used in deriving HRLs. Because these concerns have only recently come to the forefront among risk assessment scientists, there is no established approach to address them. Risk assessors and policy makers at EPA and elsewhere are exploring how best to respond to these concerns. MDH scientists are well informed of the research and discussion in this area, having actively engaged with other researchers, risk assessors, and policymakers nationwide. At this time, based on extensive research, consultation, and debate both internally and externally, MDH is presenting this revision as a reasonable and effective approach to protecting children, based on current science and policy.

In its 2007 session, the Minnesota Legislature recognized the need to update the HRL values and the methods used to derive them by enacting Minnesota Session Laws 2007, Chapter 147, Article 17, section 2. This law established HRLs for all contaminants in private domestic wells to be the more stringent of either the state standards (i.e., HRLs) or the federal standards determined by EPA (i.e., Maximum Contaminant Levels or MCLs). Consequently, MDH has adopted MCL-based HRLs for eleven chemicals effective July 1, 2007; these values remain in effect until MDH derives and promulgates revised values for these chemicals. In this revision of the HRL rules, MDH derived HRL values for three of the eleven chemicals (alachlor, benzene and 1,1,1-trichloroethane.) The MCL-based HRL values for the remaining eight chemicals (atrazine, di(2-ethylhexyl)phthalate), dichloromethane, pentachlorophenol, simazine, tetrachloroethylene, trichloroethylene, and 2(2,4,5-trichlorophenoxy)propionic acid) are included in this revision of the rules and will remain in effect until MDH develops new HRL values in future rules revisions.

In addition to these MCL-based HRLs, the MCL for nitrate (as N) is being adopted as a HRL until MDH completes its own review of current literature and calculates HRL values for that chemical.

While this revision makes some significant changes in the process for deriving a HRL, many aspects of the process have not changed. Though MDH's default values have changed, the risk assessment paradigm and the basic algorithm structure are unchanged. For linear carcinogens, EPA is still the only

statute-approved source of slope factor values. For cancer, MDH continues to use the same risk level, 1 in 100,000. For noncancer values, EPA's Integrated Risk Information System (IRIS) database is still the primary source of toxicity values, though EPA's Office of Pesticide Programs now takes precedence for pesticide values. Uncertainty and variability are still taken into account in deriving reference doses. In accordance with statute, use of a relative source contribution (RSC) factor in deriving noncancer values continues. Finally, MDH-derived HRLs are still solely based on health.

PART III. BACKGROUND

III.A. STATUTORY AUTHORITY

III.A.1. *Groundwater Protection Act of 1989*

MDH's statutory authority to adopt HRLs is found in *Minnesota Statutes*, section 103H.201, subd. (1)(a), which provides:

(a) 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.

Methods for exercising this authority are specified in *Minnesota Statutes*, section 103H.201, subd. (1)(c) and (d):

(c) For systemic toxicants that are not carcinogens, the adopted health risk limits shall be derived using United States EPA 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 EPA and determined by the commissioner to have undergone thorough scientific review.

III.A.2. Health Standards Statute of 2001

Additional authority is implicit in *Minnesota Statutes*, section 144.0751, which applies to "safe drinking water or air quality standards established or revised by the commissioner of health." This statute provides, in part:

(a) Safe drinking water or air quality standards established or revised by the commissioner of health must:

(1) be based on scientifically acceptable, peer-reviewed information; and

(2) include a reasonable margin of safety to adequately protect the health of infants, children, and adults by taking into consideration risks to each of the following health outcomes: reproductive development and function, respiratory function, immunologic suppression or hypersensitization, development of the brain and nervous system, endocrine (hormonal)

function, cancer, general infant and child development, and any other important health outcomes identified by the commissioner.

Under these statutory provisions, MDH has the necessary authority to revise the proposed rules and to include both science and policy based protections for sensitive populations, including infants and children. Because this rulemaking is a revision of rules adopted and effective prior to January 1, 1996, no additional legislative authorization is required. (See *Minnesota Statutes*, section 14.125.)

III.A.3. Health Risk Limits for Perfluorochemicals

Legislation passed in the 2007 session (Minnesota Session Laws 2007, Chapter 37) required the commissioner of health to derive and adopt by rule HRLs for perfluorooctanoic acid (PFOA), and perfluorooctane sulfonate (PFOS) by August 1, 2007. The legislation authorizes MDH to use "Good Cause Exemption" rulemaking procedures. The rules are therefore temporary and the values are only valid for two years or until they are incorporated into new, permanent HRL rules. MDH has included MDH-derived HRL values for PFOA and PFOS in the current revision of the rules.

III.A.4. Water Level Standards

Additional legislation passed in the 2007 session (Minnesota Session Laws 2007, Chapter 147, Article 17, section 2) established HRLs for all contaminants in private domestic wells to be the more stringent of either the state standards (i.e., HRLs) or the federal standards determined by EPA (i.e., Maximum Contaminant Levels or MCLs, which apply to public water supplies and can incorporate factors unrelated to risk calculations). These limits apply until MDH adopts rules setting an MDH-derived HRL value for these chemicals. MDH has identified 11 chemicals that have MCL values that are lower than the 1993/1994 HRL values:

- Alachlor - 2 µg/L
- Atrazine - 3 µg/L
- Benzene - 5 µg/L
- Bis(2-ethylhexyl)phthalate (also known as Di(2-ethylhexyl)phthalate) - 6 µg/L
- Dichloromethane - 5 µg/L
- Pentachlorophenol - 1 µg/L
- Simazine - 4 µg/L
- Tetrachloroethylene - 5 µg/L
- 1,1,1-Trichloroethane - 200 µg/L
- Trichloroethylene - 5 µg/L
- 2(2,4,5-Trichlorophenoxy)propionic acid (also known as 2,4,5-TP or Silvex) - 50 µg/L

The MCL values for these 11 chemicals were adopted as the HRL values, effective July 1, 2007. In the current revision, MDH has derived HRL values for alachlor, benzene and 1,1,1-trichloroethane. The MCL-based HRL values established by the Legislature on July 1, 2007 for the remaining eight chemicals are included in the current rules revision.

The same legislation also requires that MDH establish health risk limits for commonly detected contaminants in groundwater, and to adopt HRL rules for ten commonly detected contaminants by March 1, 2009. The legislation does not list these ten commonly detected contaminants; to identify these contaminants, MDH's Health Risk Assessment Unit (HRA) sought input from other programs

within MDH and from other state agencies, such as Minnesota Pollution Control Agency (MPCA) and the Minnesota Department of Agriculture (MDA). Each of these agencies provided lists of commonly detected chemicals to the HRA. On August 23, 2007, representatives from these agencies met to reconcile the different lists and discuss the priorities and concerns of each agency. Participants in the discussion, who included individuals with experience using HRLs in their daily work activities, were given a list of approximately 30 chemicals compiled from information provided by each agency prior to the meeting. Acting by consensus, the group classified each chemical as high-, medium- or low-priority based on frequency of detection and significance as a groundwater contaminant. A few chemicals were put into intermediate categories between high and medium, or between medium and low. The results of the prioritization process are shown in Table 1. Although the Water Level Standards legislation calls for HRL rules for the ten most commonly detected contaminants, the results of the August 23 meeting indicated a convenient dividing line at 13 chemicals (those listed as "high rank" in Table 1), a number which satisfies the law's requirements and meets the diverse needs of the various agencies that use HRLs. MCL-based HRLs are in effect for several of the chemicals on the list, including four of the "high rank" chemicals. A fifth "high rank" chemical, nitrate (as N), is included in the current rules revision as an MCL-based HRL until MDH develops a HRL using current data and the revised methodology. The federal MCL and 1993/94 MDH HRL for nitrate are both 10,000 µg/L. (This MCL adoption is being done to preserve a promulgated HRL for nitrate while MDH completes its review.)

Table 1: Priority Categories for Commonly Detected Contaminants

Priority Category	Chemical or Substance (alphabetical order within each category)
High Rank	1,2-Dichloroethylene, cis- Alachlor ESA Atrazine* Benzene Deethylatrazine (Atrazine degradate) Deisopropylatrazine (Atrazine degradate) Nitrate (as N)** Pentachlorophenol* PFOA PFOS Tetrachloroethylene (PCE)* Trichloroethylene (TCE)* Vinyl Chloride
High/Medium Rank	1,3,5-Trimethylbenzene Chloroform Arsenic Benzo(a)pyrene
Medium Rank	1,1-Dichloroethane 1,1-Dichloroethene 1,2,4-Trimethylbenzene 1,2-Dichloroethylene, trans- Acetochlor ESA Chloroethane Dichlorodifluoromethane Dichlorofluoromethane Ethylene glycol

Medium/Low Rank	Metolachlor ESA (degradate)
Low Rank	Di (2-ethylhexyl) phthalate* Ethyl ether Ethylbenzene Metribuzin degradate DADK Tetrahydrofuran Toluene Boron Manganese
*MDH is adopting an MCL-based HRL for these chemicals because the 1993/94 HRL exceeds the MCL. **MDH is adopting an MCL-based HRL for this chemical until it completes its toxicological review.	

MDH will derive HRL values for the following six "high rank" chemicals: cis-1,2-dichloroethylene, alachlor ESA, benzene, perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and vinyl chloride will be included in the current rules revision. The remaining two "high rank" chemicals (deethylatrazine and deisopropylatrazine) are breakdown products of atrazine and will be addressed in the revised rules by application of Part 4717.7900, which deals with chemical breakdown products.

III.B. MDH-DERIVED HEALTH RISK LIMITS EXPLAINED

The MDH-derived HRLs are publicly reviewed, health-based criteria available for use by state agencies and other entities that assess waters affected by pollution. MDH derived HRLs using toxicological data and scientific risk assessment methods generally prescribed in *Minnesota Statutes*, section 103H.201, subd. (1). The HRL rules provide science-based public health policy guidance that incorporates information about the risk to health associated with levels of chemicals in water used for human consumption.

The *Groundwater Protection Act* defines HRLs as follows:

"Health risk limits" means a concentration of a substance or chemical adopted by rule of the commissioner of health that is a potential drinking water contaminant because of a systemic or carcinogenic toxicological result from consumption (*Minnesota Statutes*, section 103H.005, subd. (3)).

When explaining MDH-derived HRLs to the public, MDH describes a Health Risk Limit as a concentration of a groundwater contaminant, or mixture of contaminants, that can be consumed with little or no health risk to humans, including vulnerable subpopulations. Under the current revision, noncancer HRL values are derived for up to four different exposure durations, so the appropriate value for a particular situation will depend on the circumstances, i.e., whether the exposure occurs for a few days, for a few years, or for a lifetime.

HRLs are promulgated for substances or chemicals that are found in groundwater and that are present as a result of human activities (*Minnesota Statutes*, sections 103H.201 and 103H.005, subd. (6)). In deriving HRLs, levels of contaminants are evaluated as though the groundwater were used as drinking water. This is consistent with the declaration in *Minnesota Statutes*, section 116.063(2) that the "actual or potential use of the waters of the state for potable water supply is the highest priority use" and with the stated statutory intent to protect groundwater (*Minnesota Statutes*, sections 103H.001 and 116.063(1)).

MDH-derived HRLs reflect health effects data and exposure via ingestion of water. They do not incorporate economic or technological factors, such as the cost and feasibility of treatment, as the MCLs may do. They 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 an RSC factor. Nor do HRLs address protection of the environment and the health of nonhuman species. In Minnesota, the latter are addressed by surface water regulations. MDH assumes that risk managers consider these issues when HRLs are applied.

In deriving the MDH-derived HRLs, MDH uses conservative practices that are protective of public health. Since groundwater serves as the source of drinking water for many Minnesotans, it is appropriate that MDH-derived HRLs be protective of all portions of the population. Such protection requires that both differential exposure and differential sensitivity be considered in deriving HRLs. Because children drink more water for their body weight than do adults, MDH has derived HRLs for most chemicals by adjusting daily water intake (liters of water per body weight per day) to be appropriate for the exposure duration of concern and for higher intake rates early in life. When toxicity testing shows that a particular chemical's effect is linked to exposure during a critical period of time, such as the developmental period, MDH has derived a HRL by calculating an appropriate daily water intake for that critical window of time. Finally, MDH has derived HRLs for cancer by using EPA's age-dependent cancer potency adjustment factors and intake rates to account for data indicating that early life may be more sensitive to carcinogenic action. While MDH-derived HRLs are intended to be protective, they may not be protective of individuals who experience idiosyncratic responses that may occur at the extreme ends of the distribution of possible responses within the general population.

With the exception of the water resources protection requirements (*Minnesota Statutes*, section 103H.275, subd. (1)(c)(2)), the *Groundwater Protection Act* does not specify how HRLs should be used, nor do the HRL rules specify use. MDH cannot anticipate all the situations in which HRLs might provide meaningful guidance, nor can MDH anticipate all the factors that might affect whether application of a HRL is appropriate. HRLs are but one of several sets of criteria that may be used by state groundwater and environmental protection programs to evaluate water contamination. Each program must determine whether to apply a HRL or whether site-specific characteristics justify deviation from HRLs.

As stated above, MDH's authority to promulgate HRLs under the *Groundwater Protection Act* is limited to situations where degradation has already occurred. As stated above, the process for deriving HRLs does not consider noningestion routes of exposure to water except through the application of an RSC factor. Furthermore, HRLs are not in any way intended to address impacts on non-human species or the environment. Therefore, use of HRLs to set an upper limit for degradation of water resources is not appropriate.

III.C. HISTORY

These proposed rule changes culminate more than twenty years of setting standards for drinking water contaminants. From its first statutory authority in 1986 to this seven-year effort to bring these

standards up to date, MDH has continually worked with the scientific community and the public to put the most recent accepted science into rule.

Beginning in 1986, MDH's Division of Environmental Health began providing health-based guidance for drinking water contaminants. These values, called "Drinking Water Recommended Allowable Limits" or "RALs," were based solely on the risk of potential health effects. RALs were primarily for private water supplies, but could be used for public water supplies in the absence of an applicable federal standard. By January of 1991, RALs for 196 chemicals had been developed.

The *Groundwater Protection Act*, passed in 1989, mandated that MDH promulgate Health Risk Limits (HRLs) for contaminants found in Minnesota groundwater. In 1993, MDH promulgated an equation for calculating HRLs and used that equation to calculate HRLs for 88 chemicals. MDH promulgated HRLs for 32 additional chemicals the following year.

Since the HRLs were promulgated, MDH has reviewed them on an ongoing basis. In addition, MDH has provided guidance outside the rules, as requested by state agencies.

Starting in 2001, MDH toxicologists and risk assessors conducted reviews of the risk assessment principles underlying the rules. In September of that year, MDH announced intentions to revise the rules in order to:

- provide guidance on new contaminants found in Minnesota groundwater;
- update existing HRL values with new toxicological research;
- incorporate advances in risk assessment strategies;
- reflect changes in values and policy regarding children's environmental health;
- respond to statutory directive; and
- fulfill MDH's mission of safeguarding public health.

Since announcing its intention to revise the HRLs, MDH has hosted nine public meetings to encourage participation by all stakeholders and the general public. The first of these meetings was held in 2001, and additional meetings have been held since that time, corresponding to significant milestones in the review process. In December of 2004, draft copies of the rules and SONAR were made publicly available. In addition to receiving comments from the public, MDH subjected the 2004 revised draft rules and SONAR to an independent peer review. Comments and recommended changes received by MDH during this process were considered for use in the revised draft SONAR, which was released to the public in September of 2007 in conjunction with a public meeting. See Part V.H for additional information regarding the peer review panel and the series of public meetings on the draft rules and SONAR.

Based on new guidance from the United States Environmental Protection Agency (EPA), recommendations from an external Expert Advisory Panel, comments and suggestions from stakeholders, and feedback from scientific peers, MDH has recommended that the HRL rules be revised.

III.D. NEED FOR THE PROPOSED REVISION

Minnesota Statutes, section 14.131 requires that MDH explain the need for and reasonableness of the rules as proposed. Minnesota Rule 2070 further requires that the statement explain the circumstances that created the need for the rulemaking. This section discusses the "need" for the proposed revision.

III.D.1. Generally

There are numerous reasons for revising the HRL rules at this time. Since HRLs were last promulgated, additional contaminants have been detected in Minnesota's groundwater; considerable toxicological research on environmental contaminants has been performed; risk assessment methods and guidelines have advanced; and policy makers' concerns about children and the environment have evolved. Since the 1993/1994 promulgation, MDH has been using the HRL formula, upon request, to provide advice about whether levels of chemicals measured in groundwater pose a risk to human health. As of May of 2007, MDH had provided advice to other agencies on approximately 90 chemicals that have been found in groundwater at specific sites. Promulgation of values for as many of these chemicals as practicable, as allowed by time and data availability constraints, will provide the authority and uniformity of rule and standardize the use of these values on a statewide basis. Also in 2007, the Legislature added additional impetus to the revision process by establishing a 2009 deadline for this long-standing effort.

Research has advanced the knowledge about the toxicity of many HRL chemicals. Additional testing may have shown that a given chemical is more or less potent than previously believed. Research may have shown additional toxic effects for a chemical, or it may have indicated that the events that lead to the occurrence of a toxic effect are not relevant to humans. Optimally, toxicological testing will allow the derivation of HRL values that incorporate more science, and decrease the uncertainty associated with the values.

The public policy focus on environmental risk has shifted since 1994. Both state and national legislatures have enacted laws that seek to ensure adequate protection of children. At the national level, the 1996 *Food Quality Protection Act* requires that pesticides be specifically tested for effects on development, or that pesticide regulatory values be made more conservative to account for the lack or inadequacy of such testing. In Minnesota, the *Health Standards Statute*, passed in 2001, requires that drinking water standards, such as HRLs, and air quality standards "include a reasonable margin of safety to adequately protect the health of infants, children, and adults" (*Minnesota Statutes*, section 144.0751). There is also increased concern for the combined effects of multiple chemicals to which people are exposed.

Risk assessment methods are evolving in response to the shift in public policy focus. Children's exposures are different than adults' exposures. For their body weight, children drink more water than do adults. And, because of their developing systems and rapid growth, children may be uniquely sensitive to certain chemical pollutants. Finally, because children have a longer remaining life span than adults, there is simply more time for disease to develop. A responsible risk assessment must incorporate consideration of these issues.

In 1983, the emerging practice of risk assessment was described by the National Academy of Science National Research Council as a process in which information is analyzed to determine whether an environmental hazard might cause harm to exposed persons and ecosystems (NRC 1983). In 2004, EPA, in the staff paper *Risk Assessment Principles and Practices*, described risk assessment as a tool to integrate exposure and health effects or ecological effects information into a characterization of the potential for health hazards in humans or other hazards to our environment (EPA 2004a). The

definition, the steps, and the use of risk assessment have not fundamentally changed in twenty-five years. However, there are advances in the techniques and strategies used in conducting risk assessments that result in changes between the work performed to derive the 1993/1994 HRLs and the current proposed revision. Among the most profound advances are a strong emphasis on characterizing the uncertainties and limitations of assessments; inclusion of analysis of distributions for exposures rather than single estimates of exposures; consideration of the combined risks of multiple chemicals through a variety of options; and use of benchmark doses and points of departure that are based on modeled experimental data. Many of these advances are described in EPA guidance documents on risk assessment that were released since the 1993/1994 HRLs. New guidance is now available for specific health endpoints, including reproduction, development, neurotoxicity, and cancer. EPA has also released a framework for assessing health risks to children as a result of exposures to environmental agents (EPA 2006b). The new guidance and framework is strongly reflected in this revision.

MDH has reviewed the science and policy that serve as the foundation for each element and default assumption within the HRL algorithm. The review has encompassed scientific literature; legislation and the materials evidencing the policy underlying that legislation; communication with other toxicologists, risk assessors, and regulatory agency staff across the country; and interactions with citizens and advocates for both the environment and the regulated community. The revised HRLs incorporate new scientific research and risk assessment methods and seek to align policy choices with the concerns and priorities of Minnesotans and with statutory mandates.

III.D.2. Protection of Infants and Children

Risk to children's health from environmental contaminants has been a focus of concern in recent years. When EPA strategies to assess risks from environmental contaminants were first published, they concentrated on long-term exposures and intake rates were modeled for lifetime exposures. Thus, default intake rates in risk assessment models reflected body weights and intake rates appropriate over adult life. Furthermore, toxicity testing is generally conducted using adult animals, leaving early life untested. As the field of risk assessment has advanced, scientists and policymakers have questioned whether models derived using adults are protective of children.

III.D.2.a. Reasons for Concern

Biological, physiological, and behavioral differences among adults, infants and children support concerns that standard risk assessment procedures may not adequately protect children from chemicals in the environment. Infants and children are still developing; developing organs and systems can provide unique targets or targets that are uniquely susceptible to toxic effects. Exposure to certain chemicals during critical periods can give rise to toxic responses that may result in life-long consequences. Infants' and children's exposures to drinking water are also different than those of adults: on a per body weight basis, infants and children drink more water than adults. This is especially true of newborns, whose only source of sustenance is breast milk, which is primarily derived from the mother's sources of water, or infant formula made with water. Behaviors and conditions unique to childhood, including more contact with dust and dirt, mouthing hands and objects, and a more limited variety and range of foods consumed, contribute to exposures that are different than those of adults (EPA 2005c, EPA 2006a, b).

In 1993, the NRC published a report, *Pesticides in the Diets of Infants and Children*. The question addressed in the report was whether then-current regulatory approaches for controlling pesticide residues in foods were adequately protective of infants and children (NRC 1993). The report concluded that the approaches were not sufficiently protective, and that infants and children differ both qualitatively and quantitatively from adults in their exposure to pesticide residues in foods and in their response to the toxic effects of pesticides.

. . . . Qualitative differences in toxicity are the consequence of exposures during special windows of vulnerability -- brief periods early in development when exposure to a toxicant can permanently alter the structure or function of an organ system. . . .

Quantitative differences in pesticide toxicity between children and adults are due in part to age-related differences in absorption, metabolism, detoxification, and excretion of xenobiotic compounds, that is, to differences in both pharmacokinetic and pharmacodynamic processes. Differences in size, immaturity of biochemical and physiological functions in major body systems, and variation in body composition (water, fat, protein, and mineral content) all can influence the extent of toxicity. . . . (NRC 1993)

The committee determined that dietary differences account for most of the differences in pesticide-related health risks between children and adults, so that differences in exposure generally contribute more to risk differences than age-related differences in toxicological sensitivity. Finally, the report concluded that EPA's testing requirements for pesticides were inadequate for providing a reasonable certainty of no harm to infants and children.

This report quickly gained national attention. It was recognized as having application beyond pesticide concerns and gained a reputation as the seminal work on children's environmental health risks. In the years since its publication, this report has greatly influenced the field of environmental contaminant risk assessment.

III.D.2.b. Policy and Legal Mandates

Lawmakers at both state and national levels have responded to emerging concerns about the effects of environmental contaminants on children by requiring that promulgated standards directly address children's health.

Science Policy Council. In October of 1995, the EPA Science Policy Council established an agency-wide policy to consider the risks to infants and children consistently and explicitly as part of risk assessments generated during its decision-making process, including the setting of standards to protect public health and the environment (EPA 1995b). The policy was implemented on November 1, 1995.

The Federal Food Quality Protection Act For Pesticides. The *Food Quality Protection Act* (FQPA) (21 U.S.C. § 346a), enacted in 1996, responded to concerns raised in the 1993 NRC report that pesticide regulations were not protective of children. The Act requires that EPA consider children when assessing risks from pesticide residues. In the event of "threshold effects" and absent countervailing evidence, the agency must use an additional 10-fold margin of safety "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." This specific factor is hereinafter referred to as the FQPA factor. The text of the FQPA is available in Appendix A.

The FQPA has been the subject of extensive debate both inside and outside EPA. EPA risk assessment practice already included several features that were either intended to or had the effect of extending protection to children. First, while the standard battery of tests required to evaluate pesticides for hazard to humans varies depending on the type of chemical and its use, tests required for conventional chemical pesticides applied to food crops include studies to determine effects on fetal viability, growth, and structure; multi-generation studies of effects on reproduction; and, for certain test materials, an acute delayed neurotoxicity study (40 CFR § 158.340). When routinely required data are insufficient to evaluate a pesticide, additional data requirements are imposed (40 CFR §158.75).

Second, EPA's assessment of health risks other than cancer includes a consideration of whether to implement any of a number of uncertainty and variability factors to derive a health-protective reference value. A factor (the intraspecies variability factor) is applied to account for potential variation in susceptibility within the human population, including children. EPA has also increased its use of the database uncertainty factor, which has often been implemented to account for deficiencies in developmental or reproductive data. Beyond factors for interspecies (extrapolation from animals to humans) uncertainty, intraspecies variability, and database uncertainty, EPA may apply two other uncertainty factors and a modifying factor. One commonly held view among risk assessors is that the interrelationship and overlap among factors creates a margin sufficient to account for areas not specifically addressed by any one of these uncertainty factors. Furthermore, factors are multiplied, increasing the conservativeness inherent in an assessment.

Within EPA, there has been disagreement on when the FQPA factor should be applied. Should it be applied with other uncertainty and variability factors in developing a reference dose, or is application more appropriately a matter for the risk manager during risk characterization?

While the requirements of the FQPA have been debated, there is no doubt that they fundamentally changed the process by which pesticides are regulated (though they did not necessarily change the regulation of non-pesticide chemicals). Since passage of the FQPA, EPA risk assessment has evolved to include a more conscious focus on whether regulatory standards for pesticides are sufficiently protective of infants and children. EPA believes that evolution has closed the gap between its traditional risk assessment process and the approach codified in the FQPA (EPA 2002a). In a 2002 document, EPA's Office of Pesticide Programs (OPP) stated: "the FQPA safety factor both incorporates prior Agency practice on additional safety factors and expands such prior practice." It is the OPP's view that, "the FQPA codifies, to a large extent, the Agency's pre-FQPA use of uncertainty factors in addition to the standard inter- and intraspecies factors" (EPA 2002a).

In deriving HRLs for pesticides, MDH has included, as part of the database uncertainty factor, any portion of the FQPA factor retained by EPA due to concerns that toxicity to children may be different from toxicity to adults. The FQPA factor can be conceptualized as comprising two separate components: one concerning toxicity and one concerning exposure. Because MDH is addressing children's exposures elsewhere in the revision process, any component of an OPP uncertainty factor that addresses differential exposure would not be included in the HRL derivation; only the toxicity component would be included. When the FQPA factor is retained by MDH as part of an RfD, its use is appropriate since HRLs are derived for the general population, which includes infants and children.

Executive Order 13045. President Clinton signed Executive Order 13045 in April of 1996, shortly after passage of the FQPA (President 1997). This order acknowledges that children may suffer

disproportionately from environmental health and safety risks and requires that each federal agency "identify and assess environmental health risks and safety risks that may disproportionately affect children," and "ensure that its policies, programs, activities, and standards address any disproportionate risks."

Minnesota's Health Standards Statute. In 2001, the Minnesota Legislature enacted *Minnesota Statutes*, section 144.0751 requiring additional scrutiny of environmental health hazards. This statute requires that drinking water or air quality standards established or revised by the commissioner of health:

"... include a reasonable margin of safety to adequately protect the health of infants, children, and adults by taking into consideration risks to each of the following health outcomes: reproductive development and function, respiratory function, immunologic suppression or hypersensitization, development of the brain and nervous system, endocrine (hormonal) function, cancer, general infant and child development, and any other important health outcomes identified by the commissioner."

MDH's analysis of some of the health effects listed in this statute is set out in Appendix B.

PART IV. MDH-DERIVED HEALTH RISK LIMITS

The health risk limits proposed in this promulgation are derived according to EPA risk assessment methods and conventions developed for establishing regulatory levels for contaminants in groundwater. These standard methods and conventions are implicitly referenced in *Minnesota Statutes*, section 103H.20, subd. (1)(c) and (d).

IV.A. RISK ALGORITHMS

EPA risk assessment methods consist of four separate steps: hazard identification; dose-response evaluation, or toxicity evaluation; exposure assessment; and risk characterization (NRC 1983; NRC 1994). Hazard identification is a determination of the kind of hazard posed by a chemical or substance. Dose-response or toxicity evaluation describes the quantitative relationship between the amount of exposure to a substance (i.e., dose) and the extent of toxic injury or disease. Exposure assessment typically includes the magnitude, frequency, duration, and route of exposure. Finally, risk characterization integrates the other steps to determine the likelihood that humans will experience toxicity associated with exposure to a chemical or substance.

The results of risk assessment are integrated with social, political, economic, and technological considerations to arrive at decisions about risk reduction (NRC 1994). This process is referred to as risk management.

Generally, health risk from contaminants in environmental media is considered proportional (\propto) to the toxicity of a chemical and exposure to the chemical:

$$\text{Risk} \propto (\text{Toxicity})(\text{Exposure})$$

Toxicity relates to the adverse effects that occur and the dose at which they occur. Exposure relates to the concentration of the chemical in the food, air, water, etc., and how much of the chemical is taken into the body. So specified, the equation is:

$$\text{Risk} \propto (\text{Toxicity})(\text{Concentration} \times \text{Intake Rate})$$

An MDH-derived HRL represents a concentration of a chemical in drinking water that is associated with little or no risk according to public health practice. To determine this concentration, the equation is rearranged as follows:

$$\text{Concentration} \propto (\text{Toxicity})(\text{Risk})(\text{Intake Rate})$$

To calculate the concentration, values must be supplied for risk, toxicity, and intake rate. For noncancer effects, risk and toxicity are expressed as a reference dose, referred to as an RfD. An RfD is an estimate of a dose (in milligrams of substance per kilogram of body weight per day [mg/kg-day]) for a given duration to the human population, including susceptible subgroups, that is likely to be without an appreciable risk of adverse effects. Pursuant to statute (*Minnesota Statutes*, section 103H.201, subd. (1)(c)), noncancer HRLs are calculated using a relative source contribution, or RSC. The RSC is the percent of total exposure to a substance or chemical that is allocated to drinking water. (For more information about the RSC, see Section IV.E.1.) For cancer, risk and toxicity are expressed as the dose associated with a risk of 1/100,000. In the algorithm, this appears as the risk level (1/100,000) divided by a slope factor, which is the risk per unit dose. (For more information about the risk level, see Section IV.E.2.)

MDH has sought to use available information about these variables in an objective, realistic, scientifically balanced, and reasonable way. Because of the uncertainty, variability, and data gaps in the available information and MDH's mission to protect public health, an approach that aims to avoid underestimation of risk has been chosen. The values for the input variables are selected to ensure a margin of safety for most of the potentially exposed susceptible population while also being scientifically plausible given existing uncertainty.

MDH used the following default algorithms to derive HRLs:

Noncancer HRL (nHRL).

MDH applied the various duration-specific intake rates to the default HRL algorithms for noncancer effects (nHRL):

$$\text{nHRL}_{\text{duration}} = \frac{\text{RfD}_{\text{duration}} \times \text{RSC} \times 1,000}{\text{IR}_{\text{duration}}}$$

Where:

$\text{nHRL}_{\text{duration}}$ = the noncancer health risk limit, for a given duration, expressed in units of micrograms of chemical per liter of water ($\mu\text{g/L}$).

- RfD_{duration} = the reference dose, for a given duration, expressed in units of milligram 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.
- RSC = the relative source contribution factor which represents the percentage of total exposure to a substance or chemical that is allocated to ingestion of water. The default RSC is 0.2 for highly volatile chemicals. For other chemicals the default RSC is 0.5 for acute and short-term HRLs and 0.2 for subchronic or chronic HRLs.
- 1,000 = a factor used to convert milligrams (mg) to micrograms (μg).
- IR_{duration} = the intake rate 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 of age.

MDH will depart from the above default HRL algorithm and parameter values if sufficient chemical-specific information indicates that a different duration period is more appropriate. In these cases a time-weighted intake rate would be calculated, using the same intake dataset (see Section IV.D.1), over the duration specified by the chemical-specific information. The RfD , RSC and IR values used for each chemical in deriving each nHRL are identified in the rules.

In general, it is anticipated that for a given chemical, the shorter-duration HRL values will be higher than longer-duration HRL values. However, the HRL values may not always follow the expected continuum from higher to lower for a variety of reasons. The longer-duration HRLs must be protective of short exposures that may occur within the longer duration. In the event that a shorter-duration HRL is more limiting (i.e., lower) than the calculated longer-duration HRL, the longer-duration HRL is set so as not to exceed the shorter-duration HRL. Dieldrin is an example of a case in which a longer-duration HRL (i.e., the subchronic HRL) is set at the more limiting, shorter-duration HRL (i.e., the short-term HRL) (see Appendix P).

Cancer HRL (cHRL).

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

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

Where:

cHRL = the cancer health risk limit expressed in units of micrograms of chemical per liter of water ($\mu\text{g/L}$).

- (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 $[\text{mg}/\text{kg}\text{-day}]^{-1}$).
- 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 (ADAF₁₆₊).
- 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 (IR₁₆₊).
- 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 (D₁₆₊).
- 70 years = the standard lifetime duration used by EPA in the characterization of lifetime cancer risk.

MDH will depart 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 would be applied, resulting in the following equation:

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

Where:

- (1×10^{-5}) = the additional cancer risk level.
- 1,000 = a factor used to convert milligrams (mg) to micrograms (μg).
- SF = adult-exposure based cancer slope factor.
- AF_{lifetime} = the lifetime adjustment factor based on chemical-specific data.
- 0.043 L/kg-day = 95th percentile water intake rate representative of a lifetime period.

Dieldrin and vinyl chloride are examples of cases in which a chemical specific lifetime adjustment factor was used. (See Appendix P).

EPA's model for carcinogenicity is based on a linear relationship between dose and cancer risk, with the underlying assumption that any exposure to a carcinogen, no matter how small, carries some risk of cancer. This is a conservative assumption and is the default approach in the absence of conclusive evidence of a nonlinear mechanism of action. If EPA has determined that a particular cancer-causing chemical has a threshold or otherwise exhibits nonlinearity, MDH uses that information to determine a noncancer value (a nHRL). In such cases, the health effects of concern are not cancer incidence, but some precursor to cancer. The 2005 EPA cancer guidelines recommend developing a reference dose and expressing risk as a hazard quotient (the ratio of an exposure estimate over the reference dose) (EPA 2005b).

When deriving HRLs, MDH rounded the number of significant figures at the end of the calculation to the same number of significant figures as the least precise parameter. The general rule is that for calculations involving multiplication or division, the resulting value should not possess any more significant figures than is associated with the least precise parameter in the calculation (EPA 2000c). As

a result, the HRL values were typically rounded to one significant figure. Rounding was performed as the final step in the calculation process.

The following rounding procedures were used: (1) if the digit 5, 6, 7, 8, or 9 is dropped, increase the preceding digit by one unit; (2) if the digit 0, 1, 2, 3, or 4 is dropped, do not alter the preceding digit.

The remainder of Part IV describes the individual elements that contribute to the calculation of HRLs— toxicity data, intake rate, and other exposure parameters—and explains the scientific and/or policy bases for the values assigned.

IV.B. HAZARD IDENTIFICATION

The National Research Council of the National Academy of Sciences described risk assessment in the federal government in 1983 and defined each step of risk assessment (NRC 1983). Hazard identification was described as “the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition.” The description also includes characterizing the nature and strength of the evidence of causation. (For a summary of criteria relevant to establishing causality in toxicological evaluation, see Appendix C.)

Hazard identification entails identification of the contaminants that are suspected of posing a health hazard, quantification of the concentrations at which they are present in the environment, description of the type of hazards they may pose, and an evaluation of the conditions under which toxicity might be expressed. Information for this step is typically derived from environmental monitoring data and from epidemiological and animal studies (NRC 1994).

MDH has determined that a chemical found in drinking water has the potential to be a hazard if it is known to cause toxicity in animals or humans. A chemical found in drinking water should be subjected to further analysis (toxicity and exposure evaluation). Therefore, in the HRL revision, the step of hazard identification includes identifying the chemicals that are present in Minnesota’s groundwater and determining whether toxicity data for these chemicals are available.

IV.B.1. Health Risk Limits Chemicals

Minnesota Statutes, section 103H.201, subd. (1)(a) 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 groundwater.

Minnesota Statutes, section 103H.005, subd. (6) defines “degradation” as “changing groundwater from its natural condition by human activities.”

Chemicals considered in this revision of the HRL rules include all chemicals for which HRLs have previously been promulgated, chemicals for which Minnesota agencies have subsequently asked MDH for guidance, and chemicals that Minnesota agencies specifically requested be included in the revision. The list resulting from this process comprises the chemicals and substances included for evaluation in the HRL revision. This list is attached as Appendix D.

Using time and resources judiciously, MDH has focused on the highest priority chemicals in the current revision of the rules. The current rules revision has focused on revising the methodology. Once the current revision is promulgated, it is the intent of MDH to review the remaining chemicals and amend the rules as necessary.

In preparation for the first promulgation of HRLs in 1993, MDH's Health Risk Assessment Unit (HRA), consulted groundwater monitoring and remediation programs of the Minnesota Pollution Control Agency (MPCA) and the Minnesota Department of Agriculture (MDA) to identify substances degrading groundwater. MPCA and MDA provided MDH with lists of chemicals and substances identified in groundwater at various sites, including landfills, industrial sites, monitoring wells, private wells, and municipal wells. The lists included synthetic chemicals and substances not naturally found in the environment, and naturally occurring substances detected at concentrations above background levels.

Since HRLs were last promulgated, Minnesota agencies have requested that MDH perform health risk assessments and provide provisional values for approximately 90 other chemicals and substances that have been found in Minnesota's groundwater or that had the potential to leach through soils to groundwater. In identifying chemicals and substances to include in the revision effort, HRA reviewed all recorded requests for health risk assessments, including requests for which toxicity information available at the time of the request was insufficient to complete an assessment. Pesticides constituted the majority of chemicals for which requests were made and filled. Other types of chemicals and substances include petroleum derivatives, pesticide degradates, fuel additives, and chemicals with specific applications in industry and/or consumer products. HRA also contacted MPCA, MDA, and the Drinking Water and Well Management sections at MDH and inquired as to whether there were specific chemicals or substances that they would like to see included in the revision. HRA requested verification that the chemicals and substances for which HRLs have been requested have actually been found in Minnesota groundwater. Only those chemicals and substances requested as a result of detection in groundwater were included in the revision. These chemicals provided a starting point for the MDH HRA Unit's August 2007 meeting with representatives from other MDH programs, MPCA, and MDA, as described in Section III.A.4. At this meeting, a list of more than 30 chemicals was divided into categories on the basis of their significance as a groundwater contaminant in Minnesota; a chemical's significance was characterized based on its toxicity, the frequency at which it is detected, or other factors which affect its overall impact on health. The results of the meeting are shown in Table 1 on page 13.

IV.B.2. Absence of a Health Risk Limit

The absence of a HRL for a chemical or substance does not imply that there is no health risk associated with exposure to that chemical in drinking water. The list of chemicals and substances included for consideration in the revision (see Appendix D) likely does not include all chemicals present in Minnesota groundwater as a result of human activities. First, MDH is authorized to derive HRLs for those chemicals that have been shown, through groundwater quality monitoring, to be degrading groundwater as the result of human activity (*Minnesota Statutes*, section 103H.201). Second, for a variety of reasons, Minnesota agencies may not have requested a health risk assessment for each chemical found during monitoring.

Thirdly, a HRL may not have been derived for a groundwater contaminant because toxicological information was deemed insufficient to propose a HRL. MDH will continue to review available data sources for new data concerning these chemicals.

Finally, as stated above, with the current resources, this rules revision has focused on revising the methodology and includes the highest priority chemicals. Once the current revision is promulgated, it is the intent of MDH to review the remaining chemicals and amend the rules as necessary.

IV.C. TOXICITY EVALUTION (DOSE-RESPONSE EVALUATION)

Toxicity evaluation (also called dose-response evaluation) examines the quantitative relationship between the dose and the toxic response. The desired result of toxicity evaluation is a toxicity value, which is an estimate of an amount of a substance to which a person can be exposed with little or no risk of an adverse health effect.

Generally, the risk assessor will conduct a thorough analysis of available toxicological studies. Dose-response data from epidemiology (human) studies are the preferable source of toxicity information; however, human data are rarely available. Most toxicity values are derived from laboratory animal studies conducted under controlled laboratory conditions. It is assumed that humans are at least as sensitive as the most sensitive mammalian species for which there are toxicological data. Substantial evidence that the response seen in laboratory animals is due to a mechanism that does not exist in humans can overcome this assumption. One of the best-known examples of this in the field of toxicology is a naturally occurring substance found mainly in citrus oils. While harmless to humans, female rats, and most other mammalian animals, in male rats, this substance causes a protein specific to male rats to accumulate in their kidneys and cause renal tumors.

IV.C.1. Toxic Effect

A toxic effect is an adverse biological effect that can be observed or measured. For the purpose of the MDH-derived HRLs, an adverse health effect is identified as the organ, tissue, or system in which the effect is manifested or as the occurrence of cancer. In order to constitute a toxic effect, several criteria must be satisfied. There must be a causal relationship between exposure to the substance and the biological or functional event observed. Furthermore, the effect observed must be either adverse or biologically meaningful. The body has normal compensatory responses that allow it to process a foreign substance with which it is challenged and to dispose of it without ill effect. A normal compensatory response does not in itself constitute a toxic effect, but may be identified as a precursor to an adverse effect.

Exposure to a particular chemical can cause a range of effects, depending on the dose. Generally, the number and severity of effects increase with the dose. For some chemicals, several adverse effects may be observed at the lower end of the dose range. MDH has identified all of the observed adverse effects that occur within a narrow range of the lowest dose associated with an adverse effect. For additional information, see "Critical, Co-Critical, and Secondary Effects" under Section IV.C.2. below.

In order for an effect to serve as the basis for an MDH-derived HRL, it must be adverse, or a precursor to an adverse effect. That is, it must have "biological significance." Any substance introduced into the body is likely to evoke some response. EPA has defined an "adverse effect" as "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" (EPA 2002c). The definition of "biological significance" is similar: "Biological significance is the determination that the observed effect (a biochemical change, a functional impairment, or a pathological lesion) is likely to impair the performance or reduce the ability of an individual to function or to respond to additional challenge from the agent. Biological significance is also attributed to effects that are consistent with steps in a known mode of action" (EPA 2002c).

Because some effects observed may be normal compensatory responses, professional judgment is required to decide whether any particular effect is adverse, or biologically significant. If an endpoint is quantal (i.e., all or nothing), such as birth defects or tumors, designation of an effect as "adverse" may be a straight forward decision. Similarly, a dose of a toxic substance may elicit an immediately toxic effect or may overwhelm the metabolic resources available to detoxify and eliminate it. However, for subtle effects and/or continuous measurements such as body weight or enzyme activity, this may ultimately be a qualitative decision. Professional judgment may be required to determine the point at which normal compensatory metabolic or physiological processes are compromised (EPA 2002c).

MDH determined that it would not derive HRLs for chemicals for which no adverse effects have been demonstrated. HRLs are used to establish concentrations that are "safe" in drinking water, so that it would not be appropriate to base a HRL on a data set that demonstrated only no effect levels. However, MDH determined instead that it may provide guidance for such chemicals outside the HRL rules. For example, no adverse effects have been observed in the limited testing conducted on anthracene. This does not indicate that anthracene has no effects – only that the doses tested and examinations conducted to date have not revealed any. Rather than deriving a HRL from the highest dose tested or providing no guidance for this chemical, MDH has opted to provide guidance outside the HRL rules, e.g., through the derivation of Health-Based Values (HBVs).

IV.C.2. Noncancer Effects

Toxicants can have a broad range of noncancer effects, from subcellular alterations in enzyme levels to gross morphological changes. Effects include gross alterations in organ function; pathological changes in organs; metabolic and physiological impairment, such as changes in the activities of critical metabolic enzymes or nerve impulse conduction; clinical and blood chemistry abnormalities; reduction in the ability to reproduce, including reduction in the ability to successfully bring fetuses to term; and, for the fetus, significant changes in body weight.

Generally, the number and severity of effects is assumed to increase with increasing dose. The converse assumption is that there is a dose *threshold*: below this threshold, the body is competent to process and eliminate chemicals with no ill effects. Risk assessment for noncancer effects is premised on this assumption. Reference doses for noncancer effects are usually derived by (i) identifying the lowest dose level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group (the lowest observable adverse effect level, or LOAEL); (ii) moving to the closest lower dose tested (the highest dose level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effect between the exposed population and an appropriate control group, known as the no observed adverse effect level, or NOAEL); and (iii) reducing this no effect level by a margin (e.g., uncertainty factors) to account for known differences between the laboratory animal and humans as well as gaps in the information about the chemical's toxicity. By protecting against the effect seen at

the lowest level, that is, the "critical" effect or effects, it is assumed that no other effects of concern will occur.

Alternatively, reference doses may be derived using a benchmark dose approach. A benchmark dose (BMD) approach uses mathematical models (e.g., Weibull, logistic, polynomial) to determine the dose associated with a predefined effect level; for example, a 10 percent response of a dichotomous outcome is often used as the benchmark response (BMD₁₀). The BMD approach involves an evaluation of the entire database; selection of studies and endpoints for the risk assessment; calculation of the lower confidence limit of a dose associated with a predefined effect level (e.g., BMDL₁₀); and the application of uncertainty factors. This approach has quickly gained support as an alternative for the NOAEL approach in noncancer risk assessment because it uses more of the data, providing a risk assessor with more information.

The Health Standards Statute (*Minnesota Statutes*, section 144.0751) specifies a number of health outcomes that must be considered in establishing or revising drinking water standards. Generally, adequate toxicity testing would either identify these outcomes as the critical effect, or would rule them out as other effects emerge as more sensitive; that is, occurring at lower levels. Further explanation of some of the health outcomes listed in the Health Standards Statute and how MDH has interpreted these outcomes and accounted for them in the HRL revision is found in Appendix B.

Critical, Co-critical, and Secondary Effects. Exposure to a particular chemical can cause a range of effects, depending on the dose. The toxicity evaluation identifies a "threshold" or "critical" effect; that is, the effect or effects that occur at lower doses relative to other effects. EPA defines the "critical effect" as "the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases" (EPA 2002c, 2003g).

In deriving a noncancer toxicity value, it has been standard practice to focus on only the effect or effects from a single study (the "critical study") that occurred at the lowest observed effect level (LOAEL or BMD). However, consideration of the database of available toxicity studies may show that other effects have been observed in other studies within a narrow range of the critical study LOAEL or BMD. Therefore, in the HRL rules, MDH has documented not only the critical effect(s), but also other effects that occur in close proximity to the dose level associated with the critical effect. In the revision, these effects are referred to as "co-critical effects."

Identification of co-critical effects was based on both professional judgment and practical considerations. Because the magnitudes of doses and dose intervals vary greatly from one study to the next, using a range of a set magnitude (for example, within 0.01 mg/kg-day of the LOAEL) to designate co-critical effects was not feasible. Generally, MDH considered as co-critical those effects that were observed near the critical study LOAEL or BMD. Other factors considered include the interval between the NOAEL and the LOAEL of the critical study and whether the effect under consideration occurred as a result of dosing during development. MDH includes co-critical effects in multiple-chemical risk assessments and therefore these effects are incorporated into the rules as health endpoints. (See Multiple Chemicals, Section IV.E.3., below.)

Effects within a three-fold range above the critical study LOAEL or BMD and that were not deemed co-critical effects were identified as secondary effects. Secondary effects are available from MDH in order to provide risk managers with more complete information and are not incorporated into the rules. Depending on the amount of toxicity testing to which a chemical has been subject, and because of

differences in study design, the number of effects designated as secondary varies widely, from none to a cascade of toxic events. Because of this wide variation, MDH makes no recommendations with regard to how or whether secondary effects should be considered in a risk assessment.

Calculation of a Human Equivalent Dose (HED). Mammalian animal data often form the basis for dose-response assessment and therefore an extrapolation from animals to humans is typically required. The goal of the extrapolation is to calculate the comparable externally applied exposure for humans from the lowest applied dose that elicited adverse effects in laboratory animals. The extrapolation is composed of two parts: toxicokinetics (how the body absorbs, distributes, metabolizes and eliminates the chemical) and toxicodynamics (how the body responds to the chemical). The terms pharmacokinetics and pharmacodynamics are often used interchangeably with toxicokinetics and toxicodynamics, respectively. EPA has recommended the use of dosimetric adjustment factors (DAFs) as a way to derive HEDs (EPA 2002c). The application of a DAF is typically considered to address the interspecies differences in toxicokinetics. The remaining uncertainty regarding toxicodynamics is addressed through the separate application of a partial interspecies uncertainty factor ($10^{0.5}$ or approximately 3). For additional information regarding the interspecies uncertainty factor, see the Uncertainty and Variability Factor discussion later in this Section.

EPA has a hierarchy of options for calculating HEDs (EPA 2002c, 2006c). The preferred option is to use a chemical-specific physiologically based pharmacokinetic (PBPK) model. A PBPK model 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. A formal DAF is not calculated in this process; rather the model itself serves as a DAF. However, constructing a PBPK model is an information intensive process that requires a significant quantity of chemical-specific data, including route-specific data. Such sophisticated data and models are usually available for only a small subset of chemicals that have extensive databases. For example, the HRLs for PFOS and PFOA incorporate sophisticated data on the dose *in the body* that causes an adverse effect, as opposed to the *administered* dose that causes an adverse effect. As a result, uncertainties in extrapolating from administered doses in animals to those in humans is substantially reduced, *viz.* the uncertainty factor is reduced by a factor of three. The summary sheet for PFOA is provided in Appendix P.

An intermediate option is an assessment of the available chemical-specific information, considering what is known about species differences, and toxicokinetics and toxicodynamics. This information is then used to deviate from default as appropriate (e.g., direct adjustment for toxicokinetic differences, different scaling function, different UF or combination) or to accept a default approach.

The less complex default approach scales doses between species according to body mass raised to the $\frac{3}{4}$ th power ($BW^{\frac{3}{4}}$). This adjustment can be used for estimating cross-species toxicokinetic relationships in the absence of chemical-specific information. Scaling to $BW^{\frac{3}{4}}$ is based on established allometric interspecies variation in anatomy and physiology and is a reflection of "metabolic body size." Studies have indicated that $BW^{\frac{3}{4}}$ scaling performs well at lower doses (e.g., where metabolism is not saturated and where acute, severe toxicity is not observed).

Currently EPA routinely uses $BW^{\frac{3}{4}}$ scaling in the derivation of human equivalent concentrations (HEC) for noncancer inhalation toxicity values (e.g., reference concentrations, RfC). Again, since this procedure applies only to toxicokinetic aspects of cross-species extrapolation, a separate application of a portion of the animal-to-human extrapolation ($10^{0.5}$ or approximately 3) to address the toxicodynamic portion would still be required. Scaling to $BW^{\frac{3}{4}}$ is also currently applied as a default for interspecies

extrapolation in the derivation of oral and inhalation cancer toxicity values (e.g., oral slope factor, inhalation unit risk).

The EPA Risk Assessment Forum Technical Panel has published a draft document outlining a parallel procedure for extrapolating from laboratory animal oral exposure estimates to human equivalent estimates (EPA 2006c). The current RfD approach is to apply an interspecies uncertainty factor directly to an animal experimental dose reported in mg/kg-day, which is the same as scaling by $BW^{1/1}$ and factoring uncertainty. This approach ($BW^{1/1}$ scaling) produces a higher equivalent oral dose (i.e., is less "conservative") than $BW^{3/4}$ scaling.

The typical default application of $BW^{3/4}$ scaling has been used for extrapolation from adult laboratory animals to adult humans. In most animal studies administration of a toxicant, even when the "target tissue" has been a fetus or developing pup, has been to an adult animal. Arguments have been made that varying and disproportionate growth rates among species during and around puberty would not be well characterized by $BW^{3/4}$ scaling. However, recent work has demonstrated that the $BW^{3/4}$ relationship is adequately descriptive of age-based toxicokinetic differences down to 2 months of age (EPA 2006c). Although EPA has not recommended scaling from adult animal to non-adult humans, they do note that the use of $BW^{3/4}$ scaling to derive a human equivalent dose for children yields a higher intake rate than does scaling to an adult human. These differences indicate that $BW^{3/4}$ scaling from adult animals to adult humans is a conservative approach to performing interspecies extrapolation for humans of various ages, with increased uncertainty for ages less than 2 months.

Using standard default body weights for adult mice, rats, dogs and adult humans, the corresponding $BW^{3/4}$ scaled HED would be approximately 7-, 4- and 2-fold lower than the experimental dose administered to a mouse, rat and dog, respectively. Combining the default portion of the interspecies uncertainty factor for toxicodynamic differences (a value of 3 or $10^{0.5}$) and the 7-, 4-, and 2-fold body weight scaling factors for toxicokinetic differences, the resulting cumulative interspecies adjustment would be 21-, 12-, and 6-fold for studies conducted in mice, rats and dogs. The values for rats and dogs are similar to the current 10-fold interspecies uncertainty factor; however, the value for mice is larger and would result in lower RfDs.

The EPA Risk Assessment Forum Technical Panel has not finalized its recommendations, and programs within EPA that are responsible for derivation of RfDs (e.g., EPA Integrated Risk Information Program) have not implemented a $BW^{3/4}$ scaling approach into the derivation of oral toxicity values.

Within this revision of the rules, MDH opted to use the chemical-specific physiologically based pharmacokinetic (PBPK) model and the intermediate option of incorporating chemical-specific information to calculate chemical-specific HEDs. MDH did not incorporate the default $BW^{3/4}$ scaling into the calculation of default-based HEDs. Application of the default scaling would have a limited effect on the MDH-derived nHRL values since the critical and co-critical studies were infrequently conducted in mice. MDH will revisit this decision when the recommendations are finalized and guidance on implementation is available.

Uncertainty and Variability Factors. Uncertainty and variability factors account for what is not known about a chemical's toxicity to a human population. Once the dose level (e.g., HED, NOAEL, LOAEL, or BMDL) has been selected as the point of departure (POD), it is then divided by uncertainty and/or variability factors to derive the reference dose:

$$\frac{\text{Point of Departure}}{\text{Uncertainty and Variability Factors}} = \text{Reference Dose}$$

As risk assessment methods have evolved, risk assessors have considered application of five uncertainty and variability factors. These factors account for: (i) uncertainty in extrapolating laboratory animal data to humans (the interspecies extrapolation factor); (ii) variation in sensitivity among individuals in the human population, including, for example, variation due to gender, age, genetics, and health-status (the intraspecies variability factor); (iii) uncertainty in extrapolating from effects observed in a short-term study to effects of long term exposure (the subchronic-to-chronic extrapolation factor); (iv) uncertainty in using a study in which health effects were found at all doses tested, that is, use of a LOAEL rather than a NOAEL (the LOAEL-to-NOAEL extrapolation factor); and (v) uncertainty based on existing data or deficiencies in the available data, resulting in the potential for additional data to yield a lower reference value (the database uncertainty factor) (EPA 2004a). The first two factors, those for uncertainty and variability between two species and within a single species, respectively, are nearly always applied. Application of the last factor, the database uncertainty factor, has increased over time. Application of the database uncertainty factor may incorporate an evaluation of how thorough testing is with respect to life stage assessment, endpoint assessment, and duration of exposure.

Each of the five factors is typically assigned a value between 1 and 10. Values of 1 and 10 are more common, but other values, such as $10^{0.5}$ (half of 10 on a logarithmic scale, or approximately 3), have been used. Values assigned to all factors are multiplied to determine the overall uncertainty factor. Half-power values (e.g., $10^{0.5}$) are factored as whole numbers when they occur singly but as powers or logs when they occur in tandem (EPA 2002c). Therefore, a composite UF of 3 and 10 would be expressed as $30 (3 \times 10^1)$, whereas a composite UF of 3 and 3 would be expressed as $10 (10^{0.5} \times 10^{0.5} = 10^1)$. Values assigned to all factors are multiplied to determine the total uncertainty factor (for example, $UF_{\text{Interspecies}} \times UF_{\text{Intraspecies}}$). Because the interspecies and intraspecies factors are nearly always assigned, reference doses derived from laboratory animal studies are nearly always reduced at least 100-fold below the NOAEL or BMDL. The EPA RfC/RfD Technical Panel recognized the potential overlap in the individual UFs and concluded that the application of four or more UFs is inappropriate. The Panel recommended "limiting the total UF applied for any particular chemical to no more than 3,000 and avoiding the derivation of a reference value that involves application of the full 10-fold UF in four or more areas of extrapolation" (EPA 2002c). The Panel noted that uncertainty in four areas may indicate that the database is insufficient to derive a reference value. In keeping with this 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. Chemicals with higher total uncertainty factors are not necessarily more toxic than chemicals with lower total uncertainty factors; use of a larger total uncertainty factor only means that there is less information available about the toxicity of the chemical.

Two other factors, similar to the uncertainty factors, may be applied by EPA in deriving a reference dose. First, a modifying factor may be used to account for scientific uncertainties that have not otherwise been addressed by the standard factors. This rarely-applied factor has been used less frequently as application of the database uncertainty factor has become more common.

Finally, as discussed in Section III.D.b., a *Food Quality Protection Act* (FQPA) factor may be applied to pesticides to address concerns specific to infants and children that available toxicity information and standard uncertainty factors do not adequately address. MDH considers the FQPA factor a special application of the database uncertainty factor.

Duration-Specific Reference Doses (RfDs). The EPA RfD/RfC Technical Panel (EPA 2002c) recommended that potential reference values should be calculated for each relevant and appropriate endpoint within a given duration. Data should be evaluated on the basis of a comparison of "sample" RfDs (e.g., identification of a POD, HED calculation, UF/VF application) from all available robust studies within a given duration of exposure for all relevant endpoints. Selection of the limiting RfD is the final step in the process and involves consideration of all studies and their corresponding "sample" RfDs. The selected RfD is protective of all types of adverse effects for a given duration of exposure.

Due to the concern that early life stages may be more sensitive to toxicity, MDH carefully evaluated the potential for developmental toxicity. In this rulemaking, MDH has defined a developmentally toxic effect as one which is caused by exposure sustained during a period of development, even though the health effect may manifest itself at any life stage. Developmental toxicity is an adverse effect on the developing organism that may result from exposure to either parent prior to conception, maternal exposure during prenatal development, or exposure to the organism during the postnatal period (including the period of sexual maturation). Developmental toxicity may be detected at any point in the lifespan of the organism, sometimes long after the exposure occurred. The major manifestations of developmental toxicity include: death of the developing organism, structural abnormalities, altered growth, and changes in function. The latter effect could range from the function of a single organ to a change in an organism's behavior. Some reproductive effects may be impossible to distinguish from developmental effects, and EPA has described developmental toxicity as a component of reproductive toxicity (EPA 1991a). Some toxic effects to developing organ systems may be indistinguishable from toxic effects that would occur during exposure at any other point in time. Unless it is known that such damage has no effect on function or growth, MDH considers the effect to be "developmental." MDH has used the terms developmental effect and developmental toxicity interchangeably in the SONAR.

While major developmental events occur before birth, development continues after birth and through childhood and sexual maturation. Adverse effects can result from exposure prior to conception, during pregnancy, or during infancy and childhood. Essentially every organ and system in the body can suffer an injury during the crucial time during which it is developing, even if that effect is not manifested until a much later time.

Classic examples of developmental toxicants include thalidomide, which can cause reduction or absence of limbs in offspring, and ethanol, which can cause an array of abnormalities collectively referred to as fetal alcohol syndrome. However, most developmental effects are far less obvious, and some may not be manifest until much later in life (for example, cervical and vaginal cancer in offspring of women treated with diethylstilbestrol). In fact, the laboratory animal models typically used for toxicity testing are considered inadequate for evaluating many of the more subtle deficits in neurological functioning that are currently of interest to many risk assessors.

Three different methods of testing the developmental effects of a chemical have evolved. Pregnant laboratory animals may be dosed for a short period during gestation – for example, in rats, days 6 through 15 of gestation. The dosing period generally includes the period of organogenesis. The course of the pregnancy is charted, and fetuses and sometimes neonates are observed for viability and structural malformations. In multi-generational testing, male and female laboratory animals are dosed prior to mating. Dosing continues through gestation, and through mating of one or two subsequent generations. Each generation is examined for effects related to reproductive ability and growth, but examination may occur earlier rather than later in life. In developmental neurotoxicity (DNT), testing pregnant laboratory animals are dosed from gestational day (GD) 6 through postnatal day (PND) 10,

although the requirement may soon be extended to PND 21 (i.e., until weaning) (EPA 2002c). Motor activity is measured at PND 13, 17, 21, and 60. Auditory startle is measured around weaning and at PND 60, as is a test of learning and memory. Cage-side observation of both mothers and pups is required, and neuropathology in the offspring ("pups") is required at PND 11 and at the termination of the study (usually PND 60).

Effects observed in the first type of study (i.e., dosing of pregnant laboratory animals) are the result of very short dosing periods. Dosing in multi-generational studies is generally not limited to these very brief periods; however, they can reveal effects that are different in the offspring of treated parents than in the parents themselves. These effects are presumably due to exposure during gestation and early life. The dosing period in the DNT studies is designed to cover the early postnatal period equivalent to a prenatal life stage in humans. However, there is no mechanism (i.e., direct dosing of pups) in the multi-generation or DNT study protocol to ensure adequate postnatal exposure. This is of particular importance since the chemical may not be excreted into breast milk or it may be excreted only at very low concentrations. For all three types of studies there is no long-term follow-up assessment to detect delayed effects, a situation that is arguably more worrisome for detecting developmental exposure effects than for exposure effects later in life.

MDH determined to what extent each HRL chemical had been tested for effects on or during development. While for some HRL chemicals, developmental effects were observed at lower doses than other effects, MDH observed that overall, developmental effects were not necessarily the most sensitive or "critical" effect.

MDH's recommendations in this revision are designed to protect developing fetuses and young children. MDH followed the recommendation of the EPA RfD/RfC Technical Panel that an endpoint-specific RfD for development should not be derived in isolation from RfDs for other endpoints. Thus, the RfD selected for a HRL is protective of all types of adverse effects within a given duration of exposure. If developmental toxicity was identified as the most sensitive effect, i.e., resulted in the most limiting RfD, it would form the basis of the RfD selected for the acute and short-term durations.

It is generally anticipated that the shorter-duration RfDs would be higher in absolute value than the longer-duration RfDs (e.g., acute > short-term > subchronic > chronic) for a given chemical since the dosing durations are more limited. However, the RfDs may not always follow the expected continuum from higher to lower for a variety of reasons. It is possible that the target organ for shorter durations differs from that for longer durations. The endpoint assessed in the shorter-term study may have been more sensitive or was assessed in a different species or at a different life stage. In the event that the shorter-duration RfD is more limiting (i.e., lower) than the calculated longer-duration RfD, the longer-duration RfD will be set so as not to exceed the more limiting, shorter-duration RfD value. This approach is consistent with EPA recommendations (EPA 2002c) and with recent EPA practice (EPA 2006d, EPA 2007a).

IV.C.3. Cancer Effects

In contrast to the threshold assumption operative for noncancer effects, most carcinogens are typically subject to the conservative assumption that no exposure is without risk. This leads to different procedures for estimating and regulating risk from carcinogens. The authorizing statute recognizes this by setting forth different procedures for deriving HRLs for cancer and noncancer effects. *Minnesota Statutes*, section 103H.201, subd. (1)(d) provides:

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.

EPA and other entities derive estimates of carcinogenic potency. However, *Minnesota Statutes*, section 103H.201, subd. (1)(d) restricts MDH, when deriving HRLs for cancer, to slope factors published by EPA.

Cancer Potency Estimation. Cancer potency is expressed as risk per unit dose, or slope factor (SF), which is the number of cases of cancer estimated to result from long-term dosing at the rate of one milligram of a substance per kilogram body weight per day (cancer incidence per mg/kg-day).

The incidence of cancer from the low exposure levels typically found in the environment is normally not measured in laboratory animal experiments because of cost. For example, to detect the relatively high risk of 1 in 1,000, many thousands of animals would need to be tested. Cancer risk at environmentally relevant levels is therefore estimated from laboratory animal studies that test exposures much higher than those expected to occur in the environment. Laboratory animal studies are usually designed with sufficient numbers of animals and dose groups to detect cancer in 1 in 10 animals.

Cancer risk estimation starts by determining the tumor response to doses in a laboratory animal cancer bioassay or in an epidemiological study of human exposure. Under cancer guidelines published by EPA in 1986, the lowest dose that was thought to cause cancer served as the "point of departure" for cancer risk estimation (EPA 1986a). Under EPA's long-awaited updated guidelines, published in March of 2005, this point of departure is determined starting with a curve (i.e., mathematical model) fit to the experimental data (EPA 2005b). The estimated dose associated with 1, 5, or 10 percent increase in tumor response (i.e., ED1 or "effective dose 1;" ED5 or "effective dose 5;" or ED10 or "effective dose 10," respectively) is determined from the modeled data. The lowest estimated dose (i.e., ED1, ED5, ED10) that can be supported by the data is selected, and the lower bound (lower 95 percent confidence interval) on the estimated dose serves as the point of departure (i.e., LED1, LED5, or LED10, or the lower bound on the estimated dose associated with a 1, 5, or 10 percent increase in tumor response, respectively). Units for the lower bound on the lowest estimated dose (the LED) will typically be in mg/kg-day and the percent cancer incidence is expressed as a fraction or probability (e.g., ten percent incidence is 0.1 or 1 in 10). Extrapolation to lower doses and responses, such as 1 in 100,000, is made from this point of departure from the experimental data (EPA 2005b).

Linear Assumption. A number of mathematical models and procedures have been derived for use in extrapolating from the high doses used in cancer bioassays to the relatively lower environmental doses. While chemical-specific information relevant to the mechanism of carcinogenesis should determine the choice of a low dose extrapolation method, such data are generally limited. When uncertainty exists, as it usually does, regarding the mechanism of carcinogenic action, or when there are data to indicate that the dose-response is linear below the point of departure, the EPA guidelines recommend using a low-dose linear model (EPA 2005b). To extrapolate downward, a line is drawn from the point of departure to the origin (zero) on a graph of cancer response per unit dose.

The slope of the line ("rise over run"), cancer incidence per unit dose, is the cancer slope factor. For example, the slope factor is equal to 0.05/LED5 if the dose associated with 5 percent cancer incidence

was used as the point of departure. The risk associated with any dose of a carcinogen below the point of departure is estimated using the slope of the line. The dose associated with any specific risk level, such as 1 in 100,000 can also be estimated using the slope.

Thus, at low doses (below the experimental range), the relationship between dose and cancer risk is treated as linear. This model for carcinogenicity is a mathematical expression of the "one-hit hypothesis" of carcinogenicity that suggests that exposure to even one molecule of a carcinogen can cause a heritable mutation in DNA. The hypothesis suggests that any exposure carries with it a finite, albeit low, probability of cancer. This hypothesis is based on the fact that cancer can result from a mutation in DNA. While it may be true that a single DNA lesion can lead to cancer, it is also true that the body has evolved repair mechanisms: damaged DNA can be repaired prior to replication. Therefore, while an exposure to a mutagenic carcinogen *can* result in cancer, it does not *always* result in cancer. Furthermore, not all chemicals that cause cancer do so by causing mutations. While a large number of chemicals considered carcinogenic have tested negative in mutagenicity assays and are suspected of working through nonmutagenic modes of action, researchers have identified nonmutagenic mechanisms of action for only a handful of chemicals. Absent conclusive evidence of a nonlinear mechanism of action, EPA applies the conservative assumption that any exposure to a carcinogen carries some increase in the risk of developing cancer.

Nonlinear Assumption. If, after a thorough examination, EPA determines that the dose-response relationship for a particular cancer-causing chemical has a threshold or otherwise exhibits nonlinearity, MDH will use that information to determine a value below the threshold, i.e., an RfD for which the health effects of concern will not be cancer, but some precursor to cancer.

For non-linear carcinogens that exhibit a mode of action that requires precursor events to occur (e.g., cytotoxicity with regenerative hyperplasia) before tumors develop, a dose threshold exists below which there is essentially no risk of developing cancer. The MDH approach for evaluation of non-linear carcinogens will be to ensure that the derived RfD is below the threshold for the precursor event as recommended by EPA (EPA 2005b).

Cancer Classification and Group C Carcinogens. Chemicals are classified according to their carcinogenicity. Most classifications of chemicals in EPA databases have been established pursuant to EPA's Guidelines for Carcinogenic Risk Assessment, published in 1986 (EPA 1986a). (See Appendix E for EPA's 1986 Cancer Classification Scheme.) The 1986 guidelines include, *inter alia*, group A, "human carcinogens"; group B, "probable human carcinogens"; and group C, "possible human carcinogens." *Minnesota Statutes*, section 103H.201, subd. (1)(d) restricts the derivation of HRLs for cancer to chemicals that are "known or probable carcinogens." In the 1993/1994 promulgation, MDH only derived cancer HRLs for chemicals assigned to group A or group B. For some group C chemicals, HRLs were derived by calculating a noncancer HRL and dividing by a factor of 10. However, in 1996, EPA proposed changes to the classification scheme and, even before publication of the draft final guidelines in early 2003, had begun using the new classification scheme on a piecemeal basis (EPA 1996b, 2003a). (See Appendix F for EPA's 2005 Final Guidelines for Carcinogen Risk Assessment.) The proposed classification scheme eliminates group C, "possible human carcinogens." Since the classification assigned under the 1986 guidelines will be the only classification available for a chemical until it undergoes reevaluation under the new guidelines, the rules must accommodate classification under either the 1986 guidelines or the 2005 final guidelines. MDH determined that it was necessary to shift from a technical interpretation of these terms to interpretation according to their common

meaning so that the terms would retain meaning even after implementation of the new classification scheme.^{1, 2}

When an EPA-published slope factor was available, MDH derived cancer HRLs for chemicals classified as "human carcinogens" or "probable human carcinogens" under the 1986 guidelines, or as linear carcinogens defined as "carcinogenic to humans" or "likely to be carcinogenic to humans" under the 2005 final guidelines.

Because the scientific evidence available for chemicals classified as group C, "possible human carcinogens," is more limited and encompasses a much broader range of quality, these compounds pose a specific dilemma. The external Expert Advisory Panel recommended a case-by-case evaluation of the evidence for carcinogenicity for these chemicals (ERG 2005). For this revision, an MDH committee consisting of three staff evaluated the evidence of carcinogenicity for HRL candidate chemicals currently classified in group C. When assessing a chemical's carcinogenic potential, this committee exercised professional judgment by compiling the available chemical-specific information, conducting independent reviews of the information, and discussing the weight of evidence in order to reach a consensus recommendation. These assessments included consideration of the number of studies available for review, the study design parameters, the quantity and quality of the data reported, and a review and critique of the conclusions reached by researchers and other evaluators. A list of criteria that the MDH carcinogen review committee followed is outlined in Appendix G.

In the 1993/1994 promulgation, if noncancer data were available, noncancer HRLs were derived for group C chemicals, using an additional 10-fold uncertainty factor for potential carcinogenicity. Use of this additional uncertainty factor was consistent with the practice of EPA's Office of Water (EPA 1998a). In this revision, on the recommendation of the MDH Group C committee, MDH planned to incorporate a separate uncertainty factor for Group C carcinogens to be used when a noncancer HRL is derived for a chemical for which the evidence of carcinogenic potential is strong, but still insufficient. Only one Group C chemical, cyanazine, is included in this revision. For this chemical, no HRL was developed for cancer effects because the tumors observed in animal studies were induced via a hormonal mechanism specific to the animal species and not via a genotoxic mode of action.

IV.C.4. Sources of Toxicity Data and Toxicity Values

Minnesota Statutes, section 144.0751, subdivision a, requires MDH to use "scientifically acceptable, peer-reviewed information" in deriving HRLs. Peer review ensures that the design and performance of the study meet scientific and technical standards and allows for a thorough critique of the study.

There are several components to the peer review process. Individual toxicity studies published in scientific journals are reviewed upon submission for publication. Publication makes them available for comment by the broader scientific community. EPA has indicated that studies reported in the open

¹ *Minnesota Statutes*, Section 645.08, canons of construction, states: In construing the statutes of this state. . . (1) words and phrases are construed according to rules of grammar and according to their common and approved usage; but technical words and phrases and such others as have acquired a special meaning, or are defined in this chapter, are construed according to such special meaning or their definition. . . ."

² *Minnesota Statutes*, Section 645.16, Legislative intent controls, provides in part: ". . . . Every law shall be construed, if possible, to give effect to all its provisions."

scientific literature that have been subjected to peer review as part of their evaluation are appropriate for use in assessing chemical toxicity (EPA 2002b). Studies performed at the behest of a government agency, even if they have not been published in a scientific journal, will have been reviewed, at a minimum, by other scientists within the agency. (For types of data required by the federal government for certain studies, see Appendix J.) A government agency may also assemble and critically evaluate studies for the purpose of deriving a toxicity value such as a reference dose or slope factor. Once a governmental agency has derived a toxicity value from available data, the value is subject to review and constructive criticism by the scientific and risk assessment communities.

In deriving HRLs, MDH relies upon several sources of information, all of which have been subject to peer review, though to varying degrees. Preferred sources were EPA offices that assemble toxicity studies, evaluate data from those studies, and translate those data into toxicity values. Some authorities use toxicity values to establish guidelines or standards for chemical contaminants in drinking water that do not pose a significant risk to health. MDH did not directly adopt such values, but used its own algorithm and guidelines to derive HRLs. When studies available from EPA or other authorities were limited or when evaluations did not include recent research, MDH consulted studies reported in peer-reviewed scientific literature. These studies may have served to support the toxicity value derived, may have resulted in modification of that value, or may have served as the basis for a value derived *de novo* by MDH.

For pesticides, Reregistration Eligibility Decisions (REDs) or related documents prepared by EPA's Office of Pesticide Programs, or analyses preceding formal RED evaluations, were the preferred sources. For chemicals that are not used as pesticides, EPA's Integrated Risk Information System was generally the preferred source, followed by California Office of Environmental Health Hazard Assessment and the Agency for Toxic Substances and Disease Registry. If none of these sources was available, MDH chose from among other sources, such as reports, notices, memoranda, or other documents prepared by various government agencies or research institutions. Selection criteria included the quality of the studies, the date of the assessment, the quantity of the data presented (e.g., level of detail), and consistency of the conclusions with other data and information available. MDH also conducted its own search of primary sources when formal assessments by other institutions were limited or considered outdated.

Sources of toxicity values used to derive HRL values are listed and described below. Sources are presented in approximate order of preference. Pursuant to *Minnesota Statutes*, section 103H.201, subd. (1)(d), only quantitative estimates of carcinogenic potency published by EPA can be used to develop HRLs for cancer. Therefore, of the sources listed below, only the EPA sources were used in deriving cancer HRLs.

- ◆ U.S. Environmental Protection Agency (EPA). Office of Pesticide Programs. Reregistration Eligibility Decisions (REDs). REDs summarize the results of toxicological testing required for pesticides that are subject to reregistration (that is, pesticides initially registered before November of 1984) and state risk assessment conclusions. Conclusions include toxicity values and, for REDs undertaken after 1996, a determination of the need for an additional factor to protect children. REDs form the basis for pesticide assessments on EPA's Integrated Risk Information System (IRIS) database (see paragraph immediately following) and tend to be more recent than other IRIS assessments. EPA may issue an Interim Reregistration Eligibility Decision (IRED) prior to issuing a RED. MDH has considered data and conclusions summarized in IREDs and may have used those data and conclusions in deriving a HRL. REDs and IREDs are

found at <http://cfpub.epa.gov/oppref/rereg/status.cfm?show=rereg>

In the absence of a RED or IRED, MDH may have used:

- Pesticide Tolerance Notices (published in the Federal Register);
 - Health Effects Division. Hazard Identification Assessment Review Committee Memoranda;
 - A Human Health Risk Assessment Chapter produced for a RED; or
 - A Toxicology Chapter produced for a RED.
- ◆ EPA. Integrated Risk Information System (IRIS). The Integrated Risk Information Program summarizes and evaluates toxicity testing and derives toxicity values for a large number of chemicals. IRIS is the primary toxicity database for EPA and represents a consensus opinion of EPA health scientists. IRIS files and their chemical-specific support documents have been subject to EPA's peer review policy since its issuance in 1994. IRIS is the primary source for the derivation of MDH HRLs for chemicals that are not used as pesticides. IRIS summaries can be accessed at <http://www.epa.gov/iris/>
 - ◆ California EPA. Office of Environmental Health Hazard Assessment (OEHHA). Public Health Goal technical support documents. California's OEHHA has conducted risk assessments for a number of chemicals found in drinking water. The OEHHA compiles relevant scientific studies and uses data from these studies to determine Public Health Goals (PHGs) for levels of contaminants in drinking water. PHGs are derived using methods and techniques consistent with those recommended by EPA, and are routinely subjected to internal and external peer review. Values derived and used in calculation of PHGs can be used to construct toxicity values. Technical support documents can be accessed at <http://www.oehha.ca.gov/water/phg/allphgs.html>
 - ◆ Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profiles. The U.S. Public Health Services (U.S. PHS) ATSDR has compiled "Toxicological Profiles" for more than 250 hazardous substances found at National Priorities List (NPL) sites or related to sites that are of interest to the Department of Defense (DoD) and the Department of Energy (DoE). Toxicological Profiles provide an exhaustive compilation of available toxicological and epidemiological research on a chemical. An examination, summary, and interpretation of that information results in noncancer toxicity values that are derived using the same approach as EPA. Toxicological Profiles can be accessed at <http://www.atsdr.cdc.gov/toxpro2.html>
 - ◆ EPA. National Center for Environmental Assessment (NCEA). In addition to having responsibility for maintaining IRIS, NCEA conducts a number of risk assessments for contaminants of emerging concern. While NCEA is well respected within the scientific community, toxicity values may have had less review than those from other sources. NCEA assessments summarize toxicity data and derive toxicity values. Toxicological reviews can be accessed at <http://cfpub.epa.gov/ncea/cfm/nceapublication.cfm?ActType=PublicationTopics&detype=DOCUMENT&subject=TOXICOLOGICAL+REVIEW&subjtpe=TITLE&excCol=Archive>
 - ◆ National Toxicology Program (NTP). NTP is an interagency program consisting of relevant toxicology activities involving the National Institutes of Health, the Centers for Disease Control and Prevention, and the Food and Drug Administration. NTP sponsors toxicity studies for agents of public concern and reports the results. NTP studies are among those that may be considered by EPA or other agencies. In derivation of HRLs, NTP studies that were not used to create a

toxicity value could serve to either support or reject a value based on limited data. NTP study summary reports and technical reports can be accessed at <http://ntp-server.niehs.nih.gov/>

- ◆ Primary Literature. When data summarized by other sources were limited or when toxicity assessments did not include recent research, MDH conducted a search of the published scientific literature for toxicity studies. Often, supplemental data reported by one of MDH's standard sources of toxicity data were helpful in deciding whether to accept, reject, or modify the value by applying different uncertainty and variability factors. For relatively few chemicals, MDH derived its own values from the primary literature.
- ◆ EPA Health Effects Assessment Summary Tables (HEAST) (EPA 1997). If cancer and noncancer criteria are not available through IRIS, EPA's Environmental Criteria and Assessment Office (ECAO) recommends using HEAST. This document lists the health-based criteria and references for the studies used to determine HEAST values. These are provisional risk assessment values that have been reviewed and accepted by individual agency program offices, but are not recognized agency-wide. HEAST values are used for chemicals commonly found at Superfund and Resource Conservation and Recovery Act Sites. HEAST has not been published or updated since 1997. This was taken into consideration in choosing among toxicity values.

Minnesota Department of Health Values. Generally, if EPA had published a chronic toxicity value, MDH based its evaluation on that value, including EPA's allocation of uncertainty and variability factors. However, MDH typically modified existing EPA toxicity values by adding, removing, modifying or reassigning (e.g., MDH routinely reassigned any FQPA factor as a database uncertainty factor) uncertainty and variability factors, or derived a toxicity value *de novo* from the scientific literature.

Occasionally, MDH was aware of recent research or recent concerns that were not reflected in EPA's assessment or toxicity value. In such instances, MDH turned to peer-reviewed literature to determine whether recent research indicated that EPA's toxicity value should be modified. For example, during the 1990s, EPA increased its use of the database uncertainty factor, often in response to deficits in developmental or reproductive testing. If an EPA toxicity value was derived at a time when fewer areas of uncertainty were considered or accounted for (i.e., a lack of formal developmental or reproductive testing), MDH may have increased the uncertainty factors applied for that chemical. If recent research filled a gap previously accounted for by an uncertainty factor, MDH may have removed or altered the value of that uncertainty factor. For example, if chronic studies had been lacking at the time of the EPA assessment, but had subsequently been performed, MDH could have eliminated the subchronic-to-chronic uncertainty factor. In some cases, MDH reassigned the uncertainty factors, but retained the same overall value for uncertainty.

For some chemicals and exposure durations, MDH evaluated the peer-reviewed literature and derived a HRL *de novo*. All toxicity values were reviewed internally by MDH. Draft values were made available for review on the HRL rules revision web page beginning in 2004, and again in 2007 and 2008 as values were derived. Stakeholder review of and comment on the draft values led, in some instances, to a revision of the draft values. Throughout the revision process, MDH maintained a web page summarizing its research, analysis, and results. MDH also sought input through public meetings. In December of 2004 a draft SONAR was published on the rules revision web page; the revised draft SONAR was published in September of 2007. The parameters used for each duration for each chemical were published on the rules revision draft HRL web page

(www.health.state.mn.us/divs/eh/groundwater/data/index.cfm) as the chemical reviews were completed (from September of 2007 to January of 2008).

Typically the sources listed above publish toxicity values for chronic durations. MDH used standard methods outlined by EPA (EPA 2002c) to derive RfDs for less-than-chronic durations (e.g., acute, short-term, and subchronic). EPA has published external review draft IRIS toxicological review and summary documents for two chemicals (dibutyl phthalate and 1,1,1-trichloroethane) that include derivation of less-than-chronic RfD values (EPA 2006d, 2007).

A brief explanation of any value modified or derived by MDH is provided in the table of HRL values in Part VI of this SONAR and in the example chemical summary sheets that appear in Appendix P.

Surrogates. The use of surrogates is appropriate when neither data specific to a whole mixture of chemicals, nor data specific to a chemical mixture's individual components, are available.

Use of a surrogate can allow guidance for contaminant degradates that have not been well-characterized as to their toxicity. Subject to environmental conditions, most chemicals eventually break down into degradates. The time required for this to occur depends on the chemical and the conditions. Breakdown time is measured as half-life, which is the time it takes for half of the quantity to degrade. Most chemicals have a variety of possible breakdown paths, resulting in the presence of the parent compound and a host of degradates. If degradates are known to be present and their concentrations can be accurately quantified or estimated, application of multiple-chemical risk assessment methods is appropriate.

Toxicological data for degradation products is often sparse, even when the toxicity of the parent compound is well characterized. In the absence of toxicological information specific to a degradate, it is MDH's policy to assume that a metabolite or degradation product has the same toxicological effect as its parent compound and is as potent as its parent. Degradates are typically considered to be less toxic than their parent compound, i.e., in rare instances a degradate may be more toxic than its parent, and use of the HRL of the parent compound in assessing a degradate is therefore considered to be a conservative approach. When conducting a multiple-chemical risk assessment (see Section IV.E.3.) using the common health risk index approach, the HRL derived for the parent compound will also be applied to each of its degradates in the absence of degradate-specific toxicity information.

IV.D. EXPOSURE ASSESSMENT

The exposure assessment describes "the nature and size of the population exposed to a substance and the magnitude and duration of their exposure. The evaluation could concern past or current exposures, or exposures anticipated in the future." (EPA 1985). A key component of exposure assessment is determining which exposure pathways are relevant. Each relevant exposure pathway is then quantified. The summation of the pathway-specific exposures results in an estimate of overall exposure. EPA exposure guidelines present a variety of methods for estimating exposures (EPA 1992b). The guidelines also provide recommendations for identifying populations of interest. Populations of particular interest include sensitive life stages or more highly exposed subgroups.

In deriving HRLs, MDH assumes that groundwater will serve as the primary source of drinking water for varying periods of time, and that the exposure pathway of concern is ingestion. Studies comparing water intake to age and body weight show that the period of life during which a person drinks the

greatest volume of water is during adulthood. The National Academy of Sciences Food and Nutrition Board found that the greatest range in the upper percentiles of volume of water consumed was in males between 19 and 50 years of age (NAS 2004). On a body weight basis, however, the period during which exposure to water will be greatest is during infancy and childhood. There may be some exceptions to this, such as adult athletes who consume large amounts of water due to exercise. MDH assumes that highly exposed adults are included in the higher percentiles of adult intake that have been documented in drinking water surveys. Water intake rates in infancy, childhood, and adult periods of life are all considered in the derivation of HRLs. Other pathways of exposure to a chemical in water (e.g., inhalation of volatilized chemical) or in other media (e.g., food, soil) are discussed elsewhere in the SONAR (see discussion of Relative Source Contribution in Section IV.E.1., Noncancer Risk Characterization).

IV.D.1. Water Intake Rates

Standard exposure inputs used by EPA for calculations of safe contaminant levels in drinking water use default assumptions appropriate for an adult population. Algorithms for the 1993/1994 HRLs conformed to this standard, using an adult body weight (70 kilograms) and an adult-based water intake (2 Liters/day). Expressed as a ratio, this intake rate is equivalent to approximately 0.029 liters of water per kilogram of body weight per day (L/kg-day).

Water intake is highly variable from person to person, but it is useful to note that serum osmolality, a measure of hydration, normally does not vary in a population. For example, the serum osmolality for adult males between 19 and 50 years of age ranged only between means of 279 and 281 mmol/kg (1st and 10th decile, respectively) while the corresponding mean total water intake ranged from 1.694 to 7.934 L/day (NAS 2004).³ This is because homeostatic responses (e.g., urine composition and output) compensate for over and under-hydration. Since the adult body can compensate for differing levels of water intake, there is no single water intake level that can be recommended to maintain optimal hydration.

The standard default of 0.029 L/kg-day for an adult can be compared to surveys of drinking water intake. The most recent and complete information is found in an EPA report, "Estimated Per Capita Water Ingestion and Body Weight in the United States—An Update" (EPA 2004c). EPA analyzed water ingestion from data collected in the Continuing Survey of Food Intakes by Individuals (CSFII) conducted by the U.S. Department of Agriculture for 1994-1996 (15,303 individuals) and 1998 (data for an additional 5,500 children). EPA used these survey data to derive per person and per body weight water intake distributions for the general population and subpopulations (e.g., children, pregnant women, lactating women, and women of childbearing age). EPA made a distinction between intake estimates for all people in the survey (even if they reported drinking no tap water on the days of the survey) and intakes based on only the people who drank at least some tap water ("consumers-only estimates"). The report provides water ingestion amounts by water source. Sources include community tap water, bottled water, other water (e.g., private household wells, cisterns, and springs), and all of these sources combined ("total" water). MDH followed the Science Advisory Board (SAB) recommendation that, for the purpose of deriving consumption estimates for use in assessing exposure to drinking water contaminants, consumer-only estimates be used (EPA 1999). Consumers are defined

³ Mmol/kg is millimoles per kilogram. A millimole is one thousandth of the mass in grams of 6.0225×10^{23} atoms of a substance.

as individuals who reported consuming from the water source under consideration on the day of the survey.

To obtain "consumer-only" consumption estimates for use in assessing exposure to drinking water contaminants for infants less than twelve months old, MDH contacted Jacqueline Moya, the EPA Project Manager for the Child-Specific Exposure Factors Handbook. She provided MDH with revised data for Table 4-4 of the 2006 draft Child-Specific Exposure Factors Handbook that reflected "consumer-only" intake rates (EPA 2007b).

Table 2 is an excerpt of draft values from EPA intake summary tables (EPA 2004c) and revised draft Table 4-4 of the draft Child-Specific Exposure Factors Handbook (EPA 2007b). It shows the drinking water intake rate for individuals who consume water from a community water supply. Only those that drank from a community water source were included in this analysis and the intake rate is based on their water consumption from only that source (i.e., water that they may have consumed from other sources, such as bottled water, is not included in the analysis).

Table 2: Consumer-Only Community Water Ingestion in L/kg-day

Age	Percentile				
	50 th %	75 th %	90 th %	95 th %	99 th %
Birth to < 1 month	0.155	0.198	0.269	0.269	0.269
1 to < 3 months	0.107	0.153	0.247	0.289	0.375
3 to < 6 months	0.077	0.118	0.149	0.174	0.224
6 to < 12 months	0.048	0.081	0.112	0.130	0.186
1 - 3 years	0.020	0.035	0.053	0.068	0.110
4 - 6 years	0.018	0.031	0.047	0.063	0.091
7 - 10 years	0.013	0.022	0.033	0.040	0.059
11 - 14 years	0.010	0.017	0.026	0.034	0.060
15 - 19 years	0.009	0.016	0.026	0.032	0.062
20 - 24 years	0.011	0.018	0.031	0.039	0.080
25 - 54 years	0.013	0.021	0.032	0.04	0.065
55 - 64 years	0.014	0.023	0.032	0.038	0.058
65+ years	0.016	0.024	0.032	0.037	0.053
Pregnant women	0.009	0.022	0.033	0.043	0.047
Lactating women	0.020	0.041	0.054	0.055	0.057

Sources: Age groups birth to < 12 months from revised draft Table 4-4 of the draft Child-Specific Exposure Factors Handbook (EPA 2007b) and age groups 1 year and older from EPA Estimated Per Capita Water Ingestion and Body Weight Report (EPA 2004c - Appendix E, Part IV, Table A2).

From these data it is evident that up to approximately 90 percent of adults (20 years and older) consume less than 0.029 L/kg-day and their water intake is encompassed in the 1993/1994 HRL default assumption. An exception to this is lactating women, who appear to consume more water than

other adults. For this group, the 0.029 L/kg-day default is inclusive of perhaps 60 to 65 percent of women.

The 1993/1994 HRLs were considered values for the general population, and with the exception of nitrate⁴, the 1993/1994 HRL calculations did not address exposures specifically pertinent to infants and children who, on a per body weight basis, drink more water than adults. Table 2 shows that intake rates drop sharply with age. Higher intake rates persist for approximately the first seven years of life; by age seven, intake rates are nearly the same as those of adults. These observations are not surprising, given that newborns derive all of their nutrition from liquid and that young children have a higher metabolic rate than adults. While these high intake rates persist for only a small percentage of a typical lifespan, they are important to consider when health effects can result from short periods of exposure.

IV.D.2. Exposure Duration-Specific Default Intake Rates

Generally, HRLs are thought of as protecting against adverse health effects from long-term exposures to contaminants in drinking water. However, they must also protect against effects resulting from shorter exposures. Understanding the relationship between timing and duration of exposure and the subsequent adverse effect is essential in deriving appropriate, health-protective criteria, particularly for less-than-chronic exposures. MDH considered the timing (e.g., life stage most susceptible to a toxic effect) as well as the duration of exposure necessary to elicit a toxic effect in selecting default intake rates.

The toxicity evaluation for a chemical examines the range of health effects that have been found in laboratory animal studies or epidemiological studies. Different life stages may have different sensitivities or susceptibilities to a chemical's toxic effects. It is important, therefore, to match the exposure assumptions to the life stage that is most sensitive to the toxic effects of the chemical.

A paradigm for accounting for duration of exposure by using laboratory animal experiments of acute, subchronic (e.g., 90 day bioassay) and chronic (e.g., 2 year bioassay) duration was established in 1983 by NRC (EPA 2002c). One should keep in mind the possibility that a given study duration may provide information on several different durations. For example, a chronic duration study may produce effects in the short term in addition to effects that only appear after repeated long-term dosing.

Protocols for toxicity testing do not necessarily evaluate or report effects observed at interim time points (i.e., before the end of the study). The effects reported at the end of the study could have arisen earlier and thus may have resulted from a shorter duration. MDH acknowledges this limitation and the potential to overestimate the effective dosing duration; however, in the absence of interim time point assessments the duration of the study will be used as the relevant dosing duration. When data are available, MDH assesses interim time points during the study duration, leading to a better estimate of the length of exposure required to elicit an adverse effect.

The EPA Technical Review Panel (EPA 2002c) and the external Expert Advisory Panel (ERG 2005) have recommended evaluation of less-than-chronic exposure periods to ensure that high intake rates over short periods of time (e.g., early life stages) are adequately protected. As part of their

⁴ An infant exposure of 0.64 L/day and 4 kilograms body weight was used in 1993 to calculate the nitrate HRL value.

recommendations the EPA Technical Review Panel provided the following definitions for various exposure time periods:

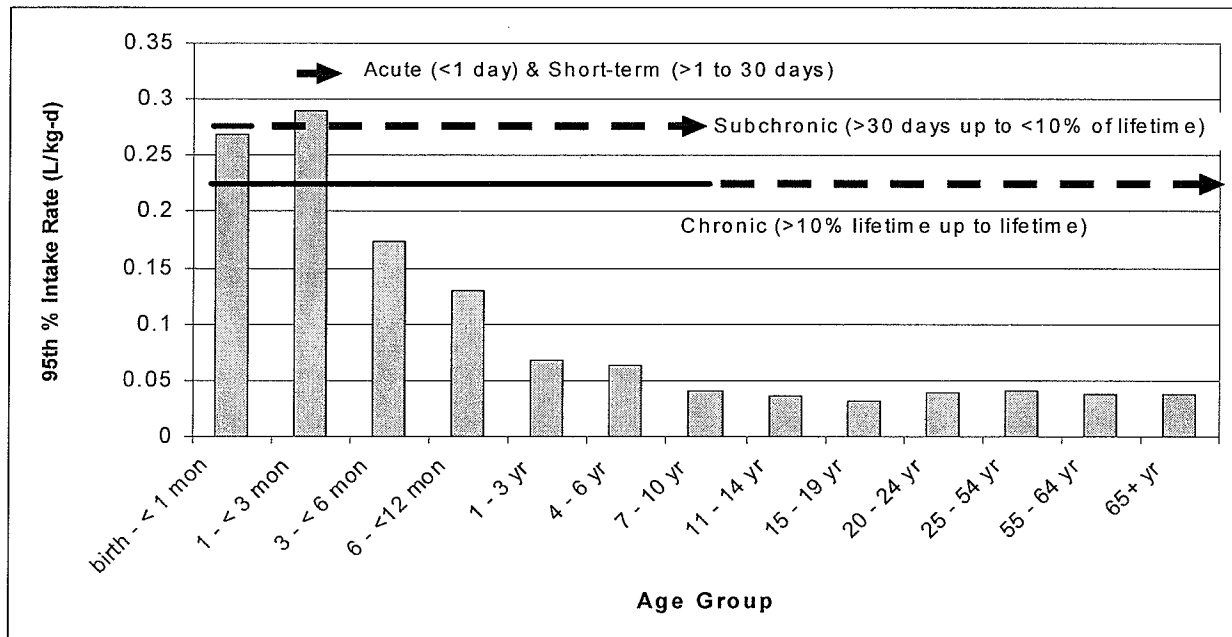
- Acute– dosing duration of 1 day or less;
- Short-term– repeated dosing for more than 1 day, up to approximately 30 days;
- Subchronic– repeated dosing for more than 30 days, up to approximately ten percent of a lifespan in humans (more than 30 days up to approximately 90 days in typical laboratory rodent studies); and
- Chronic– repeated dosing for more than approximately ten percent of a life span.

For a human residing in the United States, the current life expectancy is approximately 78 years (NCHS 2006). EPA uses a life span of approximately 70 years.

EPA usually incorporates a “high-end” exposure level in order to ensure an adequate margin of safety for most of the potentially exposed population (EPA 2004a). “High end” is defined as the part of the exposure distribution that is above the 90th percentile, but below the 99.9th percentile. The EPA SAB (EPA 1999) commented that the CSFII survey design did not allow for estimating water ingestion in subpopulations that, by choice or by circumstance, used only one source of water for ingestion. Such individuals may consume more tap water than the national estimates provide. The potential for underestimating ingestion is more pronounced for infants than other age groups since the distribution reflects a high percentage ingesting minimal amounts (insufficient to sustain life) of community water. This probably reflects infants who are breastfed or are fed pre-mixed formula or formula prepared with bottled water.

MDH has used the survey data reported in Table 2 to calculate default water intake rates for the various durations specified above (Figure 1.) The selected intake rates (L/kg-day) represent values that include most of the population (i.e., 95th percentile). This ensures that the HRL value is protective of individuals who consume a large percentage of their water from a single source, such as a private well or a community water supply.

Figure 1: Duration-Specific Intake Rates



MDH calculated a time-weighted average (TWA) of the 95th percentile intake rates within each duration of concern, as indicated by the arrows in Figure 1. The starting point of each arrow was selected so as to maximize the resulting intake rate for each duration. For effects that result from acute or short periods of dosing, a default intake rate of 0.289 L/kg-day, based on the 95th percentile intake for an infant aged 1 up to 3 months, is used in the derivation of acute or short-term HRLs. Published studies on fluid intake in young infants (Arcus-Arth *et al.* 2005, Goellner *et al.* 1981, Fomon *et al.* 1971, Leung *et al.* 1988, Neville *et al.* 1988) and daily fluid intake recommendations for infants (Kleinman 2004; Gunn and Nechyba 2002) indicate that this water intake rate is adequately protective of very young infants.

When the developmental period is identified as the most susceptible life stage, MDH carefully evaluated the available neonatal toxicity data. If the susceptible developmental period were limited to *in utero* development, the reference dose for the effect would be based on maternal exposure and the intake rate for pregnant women (0.043 L/kg-day, based on the 95th percentile intake rate) would be used to protect the developing fetus. However, development takes place after birth as well as before birth. MDH determined that, in the absence of post-natal data, developmental toxicity data (data from *in utero* exposure) would be used as the basis for evaluating health risk to neonatal humans. Infants who drink formula prepared with water are considered most exposed, and therefore most likely to be at risk. The acute and short-term default intake rate (0.289 L/kg-day), based on the 95th percentile intake rate of young infants, would be selected as the default intake rate for HRLs based on developmental effects that were not limited to *in utero* exposure. This approach was supported by the external Expert Advisory Panel (ERG 2005). The conditions for this approach to be used were not met for any of the chemicals in the current revision of the rules, but the approach is included here for potential use in future chemical assessments.

To calculate a time-weighted average (TWA) the intake data from Table 2 was used in the following equation:

$$IR_{TWA-duration} = \frac{IR_1D_1 + IR_2D_2 + IR_3D_3 + IR_4D_4 + IR_5D_5 + \dots + IR_nD_n}{D_{total}}$$

Where:

IR_{TWA} = the time-weighted water intake rate (L/kg-day).

$IR_{1,2,3\dots}$ = the water intake rate for a specific age group in Table 2 (L/kg-day).

$D_{1,2,3\dots}$ = the duration corresponding to $IR_{1,2,3\dots}$, as shown in Table 2 (years).

D_{total} = the total duration for which the TWA intake is being calculated (e.g., 8 years for subchronic).

For effects resulting from subchronic periods of dosing (e.g., periods up to less than approximately 10% of a lifetime), a time-weighted average (TWA) of the 95th percentile intake from birth up to 8 years of age was calculated as a default intake rate:

$$\begin{aligned}
 \text{IR}_{\text{TWA-subchronic}} &= \frac{(0.269 \times 0.083) + (0.289 \times 0.167) + (0.174 \times 0.25) + (0.13 \times 0.5) + (0.068 \times 3) + (0.063 \times 3) + (0.040 \times 1)}{8} \\
 &= 0.077 \frac{\text{L}}{\text{kg} - \text{day}}
 \end{aligned}$$

This approach yields a value that is conservative for adult subchronic exposure in order to be adequately protective of children.

For effects resulting from chronic dosing (e.g., periods greater than approximately 10% of a lifetime) a time-weighted average of the 95th percentile intake over a lifetime of approximately 70 years, i.e., 0.043 L/kg-day, was calculated as a default intake rate using the intake data in Table 2 and the IR_{TWA} equation above.

For carcinogenic effects, MDH selected an intake rate representative of the 95th percentile intake rate within each of the three age groups identified by EPA (EPA 2005a). For the age group from birth up to 2 years of age, MDH used the 95th percentile intake from Table A2 of Appendix E, Part IV of the EPA Estimated Per Capita Water Ingestion and Body Weight Report (EPA 2004c), i.e., 0.137 L/kg-day. For the remaining two age groups the following TWAs of the 95th percentile intake rate were calculated: 0.047 L/kg-day for 2 up to 16 years of age; and 0.039 L/kg-day for 16 years of age and older.

MDH departs from the above default intake rates if sufficient chemical-specific information indicates that a different duration or intake rate is more appropriate. In these cases MDH will use the data in Table 2 to calculate a TWA intake rate relevant for the duration specified by the chemical-specific information. The duration and intake rate for PFOA and PFOS are examples of the use of chemical-specific information. Toxicity studies indicate that adverse effects across species are consistently associated with a concentration of the chemical in serum rather than administered dose. The duration period used for PFOA and PFOS, both bioaccumulative chemicals, incorporates the chemical specific rate at which the chemicals accumulate in serum. The chemical summary sheet for PFOA is included in Appendix P.

IV.E. RISK CHARACTERIZATION

The *risk characterization* integrates the data and analysis of the first three steps of the risk assessment process to determine the likelihood that humans will experience adverse health effects as the result of the exposure conditions under evaluation. This final step summarizes assessments of health effects and assessments of exposure from multiple environmental media; identifies life stages or subpopulations at elevated risk; combines these assessments into characterizations of risk; and describes the uncertainty and variability in these characterizations (EPA 2004a). The goal of risk characterization is to provide an understanding of the type and magnitude of the potential adverse effects of an agent under the particular conditions of exposure.

Risk characterization also incorporates the conditions of exposure. Chemical exposures do not occur in isolation from one another. People are continually exposed to a mixture of chemicals that is ever-shifting in composition and in concentration.

An MDH-derived HRL represents a concentration of a chemical in drinking water that is associated with little or no health risk according to public health practice. In deriving HRLs for individual chemicals MDH selected toxicity values based on the most sensitive health effect(s) (e.g., RfD for noncancer effects and slope factors for cancer effects) for various exposure durations. MDH also selected duration-specific intake rates based on life stages or subpopulations at elevated risk due to sensitivity or increased exposure. Furthermore, MDH accounted for exposure from multiple environmental media (e.g., RSC) and adopted an approach to account for multiple exposures from multiple chemicals. This section summarizes the rationale for these decisions and also describes the key sources of uncertainty.

IV.E.1. Noncancer

In the HRL rules, the goal for chemicals that exhibit a threshold for toxicity is to prevent exposures from exceeding the threshold. The reference dose is the dose (expressed in mg/kg-day) that is without significant health risk, therefore, the HRL is based on a reference dose for noncancer health effects.

A reference dose (RfD) may be based on a few days of exposure (e.g., dosing to the pregnant rat in a developmental study) or on a long-term or chronic exposure (e.g., a 2-year chronic toxicity study in rats). Reference doses for a chemical are intended to be protective of all types of adverse effects for a given duration of exposure. Therefore, HRLs also protect from exposures of varying durations.

The challenge in deriving a HRL is to consider combinations of exposures (in terms of drinking water intake) and sensitive time points (such as life stages) of exposure in order to select an appropriate exposure interval for a particular reference dose. To address this challenge, MDH considered developmental as well as nondevelopmental effects that may occur as the result of acute, short-term, subchronic and chronic exposures.

Developmental Effects. Deriving values that will protect infants from chemical insult involves unique challenges. During pre-natal and post-natal periods, the fetus and neonate is growing and changing rapidly. In humans, organogenesis occurs between gestation days 21 and 46; upper limb buds form on days 29-30, lower limb buds on days 31-32, testes differentiation occurs on day 43, and heart septation on days 46-47 (Rogers, 1996). For some chemicals, exposures of only a few days in length can change the course of development. The most dramatic of such exposures was the effect that thalidomide exposure during gestation had on limb bud development of babies. Another example is the lifelong cognitive and behavioral effects that lead has on babies exposed after birth. MDH has given serious consideration to how to address these concerns when creating HRLs for chemicals that have their greatest effect during developmental periods.

Three different methods of testing the developmental effects of a chemical have evolved: standard developmental studies, multigenerational studies, and developmental neurotoxicity studies. Standard developmental studies provide data on maternal and fetal toxicity from laboratory animal studies. Multigenerational studies provide toxicity data for animals dosed from conception – or before – and into adulthood in more than one generation. In developmental neurotoxicity studies pregnant animals are dosed during gestation through postnatal day 10. Motor activity of the offspring is measured at various time points through young adulthood.

The standard developmental studies fall short of providing the information needed because they do not dose or evaluate toxicity during the post-natal period. The latter studies (multigenerational and

developmental neurotoxicity) fall short because the actual dose received by the neonate is often unknown due to difficulty in quantification. Moreover, it is unclear whether an effect observed at the termination of dosing or at the termination of the study is a result of cumulative exposure or the manifestation of a latent response from early-life exposure. All studies require extrapolation from laboratory animals to humans. Rodents, the most common mammalian laboratory animals, are less developed at birth than humans.

MDH has assumed that a human newborn is as susceptible to developmental toxicity as the fetus or pup that was evaluated in a laboratory study. This assumption may be overprotective, or it may not be protective enough. The developmental endpoints most often measured in mammalian laboratory animal studies, including low body weight, delayed physical development, and mortality, are effects that can occur after birth as well as *in utero*. Many of the more subtle functional endpoints that are a concern today are not tested in laboratory animal studies.

Selecting an intake rate appropriate to developmental periods is another challenge. Doses of concern for developmental toxicants in fetuses are based on maternal intake. However, MDH must also consider development that occurs after birth and the appropriate exposure level for a developing infant. The actual dose received by the fetus in a developmental study is not known because the dose is mediated by the mother's body. For the purpose of protecting the fetus, the maternal dose associated with no effects to the fetus during the course of the pregnancy is all that matters. However, at birth, the neonate begins drinking directly and at its own rate. The newborn that is given formula prepared with water will have a water intake rate that is higher than that of its mother. Exposure criteria for developmental toxicants that are based only on an adult intake rate may not protect the developing infant. MDH has determined that an intake rate appropriate for infants should be used in deriving HRLs for developmental effects. The infants that are the greatest concern to MDH are those that are dependent on formula prepared with tap water. The intake rate used for acute and short-term exposure (i.e., an infant intake rate) will also be used for the derivation of noncancer HRLs based on developmental effects. However, if the developmental effect could only occur *in utero*, the intake rate for a pregnant woman (0.043 L/kg-day) rather than a young infant would be used.

The external Expert Advisory Panel agreed that the practice of using prenatal (fetal) developmental toxicity information, in the absence of appropriate neonatal toxicity data, to protect neonates is reasonable and health-protective (ERG 2005). The Panel also supported the need to incorporate water consumption rates representative of infant intake rates.

Noncancer Effects Other than Development. MDH also considered what period of time should be used for averaging intake rate when developmental effects are not the critical effect. As described in Section IV.D.1., intake rates on a per body weight basis are quite high at birth and then drop sharply with age. By seven to eight years of age the per body weight intake rates are similar to adults.

EPA (EPA 2002c) has defined a variety of exposure durations ranging from acute (up to one day) to a lifetime:

- Acute - dosing duration of 1 day or less;
- Short-term – repeated dosing for more than 1 day, up to approximately 30 days;
- Subchronic – repeated dosing for more than 30 days, up to approximately ten percent of a lifespan in humans (more than 30 days up to approximately 90 days in typical laboratory rodent studies); and
- Chronic - repeated dosing for more than approximately ten percent of a life span

MDH selected duration-specific periods that incorporated the higher intake rates during early life so that childhood was specifically addressed in the HRL algorithm. In deriving HRLs for acute, short-term, subchronic and chronic effects MDH will use the following default algorithm.

$$\text{nHRL}_{\text{duration}} = \frac{\text{RfD}_{\text{duration}} \times \text{RSC} \times 1,000}{\text{IR}_{\text{duration}}}$$

Where:

- nHRL_{duration} = the noncancer health risk limit, for a given duration, expressed in units of micrograms of chemical per liter of water (µg/L).
- RfD_{duration} = the reference dose, for a given duration, expressed in units of milligram 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.
- RSC = the relative source contribution factor which represents the percentage of total exposure to a substance or chemical that is allocated to ingestion of water. The default RSC is 0.2 for highly volatile chemicals. For other chemicals the default RSC is 0.5 for acute and short-term HRLs and 0.2 for subchronic or chronic HRLs.
- 1,000 = a factor used to convert milligrams (mg) to micrograms (µg).
- IR_{duration} = the intake rate 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 birth - 1 month 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 of age.

MDH will depart from the above default noncancer HRL algorithm and parameter values if sufficient chemical-specific information indicates that a different duration or intake rate is warranted. In these cases a time-weighted intake rate would be calculated, using the same intake dataset (see Section IV.D.1), over the duration specified by the chemical-specific information. The RfD, RSC and IR values used for each chemical in deriving each nHRL will be identified in the rules.

In general, it is anticipated that for a given chemical the shorter-duration HRL will be higher than the longer-duration HRL. However, the HRL values may not always follow the expected continuum from higher to lower for a variety of reasons. The longer-duration HRLs must be protective of short exposures that may occur within the longer duration. In the event that a shorter-duration HRL is more limiting than the calculated longer-duration HRL, the longer-duration HRL will be set so as not to exceed the shorter-duration HRL. Dieldrin is an example of a case in which a longer-duration HRL (i.e.,

the subchronic HRL) was set at the more limiting, shorter-duration HRL (i.e., the short-term HRL) (see Appendix P).

Relative Source Contribution. The relative source contribution, or RSC, is a factor used in drinking water risk assessment to allocate only a portion of the RfD to exposure from ingestion of water, and reserves the remainder of the RfD 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 HRLs for noncarcinogens, requires that an RSC be used in deriving noncancer HRLs.

The external Expert Advisory Panel encouraged development of an exposure modeling analysis for definition of a family of RSC values (ERG 2005). Separation of volatile and nonvolatile agents was suggested as a first approach.

Because reliable data suitable for application to the general case (e.g., non-site-specific) are not available, RSC values for the revised HRL rules have been derived in a qualitative manner using a decision tree process produced by EPA in its Ambient Water Quality Criteria document (EPA 2000c). In that guidance, EPA presents a series of decision points at which the quality and quantity of available data are evaluated; at each decision point the derivation of an RSC is steered towards another decision point, and ultimately to one of several conclusions indicating an appropriate RSC. In general, a lack of statistically significant data relating to fate and transport, exposure, and physical/chemical properties will tend to result in a more conservative (i.e., lower) RSC. EPA recommends a floor value of 20 percent (0.2) and a ceiling value of 80 percent (0.8) for the RSC. The use of an 80 percent ceiling is intended "to ensure that the health-based goal will be low enough to provide adequate protection for individuals whose total exposure to a contaminant is, due to any of the exposure sources, higher than currently indicated by the available data" (EPA 2000c). The 20 percent floor incorporates an assumption that the major portion (80 percent) of the total exposure comes from other sources, such as diet. Because the decision tree model is intended for use in site-specific applications, its use in the general case has resulted in a default RSC of 0.2 for most chemicals and most exposed populations. The exceptions to this conclusion are the cases of infant exposure to chemicals *other than* highly volatile chemicals; the narrow range of environments encountered by an infant during the first month of life justified the use of a default RSC of 0.5 for those exposure scenarios. Highly volatile chemicals were assigned an RSC of 0.2 for all populations because the exception for infants was not expected to apply to chemicals whose principal route of exposure is inhalation. MDH's derivation of the default RSC values using EPA's decision tree process is documented in Appendix K.

The RSC scheme outlined above requires a classification of the volatility of each chemical for which a HRL is derived. To that end, MDH has classified each HRL chemical as being nonvolatile, highly volatile, moderately volatile, or of low volatility using criteria developed by ATSDR (2001). Under those criteria, highly volatile chemicals are defined as those with a Henry's Law constant greater than 1×10^{-3} atm³/mol; these chemicals would have a default RSC of 0.2 for the first month of life. Other chemicals would have a default RSC of 0.5 for the first month of life. While a nonvolatile, low-volatility, or moderate-volatility chemical may still be present in air, concentrations will generally not be high enough to contribute significantly to total exposure. This information will permit the risk manager to determine whether additional protections beyond those in the HRL are advisable to protect the health of potentially exposed individuals. (See Appendix L for more information about volatilization.)

IV.E.2. Cancer

The risk characterization step for a carcinogenic chemical combines exposure assessment and toxicity evaluation to derive an expression of risk. The risk for carcinogens is expressed as a probability of developing cancer. As described above in the discussion of Cancer Potency Estimation in Section IV.C.3., Cancer Effects, results of laboratory animal assays are expressed as a probability of cancer. For example, a pathologist may find that 4 of 10 animals have one or more malignant tumors when the study is terminated after two years of daily dosing. The risk of an animal developing one or more tumors is 4 in 10. The data are modeled in various ways, and a confidence level is calculated for the data. The final expression of cancer potency (cancer incidence per mg/kg-day) represents a high confidence (95 percent) that the true risk is lower. Simple multiplication of the estimated daily dose in mg/kg-day and the cancer potency results in a cancer incidence (risk).

In the case of the HRL rules, a risk level must be chosen so that the exposure level (i.e., the HRL) that prevents higher risk can be calculated. This risk level is termed "additional cancer risk." Longstanding public health practice in Minnesota has been to use an additional cancer risk of 1 in 100,000 when considering environmental contaminant impacts on human health. An additional cancer risk of 1 in 100,000 means that if a population of 100,000 people were exposed, to a specific concentration of a carcinogen, at most, one case of cancer would be expected to result from this exposure. Because the calculations use a 95 percent confidence interval, the true risk is likely to be lower. To put this 1 in a 100,000 risk in perspective, currently one of every two Minnesotans will have some type of cancer by the end of their lifetime (a cancer risk of 50,000 per 100,000). This is considered the background cancer risk in Minnesota and in the United States over all. The risk from exposure to a HRL chemical is considered an additional cancer risk.

To calculate a cancer HRL an appropriate intake rate and a cancer potency factor must be selected. Current cancer risk assessment models for drinking water standards typically make no assumption about the duration of exposure or variability in exposure over a lifetime, but use a standard default intake of 2 L and 70 kg, which is appropriate for adults.

In many other risk assessment applications, risk assessors use lifetime time-weighted average intake rates; that is, the total dose received is averaged over a lifetime to determine additional cancer risk. A corollary of the use of lifetime average daily dose (LADD) in assessing cancer is that the same cumulative dose is assumed to give rise to the same cancer response regardless of the time period over which that dose is received. A second corollary of the use of LADD is that it does not matter when a dose is received: no period of life is considered any more sensitive than any other period of life.

The appeal of using LADD with expressions of cancer potency lies in its simplicity and its appearance of being risk neutral with regard to timing of exposure. It is not, however, compatible with current dose-response models of carcinogenesis (EPA 2005a, b). These models predict that cancer risks are not necessarily proportional to exposure duration and can depend on the nature of the carcinogen and the timing of exposure. Differences in molecular and biochemical processes among adults, adolescents, children, infants, and fetuses may influence the development and progression of cancer. Cell proliferation and programmed cell death (and the balance between the two), critical for the development and maintenance of normal tissue, are also important elements of the carcinogenic process. Cell proliferation and programmed cell death are most rapid during the developmental years. Rapid cell division during development can cause enhanced expression of mutations due to reduced

time available for DNA (deoxyribonucleic acid) repair. Also, some embryonic cells lack key DNA repair enzymes.

The assumption implicit in LADD that the timing of the dose does not matter is fundamental to the standard method that has evolved for testing chemicals for carcinogenic potential. However, EPA has recently acknowledged that there is evidence that this assumption is not always correct (EPA 2005a). In the classic laboratory animal cancer bioassay, rats are dosed essentially daily (usually five days/week) for two years, beginning at approximately six to eight weeks of age. In terms of physiological maturity, a six to eight week old rat is considered analogous to a fifteen to eighteen year old human. Therefore, the cancer bioassay does not include early life, and may only touch on later puberty. Since under LADD, timing of the dose is irrelevant, this gap in testing (birth to weaning) has largely been ignored. It is very difficult for toxicologists to directly dose a neonate and there has been little incentive for toxicity testing for this life stage.

MDH considered the age at which laboratory animals are first exposed in an experimental study, the time points at which tumor development is assessed, the effect of intermittent or short-term dosing on long term tumor development, and how all of these relate to human exposure to contaminated drinking water.

Data from short-term exposure studies indicate that the lack of early-life-stage testing and lifetime averaging may in fact result in a gap in public protection. MDH has considered several types of studies that examine whether the timing and duration of an exposure to a carcinogen make a difference in the development of cancer. The relevant studies are of several types:

- ◆ "Stop exposure" studies – Standard cancer bioassays generally involve exposure of adult laboratory animals for 2 years. In the "stop-exposure" study, a subgroup of adult animals in the standard chronic cancer bioassay are dosed for a short period of time and are then maintained until the end of the study. The tumor incidence rates from the short period of time are compared to tumor incidence rates resulting from the standard chronic cancer bioassay. "Stop exposure" studies evaluate the assumption that exposures of limited duration are associated with a proportional reduction in risk.
- ◆ "Single dose" or acute exposure studies – The tumor incidences resulting from a single dose administered at different life stages are compared. Doses may be administered during early life, including gestation, and tumorigenesis is typically evaluated late in life. Dosing test laboratory animals at different times of life allows a comparison of cancer potency (incidence per mg/kg-day) at different stages of life.
- ◆ "Short-term repeated" studies – The tumor incidence resulting from short-term repeated dosing during the early postnatal to juvenile period is compared to the tumor incidence resulting from the standard chronic adult-only cancer bioassay. The objective of this comparison is to estimate the incidence attributable to early-life exposures.
- ◆ "Lifetime exposure" studies – The tumor incidence in laboratory animals dosed for a "lifetime" (beginning at or before birth and continuing through adulthood) is compared to the tumor incidence resulting from the standard chronic adult-only cancer bioassay. The objective of this comparison is to evaluate whether dosing during early life contributes disproportionately to the lifetime incidence of cancer.

A brief summary of recent evaluations of each study type is presented below. A more detailed summary of evaluations is presented in Appendix M.

“Stop-exposure” studies. In 2000, Halmes, Roberts, Tolson, and Portier tested the cumulative dose assumption by comparing observations from eleven “stop exposure” studies conducted by the National Toxicology Program (NTP) (Halmes *et al.* 2000). The NTP stop-exposure studies followed the standard cancer bioassay design, but included a subset of animals exposed for shorter periods of time. The objective of the study was to test the hypothesis that short-term adult exposure, when compared to long-term adult exposure, results in a proportional decrease in risk.

For more than half of the eleven chemicals evaluated, the shorter exposures resulted in disproportionately higher cancer incidence. Consistency in cancer potency between the short-term and standard continuous exposures was only achieved when the short-term doses were averaged over periods of less than a lifetime. In some cases, the equivalent averaging time was as short as the exposure duration itself. The authors noted that no obvious relationship could be deduced between genotoxicity and the influence of exposure duration on tumor response for the eleven chemicals evaluated when the exposure was averaged over longer periods. The observations from this analysis suggest that, more often than not, lifetime averaging of short-term exposure underestimates the cancer risk.

“Single-dose” or Acute exposure studies. In the *Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens* (EPA 2005a), EPA scientists performed a quantitative evaluation of tumor incidence rates resulting from a single dose administered either during the first weeks of life or during young adulthood. Studies were available for eleven mutagenic chemicals and doses were typically administered by injection. The tumor incidence resulting from the single exposure during the first weeks of life was compared to the tumor incidence resulting from the same single dose as a young adult (e.g., tumor incidence_{early-life}/ tumor incidence_{adult}). When ratios for all tissues were combined, 55 percent of the ratios were greater than 1 (range 0.01 to 178, with a geometric mean ratio of 1.5) (Barton *et al.* 2005; EPA 2005a, Table 8). This means that for the majority of the studies conducted with these eleven chemicals, a single exposure early in life was more potent than that same exposure to an adult.

In 2003, Ginsberg⁵ also conducted a literature-based review of early-life-stage exposure data (Ginsberg 2003). Ginsberg compared the results of acute exposures during early life stages to the results of acute exposures in adults. The comparison was conducted for eight mutagenic chemicals. The comparison for all eight chemicals showed at least a two-fold increase in sensitivity in juvenile laboratory animals. Overall, the differences were commonly between three- and ten-fold, with evidence that for certain carcinogens and tissues the difference could be greater than an order of magnitude.

“Short-term repeated dose” studies. Researchers have also compared tumor incidence rates resulting from short-term exposures during the juvenile period to rates resulting from chronic exposure during adulthood (i.e., the standard cancer bioassay design) (EPA 2003f, 2005a; Ginsberg 2003).

⁵ Dr. Gary Ginsberg is associated with the Connecticut Department of Public Health, Division of Environmental Epidemiology & Occupational Medicine.

Hattis⁶ and his colleagues have recently conducted a more formal analysis of the data assembled by EPA (Hattis *et al.* 2004a, 2004b).

The objective of the EPA analysis was to estimate the increased tumor incidence attributable to early-life exposure. To do this, EPA scientists normalized the incidence data for the exposure duration (for example tumors per week of exposure). Tumor incidence rates from short-term exposure during early life were compared to tumor incidence from chronic adult exposure (Barton *et al.* 2005; EPA 2005a, Table 8). Studies were available for four mutagenic and six nonmutagenic chemicals. Forty-two percent of the ratios for the four mutagenic chemicals were greater than 1 (range 0.12 to 111, with a geometric mean ratio of 10.5). Twenty-seven percent of the ratios for the six nonmutagenic chemicals were greater than 1 (range 0.06 – 13, with a geometric mean ratio of 2.2). These ratios show that for some, but not all, of the eleven chemicals studied, a brief period of multiple exposures during early life was more potent than a comparable dose given over a longer period later in life.

Ginsberg evaluated studies for ten carcinogens to determine whether exposure during early life would result in additional tumors and/or higher potency than adult-only exposure. The studies with similar administered dose rates (mg/kg-day during the dosing period) were selected to facilitate direct comparison of the tumor response. The short-term early-life versus chronic adult comparisons did not show a large difference in response. Nine of the ten carcinogens provided evidence of similar tumor response per unit of administered dose for short-term early-life exposure as compared to chronic adult exposure. This suggests that short-term exposures early in life are just as important as long-term exposures that begin later in life.

In 2004, Hattis and colleagues conducted a more formal statistically-weighted evaluation of studies assembled by EPA. Rather than simply compare tumor incidence rates resulting from exposure during different life stages, Hattis *et al.* quantified cancer potency in terms of cancer transformations per animal per unit dose for three different age groups (fetal, birth-to-weaning, and weaning-to-60 days) relative to comparably dosed adults. The unit dose was expressed as dose/kg^{0.75}-day. This analysis suggested that, for mutagens, the birth-to-weaning age group exhibited the highest sensitivity, followed by the fetal period and the weaning-to-60 day period. The magnitude of increased sensitivity, for the birth-to-weaning age group was similar to EPA's estimate (i.e., 10-20) for short-term repeated exposure to mutagenic chemicals.

The California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) has also evaluated the effects of carcinogenic exposures early in life (Sandy *et al.* 2006). In this analysis OEHHA did not separate the carcinogens evaluated as mutagenic or nonmutagenic. Age Sensitivity Factors (ASFs) were derived for the following age windows: prenatal (*in utero*), postnatal (birth to weaning), juvenile (weaning to sexual maturity), and adult (sexual maturity onwards).

For the prenatal age window the ASF distributions ranged from less than 0.1 up to greater than 100, with a weighted median value of 2.38. For the postnatal age window the ASF distributions, based on 18 carcinogens, ranged from greater than 1 up to greater than 100, with a weighted median value of 7.66; the mean of the trimmed distribution (1st-99th percentile range) was 15.95. For the juvenile age window the ASF distributions, based on 5 carcinogens, ranged from less than 0.1 up to greater than 10, with a weighted median value of 3.03; the mean of the trimmed distribution (1st-99th percentile range) was 3.88.

⁶ Dr. Dale Hattis is with Clark University.

OEHHA has drafted a technical support document to provide guidance on how best to incorporate concerns about children's exposures and children's sensitivity into environmental standards. This document includes the evaluation of increased sensitivity, discussed above. OEHHA will be integrating information regarding sensitivity as well as exposure differences into risk assessment guidance. This guidance is available as a draft document that is being publically reviewed at this time (OEHHA 2008).

"Lifetime" exposure studies. The evaluation by Ginsberg suggested that short-term exposure early in life could result in a tumor response rate similar to chronic adult exposure. If this is true, one would expect that bioassays that combine early-life and adult exposures ("lifetime") would yield higher tumor rates than in the chronic adult exposure alone. EPA (EPA 2005a) evaluated the impact of lifetime (combined prenatal and adult) exposure vs. chronic later life dosing. Studies were available for three mutagenic and five nonmutagenic chemicals (EPA 2005a, Table 8). Sixty-seven percent of the ratios for mutagenic chemicals were greater than 1 (range 0.18 to 79, with a geometric mean ratio of 8.7). Twenty-one percent of the ratios for the nonmutagenic chemicals were greater than 1 (range 0.15-36, with a geometric mean ratio of 3.4). These ratios show that for many, but not all of the eight chemicals studied, multiple exposures over a lifetime (prenatal and adult) are more potent than multiple exposures to a comparable dose administered later in life (adulthood).

Summary. The standard methods that have evolved for evaluating cancer risk use lifetime dose averaging. Results from short-term early-life exposure studies indicate that cancer incidence from short exposures early in life can be as high as, and in some cases higher than, cancer incidence from longer exposures during adult life. Stop-exposure studies in adult laboratory animals indicate that a lifetime of exposure is not necessary to give rise to cancer and that averaging short-term exposures over a lifetime can underestimate risk.

Available early-life and lifetime studies indicate that exposure to some carcinogens during early life may result in increased cancer rates, even when the dose rate remains constant. One interpretation of these data is that exposures during early life may be more potent than the same exposure later in life. There may be many reasons for an increase in potency. Increased tumor rates could be the result of increased susceptibility (e.g., rapid cell division), differences in dosing (e.g., many of the "short-term" and "lifetime" studies were dietary and the actual dose early in life was not measured), a longer time for tumors to develop (i.e., dosing began earlier in life), a higher cumulative dose in the case of "lifetime" studies, or a combination of these factors. While available data are not amenable to rigorous quantitative analysis, MDH cannot ignore their import.

The external Expert Advisory Panel agreed that although the scientific literature is sparse, the available data clearly indicate that for many carcinogens there is evidence of early-life sensitivity (ERG 2005). With the exception of one panelist, the opinion of the panel members was that the data are sufficient to warrant application of adjustment factors to address early-life sensitivity. MDH was advised to give the EPA approach outlined in the *Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens* (EPA 2005a) serious consideration. The panel also felt that separate adjustments to potency and exposure to address life stage sensitivity and intake rates, respectively, were reasonable and that an overall adjustment of 6-fold (relative to adult-based calculation) was reasonable and prudent.

Based on the available scientific information, input received from public stakeholders, and recommendations made by the convened expert panel, MDH will use the EPA approach outlined in the

Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens (EPA 2005a). The EPA approach consists of three life-stage windows (< 2 years, 2 to < 16 years, and > 16 years). MDH will use the following age dependent adjustment factors (ADAF) and intake rates:

- < 2 years: 10 ADAF × Cancer Slope Factor and 0.137 L/kg-day;
- 2-<16 years: 3 ADAF × Cancer Slope Factor and 0.047 L/kg-day; and
- ≥16 years: 1 ADAF × Cancer Slope Factor and 0.039 L/kg-day.

The sum of the risks associated with each life-stage window is averaged over a lifetime duration of 70 years. The ADAFs of 10, 3 and 1 are based on the EPA Supplemental Guidance. The age-specific intake rates are time-weighted average (TWA) of the 95th percentile intake rates based on the intake rate data summarized in Table 2 (see Section IV.D.1.) Application of the EPA early-life sensitivity model would yield the following cancer HRL (cHRL) algorithm:

$$\text{cHRL} = \frac{(1 \times 10^{-5}) \times 1,000 \frac{\mu\text{g}}{\text{mg}}}{[(\text{SF} \times \text{ADAF}_{<2} \times \text{IR}_{<2} \times \text{D}_{<2}) + (\text{SF} \times \text{ADAF}_{2<16} \times \text{IR}_{2<16} \times \text{D}_{2<16}) + (\text{SF} \times \text{ADAF}_{16+} \times \text{IR}_{16+} \times \text{D}_{16+})] \div 70 \text{ years}}$$

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 risk per mg/kg-day] or [mg/kg-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 (ADAF₁₆₊).

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 (IR₁₆₊).

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 (D₁₆₊).

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

The resulting overall adjustment (i.e., potency and exposure) is a factor of approximately 3.3.

EPA has recommended that the supplemental approach be applied to carcinogens with a mutagenic mode of action. However, the EPA Science Advisory Board suggested that EPA reconsider limiting the application of adjustment factors only to mutagenic agents and instead apply a default approach to both mutagenic and to non-mutagenic chemicals for which the mechanism of action remains unknown or insufficiently characterized (EPA 2004b). EPA acknowledged that the nonmutagenic studies provided evidence that early life stages can be more susceptible to exposures to chemicals causing cancer through a variety of modes of action other than mutagenicity. However, a major factor that

complicated the interpretation of the results was that most of these studies involved dietary feeding initially to the mother, resulting in uncertainty regarding dose received during early life. EPA chose to continue to limit application of the ADAFs to only carcinogens acting through a mutagenic mode of action based in part on the analysis of available data, but also on EPA's long-standing science policy decision regarding the conservativeness of low-dose linear extrapolation. It is interesting to note that OEHHA did not separate carcinogens based on mode of action in their analysis, and the weighted median value for the postnatal and juvenile age windows (i.e., 7.66 and 3.03) are very similar to the EPA ADAFs (i.e., 10 and 3). Also, in their technical support document for cancer potency factors, OEHHA has indicated that in the absence of chemical-specific information, they will apply the EPA ADAFs to all carcinogens regardless of mode of action (OEHHA 2008).

The use of mechanism of action in selecting the appropriate low-dose extrapolation model (e.g., linear non-threshold versus nonlinear threshold) is an area of active discussion. There is a wide range of scientific opinion, making it evident that additional research is needed. The external Expert Advisory Panel (ERG 2005) had a far-ranging discussion, expressing a diversity of opinion that reflected the ongoing debate on this topic. Unlike mutagens, the case for nonmutagens is less data-rich and less supported by a consistent mechanistic framework. Ideally, data regarding early-life sensitivity would be available to inform the decision; however, in most cases, such data will not be available. Some panelists noted that several nonmutagens appear to exhibit early-life sensitivity and that it would be premature to conclude that for any particular nonmutagenic carcinogen, there are no sensitivity issues for early life. In the face of such limited data they considered it prudent to take the more health-protective approach as the default, and to be flexible to move from the default if MDH has data indicating that the specific nonmutagenic mechanism is not a vulnerability issue for early life.

Panelists also expressed concern that many carcinogens may have multiple mechanisms of action involving nongenotoxic (e.g., nonmutagenic) as well as genetic actions. Thus, it may be difficult to categorize carcinogens as strictly mutagenic or nonmutagenic. One panel member advised that it might be more productive to think about whether the cancer assessment is based on a linear or nonlinear dose extrapolation approach. A cancer assessment based on linear dose extrapolation may warrant use of the early-life sensitivity factor (regardless of the mechanism of action), as the linear low dose extrapolation is used in cases of receptor-mediated mechanisms, for mutagens, or in cases where the mechanism is too uncertain to document a threshold. If a nonlinear approach had been used, data documenting a threshold mechanism would already exist.

The EPA RfD/RfC Technical Panel (EPA 2002c) recommended that the dose-response relationship (e.g., linear or nonlinear) as well as the underlying mode of action (e.g., mutagenic) should be taken into consideration when selecting a low-dose extrapolation model. This approach recognizes that some mutagenic carcinogenic agents may work through nonlinear mechanisms and some chemicals that produce effects other than cancer may work through linear mechanisms.

EPA has recently released a draft framework for determining mutagenic mode of action (EPA 2007c). The intent of the draft document is to assist risk assessors in determining whether data are adequate to support a finding of a mutagenic mode of action (MOA) for carcinogenicity. Critical review of the draft document by the scientific community during the public comment period suggests that the draft document needs to be revised (EPA 2008a). EPA also contracted to have an independent peer review of the External Review Draft of the Framework conducted. In both cases, reviewers have questioned the health protectiveness of the framework, noting that the burden of proof was unrealistically onerous and inconsistent with the current state of the science. Several reviewers question whether the

mutagenic carcinogens upon which the ADAFs in the Supplemental Guidance are based would meet the requirements. Specific comments include: inconsistency in the definition of mutagen; inadequate characterization of the complexity of mechanisms of carcinogenicity (e.g., multiple MOAs, non-mutagenic genotoxicity); and failure to address uncertainty of extrapolating MOA across life stages.

Given the significance of early-life sensitivity and the uncertainties surrounding mechanism of action, MDH, like OEHHA, has chosen to apply the EPA approach as a default approach for linear carcinogens, regardless of the mechanism of action. The application of the EPA algorithm as a default approach for linear carcinogens is a policy decision informed by the scientific evidence described above. Chemical-specific information regarding early-life sensitivity will be used in place of the default approach whenever possible. When available, the chemical-specific information would be used in the following cancer HRL algorithm:

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

Where:

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

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

SF = adult-exposure based cancer slope factor ($[\text{mg}/\text{kg-day}]^{-1}$).

$\text{AF}_{\text{lifetime}}$ = the lifetime adjustment factor based on chemical-specific data.

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

An example of a chemical-specific adjustment is EPA's derivation of oral slope factors for vinyl chloride, which is included in the sample summary sheets in Appendix P. The angiosarcoma incidence after short-term, early-life exposure to vinyl chloride was approximately equal to that of long-term exposure starting after maturity. Hepatoma incidences also differed for these two exposure periods. Based on these observations, EPA determined that continuous lifetime exposure from birth would about double cancer risk. EPA derived two oral slope factors: 0.72 per mg/kg-day for continuous exposure during adulthood and 1.4 per mg/kg-day for continuous lifetime exposure from birth (EPA 2000d).

For nonlinear carcinogens, current theories propose that these compounds exhibit a mode of action that requires precursor events to occur (e.g., cytotoxicity with regenerative hyperplasia), and that a dose threshold exists below which there is essentially no risk of developing cancer. The MDH approach for evaluation of non-linear carcinogens will be to ensure that the derived RfD is below the threshold for the precursor event.

The MDH methodology reflects a public health-protective approach in light of the limited information currently available on the nature of the dose-response relationship at the low end of the dose range. MDH will revisit this policy when additional data and/or generally accepted methods become available.

The cancer HRLs are based on lifetime consumption and represent a concentration in water that, if consumed over a lifetime, will not result in an additional lifetime cancer risk of greater than 1×10^5 (i.e., 1 in 100,000). The stop-exposure studies in adults and early-life short-term exposure studies have indicated that lifetime averaging of less-than-lifetime exposures may underestimate cancer risk.

Therefore, prorating the cancer HRL for less-than-lifetime exposures is not advisable because it may underestimate the risk and may not be protective of health.

For a more in-depth discussion of lifetime and early-life exposure studies, see Appendix M.

IV.E.3. Multiple Chemicals

In general, the RfDs and cancer potency slopes used to derive HRLs are calculated for a single chemical or compound. In many situations, multiple chemicals are found in a sample of groundwater. Chemicals in combination may cause adverse effects that would not be predicted based on separate exposures to individual chemicals. Thus, evaluating the safety of a mixture of chemicals based on individual HRLs may not provide an adequate margin of safety. Unfortunately, few data address the toxicology of mixtures, and derivation of risk assessment tools to handle complex mixtures has been protracted.

Adding by the shared health risk index endpoint is the default approach for assessing risk from multiple chemicals. The procedures set forth in the revised HRL rules for determining whether the health risk limit for multiple chemicals has been exceeded, whether the effect is cancer or otherwise, are based on the additive model. Following the EPA's guidelines for mixtures (EPA 1986b, 2000b), chemicals that share the same health risk endpoint are all evaluated together. For each chemical sharing a health risk endpoint, a hazard quotient is formed by comparing the groundwater concentration of the chemical to the duration-specific HRL for that chemical. The ratios are grouped by duration, summed within each health endpoint group, and compared to the multiple-chemical health risk index of one.

The term "shared health risk endpoints" is construed broadly for the purpose of assessing risk from multiple chemicals. Generally, a shared health risk endpoint is an organ or a system, for example, hepatic system or nervous system. Because cancers all share the same proliferative mechanism and because they may metastasize, all cancers are considered a single, shared health endpoint. A slightly different approach is taken for the developing organism. Because development is considered a process, and that process may go awry, all chemicals that affect any aspect of development are evaluated together, regardless of the specific target affected. Also, because body weight is crucial for the developing organism, body weight is included in the multiple chemical health risk assessment when the impact is during the developmental period. Body weight changes in an adult could reflect any number of subtle toxicological effects within the body, or merely decreased palatability due to the presence of a chemical. While a change in adult body weight may be the lowest observed effect, and while a HRL may be derived based on a change in body weight, for adults body weight changes are not considered additive, and "body weight" is not a health index endpoint for evaluating risks from exposure to multiple chemicals.

The multiple-chemical health risk limit applicable when multiple chemicals are found in groundwater is equal to one. To determine whether the multiple-chemical health risk limit for noncarcinogens has been exceeded, the chemicals are grouped according to their shared HRL health endpoints, e.g., liver, kidney, nervous system. A ratio of the measured concentration of each chemical in groundwater to the health risk limit for the individual chemical is constructed for each chemical and for each exposure duration. Ratios are added for chemicals within a group and compared to the multiple-chemical health risk limit of one. For example:

$$\text{Noncancer Health Risk Index}_{\text{duration}} = \frac{C_1}{\text{nHRL}_{1 \text{ duration}}} + \frac{C_2}{\text{nHRL}_{2 \text{ duration}}} + \dots + \frac{C_N}{\text{nHRL}_{N \text{ duration}}}$$

Where:

C_1, C_2, \dots, C_N = the concentration of the first, second, ..., N^{th} chemical that has been detected in groundwater and that causes a specific noncancer effect ($\mu\text{g/L}$).

$\text{nHRL}_{1 \text{ chronic}}, \text{nHRL}_{2 \text{ chronic}}, \dots, \text{nHRL}_{N \text{ chronic}}$ = the duration-specific noncancer health risk limit of the first, second, ..., N^{th} chemical that has been detected in groundwater ($\mu\text{g/L}$).

All carcinogens are treated as members of the same group. A ratio of the measured concentration of each individual carcinogen in groundwater to the health risk limit for that carcinogen is constructed. Ratios are added and compared to the multiple-chemical health risk limit of one. For example:

$$\text{Cancer Health Risk Index} = \frac{C_1}{\text{cHRL}_1} + \frac{C_2}{\text{cHRL}_2} + \dots + \frac{C_N}{\text{cHRL}_N}$$

Where:

C_1, C_2, \dots, C_N = the concentration of the first, second, ..., N^{th} chemical that has been detected in groundwater and that causes cancer ($\mu\text{g/L}$).

$\text{cHRL}_{1 \text{ duration}}, \text{cHRL}_{2 \text{ duration}}, \dots, \text{cHRL}_{N \text{ duration}}$ = the cancer health risk limit of the first, second, ..., N^{th} chemical that has been detected in groundwater ($\mu\text{g/L}$).

The multiple-chemical health risk limit for carcinogens incorporates MDH's additional risk level of 1/100,000.

The equations above follow guidelines published by EPA in 1986 (EPA 1986b). The 1986 guidelines established a hierarchical approach. Data on the defined mixture of concern are preferred, followed by data on similar defined mixtures. If data on the specific mixture or a similar mixture are not available, the guidelines recommend applying an additive model, such as the equation above, to data on mixture components. Dose additive models are not the most biologically plausible approach for compounds that do not share the same mode of toxicological action. However, since the mechanism of action for most compounds is not well understood, it is assumed that dose addition will often be limited to similarities in toxicokinetics and toxicological characteristics. Most studies on toxicity report only descriptions of the effects. EPA issued supplementary guidance in 2000 (EPA 2000b). The supplement continues the hierarchical approach, but describes more detailed procedures.⁷ Both documents acknowledge that data on defined whole mixtures – whether the mixture of concern or a similar mixture – are limited. Thus, the additive model is usually the default. The additive model does not account for synergism, potentiation, antagonism, masking, or inhibition, or for the absence of contaminant chemical interactions; however, the model is a reasonable approach for evaluating the health risk of multiple chemicals. EPA also suggests that based on current information, additive assumptions are expected to

⁷ In the preface, the 2000 guidelines state: "The 1986 Guidelines represent the Agency's science policy and are a procedural guide for evaluating data on the health effects from exposures to chemical mixtures. The principles and concepts put forth in the Guidelines remain in effect. However, where the Guidelines describe broad principles and include few specific procedures, the present guidance is a supplement that is intended to provide more detail on these principles and procedures." (EPA 2000b)

yield generally neutral risk estimates (i.e., neither conservative nor lenient) and are plausible for component compounds that induce similar types of health effects.

In conformity with EPA recommendations, MDH has used the most specific data available to evaluate chemicals found together in groundwater. Given limited data, however, most HRLs are derived for individual chemicals. When multiple chemicals are present, MDH uses the shared health risk index approach described above as a default to derive a duration-specific health risk index for chemicals with shared health risk endpoints. MDH encourages risk managers to use more specific data when such data are available. However, in order to safeguard public health, approaches adopted for assessing risk from multiple chemicals should always err on the side of inclusion. Appendix N discusses these alternative approaches.

Example Health Risk Index Calculations:

To determine the health risks when benzene, chloroform and vinyl chloride are present, the duration-specific ratio for each health endpoint is added together to derive a duration-specific health risk index for each endpoint.

Chemical	Amount detected in water (µg/L)	Duration	HRL (µg/L)	Health Endpoint
Benzene	2.8	Acute	10	Developmental
		Short-term	10	Hematologic; Immune
		Subchronic	3	Hematologic; Immune
		Chronic	3	Hematologic; Immune
		Cancer	2	Cancer
Chloroform	1.5	Acute	ND	
		Short-term	30	Developmental; Hepatic; Immune
		Subchronic	30	Developmental; Hepatic; Immune; Male Reproductive
		Chronic	30	Developmental; Hepatic; Immune; Male Reproductive
		Cancer	NA	
Vinyl chloride	0.4	Acute	ND	
		Short-term	20	Hepatic
		Subchronic	20	Hepatic
		Chronic	10	Hepatic
		Cancer	0.2	Cancer

NA = Not Available

ND = Not Derived (due to absence or paucity of toxicity information)

There are no common health endpoints for the acute duration. For the short-term duration, the immune system is a common health endpoint for benzene and chloroform. The short-term hazard index for immune effects is:

$$\text{Noncancer Immune Health Risk Index}_{\text{short-term}} = \frac{2.8}{10} + \frac{1.5}{30} = 0.3 + 0.05 = 0.35$$

For the subchronic duration, the immune system is a common health endpoint for benzene and chloroform and the hepatic system is a common health endpoint for chloroform and vinyl chloride. The subchronic hazard index for immune effects is:

$$\text{Noncancer Immune Health Risk Index}_{\text{subchronic}} = \frac{2.8}{3} + \frac{1.5}{30} = 0.9 + 0.05 = 0.95$$

The subchronic hazard index for hepatic effects is:

$$\text{Noncancer Hepatic Health Risk Index} = \frac{1.5}{30} + \frac{0.4}{20} = 0.05 + 0.02 = 0.07$$

For the chronic duration, the immune and hepatic systems are common health endpoints for the same pairings of chemicals as in the subchronic case. The chronic hazard index for immune effects is:

$$\text{Noncancer Immune Health Risk Index}_{\text{chronic}} = \frac{2.8}{3} + \frac{1.5}{30} = 0.9 + 0.05 = 0.95$$

The chronic hazard index for hepatic effects is:

$$\text{Noncancer Hepatic Health Risk Index} = \frac{1.5}{30} + \frac{0.4}{10} = 0.05 + 0.04 = 0.09$$

Cancer is a common health endpoint for benzene and vinyl chloride. The cancer hazard index is:

$$\text{Cancer Health Risk Index} = \frac{2.8}{2} + \frac{0.4}{0.2} = 1.4 + 2 = 3.4$$

Defined Mixtures of Chemicals. Groundwater samples often contain multiple chemicals. Optimally, toxicity data would be available on the actual mixture present – that is, all the chemicals present, only the chemicals present, and in the same proportion present. However, this is rarely the case. As discussed above, toxicity testing focuses on individual chemicals and risk from environmental mixtures is usually assessed by some method of melding individual assessments (see discussion above and in Appendix N.) While defined mixtures are sometimes tested for toxicity, due to the infinite number of combinations of chemicals possible, it is unlikely that the mixture in question will exactly match a mixture for which toxicity data are available. However, when data on a mixture similar to that present are available, risk assessors may use that data, rather than relying on individual chemical assessments (EPA 2000b).

An example of a defined chemical mixture is xylenes. In 1993, a HRL was promulgated for a mixture of m-, p- and o-xylenes. The RfD for xylenes was based on a toxicity evaluation of a defined mixture comprised of 60% m-xylene, 13.6% p-xylene, and 9.1% o-xylene and 17% ethylbenzene. There are no defined mixtures included in the current rules revision.

IV.E.4. Uncertainty Analysis

Risk assessment involves a series of judgments, all based, to a greater or lesser extent, on science. Risk assessors and managers must evaluate the science and make decisions. Uncertainty is inherent in every step of risk assessment. This section reviews key sources of uncertainty for each step in the context of derivation of health risk limits.

Uncertainties in Hazard Identification. A primary but often over-looked source of uncertainty in hazard identification is whether chemicals present in groundwater have actually been identified. The operative assumption is that groundwater is pristine – or at least free of man-made chemicals. Relatively high levels of most chemicals must be present before they can be detected by odor or taste. Therefore, absent evidence of spill, a leak, a discharge, or a known routine use or release of chemicals into the environment, there is little reason to suspect and test for the presence of chemicals in groundwater. Even when contamination is suspected and groundwater is collected and analyzed, the list of chemicals for which testing is performed is the result of an educated though perhaps biased assessment of what might be found. Additionally, convenient, replicable or affordable laboratory methods for analyses of some chemicals are sometimes unavailable.

Uncertainties in Toxicity Evaluation. In toxicity evaluation, the risk assessor must inquire whether the doses at which effects were observed in laboratory animals are relevant to humans, or whether extrapolation of effects to humans requires that the doses tested in animals be modified to account for, for example, differences in body weight or metabolism.

The risk assessor must also make many choices in interpreting data. There is uncertainty inherent in each of these choices. Decisions made by the risk assessor in interpreting the data influence the appearance of the dose-response curve (NRC 1994). A related concern is interpretation of trends that do not reach statistical significance. For example, a larger sample size might have resulted in statistical significance.

For many chemicals, only limited data are available. Because of a lack of data, the risk assessor may not be able to assess short duration exposures, and may be required to extrapolate from effects seen after short duration exposures to long duration exposures, or from an effect level to a no-effect level. When a study using the exposure route of interest is not available, risk assessors may extrapolate between routes.

The age of the test animals and the duration of exposure may pose particular problems. Chemicals may be tested for developmental toxicity by exposing pregnant rats and evaluating effects on offspring. Maternal metabolism of the chemical, circulating blood level of the chemical, and perfusion of fetal tissue are not typically evaluated and the actual dose to the fetus is unknown. The dose delivered to the fetus may be lower than the dose given to the mother as a result of maternal metabolism and excretion of a portion of the chemical before it reaches the fetus. It is also possible that the dose to the fetus may be higher if the chemical is metabolized to a more toxic form. However, since the fetal dose will always be mediated by the mother, if no effects are observed in the offspring at a certain maternal dose, it is safe to assume that this dose poses no risk to the offspring. Uncertainties in identifying the dose to the mother that is safe for a developing fetus include concerns about whether all species metabolize and circulate a maternal dose in the same manner.

At birth, the neonate's dose is no longer mediated by the mother. Very little oral toxicity testing of neonates has been performed because of the difficulty in delivering doses to a newborn rodent, the species most commonly used for toxicity testing. For purposes of risk evaluation, MDH has chosen to use the maternal dose protective of the fetus as a surrogate for a protective dose to a newborn. This dose (in mg/kg-day) is used as a safe exposure for human infants, whether breast-fed or fed formula prepared with drinking water. There are many uncertainties in making this extrapolation; chief among them is the possibility that the dose to the fetus that disrupted fetal development was actually lower than the dose to the mother (because the mother may detoxify a chemical before it circulates to the fetus). This would lead to an underestimate of the true magnitude of risk to the newborn. An important uncertainty in extrapolating results to neonates is that the newborn may not be susceptible to the same developmental disruptions that were a concern *in utero*. This may lead to an overestimate of the true magnitude of risk or a misidentification of the true health effect of concern to the newborn.

The neonate may have the same sensitivity as an adult to a chemical's effects. This means that the chemical is not necessarily a developmental toxicant, but might have the appearance of affecting a developing organism. In the revised HRL rules, if an effect results from exposure during a developmental period or within an acute or short-term duration, an infant intake rate is used.

MDH partially addressed the issue of accounting for duration, rather than timing (e.g., sensitive life stage), by using bioassays of different durations: acute, short-term, subchronic (e.g., 90 day bioassay) and chronic (e.g., 2 year bioassay). A study of a given duration may provide information on endpoints observed at more than one duration. For example, a chronic duration study may result in effects, which occur immediately (acute) as well as health effects that only appear after repeated chronic dosing.

Currently, laboratory animal studies are mainly conducted to characterize a dose-response relationship and rarely to explicitly evaluate the effects of various durations of exposure (EPA 2002c). The timing of both exposure and the initial occurrence of toxic effects are important considerations in assessing risk from less-than-lifetime exposures. Understanding the biological relationship between timing and duration of exposure and subsequent toxic effects is essential in deriving health-protective HRLs.

Current standard study protocols typically use dosing regimens that involve young adult animals. The exposure protocols do not include the pre- or postnatal development period. Reproductive and generational studies do provide data on subchronic exposure in animals exposed before birth, through prenatal and postnatal development up to mating of the F1 males and females and through pregnancy (F1 young adult females). The focus, however, may be limited to reproductive-related endpoints.

Short-term and subchronic studies are often conducted to identify potential toxicity to selected major organ systems. This information can then be used to determine where to look in more detail at specific organ system structure and function. The chronic studies, which are usually done in combination with a carcinogenicity study, evaluate general toxicity in all major organ systems.

Effects seen at the termination of a study may be due to cumulative damage from a continued repeated chemical insult, but they could also be a latent response from an exposure early in the study that had an effect during a short period of vulnerability. Specific information on the latency of a response would follow only from a clear understanding of the effect and from actual "stop-exposure" protocols (e.g., short-term exposure with follow-up over a long period of time).

In addition to the recommendation to assess less-than-chronic durations the EPA Technical Panel (EPA 2002c) also made the following recommendations regarding study designs:

- Develop protocols for acute and short-term studies that provide more comprehensive data for setting reference values,
- Modify existing guideline study protocols to provide more comprehensive coverage of life stages for both exposure and outcomes, and
- Collect more information from less-than-lifetime exposures to evaluate latency to effect and reversibility of effect.

Data from current study designs can be improved by incorporating stop-exposure subgroups to evaluate latency, serial sacrifice time points, or even simply increased reporting of time point data currently collected. MDH has attempted to derive RfDs and nHRLs for acute, short-term, and subchronic durations, as well as chronic durations whenever possible. If adequate data were not available or include only severe effects (e.g., death), HRL values were not derived for that exposure duration.

For noncancer effects, risk assessors have traditionally applied factors to account for some specific uncertainties. (See discussion of Noncancer in Toxicity Evaluation, Section IV.C.2.) Briefly, an uncertainty factor of 10 is usually applied for extrapolation between laboratory animals and humans, and a variability factor of 10 for differences in sensitivity among humans. When a subchronic study is used to derive a value that will apply to chronic situations, another uncertainty factor is usually applied (typically 3 or 10). If all doses caused adverse effects, the lowest dose tested may not be protective; a factor, most often ten-fold, is applied to account for the fact a no-effect level has not been identified. Finally, a database uncertainty factor may be applied if there are obvious gaps in testing.

A fundamental uncertainty in cancer assessment is whether a chemical is a human carcinogen. The classification system provides information about scientists' assessment as to whether a chemical may cause cancer in humans. (See Appendices E through I for information about cancer classification schemes.) MDH has attempted to reduce uncertainty by more carefully considering group C carcinogens (possible human carcinogens). (See the discussion of group C carcinogens in Section IV.C.3., cancer effects, for an explanation of MDH's decision.) A convention in identifying a cancer dose or an effect level of concern has been to calculate confidence intervals on data points (similar statistical manipulations are now being used with noncancer effects as well—for example, benchmark dose calculations). Risk assessors do not consider this an adjustment linked to uncertainty in the risk assessment, but simply an expression of the appropriate selection of a dose of concern. That is, scientists can be confident that the true dose of concern is not outside of this confidence interval. Others may characterize this as unwarranted conservatism. It is, however, a well-established convention in risk assessment for public health protection. EPA practice has been to use a lower bound as the point of departure (POD) for cancer risk estimation. This practice "reflects the Agency's appraisal of the relative consequences of overestimating or underestimating the POD. It also ensures that the POD considers the variance of the estimated dose, which can depend on a study's design, sample size, and quality" (EPA 2005b).

For cancer, especially, effects seen at high doses are extrapolated to low doses. Cancer risk assessment has traditionally assumed that carcinogens have no threshold; that is, the response is linear, from the upper confidence limit on the lowest dose that caused cancer, all the way down to a dose of zero. In fact, as data accumulate, it is clear that for some carcinogens, the dose-response

relationship in the low dose region may also be sublinear or supralinear, or there may be a threshold. In addition, for both noncarcinogens and carcinogens, there may be the possibility of biphasic dose-response curves in the low dose-region of the curve or paradoxical dose-response relationships such as hormesis (low doses appear to confer health benefits) or U-shaped dose-response curves (a dose appears to confer health benefits not replicated at lower or higher doses). These possibilities add to the uncertainty in a simple linear extrapolation from high doses (in the experimental range) to low doses (in the environmental exposure range). In the absence of evidence of a threshold (nonlinear dose-response curve), the linear extrapolation model is a reasonable choice.

EPA recommends that the supplemental approach be applied only to carcinogens with a mutagenic mode of action. In response to the EPA Science Advisory Board suggestion that EPA reconsider this limitation, EPA acknowledged that the nonmutagenic studies provided evidence that early life stages can be more susceptible to exposures to chemicals that cause cancer through modes of action other than mutagenicity. EPA chose to continue to limit application of the ADAFs only to carcinogens which act through a mutagenic mode of action. This decision was based in part on the analysis of available data, but also on EPA's long-standing science policy decision regarding the conservativeness of low-dose linear extrapolation. The external Expert Advisory Panel (ERG 2005) expressed a diversity of opinion that reflected the ongoing debate on this topic. Ideally, data regarding early-life sensitivity would be available to inform the decision; however, in most cases, such data will not be available. In the face of such limited data the majority of the external Expert Advisory Panel considered it prudent to take the more health-protective approach as the default, and to be flexible to move from the default if MDH has data indicating that the specific nonmutagenic mechanism is not a vulnerability issue for early life.

Mode of action analysis is inherently difficult to experimentally discern. These difficulties are apparent in the comments received on the recently released EPA draft framework for determining mutagenic mode of action. Several reviewers have questioned the health protectiveness of limiting the default adjustment approach to mutagenic mode of action carcinogens only.

MDH has chosen to utilize EPA's Supplemental Guidance (EPA 2005a) to address uncertainty about the extent to which early-life exposures may give rise to increased incidence of cancer and to extend this approach to linear carcinogens, including those with unknown modes of action. There is scientific justification for concerns that early-life exposures may give rise to higher cancer incidence than exposures later in life, and there are data substantiating these concerns for both mutagenic and nonmutagenic carcinogens. Studies that allow an evaluation of risk from early life or whole life exposure versus risk from adult life exposure have been performed for a limited number of chemicals. Overall, these studies indicate that risk from early-life exposure is higher than similar exposures later in life.

Uncertainties in Exposure Assessment. In estimating drinking water exposures for Minnesotans, MDH used data from an EPA analysis of the Continuing Survey of Food Intakes by Individuals (CSFII) (EPA 2004c, 2007b). While the CSFII and the supplemental data are the best data available, there are legitimate concerns about its application in the derivation of HRLs.

The CSFII sampled more than 15,000 individuals across the nation. Results might be slightly different for Minnesotans. In using the CSFII data, MDH had to select from among several different sets of data. The survey collected data on different types or sources of water, and data were tabulated both for "consumers only" and for "all individuals (consumers and nonconsumers)." MDH determined that, for

the purpose of HRLs, data for direct and indirect (total) community water consumption by consumers only were the most appropriate. Direct water is water consumed as drinking water; indirect water is water used in the preparation of foods and beverages at home, or by food establishments. Use of an individual's total water consumption is likely to result in overly conservative HRL values for those individuals who are served by several different sources of water. However, for those parts of the population likely to spend most of their time in the home, including small children not in daycare, stay-at-home parents, home workers, and the elderly, these values will not be overly conservative. Thus, use of data for direct and indirect community water consumers is appropriate.

There are uncertainties in the analysis and use of the CSFII. In the survey, reports of water ingested on two non-consecutive days were averaged for each participant. This likely produces a valid population estimate for water ingestion. However, MDH required data on water ingestion for various life stages and durations up to a lifetime. The SAB has suggested that the range of intake rates may narrow as averaging time increases (EPA 1999). Essentially, this means that the individuals whose intake rates place them on the extreme ends of the distribution at a particular point in time are unlikely to continue to consume at that rate over long periods of time. In short, it would be preferable to have data for the same set of individuals for several years in order to understand how an individual's intake varies over time, rather than averaging the data for different individuals of different ages over the default durations.

The CSFII and supplementary data included data from infants who were exclusively bottle-fed formula prepared with tap water, as well as data for infants who consumed combinations of breast milk, plain tap water, and formula prepared with or without tap water. Inclusion of this latter group has the potential for skewing percentile estimates of consumption by infants downward. While the upper percentiles of the distribution will be less affected than the lower percentiles, they will none-the-less be impacted, adding to the uncertainty of correctly describing the distribution of intake values for the subpopulation of infants who are reliant on tap water. Currently, MDH cannot estimate the magnitude of this effect, as the summary tables of the survey data do not distinguish between these groups. However, published studies on fluid intake in very young infants are consistent with the CSFII upper percentile intake rates (> 90th percentile) for infants.

Uncertainties in Risk Characterization. MDH has attempted to include information in the rules that will inform users of the factors and decisions that went into the derivation of the HRL value, as well as the value itself. The rules list not just the endpoint identified as critical but also other endpoints that were observed within a close range of the dose associated with the critical endpoint. This strategy more fully informs risk managers of potential hazards and is instrumental in the effort to assess risk from multiple chemicals.

A variety of population subgroups (e.g., infants) and exposure durations may be of concern to the risk managers. If sufficient toxicity data exist, MDH will derive noncancer HRLs for a range of exposure durations. This additional information will allow risk managers to select the most appropriate values for the situation under consideration.

Information about volatility allows risk managers to consider additional sources of exposures. In particular, MDH recommends a site-specific evaluation of inhalation exposure be conducted in situations where highly volatile chemicals have contaminated the groundwater and this groundwater is used for domestic purposes (e.g., bathing, showering, etc.).

Despite MDH's best efforts, it is impossible to capture in a single value or brief narrative all the considerations that went into the derivation of a HRL value. However, MDH maintains the information it has collected that support its selection of the HRL values. This information is available upon request.

Since EPA first issued guidelines on risk assessment for exposures to mixtures of chemicals more than a decade ago, there has been little reduction of uncertainty in this crucial area (EPA 1986b, 2000b). The Agency has issued supplemental guidance providing more detailed methodologies. However, these methodologies are of little use without testing data on mixtures. Data are only available for a very limited number of common mixtures, and this situation is not likely to change soon. Therefore, the uncertainties presented by the common health risk index endpoint model (i.e., the additive model) – that it does not account for synergism, potentiation, antagonism, masking, or inhibition, or for the absence of contaminant chemical interactions – are likely to continue.

IV.F. RISK MANAGEMENT FOR DRINKING WATER

Risk management leads to decisions about the need and methods for risk reduction (NRC 1994). In the regulatory context, risk management begins with decisions about what risks should be considered and how much risk will be tolerated. In the derivation of regulatory values, these decisions are manifested in the additional cancer risk level (e.g., 1/100,000) and the use of a no effect level for a noncancer value (e.g., RfD). Societal values and, in some cases, statements of political will as set forth in laws, rules, and orders, also provide some direction to this first phase of risk management. Those responsible for applying regulatory values engage in a second phase of risk management as they make decisions about whether to apply a value or to modify it, and what technology to use to achieve a reduction in contaminant exposure. Decisions made in this phase of risk management should not be determined solely by the outcome of the risk assessment, but should encompass all relevant factors. At a specific site, these factors might include the social, cultural, political, and economic conditions of the population. On a more general level, factors include whether the regulatory goal can be achieved by available technology, the cost of that technology, and a balancing of the costs versus the benefits (EPA 1995a).

HRLs are derived as health-protective upper limits for contaminants found in groundwater. They are intended to be generally applicable to contaminated groundwater that may be used as a drinking water. Potential human health effects resulting from ingestion of water is the only consideration in derivation of HRLs. HRLs do not directly address human exposure resulting from non-ingestion exposure to water (e.g., dermal, inhalation of volatilized chemicals) or contact with other contaminated media; these exposures are acknowledged through the use of a Relative Source Contribution (RSC) factor, but are not quantified beyond that gross level. They also do not address the protection of aquatic life, animal life, or links between ecological and human health. Additionally, HRLs for individual chemicals do not protect from exposure to multiple chemicals. Thus, HRLs are not intended as levels generally appropriate for protection of the environment. Use of HRLs as "pollute up to" standards would not be a conservative, health-protective approach.

MDH does not specify application of HRLs or enforce any application of HRLs. Agencies may adopt HRLs for regulatory purposes. Depending on the circumstances of a particular site, a risk manager may consider modifying the HRLs, e.g., by applying a site-specific RSC. Since economics and technological feasibility are not considered in derivation of HRLs, the risk manager may need to take these into account in order to establish realistic goals for remediation or protection of groundwater. Other factors to consider include the characteristics of the population likely to be exposed, the source of the

pollution, the chemical, and the nature and duration – if known – of the exposure. For example, a risk manager may want to deviate from the HRLs if the chemicals in question are volatile.

Several topics of potential interest to risk managers are discussed in Appendix O.

PART V. REQUIRED INFORMATION

Minnesota Statutes, section 14.131, lists factors that agencies must include in the Statement of Need and Reasonableness (SONAR). This section addresses these required factors.

V.A. Classes of Persons Affected by the Proposed Rules, Including Classes that will bear the Costs and Classes that will Benefit

This proposed revision of the HRL rules could potentially affect all persons living in Minnesota. Because application of HRLs is generally left to the discretion of state agencies charged with protecting Minnesota's environment and water resources, the best predictor of who will be affected by the rules is to review the way the HRLs are applied.

Generally, the proposed rules can benefit the entire state because HRLs are used as benchmarks that play a role in state groundwater monitoring and contamination response programs. The incorporation of HRLs and related chemical data into other state rules intended to protect Minnesota's water resources (e.g., the Minnesota Pollution Control Agency's (MPCA's) solid waste rules and MPCA's surface water rules) is also a benefit to the entire state.

More specifically, the proposed rules can affect individuals or populations when a private water supply or when a public water supply becomes contaminated and federal Maximum Contaminant Levels (MCLs) are unavailable. In these instances, the risks from consuming contaminated water are estimated using HRLs, and advice on eliminating or reducing risks is conveyed to the consumer, responsible governmental unit, or water operator. On the pollution control side of a groundwater contamination scenario, HRLs are the benchmarks most often used to direct monitoring and remediation.

The revisions in the proposed rules that pertain to sensitive or highly exposed sub-populations (i.e., children) will provide a greater degree of protection than afforded in the previous version of the rules. Risk managers have the option of applying HRLs to the general population, or adjusting them for sub-populations.

V.B. Estimate of the Probable Costs of Implementation and Enforcement and Any Anticipated Effect on State Revenues

This rulemaking has no direct impact on state revenues. There are no fees associated with the rules, nor are there any specific implementation or enforcement costs. The rules simply provide health-based levels for certain groundwater contaminants. To the extent that state agencies apply the proposed HRLs, those agencies will have to determine costs on a case-by-case basis.

V.C. Determination of Whether there are Less Costly or Less Intrusive Methods for Achieving the Rules' Purpose and a Description of Alternative Methods Considered and Why They Were Rejected

State statutes define the methods by which HRLs are derived and the policy goals they serve. *Minnesota Statutes*, section 103H.201, subd. (1), authorizes the Commissioner of the Department of Health to promulgate HRLs. Methods to be used in deriving HRLs are stated in paragraphs (c) and (d) of subdivision 1. In addition, *Minnesota Statutes*, section 144.0751(a)(1), requires that safe drinking water standards "be based on scientifically acceptable, peer-reviewed information." *Minnesota Statutes*, section 144.0751(a)(2) requires that safe drinking water standards "include a reasonable margin of safety to adequately protect the health of infants, children, and adults." In addition to being statute, this is prudent public health policy, since groundwater is a primary source of drinking water for all Minnesotans, including the very young, the very old, the sick and the infirm. These statutory mandates provide the boundaries of MDH's discretion in deriving HRLs.

Accordingly, MDH derived its HRLs using scientifically sound sources and methods that ensure the protection of all Minnesotans. If the agency in charge of an investigation determines that certain groups will not be exposed, that agency can exercise its discretion to apply a different value or manage known and potential risks in other ways.

The MDH-derived HRLs provide uniform, science-based rules that can be applied to the protection of the health of the general public that uses groundwater as a source of drinking water. The MDH-derived HRLs have been derived through a process designed to inform and engage the public. MDH has fully discussed and considered the comments provided by individuals and groups, and their input is reflected in the changes to the rules and SONAR made between publication of the 2004 draft and publication of the current edition.

HRLs are superior to the Health-Based Values (HBVs) that MDH derives from time to time to meet a specific need communicated to MDH by other state agencies. While HBVs are based on consistent, science-based analysis, state agencies and the regulated community often consider them to be transient in nature, while a HRL is considered more permanent and therefore more useful in planning long-term risk management strategies.

Consequently, these rules represent the soundest calculations that MDH can supply to fulfill its mission without unduly restricting the parties who ultimately must observe them.

V.D. Estimate of the Probable Costs of Complying with the Proposed Rules Revision

Because the HRL rules do not specify how the health-protective numbers are to be applied, the probable cost of complying with the proposed rules cannot be estimated. HRLs are only one set of criteria used to evaluate whether the concentration of a contaminant found in groundwater is associated with a risk to health. HRLs are not intended to be bright lines between "acceptable" and "unacceptable" concentrations. As previously stated, MDH derived its HRLs using conservative methods so that exposures below a HRL would be expected to present minimal if any risk to human health. Similarly, a contaminant concentration above a HRL, without consideration of other information, may not necessarily indicate a public health problem. However, since some of the HRL values in the revised rules are lower than the 1993/1994 values, the cost of remediating or preventing water contamination

may increase. On the other hand, some of the HRL values in the revised rules are higher than the 1993/94 values and therefore, the cost may decrease.

V.E. Probable Costs or Consequences of Not Adopting the Proposed Revision

The probable costs or consequences of not adopting the proposed revision 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.

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. HRLs allow authorities to evaluate groundwater to ensure that there is minimal risk to human health from using the groundwater for drinking water. A reliable source of groundwater, safe for human consumption, is essential to the ability of a state to offer a high standard of living to its citizens.

Failure to revise the rules would ignore legislative directives and leave in place an outdated set of standards that provide only limited protections to segments of the population.

V.F. Differences Between the Proposed Rules and Existing Federal Regulations, and the Need for and Reasonableness of Each Difference

EPA's Office of Water publishes several sets of standards and health advisories relevant to water consumed as drinking water. While each of these standards and advisories is similar to MDH-derived HRLs in some respects, they differ in important ways. Furthermore, for any given chemical, all, several, one, or none of these standards and advisories may have been derived.

MDH-derived HRLs differ from existing federal regulations and advisory values in three primary ways. First, MDH-derived HRLs are strictly health-based. Second, MDH-derived HRLs provide guidance for both cancer and noncancer effects. Finally, calculation of the revised MDH-derived HRLs explicitly addresses infants and children, considered to potentially be at higher risk than adults. While some federal regulations or advisory values might adhere to one or two of these conditions, none adheres to all conditions.

EPA-derived Maximum Contaminant Level Goals, or MCLGs, are advisory values based solely on considerations of human health. However, by definition, the MCLG for any chemical that causes cancer is zero. Since 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 Maximum Contaminant Levels, or MCLs, are federal standards adopted for regulation of public drinking water in Minnesota. However, MCLs incorporate a consideration of the costs required to reduce contaminant concentrations of a given level and the technological feasibility of reaching that level. The factors that determine economic and technological feasibility for public drinking water systems may not be relevant to private drinking water wells or to other sites impacted by contamination.

Legislation passed in the 2007 session (Chapter 147, Article 17, section 2) declared HRLs for all contaminants in private domestic wells to be the more stringent of either the state standards or the federal MCLs. These MCL-based HRL values apply until MDH adopts rules setting an MDH-derived HRL value for these chemicals. MDH has identified 11 chemicals that have MCL values that are lower than the 1993/1994 HRL values (see Section III.A. for list of chemicals). The MCL-based values for these 11 chemicals were adopted as the HRL values, effective July 1, 2007. MDH has derived HRL values for three of these 11 chemicals (alachlor, benzene and 1,1,1-trichloroethane). By including these MCL-based HRL values in the current revision of the rules, the MCL-based HRL values for the remaining eight chemicals will remain in effect until MDH revises the HRL rules for these chemicals.

EPA-derived Drinking Water Equivalent Levels (DWELs) and Health Advisories (HAs) are estimates of acceptable drinking water levels of noncarcinogens based on health effects information. DWELs and HAs serve as 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. HRLs 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 a Relative Source Contribution (RSC)). HAs may also be derived for exposure durations of one day, ten days, or a lifetime. One-day and ten-day HAs incorporate intake and body weight parameters appropriate for children but do not incorporate an RSC. MCLGs, MCLs, DWELs, and lifetime HAs are calculated for adult intake and body weight.

V.G. Performance-Based Rules

Minnesota Statutes, sections 14.002 and 14.131, require that the SONAR describe how the agency, in developing the amendments to the rules, considered and implemented performance-based standards that emphasize superior achievement in meeting the agency's regulatory objectives and maximum flexibility for the regulated party and the agency in meeting those goals.

The proposed HRL rules allow risk managers and stakeholders flexibility in determining how best to protect public from potentially harmful substances. The MDH-derived HRLs provide a scientific and policy context within which the risks posed by a particular situation may be analyzed. After the analysis of risk, stakeholders, which may include other regulatory agencies, may examine options, make decisions about which options to implement, take action, and evaluate the results of those actions taken.

V.H. Additional Notice

MDH will mail the rules and Notice of Intent to Adopt to each party on MDH's rule-making mailing list, as stipulated by *Minnesota Statutes*, section 14.14, subd. (1)(a). MDH will also give notice to the Legislature per *Minnesota Statutes*, section 14.116. MDH will post an electronic copy of the rules and SONAR on the MDH HRL Rules Revision webpage (<http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/index.html>) and will send an email announcement to individuals on the HRL rules revision GovDelivery subscription list. Copies will be made available at no cost to individuals upon request.

Promulgation of rules by administrative agencies is governed by the *Minnesota Administrative Procedure Act (APA)* (*Minnesota Statutes*, sections 14.001 *et seq.*). The purposes of the APA include increasing public access to information and public participation in the formulation of rules. The Act also

notes that these objectives must be balanced with the need for efficient, economical, and effective government administration. This section describes the efforts of MDH to inform and engage the public in the revision process.

Request for Comments. MDH published a notice in the *State Register* soliciting outside public opinion on the planned revision of the HRLs. The first notice appeared in the *State Register* on September 24, 2001 (26 SR 462). This notice simply informed the public that MDH was considering revising the HRLs. MDH received no letters in response to this notice.

Likewise, MDH published a second notice in the *State Register* on December 27, 2004, again notifying the public that MDH was considering revisions to the HRL rules. It also stated that details about public and requested meetings and a draft editions of the rules and SONAR were available via the MDH website or from the agency's contact person. MDH received comments in response to this notice and posted these comments on its website.

MDH published a third notice in the *State Register* on September 10, 2007. This notice contained the same information on information access as the second notice. MDH received one comment in response to this notice and posted it on the MDH website.

Public Meetings. MDH has hosted nine public meetings to encourage participation by all stakeholders and the general public in the revision of the HRLs. These public meetings allowed all stakeholders an equal opportunity to participate in the revision process and optimize MDH resources. In addition to responding to *Minnesota Administrative Procedure Act* (APA) goals vis-à-vis public access to and input on rules, these meetings partially fulfill MDH's need for public input into the scientific and policy rationales for the derivation of health-based contaminant levels in groundwater.

MDH held its first public meeting on October 31, 2001. The purpose of this meeting was to provide a venue in which Minnesota residents and other stakeholders could identify issues concerning HRLs so that MDH might be better informed as it revises the HRL rules. The second meeting was held on October 30, 2002. The purpose of the second meeting was to draw participants into the discussion about MDH's planned changes in methods and data. The third meeting, held on June 24, 2003, centered on children's exposures, children's risks, and protection of children, all within the context of the HRL rules. At this meeting MDH presented its research, communications, and analysis of issues related to children. The fourth meeting, held on July 13, 2004, consisted of independent morning and afternoon sessions. In the morning session, MDH reviewed how its recommendations had changed since the 2003 meeting; summarized how recommendations differed from the 1993/1994 promulgation; distinguished between the science and the policy decisions; and reviewed several chemicals that either had been requested by stakeholders or represented a particular issue encountered in the revision. In the afternoon session, management from MDH, the Minnesota Department of Agriculture, and the Minnesota Pollution Control Agency discussed their programs' use of HRLs and the potential effects of the revision.

In December 2004, MDH made draft editions of the rules and SONAR publicly available. The fifth meeting, held on March 14, 2005, reviewed and responded to comments received on the December 2004 draft. MDH also discussed the process for assembling an external Expert Advisory Panel to review the 2004 draft documents.

MDH subjected the December 2004 revised draft rules and SONAR to an independent peer review. An independent contractor, Eastern Research Group, Incorporated (ERG), identified and recruited national experts to serve on the panel. The panel was composed of experts in risk assessment, toxicology, exposure science, and public health. The sixth public meeting, held on November 16-17, 2005, addressed the external Expert Advisory Panel's comments on the 2004 draft documents. The panel considered whether the public health policy decisions in the proposed revised rules were consistent with the *Minnesota Health Standards Statute (Minnesota Statutes, section 144.0751)* to protect sensitive subpopulations, and the *Groundwater Protection Act (Minnesota Statutes, sections 103H.201 - 103H.280)*, which directs MDH to use certain risk assessment procedures to derive HRLs.

The panel answered the general question "Are the methods to protect public health that are proposed in the revision of the Health Risk Limits rules prudent and reasonable interpretations of the legislative directives?", as well as specific charge questions related to the revision. The meeting was open to the public and observers were allowed to provide oral comments.

MDH posted its final external Expert Advisory Panel report, containing the list of charge questions, panel deliberations (including recommendations), comments from the individual members of the panel, and comments from members of the public, on the MDH rules revision web page in December of 2005.

The seventh meeting, held on April 5, 2007, focused on MDH's plans to revise the 2004 draft recommendations. This meeting provided participants with an overview of the revised recommendations.

An eighth meeting was held on September 13, 2007 to introduce the revised draft SONAR. MDH staff presentations focused on significant differences in procedures and concepts between the new rules and current methods.

The ninth meeting, held on October 11, 2007, included brief presentations on four chemicals undergoing the revision process. MDH staff described the key studies and stepped through the evaluation process, showing how multiple-duration HRLs were derived from the available toxicological data.

At each meeting, MDH encouraged attendees to ask questions and engage in discussion with MDH and one another. MDH also encouraged attendees and other interested parties to submit written comments at any time. MDH also suggested that stakeholders request meetings with MDH to discuss their concerns directly. MDH considered all comments received, whether verbal or written.

To allow interested parties who were not able to attend the meetings access to the proceedings of each meeting, MDH posted a summary of each meeting on a revision web page maintained by MDH (<http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/meetings.htm>).

Requested Meetings. Beginning in November of 2002, MDH received requests for meetings and met individually with different groups representing specific interests. A record of these meetings and the general subject matter discussed is available on the web at <http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/meetings.htm>.

Web Site. MDH created and maintained a web page containing information about the revision process. See <http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/index.html>. MDH posted notices and

summaries of all public meetings were posted on its website. In addition, the website contains summaries of science and policy recommendations by MDH research scientists (<http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/changes.html>), as well as public comments (<http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/comment/index.html>). Throughout the revision process, MDH has updated the web page to reflect new information pertaining to the revision effort.

As toxicological evaluations were completed, MDH posted toxicological summaries for each chemical. The summaries include draft HRL values and endpoints, the source and basis of the values, and research status relevant to the Health Standards Statute. Stakeholders responded to draft values with comments on overall risk assessment strategies; with questions about the derivation of draft values for certain chemicals; and, in some instances, with offers to serve as liaisons in obtaining further data for MDH. Stakeholder actions resulted in modifications of some procedures; inclusion of more information in the SONAR; and modification or elimination of certain draft values.

Distribution List. MDH routinely emails the "Request for Comments," meeting notices, and notices of the periodic web updates to individuals on a distribution list maintained by MDH. The distribution list includes persons or entities self-identified or identified by MDH or others as interested in the revision. MDH has actively sought to add parties to the distribution list throughout the revision process. In November of 2004, MDH implemented a free notification system (through the GovDelivery.com subscription management service) that automatically notifies interested parties whenever the revision web page is updated. The automatic email includes a direct link to the appropriate web page.

Outside Expertise. As MDH developed its recommendations for changing its methods and data for the rule revision, MDH staff met with representatives of other programs and other state agencies to communicate the direction MDH was considering taking on relevant issues, to respond to questions, and to seek input on how the revision of the rules would affect other programs.

MDH has solicited technical and practical advice from EPA, from agencies working on similar issues in other states, and from toxicologists and risk assessors with specialized knowledge in areas of interest.

MDH has presented risk assessment issues, ideas, and advances at a variety of scientific meetings and seminars to share and discuss these ideas with other scientists working in public health protection. A record of these meetings and a copy of the presentations are available on the web at <http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/present/index.html> .

Routine Communications. MDH has responded to numerous emails and verbal inquiries from stakeholders.

V. I. Consultation with Finance on Local Government Impact

As required by Minnesota Statutes, section 14.131, the Department has consulted with the Commissioner of Finance. We did this by sending to the Commissioner of Finance copies of the documents sent to the Governor's Office for review and approval by the Governor's Office prior to the Department publishing the Notice of Intent to Adopt.

PART VI. RULE-BY-RULE ANALYSIS

Minnesota Statutes, section 14.131 requires that MDH prepare a written statement of the proposed rules' need and reasonableness. *Minnesota Rules*, part 1400.2070 expands upon that requirement:

The statement of need and reasonableness must summarize the evidence and argument that the agency is relying on to justify both the need for and the reasonableness of the proposed rules, and must state how the evidence rationally relates to the choice of action taken. The statement must explain the circumstances that created the need for the rulemaking and why the proposed rulemaking is a reasonable solution for meeting the need.

Part VI summarizes the subject matter of each rule revision for HRLs.

4717.7810. HEALTH RISK LIMITS; PURPOSE AND SCOPE.

Subpart 1. **Purpose.** Subpart 1 states the purpose of the proposed rules and identifies their numerical range within *Minnesota Rules*. The proposed rules specify the methods and factors that MDH used to calculate the health risk limits, along with the values calculated using those methods and factors. However, the proposed rules stop short of specifying how the HRLs are to be applied.

The *Groundwater Protection Act* specifies only one application for the HRLs. section 103H.275, Management of Pollutants Where Groundwater Is Polluted, states that the Pollution Control Agency or the Commissioner of Agriculture may adopt water [re]source protection requirements if implementation of best management practices has proven to be ineffective [*Minnesota Statutes*, section 103H.275, subdivision 1, item (b)]. If water resource protection requirements are adopted, then the HRLs must be used in their development. *Minnesota Statutes*, section 103H.275, subdivision 1, item (c) requires, *inter alia*, that water resources protection requirements be designed to prevent the concentrations of contaminants from exceeding the HRLs.

The HRLs provide guidance as to whether water is fit for human consumption. However, the HRLs are but one of several factors that may State agencies responsible for addressing groundwater issues might consider.

Subpart 2. **Scope.** Subpart 2 contains introductory information about the HRLs that is taken from the *Minnesota Groundwater Protection Act*. This restatement clarifies what the HRLs are and how they might be used.

Item A indicates that HRLs are developed for cancer and noncancer effects. This is a change in wording from the *Minnesota Groundwater Protection Act*. *Minnesota Statutes*, section 103H.005, Subd. 3, and section 103H.201, subd. 1, juxtapose carcinogens and "systemic" toxicants. "Systemic" means "relating to or affecting a given body system." Thus, "noncarcinogen" and "noncancer" would be more appropriately used in juxtaposition to "carcinogen" or "cancer." A chemical may have both noncancer and cancer effects. MDH has added precision to the Legislature's intention that HRLs be developed for both types of effects.

Item B points out that HRLs are developed to evaluate concerns about risks to human health from ingesting water. The HRLs do not consider non-ingestion routes of exposure (e.g., dermal or inhalation) except through the application of an RSC factor. Factors in addition to human health might also be relevant in the application of the HRLs. These factors, however, do not play a role in the development of HRLs. For example, HRLs do not consider aquatic life. Nor do HRLs consider implications to human health from effects on aquatic life. Application of the HRLs as general environmental levels would therefore not be appropriate.

4717.7820. DEFINITIONS.

This part defines the technical terms used in the Rules and the terms that are not ascribed their commonly understood meaning when used within the Rules.

Subpart 1. **Scope.** Application of the definitions stated in the Rules is limited to the sequence of parts that constitute the Rules. The need for this provision is self-evident.

Subpart 2. **AF_{lifetime} or lifetime adjustment factor.** This term refers to an adjustment factor used to adjust the adult based cancer slope factor for lifetime exposure based on chemical-specific data.

Subpart 3. **ADAFs or Age-Dependent Adjustment Factor.** To account for increased sensitivity to exposure during early life, the ADAF, a default adjustment to the cancer slope factor, is incorporated into the denominator of the cancer HRL equation in the absence of chemical-specific data. For the default derivation of cancer HRLs, the following ADAFs corresponding age groups are used: ADAF_{<2} = 10, for birth until 2 years of age; ADAF_{2 to <16} = 3, for 2 up to 16 years of age; and ADAF₁₆₊ = 1, for 16 years of age and older.

Subpart 4. **Additional lifetime cancer risk.** Additional cancer risk is a mathematical probability of risk of cancer that has been selected by MDH for use in calculating HRLs. It can be used to describe both an individual's added risk of developing cancer and an increase in the rate of cancer in an exposed population.

MDH uses an additional cancer risk level of 1×10^{-5} (or 1/100,000) in deriving maximum human health-based concentrations for contaminants in air and groundwater. 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 carcinogen at a concentration equal to its 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 might be lower.

Additional cancer risk is risk added to the background cancer rate. Currently one of every two Minnesotans will have some type of cancer by the end of their lifetime (a cancer risk of 50,000/100,000). This is considered the background cancer risk in Minnesota and in the United States as a whole. Therefore, in a population of 100,000 individuals exposed to a carcinogenic chemical at a concentration equal to its HRL, the lifetime incidence of cancer would be expected, at most, to increase from 50,000 cases to 50,001 cases.

Another Minnesota agency, the Minnesota Pollution Control Agency, has adopted the same 1×10^{-5} additional cancer risk level in rules, that is, the Solid Waste Rules [*Minnesota Rules*, part 7035.2815, Subpart 4, item H, subitem (5)(b)] and the Surface Water Rules [*Minnesota Rules*, part 7050.0218,

Subpart 6, item C]. However, other regulatory agencies might use different additional cancer risk levels. The EPA recommends using a lifetime risk level between 1×10^{-4} and 1×10^{-6} , but the choice of a specific lifetime risk level is left to the discretion of the regulatory agency.

Subpart 5. **Carcinogen.** The term "carcinogen" is used throughout the proposed rule for chemicals that cause cancer. *Minnesota Statutes*, section 103H.201, subd.1(d), restricts HRLs to those chemicals for which the EPA has published a slope factor, or an estimate of carcinogenic potency.

Statutory language authorizes derivation of health risk limits using a quantitative estimate of carcinogenic potency to toxicants "that are known or probable carcinogens." This language reflects the scheme for classification of chemical carcinogenicity set in place by the Risk Assessment Guidelines of 1986 (EPA 1986a). The 1986 Guidelines established five classifications for carcinogens: "A, human carcinogen;" "B, probable human carcinogen;" "C, possible human carcinogen;" "D, not classifiable as to human carcinogenicity;" and "E, evidence of non-carcinogenicity for humans." In EPA's Final Guidelines for Carcinogenic Risk Assessment, (EPA 2005b), these classifications are supplanted by a set of narrative descriptors which reflect the use of a "weight of the evidence" narrative to characterize cancer hazard. To provide some measure of clarity and consistency, the Agency recommends five standard hazard descriptors: "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." While these new descriptors loosely parallel the A through E classes of the older guidance, they are not equivalent, and a chemical's classification under the old system does not directly translate into a classification under the new system without a review of the chemical's carcinogenic potential. For example, under the new classification system, some chemicals are classified as not likely to be carcinogenic at low doses, but likely to be carcinogenic at high doses.

In the 1993 and 1994 promulgations, MDH developed cancer HRLs only for those chemicals classified as "A, human carcinogen" or "B, probable human carcinogen." Where data allowed, MDH developed HRLs for chemicals classified as "C, possible human carcinogen" using noncancer data and an additional ten-fold uncertainty factor to account for possible carcinogenicity. Because the letter-based classes described in the statutory text are being replaced by new narrative descriptors, continuing the practice of interpreting the statutory language as referring to specific assignments of carcinogenic potential would render this portion of the statute meaningless. Therefore, in this revision, MDH shifted away from interpretation of the language "known or probable carcinogens" as referring specifically to classifications established by the 1986 cancer guidelines. MDH will instead interpret this phrase according to its common usage.

Typically, there are sufficient data from EPA to develop a HRL based on cancer for chemicals with a classification of "A, human carcinogen" or "B, probable human carcinogen" under the 1986 guidelines, or "carcinogenic to humans" or "likely to be carcinogenic to humans" under the 2005 guidelines. If the EPA has derived a slope factor for a chemical with a classification of "C, possible human carcinogen" under the 1986 guidelines an MDH review panel, made up of three staff members, evaluated the evidence supporting the finding of carcinogenicity and the slope factor and exercised professional judgment to determine whether to develop a cancer HRL. The MDH carcinogen review committee guidelines are presented in Appendix G. (For cancer classifications used by NTP and IARC, see Appendices H and I. The 1986 and 2005 EPA guidelines are presented in Appendices E and F, respectively.) Some factors considered include the strength of the findings, the number of studies conducted, the relative proportions of studies positive for carcinogenicity and negative for

carcinogenicity, whether studies have been conducted in more than one species, and the results of mutagenicity assays. If there was adequate evidence for carcinogenicity and an EPA cancer slope factor was available, a cancer HRL was derived. In the absence of an EPA cancer slope factor, application of a Group C factor was considered (see Section IV.C.3.) If evidence of carcinogenicity was inadequate, then a noncancer HRL value was derived. The calculated noncancer HRL value does not incorporate a Group C factor.

See 4717.7820, Subpart 20 for definition of nonlinear carcinogen.

Subpart 6. **Chemical.** This definition is included so that the term "chemical" is confined to a chemical or a defined mixture of chemicals throughout the rules. While HRLs are derived for individual chemicals whenever possible, toxicity data are sometimes available for chemical mixtures whose constituent parts are well-defined. An example of a defined chemical mixture is xylenes. In 1993, a HRL was promulgated for a mixture of m-, p- and o-xylenes. The RfD for xylenes was based on a toxicity evaluation of a defined mixture comprised of 60% m-xylene, 13.6% p-xylene, and 9.1% o-xylene and 17% ethylbenzene. There are no defined mixtures included in the current rules revision, but HRLs for mixtures may be added in the future.

Subpart 7. **Chemical abstracts service registry number or CAS number.** The "Chemical Abstracts Service registry number" or "CAS number" is a unique identifier established and maintained by the Chemical Abstracts Service, a division of the American Chemical Society. This chemical substance identification system is the standard used by scientists, industry, and regulatory bodies. A CAS number links systematic, generic, and proprietary names to a unique chemical structure. A single chemical may be known by many names, including trade names, so incorporation of the CAS number into the rule ensures that HRLs will be consistently identified with the proper substance, regardless of the nomenclature used. MDH has incorporated a CAS number for all chemicals for which a CAS number was available. For some chemicals, more than one CAS number is applicable due to multiple forms of the chemical being grouped together, e.g., PFOA and its salts.

Subpart 8. **Developmental health endpoint.** This term refers to an exposure that results in an adverse health effect based on its timing, rather than on a particular type of adverse health effect. This definition also describes the range of impacts that may occur as a result of exposure during development and specifies that impacts may be latent for many years and appear in subsequent generations. Development of an organism can be altered during a brief chemical insult during pre-natal and post-natal periods. The developmental effects of a particular chemical are assessed using standard developmental studies, multigenerational studies and developmental neurotoxicity studies. Standard developmental studies provide data on maternal and fetal toxicity in laboratory animals. Multigenerational studies provide toxicity data for animals dosed from a point at or before conception up to adulthood in more than one generation. Finally, developmental neurotoxicity studies provide data on offspring born to pregnant animals dosed during gestation through postnatal day 10. Motor activity of the offspring is monitored through young adulthood. Examples of developmental effects are lack of growth, skeletal malformation, mortality, and latent effects such as learning difficulties, memory damage and changes in reproductive behavior.

Subpart 9. **Duration.** This term refers to the length of an exposure period. The EPA Technical Review Panel (EPA 2002c) and the external Expert Advisory Panel (ERG 2005) have recommended evaluation of less-than-chronic exposure periods to ensure adequate protection during early life (i.e. the

developmental period) and periods of high intake. As part of their recommendations, the EPA Technical Review Panel provided the following definitions for the various exposure time periods:

Acute - A period of 24 hours or less.

Short-term - A period greater than 24 hours and up to 30 days.

Subchronic - A period of greater than 30 days and up to approximately 10% of the life span in humans.

Chronic - A period of greater than approximately 10% of the life span in humans.

In the United States life expectancy is approximately 78 years (NCHS 2006). EPA uses a life span of approximately 70 years.

The default durations evaluated for cancer health effects correspond to the age groups upon which the age dependent adjustment factors (ADAFs) are based. These age groups were identified in the "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens," United States Environmental Protection Agency, Risk Assessment Forum (EPA 2005a). 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, if the noncancer health effect is linked to a specific time point at which the concentration of the chemical in the blood reaches a critical level, a duration corresponding to that time point is used. Or, if the cancer slope factor is based on a lifetime rather than an adult-only exposure protocol, the lifetime duration rather than the three age groups identified above is used.

Subpart 10. Endocrine or (E). This definition explains the meaning of the designation "(E)" when attached to a health endpoint for a health risk limit. MDH added this designator in consideration of the Health Standards Statute. This statute requires that water standards include a reasonable margin of safety, given certain specified health outcomes, including "endocrine (hormonal) function." While other specified health outcomes tend to be associated with specific organs or organ systems, changes in endocrine function have the potential to impact nearly every organ, system, or process in the body.

Because of the many organs and tissues that secrete and/or are affected by hormones, MDH has not considered the endocrine system to be a discrete classification of toxicity, but rather a mechanism through which toxicity is caused or manifested. An effect will only be considered an "endocrine effect" if a change in circulating hormones or receptor interactions has been measured. The toxic endpoint may be either an organ that produces the hormone measured or an organ that is affected by the hormone measured. In this revision of the HRLs, endocrine effects are indicated in the HRL tables with the designation "(E);" for example, "thyroid (E)."

Subpart 11. Health risk index. This term is used in the discussion of multiple chemical health risk limits (Subp. 19.) Contaminants are grouped on the basis of the health effects (or "endpoints") observed at each of the four exposure durations (acute, short-term, subchronic, and chronic.) For each health endpoint, an acute, short-term, subchronic, and chronic health risk index may be expressed as the sum of the ratios of the measured concentration of each chemical in the group to its respective HRL. The health risk index is compared with the multiple-chemical health risk limit, which is equal to one, to evaluate the hazard posed by exposure to multiple chemicals. The equation to calculate multiple-chemical HRLs and a sample calculation are found in Section IV.A.

Subpart 12. **Health risk index endpoint or health endpoint.** The "health risk index endpoint" or "health endpoint" is a general description of toxic effects used to group chemicals for the purpose of calculating a health risk index. For example, a chemical with the toxic effect "acetylcholinesterase inhibition" would have the health risk index endpoint "nervous system" and would be grouped with all chemicals that affect the nervous system. A health endpoint may also have the additional descriptor ("E") that indicates an associated change in hormone levels (see Subp. 10). Note that for a given chemical, the health endpoint(s) may vary with exposure duration, i.e., the short-term endpoint may be different from the chronic endpoint.

Subpart 13. **Health Risk Limit (HRL).** *Minnesota Statutes*, section 103H.005, subdivision 3 defines "health risk limit." *Minnesota Statutes*, section 103H.201, subd. 1 (c) and (d) provide further context by setting forth methods for deriving HRLs. The methods required are standard risk assessment methods, which, when applied, result in an estimate of a dose that, even when consumed daily, is associated with little or no risk to human health. Because these two statutory provisions must be read in conjunction with one another, MDH interprets "health risk limit" to mean the concentration of a groundwater contaminant, or multiple contaminants, that can be consumed daily with little or no risk to health. Health Risk Limits are derived and promulgated under rule.

HRLs are intended to be protective of varying durations. Therefore, if there is adequate information, MDH derives and promulgates multiple-duration noncancer HRLs. The durations are as specified above in 4717.4820, Subpart 9.

The magnitude of the HRL value is a function of the reference dose (RfD) and the intake rate. In general, for a given chemical, the shorter-duration RfD values will be higher than 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. In most cases, therefore, the calculated HRL values decrease with increasing duration, e.g., acute HRLs are greater than short-term HRLs, short-term HRLs are greater than subchronic HRLs, and so on. It is possible, however, that the RfD for a shorter-duration is the same, or in rare cases lower, than the RfD for a longer-duration. This could result if a short-duration was sufficient to elicit an adverse effect, if a more sensitive endpoint was assessed in the shorter-duration study, or if a different species or life stage was assessed. The intake rate also impacts the magnitude of the HRL value. As shown above the shorter-duration intake rates are higher than the longer-term intake rates. These factors may cause a calculated shorter-duration HRL to be less (lower) than a 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 any higher shorter-term exposure that occurs within its defined time span.

A HRL has the units of micrograms per liter ($\mu\text{g/L}$), which is equivalent to one part per billion (ppb) or one one-thousandth of a milligram per liter (mg/L).

Subpart 14. **Intake rate or (IR).** For water consumption, the intake rate is the volume of water, on a per body weight basis, ingested per day (liters per kg body weight per day, or L/kg-day) for a specified duration. The EPA Technical Review Panel (EPA 2002c) and the external Expert Advisory Panel (ERG 2005) have recommended the evaluation of less-than-chronic exposure periods to ensure that high intake rates over short periods of time, e.g. infants, are adequately protected. (The highest short-term water intakes on a unit body weight basis occur in young infants.) For noncancer HRL derivation, a time-weighted average value of the 95th percentile intake rate for the relevant duration is used. The

starting and ending ages for the durations used in calculating this time-weighted average are selected in such a way as to maximize the resulting intake rate; this is done by including infancy and childhood in the period being measured, because these ages have higher water intake rates per unit body weight. Maximizing the intake rate ensures that the resulting HRLs will be protective regardless of at what point exposure occurs during a person's lifetime. For acute and short term duration, the intake rate is 0.289 L/kg-d; this value is the highest 95th percentile intake for any 30-day period during a lifetime, and happens to occur during the second and third months of life. The subchronic duration intake rate is 0.077 L/kg-d and the chronic duration intake rate is 0.043 L/kg-d.

MDH will depart from the above default intake rates if sufficient chemical-specific information indicates that a different duration or intake rate is more appropriate, e.g. perfluorochemicals-PFOS and PFOA. In these cases MDH will use the data presented in Table 2 to calculate an appropriate TWA intake rate for the duration specified by the chemical-specific information.

MDH has adopted EPA's approach for integrating age-dependent sensitivity adjustment factors and exposure information for the derivation of HRLs for linear carcinogens. The default intake rates corresponding to the age-dependent adjustment factor age groups used in deriving cancer HRLs, which are based on the TWA of the 95th percentile intake rate for each age range, are 0.137 (up to 2 years of age), 0.047 (2 to up to 16 years of age), and 0.039 (16 years of age and older) L/kg-day. The lifetime duration used by EPA to characterize lifetime cancer risk is 70 years.

MDH will depart from the above default age group intake rates if sufficient chemical-specific information permits the derivation of a lifetime adjustment factor, e.g. dieldrin and vinyl chloride. In these cases MDH used the data presented in Table 2 to calculate a TWA intake rate over a lifetime of approximately 70 years, i.e., 0.043 L/kg-day).

Subpart 15. Maximum Contaminant Level or MCL. The MCL is a federal health-protective standard determined by the United States Environmental Protection Agency and intended for public water supplies. MCLs take into account chemical health risk, as well as other factors such as chemical detection limits, treatment potential, and cost. HRLs, by contrast, are based only on health effects.

Subpart 16. Maximum Contaminant level-based Health Risk Limit or MCL-based HRL. An MCL-based HRL is defined as an existing MCL value that is adopted as a HRL value. Legislation passed in 2007 (Minnesota Session Laws 2007, Chapter 147, Article 17, section 2) established HRLs for contaminants in private domestic wells to be the more stringent of either the existing HRL or the EPA-derived MCL. As a result, MCL values for eleven chemicals were adopted as HRL values in July 2007. MDH has derived HRLs for three of the eleven chemicals (alachlor, benzene, and 1,1,1-trichloroethane). The MCL-based HRLs for the remaining eight chemicals will be kept until MDH derives and promulgates revised values for these chemicals. An MCL-based HRL for nitrate (as N) has also been incorporated into the revised rules to preserve a promulgated HRL for this common contaminant until MDH completes its review. See Section III.A.

Subpart 17. Microgram per liter. "µg/L" refers to micrograms of chemical per liter of water, which are the units of measure used for HRLs throughout the Rules. One microgram is 1×10^{-6} grams or 1×10^{-3} milligrams.

Subpart 18. Milligram per kilogram per day. "mg/kg-day" refers to milligrams of chemical per kilogram of body weight per day, which are the units used in toxicity values from which non-cancer

reference doses, used to calculate non-cancer HRLs, are derived. For cancer, the slope factor used to derive cancer HRL is in units of inverse (mg/kg-day), or (mg/kg-day)⁻¹.

Subpart 19. **Multiple chemical HRL.** Exposures to individual chemicals do not occur in isolation from one another; people are continually exposed to multiple chemicals. In contrast, groundwater standards are typically derived chemical by chemical without consideration of the presence of other chemicals. This definition provides guidance in situations where more than one HRL chemical is present.

The multiple chemical health risk limit is a concept used to evaluate whether multiple substances or chemicals present in groundwater pose a risk to human health. To determine this, risks from exposures to multiple agents, all of which have the potential to affect the same organ, system, or process, are combined (EPA 2003b). First, chemicals present in groundwater are identified. Then the toxicity of each of the chemicals is characterized for a given duration, and chemicals are grouped according to health endpoint. Because more than one health endpoint might be associated with a chemical, a chemical may be included in more than one endpoint grouping. The measured concentration of each chemical within a group is divided by that chemical's HRL to yield a hazard quotient. Hazard quotients for all chemicals within a given duration with the same health endpoint are summed. If the sum for any health endpoint within a given duration exceeds unity, the multiple chemical health risk limit has been exceeded.

Subpart 20: **Nonlinear Carcinogen.** This term refers to a chemical for which, at low doses, the risk for cancer does not increase in direct proportion with the exposure duration. Nonlinearity implies that there is a threshold level of exposure below which there is no cancer risk. For nonlinear carcinogens, MDH will use available information to derive an RfD-based HRL that is likely to be without appreciable risk of adverse health effects, including cancer, during a lifetime.

A linear carcinogen, by contrast, is one where there is no threshold below which there is no risk. HRLs for linear carcinogens are calculated using a slope factor instead of a reference dose.

Subpart 21: **Reference Dose (RfD).** This definition is based on that provided by the EPA in *A Review of the Reference Dose and Reference Concentration Processes* (EPA 2002c),⁸ but the use and definition of the RfD in the HRL process differs from the source definition in several substantive ways. First, it substitutes "an exposure for a given duration" for "a daily oral exposure." This change reflects the fact that HRLs may be derived not only for risks associated with long-term exposure, but also for risks incurred from exposures of much shorter duration, such as exposures during a short yet critical window of time during which a structure or system is developing. Consideration of these short-term exposures is necessary to fulfill MDH's mission of protecting public health; to comply with strictures of the Health

⁸ IRIS and the 2002 document, "A Review of the Reference Dose and Reference Concentration Processes," defines "Reference Dose" as "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally it is used in the EPA's noncancer health assessments. [duration includes acute, short-term, subchronic, and chronic which are individually defined in the IRIS glossary] "

Standards Statute;⁹ and to be internally consistent with the remainder of the RfD definition, which specifies that "sensitive subgroups" are within the population that the RfD aims to protect. Second, it substitutes "during a lifetime" for "over a lifetime" in specifying the period over which adverse effects may develop. The rationale for this change is similar to that for the first change, acknowledging that adverse effects will be considered whenever they arise during the course of a lifetime, and not only at the end of a lifetime. Third, it replaces specific descriptions of the various points of departure with a more general description – "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." Fourth, it replaces "uncertainty factors" with "uncertainty and variability factors." This change acknowledges that some of the factors that have been termed "uncertainty factors" in the past actually reflect measures of variability rather than uncertainty. Fifth, MDH's definition of the RfD acknowledges that uncertainty and variability factors may be applied for limitations in methods, as well as for limitations in data. Finally, the definition in the Rules eliminates the requirement that exposure be via the oral route, thus allowing for HRLs to be developed using route-to-route extrapolation from routes of exposure other than oral.

Reference doses are intended to be protective of all types of adverse effects for a given duration. The EPA RfC/RfD Technical Panel (EPA 2002c) considered the relationship between exposure duration, life stage and subsequent adverse health effect and recommended that RfDs for acute, short-term, subchronic and chronic durations be calculated for each identified endpoint. Multiple-duration exposure analysis is protective of all sensitive life stages (e.g. development) and short periods of high exposure (e.g. infancy). From the available studies, MDH derived RfDs for the durations specified by EPA. MDH evaluated toxicological data from available studies, determined the point of departure, assigned an uncertainty factor, selected the appropriate endpoint, and calculated the RfDs. Selection of the critical RfD (often the lowest RfD) for each exposure duration involved consideration of the robustness of the study and the range of health endpoints observed. The selected RfD for a given exposure duration is protective of all types of adverse effects.

Subpart 22. **Relative Source Contribution (RSC):** The RSC is a measure of the proportion of an individual's total permissible exposure that is allocated to ingestion of water. Application of this factor takes into account the possibility that exposure may occur from water through means other than ingestion (e.g., dermal contact with water or inhalation of volatilized chemicals from water), or from exposure to media other than water, such as air, food, and soil. By using an RSC, exposure from ingestion of drinking water is constrained to "use up" only a fraction of the reference dose, leaving the remainder for any other potential sources, known or unknown. The *Minnesota Groundwater Protection Act*, in *Minnesota Statutes*, section 103H.201, subd. (1)(d), requires that the Minnesota Department of Health use a relative source contribution in deriving health risk limits for systemic toxicants. MDH relied upon EPA's Exposure Decision Tree approach (EPA 2000c) to determine appropriate RSC values.

Using a qualitative evaluation and EPA's Exposure Decision Tree, MDH determined the following default RSC values: for highly volatile contaminants (chemicals with a Henry's Law Constant greater than 1×10^{-3} atm-m³/mole), the RSC is 0.2 for all persons. For chemicals that are not highly volatile, the RSC is 0.5 for young infants or 0.2 for all other persons. The value of 0.5 was selected for young infants because they encounter a far narrower range of environments than older infants, children, or adults; in

⁹ The health standards statute, *Minnesota Statutes* 144.0751, provides, in part: "(a) Safe drinking water or air quality standards established or revised by the commissioner of health must . . . include a reasonable margin of safety to protect the health of infants, children, and adults . . ."

contrast, the RSC is 0.2 for all ages for highly volatile chemicals because inhalation exposure would be a concern for exposure at any age, including infancy.

These RSC values are intended to be applicable to a broad range of potential uses of the HRLs and potentially exposed populations. When applying HRLs, risk assessors may find that the level of contamination in each medium and the populations potentially exposed vary from site to site and from chemical to chemical. Therefore, there may be situations where the Exposure Decision Tree process could be used in conjunction with site-specific information to derive a site-specific RSC that varies from the above values. Per EPA guidance, the RSC should not be less than 0.2 or greater than 0.8.

Subpart 23. **Slope factor or SF.** The SF is the slope of a curve expressing the relationship between cancer risk and dose. Is an upper-bound estimate of risk per unit dose, expressed in units of the inverse of milligrams per kilogram of body weight per day ($[\text{cancer risk per mg/kg-d}]$ or $[\text{mg/kg-d}]^{-1}$). This estimate is generally used only in the low-dose range of the dose-response relationship, i.e., for exposures corresponding to risks less than or equal to 1 in 100 (EPA 2003g). Within that range, the dose-response relationship closely approximates a straight line whose slope is equal to the SF. Because the linear carcinogenic model is essential to the concept of a slope factor, the SF is not used for assessment of nonlinear carcinogens.

Subpart 24: **Toxic Effect(s).** A toxic effect is a measurable or observable deleterious effect on an organ, tissue, or biological systems. Identification of a toxic effect requires a clear causal relationship between exposure to the substance and observed effect, which is often adverse or biologically significant. The United States Environmental Protection Agency (EPA) defines "adverse effect" as "a biological 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" (EPA 2002c). The EPA defines an effect as "biologically significant" if "the observed effect (a biological change, a functional impairment, or a pathological lesion) is likely to impair the performance or reduce the ability of an individual to function or to respond to additional challenge from the agent. Biological significance is also attributed to effects that are consistent with steps in a known mode of action" (EPA 2002c). The body has a built-in repair mechanism to protect against assault from foreign substances. Effects as a result from this process are not considered a toxic effect, but may be a precursor to an adverse effect that occurs with longer exposure or at a higher dose.

Subpart 25: **Volatility.** Volatility, in chemical parlance, is the tendency of a chemical to vaporize. The use of water during regular household activities may significantly contribute to an individual's exposure to chemicals present in the water because they may volatilize from water to air. Although inhalation exposure was not considered in the HRL rule, information about the tendency of a chemical to evaporate provides a complete risk assessment picture and may be useful to risk managers. Therefore, volatility information of each chemical is included in the HRL rule. Chemicals are classified as to their volatility using the Henry's Law constant, a commonly used and measured chemical property defined as the ratio of the concentration of volatilized chemical in the air to the concentration of the chemical in water (C_a/C_w) at equilibrium:

Nonvolatile – Henry's Law constant $< 3 \times 10^{-7}$ atm-m³/mol

Low volatility – Henry's Law constant $> 3 \times 10^{-7}$ to 1×10^{-5} atm-m³/mol

Moderate volatility – Henry's Law constant $> 1 \times 10^{-5}$ to 1×10^{-3} atm-m³/mol

High volatility – Henry's Law constant $> 1 \times 10^{-3}$ atm-m³/mol

4717.7830 FOR TOXIC EFFECTS OTHER THAN CANCER.

This part describes the proposed methods for calculating a HRL for a toxic effect other than cancer. The proposed methods comply with the procedure for deriving health risk limits for "systemic toxicants that are not carcinogens" in *Minnesota Statutes*, section 103H.201, subd. 1(c):

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

Subpart 1. **Scope.** This Subpart specifies that the equation in this part applies to toxic effects other than cancer.

Subpart 2. Equation for toxic effects other than cancer or MCL-based HRLs.

This part describes the proposed methods for calculating HRLs for noncancer effects, and defines each component of the equation. The equation for calculating cancer HRLs will be covered in 4717.7840 and MCL-based HRLs will be covered in 4717.7850.

Item A specifies units of measurement and duration for the noncancer health risk limit as defined in 4717.7820, Subpart 14 and 4717.7820, Subpart 9, respectively.

Item B specifies the reference dose (RfD) as defined in 4717.7820, Subpart 21.

Item C specifies the relative source contribution (RSC), which represents the fraction of total exposure to contaminant that is attributed to water ingestion. MDH determined the default RSC values to be 0.2 for all durations and chemicals, with one exception: the RSC is 0.5 for acute and short-term durations when assessing chemicals that are *not* highly volatile.

Item D is a conversion factor that allows expression of the HRL in units of micrograms per liter ($\mu\text{g/L}$), rather than milligrams per liter (mg/L). Micrograms per liter are a more convenient expression of concentration of a HRL than milligrams per liter. There are 1,000 micrograms in one milligram.

Item E specifies the intake rate of water ingestion, which is a ratio of daily adult water intake to body weight (liters per kg body weight per day or L/kg-day). It is a time-weighted average (TWA) of the 95th percentile intake rate for a given duration. The intake rate for acute and short-term duration is 0.289 L/Kg-d , based on intake for from 1 to 3 months of age; the subchronic duration intake rate is 0.077 L/Kg-d based on a TWA up to 8 years of age; and the chronic exposure duration intake rate is 0.043 L/Kg-d , based on a TWA over a lifetime of approximately 70 years of age.

4717.7840 FOR CANCER.

This part describes the proposed methods for calculation of a HRL for cancer. The proposed methods comply with the procedure for deriving health risk limits for "toxicants that are known or probable carcinogens," as stated in *Minnesota Statutes*, section 103H.201, subd. 1(c):

- (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 EPA and determined by the commissioner to have undergone thorough scientific review.

Methods for deriving estimates of carcinogenic potency are set forth in *The Risk Assessment Guidelines of 1986* (EPA 1987) and in the Draft Final Guidelines for Carcinogenic Risk Assessment (EPA 2003a).

Subpart 1. **Scope.** This Subpart specifies that the equation in this part applies to cancer effects that are subject to the linear default assumption.

Subpart 2. **Equation for cancer for chemicals other than chemicals for which a lifetime adjustment factor has been derived or nonlinear carcinogens.** Subpart 2 provides the general equation for calculating a HRL for cancer effects that follow the linear default assumption. If there is lack of evidence for nonlinear mode of action, then the default model for carcinogenicity is based on a linear relationship between dose and cancer risk with the assumption that exposure to any amount of a carcinogen, no matter how small, carries some risk for cancer. If there is adequate information to derive a chemical-specific lifetime adjustment factor MDH will use the equation in Subpart 3 to derive a cancer HRL. If the EPA has determined that a particular carcinogen is nonlinear, MDH will use that information to determine a noncancer HRL value that will be protective of cancer, as recommended by the EPA 2005 cancer guidelines (EPA 2005b).

Item A specifies the units of measurement for the cancer HRL ($\mu\text{g/L}$).

Item B refers to the additional lifetime cancer risk level, which is 1×10^{-5} . See section 4717.7820, Subp. 4.

Item C is a factor used to convert milligrams (mg) to micrograms (μg). There are 1,000 micrograms in one milligram.

Item D refers to the cancer slope factor based on adult exposure, expressed in units of the inverse of milligrams per kilogram of body weight per day ($[\text{cancer risk per mg/kg-day}]$ or $[\text{mg/kg-day}]^{-1}$).

Item E refers to the age-dependent adjustment factors; see 4717.7820, Subpart 3.

Item F refers to the water intake rate corresponding to the age-dependent adjustment factor age groups, calculated as the 95th percentile intake rate for each age range; see 4717.7820, Subpart 14.

Item G is the duration corresponding to each age group: 2 years, for up to 2 years of age ($D_{<2}$); 14 years, for 2 up to 16 years of age ($D_{2 \text{ to } <16}$); and 54 years, for 16 years of age and older (D_{16+}).

Item H is the standard lifetime duration of 70 years, as defined by the EPA in their assessment of lifetime cancer risk.

Subpart 3. **Equation for cancer for chemicals for which a lifetime adjustment factor has been derived.** Subpart 3 provides the general equation for calculating a HRL for cancer effects when an adjustment factor could be based on chemical-specific information.

Item A specifies the units of measurement for the cancer HRL ($\mu\text{g/L}$), the additional lifetime cancer risk level, the milligrams to micrograms conversion factor, and cancer slope factor based on adult exposure, respectively, as described in 4717.7840, Subpart 2.

Item B refers to the lifetime adjustment factor used to modify the adult based slope factor for lifetime exposure based on chemical-specific information; see 4717.7820, Subpart 2.

Item C is the water intake rate, calculated as the 95th percentile water intake rate over a lifetime; see 4717.7820, Subpart 14.

4717.7850 USE OF MAXIMUM CONTAMINANT LEVELS..

This part describes the adoption of Maximum Contaminant Levels (MCLs), a federal standard developed by EPA, as Health Risk Limits (see the definition of MCL-based HRLs in 4717.7820, Subpart 18.) MDH will include these MCL values in revisions to the rules until MDH derives and promulgates HRL values for them.

Subpart 1. **Scope.** This part establishes the methods for determining a health risk limit based on a maximum contaminant level.

Subpart 2. **Water levels standards.** As authorized by Session Laws 2007 (Chapter 147, Article 17, section 2), MCL values for eleven chemicals were adopted as HRL values in July of 2007. MDH derived HRLs for three of the eleven chemicals (alachlor, benzene, and 1,1,1-trichloroethane). The MCL-based HRLs for the remaining eight chemicals will remain in effect until MDH derives and promulgates revised values for these chemicals. A MCL-based HRL for nitrate (as N) has also been adopted to preserve a promulgated HRL for this common contaminant until MDH completes its review. Therefore MCLs are adopted as HRLs for the following nine chemicals:

- A. Atrazine;
- B. Dichloromethane;
- C. Di (2-ethylhexyl) phthalate;
- D. Nitrate (as N);
- E. Pentachlorophenol;
- F. Simazine;
- G. 1,1,2,2-Tetrachloroethylene;
- H. 1,1,2-Trichloroethylene; and
- I. 2(2,4,5-Trichlorophenoxy)propionic acid.

4717.7860 HEALTH RISK LIMITS TABLE.

Subpart 1. The Health risk limits table includes the year the HRL is promulgated, a Chemical Abstract Service (CAS) Registry Number which uniquely identifies each chemical, and classification for chemical volatility (low, moderate or high).

If the HRL is developed by MDH, the following information is provided:

The nHRLs listed in the table have been derived for each duration using the equation stated in part 4717.7830 of the Rules. For each chemical with an MDH-developed noncancer HRL, MDH has listed the

reference dose (RfD) and the health endpoint for acute, short-term, subchronic and chronic durations, where applicable. In general, for a given chemical, the shorter-term HRL values are higher than the longer-term HRL values, i.e., acute \geq short-term \geq subchronic \geq chronic. However, if MDH's calculation of a HRL for a longer duration yielded a higher value than that for a shorter duration, MDH set the longer-duration HRL equal to the shorter-duration value and made a notation in the table. In some instances, when such a substitution is made, the list of health endpoints may include endpoints for the longer duration that do not apply to the shorter-duration HRL that is being imputed. The table also lists duration-specific relative source contribution (RSC) and default water intake rates.

For chemicals with MCL-based HRL values, the MCL value is listed in lieu of the descriptions and table that are provided for MDH-derived HRLs.

If the chemical is a linear carcinogen, cancer is listed as a health endpoint. The table lists a cancer HRL that has been derived using the equation presented in part 4717.7840, Subpart 2 or Subpart 3, and the slope factor used in deriving the cHRL is provided. The table also lists, where applicable, chemical-specific information such as the age-dependent adjustment factor (for example, see benzene) and chemical adjustment factor (for example, see dieldrin and vinyl chloride.)

Subpart 2. **Explanation of the table in this section.**

- A. "-" symbol means not relevant.
- B. "NA" means not applicable.
- C. "ND" means not derived due to absence or paucity of toxicity information.
- D. "None" means not applicable for inclusion in the health risk index.
- E. The following explanations apply where noted:
 - (1) If the calculated HRL value is greater than the acute value, to be protective of acute exposures, the HRL is set to equal the acute HRL value.
 - (2) If the calculated HRL value is greater than the short-term HRL value, to be protective of short-term exposures, the HRL is set equal to the short-term HRL value.
 - (3) If the calculated HRL is greater than the subchronic HRL, to be protective of subchronic exposures, the HRL is set to equal the subchronic HRL value.

Subpart 3. **Acetochlor.**

CAS number: 34256-82-1

Year Established: 2008

Volatility: Nonvolatile

Acute and Short-term durations.

The reference dose is 0.021 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability and 10 for database insufficiencies due to lack of developmental neurotoxicity study and short-term studies in a more sensitive species, i.e. the dog). The source of the reference dose and uncertainty factor allocation is MDH. The point of departure NOAEL is 21.2 mg/kg-d and the LOAEL is 65.6 mg/kg-d from EPA (2006), based on developmental effects observed in a 2-generation study in rats.

Subchronic duration.

The intake rate used to calculate the subchronic HRL is lower (0.077 L/kg-day) than the acute and short-term intake rate (0.289 L/kg-day) and resulted in a higher calculated subchronic HRL despite nearly identical RfD values (0.02 mg/kg-d for subchronic versus 0.021 mg/kg-d for acute and short-term). The subchronic HRL must be protective of the short-term exposures that occur within the subchronic period, so the subchronic nHRL was set equal to the short-term non-cancer HRL.

Chronic duration.

The reference dose is 0.002 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability and 10 for subchronic to chronic extrapolation). MDH is the source of the reference dose and uncertainty factor allocation. The point of departure NOAEL is 2 mg/kg-d and LOAEL is 10 mg/kg-d, from EPA (2006), based on adverse effects in the hepatic (liver), male reproductive, nervous and renal (kidney) systems in a 1-year oral study in dogs. Bronchiolar hyperplasia and renal tubular hyperplasia were observed as co-critical effects.

Cancer.

EPA’s Final Guideline for Cancer Assessment Review Committee reevaluated the carcinogenic potential of acetochlor, and has classified it as having “suggestive evidence of carcinogenic potential” (EPA 2006). Acetochlor mode of action data supports a nonlinear dose-response relationship. In addition, the data did not indicate significant mutagenic potential. Following EPA’s recommended approach for nonlinear carcinogens, MDH has derived a chronic RfD of 0.002 mg/kg-d that is protective against cancer effects.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	40	40	40 (2)	9	NA
RfD (mg/kg-d)	0.021	0.021	(2)	0.002	-
RSC	0.5	0.5	(2)	0.2	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-d)	0.289	0.289	(2)	0.043	-
Endpoint(s)	developmental	developmental	developmental	hepatic (liver) system, male reproductive system, nervous system, renal (kidney) system, respiratory system	-

Subpart 4. **Alachlor.**

CAS number: 15972-60-8

Year Established: 2008

Volatility: Nonvolatile

Acute duration. Not derived due to insufficient data.

Short-term duration.

The reference dose is 0.1 mg/kg-d and the total uncertainty factor is 100 (10 for interspecies extrapolation and 10 for intraspecies variability). The source of the reference dose and uncertainty factor allocation is MDH. The point of departure NOAEL is 10 mg/kg-d and the LOAEL is 30 mg/kg-d from EPA (1998), based on renal (kidney) effects observed in a 3-generation rat reproductive study.

Subchronic duration.

The reference dose is 0.01 mg/kg-d and the total uncertainty factor is 100 (10 for interspecies extrapolation and 10 for intraspecies variability). The source for the reference dose and the uncertainty factor allocation is MDH. The point of departure NOAEL is 1 mg/kg-d and the LOAEL is 3 mg/kg-d from EPA (1998), based on hepatic (liver) and hematologic (blood) system effects observed in a 1 year oral study in dogs.

Chronic duration.

The reference dose is 0.001 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability, an additional factor of 10 is applied to account for subchronic to chronic extrapolation based on evidence of increased severity of effects with longer duration). The source for the reference dose and the uncertainty factor allocation is MDH. The point of departure NOAEL is 1 mg/kg-d and the LOAEL is 3 mg/kg-d from EPA (1998), based on hepatic (liver) and hematologic (blood) system effects observed in a 1 year oral study in dogs.

Cancer.

EPA, in agreement with FIFRA Scientific Advisory Panel on the mode of action data on carcinogenic potential of alachlor, has classified alachlor as "likely to be carcinogenic at high dose, but not likely at low dose, by all routes of exposure" (EPA 2004). Alachlor is considered a nonlinear carcinogen. Following EPA's recommended approach for nonlinear carcinogens, MDH derived a chronic RfD of 0.001 mg/kg-d that is protective against cancer effects.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	200	30	5	NA
RfD (mg/kg-d)	-	0.1	0.01	0.001	-
RSC	-	0.5	0.2	0.2	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-day)	-	0.289	0.077	0.043	-
Endpoint(s)	-	Renal (kidney) system	hepatic (liver) system, hematological (blood) system	hepatic (liver) system, hematological (blood)	-

Subpart 5. **Alachlor ESA.**

CAS number: 142363-53-9

Year Established: 2008

Volatility: Nonvolatile

Acute duration. Not derived due to insufficient data.

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

Subchronic duration.

The reference dose is 0.053 mg/kg-d and the total uncertainty factor is 300 (10 for interspecies extrapolation, 10 for intraspecies variability and 3 for database insufficiencies due to lack of adequate developmental and reproductive studies). The source for the reference dose and the uncertainty factor allocation is MDH. Point of departure NOAEL is 16 mg/kg-d and the LOAEL is 157 mg/kg-d from EPA (1998) and Wisconsin Department of Health and Family Services (WDHFS) (2005), based on hematologic (blood) system effect observed in a 91-day oral study in rats.

Chronic duration.

The reference dose is 0.0053 mg/kg-d and the total uncertainty factor is 3000 (10 for interspecies extrapolation, 10 for intraspecies variability and 10 for subchronic to chronic extrapolation and 3 for database insufficiencies). The source of the reference dose and uncertainty factor allocation is MDH. Point of departure NOAEL is 16 mg/kg-d and LOAEL is 157 mg/kg-d from EPA (1998) and WDHFS (2005), based on hematologic (blood) system effects observed in a 91-day oral study in rats.

Cancer.

The carcinogenic potential of acetochlor ESA has not been evaluated and a cancer classification is currently not available. However, EPA concluded that the following factors make alachlor ESA less likely to be a carcinogen in a long-term cancer study: 1) alachlor ESA is highly polar and is easily excreted from the body; 2) compared with alachlor, the parent compound, alachlor ESA does not produce a highly reactive metabolite capable of inducing tumor formation in animals; and 3) alachlor ESA has shown low affinity for protein binding EPA (1998).

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	100	20	NA
RfD (mg/kg-d)	-	-	0.053	0.0053	-
RSC	-	-	0.2	0.2	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-d)	-	-	0.077	0.043	-
Endpoint(s)	-	-	hematological (blood) system	hematological (blood) system	-

Subpart 6. **Atrazine.**

CAS number: 1912-24-9

Year Established: 2008

Volatility: Nonvolatile

MCL-based HRL: 3 µg/L

A Maximum Contaminant Level-based HRL value of 3 µg/L, based on a federal regulatory standard developed by EPA, is adopted for atrazine; see definition of MCL-based HRL values in 4717.7820, Subpart 16. This limit will apply until MDH derives and promulgates a HRL value.

Subpart 7. **Benzene.**

CAS number: 71-43-2

Year Established: 2008

Volatility: High

Acute duration.

The reference dose is 0.015 mg/kg-d and total uncertainty factor is 300 (10 for interspecies extrapolation, 10 for intraspecies variability and 3 for database insufficiencies due to lack of adequate developmental studies examining critical endpoints of concern for benzene exposure such as hematological (blood), immune and neurological effects). MDH is the source for the reference dose as well as the uncertainty factor allocation. The point of departure NOAEL is 4.6 mg/kg-d and the LOAEL is 11.4 mg/kg-d from Coate et al. (1984), based on developmental effects observed in a rat inhalation study. MDH used the route-to-route methodology developed by EPA (EPA 2002).

Short-term durations.

The reference dose is 0.014 mg/kg-d and the total uncertainty factor is 100 (10 for interspecies extrapolation and 10 for intraspecies variability). MDH is the source of the reference dose and the uncertainty factor allocation. The point of departure BMDL is 1.4 mg/kg-d and the BMD is 2.2 mg/kg-d from EPA-IRIS (2002), based on blood and the immune system toxicity observed in a 28-day oral study in mice (Hsieh et al. 1998a).

Subchronic duration.

The reference dose is 0.0013 mg/kg-d and the total uncertainty factor is 10 (10 for intraspecies variability). MDH is the source of the reference dose and the uncertainty factor allocation. The point of departure was identified by ATSDR as $BMCL_{0.25sd}$ 0.1 ppm and the LOAEL as 0.57 ppm, based on hematological (blood) and immune system effects observed in a study of occupationally exposed workers (Lan et al. 2004). Using the route-to-route conversion equation provided by EPA (EPA 2002) the ATSDR derived a point of departure $BMCL_{0.25sd}$ of 0.013 and a BMC of 0.074 mg/kg-d.

Chronic duration.

The intake rate used to calculate the chronic HRL is lower (0.043 L/kg-day) than the subchronic intake rate (0.077 L/kg-day) and resulted in a higher calculated chronic HRL despite identical RfD values (0.0013 mg/kg-d). The chronic HRL must be protective of the subchronic exposures that occur within the chronic period and so, the chronic nHRL was set equal to the subchronic non-cancer HRL.

Cancer.

Benzene is classified as Group A, "a known human carcinogen," by EPA (EPA 2000). Benzene is a linear carcinogen with a slope factor of $0.055 \text{ (mg/kg-d)}^{-1}$ from EPA-IRIS (2000) based on occupational studies, which reported leukemia as the endpoint. Due to early life sensitivity to benzene exposure, default intake rates (IR) corresponding to age-dependent adjustment factor age groups were used in the cancer HRL calculation. In addition, Age-Dependent Adjustment Factor (ADAFs), a default adjustment to the cancer slope factor that recognizes the increased susceptibility to cancer from early life exposures to linear carcinogens, was also incorporated into the denominator of the cancer HRL equation.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL ($\mu\text{g/L}$)	10	10	3	3 (3)	2
RfD (mg/kg-d)	0.015	0.014	0.0013	(3)	-
RSC	0.2	0.2	0.2	(3)	-
SF (per mg/kg-d)	-	-	-	-	0.055
ADAF	-	-	-	-	10 (ADAF _{<2}) 3 (ADAF _{2 to <16}) 1 (ADAF ₁₆₊)
Intake Rate (L/kg-d)	0.289	0.289	0.077	(3)	0.137 (<2) 0.047 (2 to <16) 0.039 (16+)
Endpoint(s)	developmental, immune system	hematological (blood) system, immune system	hematological (blood) system, immune system	hematological (blood) system, immune system (3)	cancer

Subpart 8. **Chloroform.**

CAS number: 67-66-3
 Year Established: 2008
 Volatility: High

Acute duration. Not derived due to insufficient data.

Short-term duration.

The reference dose is 0.05 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability and 10 for LOAEL-to-NOAEL extrapolation). The source for the reference dose and the uncertainty factor allocation is MDH. The point of departure LOAEL is 50 mg/kg-d from Munson et al., (1982), based on hepatic (liver) and immune system effects observed in a 90-day oral immunology rat study. Co-critical effects include increased relative liver weight with fatty changes to the liver, and decreased body weight gain in pups. The study did not establish a NOAEL.

Subchronic duration.

The intake rate used to calculate the subchronic HRL is lower (0.077 L/kg-day) than the short-term intake rate (0.289 L/kg-day) and resulted in a higher calculated subchronic HRL despite identical RfD values (0.05 mg/kg-d). The subchronic HRL must be protective of the short-term exposures that occur within the subchronic period and so, the subchronic nHRL was set equal to the short-term non-cancer HRL. Male reproductive co-critical effects observed at the subchronic duration are included as additivity endpoints.

Chronic duration.

The intake rate used to calculate the chronic HRL is lower (0.043 L/kg-day) than the short-term (0.289 L/kg-day) and subchronic (0.077 L/kg-day) and resulted in a higher calculated chronic HRL despite a 5-fold lower RfD value (0.01 mg/kg-day versus 0.05 mg/kg-d). The chronic HRL must be protective of the short-term and subchronic exposures that occur within the chronic period and so, the chronic nHRL was also set equal to the short-term non-cancer HRL. Male reproductive co-critical effects observed at the subchronic duration are included as chronic additivity endpoints.

Cancer.

EPA has classified chloroform as carcinogenic to humans by all exposure routes at high doses but not at low doses. At high doses exposure to chloroform leads to tumor formation in the kidney and the liver. Chloroform is considered a nonlinear carcinogen. Following EPA recommendations MDH has used the chronic RfD of 0.01 mg/kg-d derived by EPA-IRIS to generate a chronic HRL that will be protective against cancer. EPA states that the RfD is protective against cancer.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	30	30 (2)	30 (2)	NA
RfD (mg/kg-d)	-	0.05	(2)	(2)	-
RSC	-	0.2	(2)	(2)	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-d)	-	0.289	(2)	(2)	-
Endpoint(s)	-	developmental, hepatic (liver) system, immune system	developmental, hepatic (liver) system, immune system, male reproductive system	developmental, hepatic (liver) system, immune system, male reproductive system	-

Subpart 9. **Cyanazine.**

CAS number: 21725-46-2

Year Established: 2008

Volatility: Nonvolatile

Acute and Short-term durations.

The reference dose is 0.001 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability and 10 for database insufficiencies for lack of studies in the database that address the neuroendocrine endpoint). The source for the reference dose and the uncertainty factor allocation is MDH. The point of departure NOAEL is 1.0 mg/kg-d and the LOAEL is 2 mg/kg-d from Tunstall 1982 as cited by World Health Organization (WHO) (2003), based on developmental effects observed in a teratology rabbit study.

Subchronic duration.

The reference dose is 0.00063 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability and 10 for database insufficiencies for lack of studies in the database that address the neuroendocrine endpoint). MDH is the source for the reference dose and uncertainty factor allocation. The point of departure NOAEL is 0.625 mg/kg-d and the LOAEL is 2.5 mg/kg-d from Dickie 1986 as cited by EPA (1991) & WHO (2003), based on hepatic (liver) and renal (kidney) effects observed in a 1 year oral study in dogs.

Chronic duration.

The reference dose is 0.00026 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability and 10 for database insufficiencies for lack of studies in the database that address the neuroendocrine endpoint). MDH is the source of the reference dose and the uncertainty factor allocation. The point of departure NOAEL is 0.259 mg/kg-d and LOAEL is 1.37 mg/kg-d from Bogdanffy et al. (2000), based on decreased adult body weight and food efficiency in a chronic feeding study in rats.

Cancer.

The EPA has classified cyanazine as Group C, "a possible human carcinogen," with a slope factor of 1.0 (mg/kg-d)⁻¹, based on mammary tumor formation in rats. However, EPA has since determined that the neuroendocrine mechanism of action through which chloro-s-triazines produce mammary tumors is not relevant to humans. The MDH Group C Carcinogens Review Committee, following the 2005 EPA Final Guideline for Carcinogenic Risk Assessment, reviewed the weight-of-evidence regarding carcinogenicity of cyanazine. The committee concluded that, for cyanazine there is "suggestive evidence of carcinogenic potential" and concurred with EPA that based on the scientific evidence for cyanazine and chloro-s-triazines in general, the mode of action for tumor formation is not relevant to humans. Therefore, the chronic nHRL is considered to be protective against cancer.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	2	2	2	1	NA
RfD (mg/kg-d)	0.001	0.001	0.00063	0.00026	-
RSC	0.5	0.5	0.2	0.2	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-d)	0.289	0.289	0.077	0.043	-
Endpoint(s)	developmental	developmental	hepatic (liver) system, renal (kidney) system	None	-

Subpart 10. **cis 1,2-Dichloroethylene.**

CAS number: 156-59-2

Year Established: 2008

Volatility: High

Acute duration. Not derived due to insufficient data.

Short-term duration.

The reference dose is 0.097 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability and 10 for database insufficiencies due to lack of developmental and reproductive studies). MDH is the source of the reference dose and uncertainty factor allocation. The point of departure NOAEL is 97 mg/kg-d and LOAEL is 290 mg/kg-d from McCauley et al. (1995), based on adverse hematologic (blood) system effects observed in a 14-day oral study in rats.

Subchronic duration.

The intake rate used to calculate the subchronic HRL is lower (0.077 L/kg-day) than the short-term (0.289 L/kg-day) intake rate and results in a higher calculated subchronic HRL despite a 3-fold lower RfD value (0.032 mg/kg-day versus 0.097 mg/kg-d). The subchronic HRL must be protective of the short-term exposures that occur within the subchronic period and so, the subchronic nHRL was set equal to the short-term non-cancer HRL.

Chronic duration.

The reference dose is 0.011 mg/kg-d and the total uncertainty factor is 3000 (10 for interspecies extrapolation, 10 for intraspecies variability, 3 for subchronic to chronic extrapolation, and 10 for database insufficiency due to lack of adequate developmental and reproductive studies). The source of the reference dose and uncertainty factor allocation is MDH. The point of departure is NOAEL is 32 mg/kg-d and the LOAEL is 870 mg/kg-d from McCauley et al. (1995), based on adverse hematologic (blood) system effects observed in a 90-day oral study in rats.

Cancer.

EPA has classified cis-1,2-dichloroethylene as Group D, "not classifiable as to human carcinogenicity."

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	70	70 (2)	50	NA
RfD (mg/kg-d)	-	0.097	(2)	0.011	-
RSC	-	0.2	(2)	0.2	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-d)	-	0.289	(2)	0.043	-
Endpoint(s)	-	hematological (blood) system	hematological (blood) system	hematological (blood) system	-

Subpart 11. **Dichloromethane.**

CAS number: 75-09-2
Year Established: 2008
Volatility: High
MCL-based HRL: 5 µg/L

A Maximum Contaminant Level-based HRL value of 5 µg/L, based on a federal regulatory standard developed by EPA, is adopted for dichloromethane; see definition of MCL-based HRL values in 4717.7820, Subpart 16. This limit will apply until MDH derives and promulgates a HRL value.

Subpart 12. **Dieldrin.**

CAS number: 60-57-1
Year Established: 2008
Volatility: Nonvolatile

Acute duration.

The reference dose is 0.0001 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies and 10 for application of a LOAEL instead of a NOAEL). MDH is the source of the reference dose and uncertainty factor allocation. The point of departure LOAEL is 0.1 mg/kg-d from Richardson et al. (2006) based on alterations in dopamine transporter levels and vulnerability of dopamine neurons observed in a mouse developmental neurotoxicity study. Co-critical effects include hepatic lesions in pups and decreased pup viability. The study did not establish a NOAEL.

Short-term duration.

The reference dose is 0.0001 mg/kg-d and the total uncertainty factor is 100 (10 for interspecies extrapolation and 10 for intraspecies variability). ATSDR is the source of the reference dose and the uncertainty factor allocation. The point of departure NOAEL is 0.01 mg/kg-d and the LOAEL is 0.1 mg/kg-d from Smith et al. (1976), based on adverse effect to the nervous system i.e. impaired learning, which was observed after 15 days of treatment in a 55-day oral study in monkeys. Co-critical effects include hepatic lesions in pups, dopamine effects, decreased pup viability, and decreased antigen processing and tumor cell killing ability.

Subchronic duration.

The intake rate used to calculate the subchronic HRL is lower (0.077 L/kg-day) than the short-term (0.289 L/kg-day) intake rate and results in a higher calculated subchronic HRL despite identical RfD values (0.0001 mg/kg-day). The subchronic HRL must be protective of the short-term exposures that occur within the subchronic period and so, the subchronic nHRL was set equal to the short-term non-cancer HRL.

Chronic duration.

The reference dose is 0.00005 mg/kg-d and the total uncertainty factor is 100 (10 for interspecies extrapolation and 10 for intraspecies variability). The source for the reference dose and uncertainty factor allocation is EPA-IRIS (1990). The point of departure NOAEL is 0.005 mg/kg-d and the LOAEL is

0.05 mg/kg-d from EPA-IRIS (2003), based on adverse hepatic (liver) effects observed in a chronic dietary study in rats. Co-critical effects include significantly increased plasma alkaline phosphatase activity, significant decrease in serum protein in males, increased relative liver weight in females, and cerebral edema.

Cancer.

Under the 1996/99 EPA Cancer Guideline, dieldrin is classified as Group B2, "a probable human carcinogen." Dieldrin is a linear carcinogen with a slope factor of 16 (mg/kg-d)⁻¹ from EPA-IRIS (1993). The slope factor is a geometric mean of 13 slope factors calculated from liver carcinoma observed in several strains of adult mice using the linearized multistage extra risk procedure. A study by Vesselinovitch et al. (1979), reported evidence of life-stage sensitivity following exposure to dieldrin. The tumor incidence following perinatal plus adult exposure was 2.5-fold higher than adult only exposure. Therefore, to protect sensitive subgroups such as infants and young children, MDH incorporated chemical specific adjustment factor of 2.5 to the denominator of the cancer algorithm.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	0.2	0.2	0.2 (2)	0.2	0.006
RfD (mg/kg-d)	0.0001	0.0001	(2)	0.00005	-
RSC	0.5	0.5	(2)	0.2	-
SF (per mg/kg-d)	-	-	-	-	16
AF _{lifetime}	-	-	-	-	2.5
Intake Rate (L/kg-d)	0.289	0.289	(2)	0.043	0.043
Endpoint(s)	developmental	developmental, immune system, nervous system	developmental, immune system, nervous system	hepatic (liver) system, nervous system	cancer

Subpart 13. Di-(2-ethylhexyl)phthalate.

CAS Number: 117-81-7
 Year Established: 2008
 Volatility: Moderate
 MCL-based HRL: 6 µg/L

Maximum Contaminant Level-based HRL value of 6 µg/L, based on a federal regulatory standard developed by EPA, is adopted for di-(2-ethylhexyl)phthalate; see definition of MCL-based HRL values in 4717.7820, Subpart 16. This limit will apply until MDH derives and promulgates a HRL value.

Subpart 14. Nitrate (as N).

CAS Number: 14797-55-8
 Year Established: 2008
 Volatility: Nonvolatile
 MCL-based HRL: 10,000 µg/L

Maximum Contaminant Level-based HRL value of 10,000 µg/L, based on a federal regulatory standard developed by EPA, is adopted for nitrate; see definition of MCL-based HRL values in 4717.7820, Subpart 16. This limit will apply until MDH derives and promulgates a HRL value.

Subpart 15. **Pentachlorophenol.**

CAS Number: 87-86-5
Year Established: 2008
Volatility: Nonvolatile
MCL-based HRL: 1 µg/L

Maximum Contaminant Level-based HRL value of 1 µg/L, based on a federal regulatory standard developed by EPA, is adopted for pentachlorophenol; see definition of MCL-based HRL values in 4717.7820, Subpart 16. This limit will apply until MDH derives and promulgates a HRL value.

Subpart 16. **Perfluorooctane sulfonate (PFOS) and salts.**

CAS number: 1763-23-1; 29081-56-9; 2795-39-3; 70225-14-8; and 29457-72-5
Year Established: 2008
Volatility: Nonvolatile

Serum concentrations appear to be the best dose metric for extrapolating from laboratory animals to humans. At the present time, the information necessary to estimate less-than-chronic doses (i.e., acute, short-term or subchronic) that would result in a given serum concentration is not available. Additional uncertainty exists regarding toxicokinetics in early life. Therefore, acute, short-term and subchronic HRLs will not be derived at this time.

Acute duration. Not derived due to insufficient data.

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

Subchronic duration. Not derived due to insufficient data.

Chronic duration.

The reference dose is 0.00008 mg/kg-d and the total uncertainty factor is 30 (3 for interspecies toxicodynamic difference 10 for intraspecies variability). Interspecies toxicokinetic differences were incorporated into the Human Equivalent Dose (HED) calculation. MDH is the source of the reference dose and uncertainty factor allocation. The point of departure is 35 µg/mL serum levels corresponding to BMDL₁₀ for cholesterol, liver and thyroid effects reported by Thomford et al. (2002) as cited by OECD (2002) and Seacat et al. (2002), in a 26-week oral study in monkeys. The HED is 0.0025 mg/kg-d, based on calculation by MDH from serum concentration corresponding to the BMDL₁₀ and the half life and volume of distribution of PFOS in humans. MDH used a time-weighted intake rate corresponding to 95% intake rate over the first 27 years of life, the duration to achieve steady-state serum concentration based on a half-life of 5.4 years.

Cancer.

In an external review draft document, EPA indicated that based on the available data and the weight of evidence PFOS would be classified as having "suggestive evidence of carcinogenicity", but not enough to assess carcinogenicity potential in humans (EPA 2003). At the present time, the evidence to assess carcinogenic potential in humans is unavailable.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	ND	0.3	NA
RfD (mg/kg-d)	-	-	-	0.00008	-
RSC	-	-	-	0.2	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-d)	-	-	-	0.049	-
Endpoint(s)	-	-	-	developmental, hepatic (liver) system, thyroid (E)	-

Subpart 17. Perfluorooctanoic acid (PFOA) and salts.

CAS number: 335-67-1; 3825-26-1; 2395-00-8; 335-93-3 and 335-95-5

Year Established: 2008

Volatility: Nonvolatile

Serum concentrations appear to be the best dose metric for extrapolating to humans. At the present time, the information necessary to estimate less than chronic doses (i.e., acute, short-term or subchronic) that would result in a given serum concentration is not available. Additional uncertainty exists regarding toxicokinetics in early life. Therefore, acute, short-term and subchronic HRLs will not be derived at this time.

Acute duration. Not derived due to insufficient data.

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

Subchronic duration. Not derived due to insufficient data.

Chronic duration.

The reference dose is 0.000077 mg/kg-d and the total uncertainty factor is 30 (3 for interspecies toxicodynamic difference and 10 for intraspecies variability). The interspecies toxicokinetic differences are incorporated into the Human Equivalent Dose (HED) calculation. MDH is the source for the reference dose and the uncertainty factor allocation. The point of departure is 23 µg/mL serum levels corresponding to the BMDL₁₀ for liver effects reported by Thomford et al. (2002) and Butenhoff et al. (2002), observed in a 26-week oral study in monkeys. Developmental and immune system effects were identified as co-critical effects. The HED used to calculate the toxicity value is 0.0023 mg/kg-d based on calculation by MDH from serum concentration corresponding to the BMDL₁₀ and the half life of PFOA

and volume of distribution in humans. MDH used a time-weighted intake rate corresponding to 95% intake rate over the first 19 years of life, an estimate of duration to achieve steady-state serum concentration based on a half-life of 3.8 years.

Cancer.

In the 2005 draft PFOA risk assessment, EPA recommended the classification of “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential.” No slope factor has been derived by EPA. The majority of EPA’s Science Advisory Panel (SAP) recommended that PFOA be classified as “likely to be carcinogenic” based on the available information. The SAP also acknowledged that additional research was needed and that the carcinogenic effects may not be the most sensitive. MDH has used a nonlinear approach to derive a chronic RfD that is adequately protective against cancer.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	ND	0.3	NA
RfD (mg/kg-d)	-	-	-	0.000077	-
RSC	-	-	-	0.2	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-d)	-	-	-	0.053	-
Endpoint(s)	-	-	-	developmental, hepatic (liver) system, immune system	-

Subpart 18. **Simazine.**

CAS Number: 122-34-9
 Year Established: 2008
 Volatility: Nonvolatile
 MCL-based HRL: 4 µg/L

Maximum Contaminant Level-based HRL value of 4 µg/L, based on a federal regulatory standard developed by EPA, is adopted for simazine; see definition of MCL-based HRL values in 4717.7820, Subpart 16. This limit will apply until MDH derives and promulgates a HRL value.

Subpart 19. **1,1,2,2-Tetrachloroethylene.**

CAS Number: 127-18-4
 Year Established: 2008
 Volatility: High
 MCL-based HRL: 5 µg/L

Maximum Contaminant Level-based HRL value of 5 µg/L, based on a federal regulatory standard developed by EPA, is adopted for 1,1,2,2-Tetrachloroethylene; see definition of MCL-based HRL values in 4717.7820, Subpart 16. This limit will apply until MDH derives and promulgates a HRL value.

Subpart 20. **1,1,1-Trichloroethane.**

CAS number: 71-55-6
 Year Established: 2008
 Volatility: High

Acute duration. Not derived due to insufficient data.

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

Subchronic duration.

The reference dose is 7 mg/kg-d and the total uncertainty factor is 300 (10 for interspecies extrapolation, 10 for intraspecies variability and 3 for database insufficiencies due to inadequate evaluation of neurological effect which is identified as a sensitive endpoint in inhalation studies and lack of a LOAEL from oral reproductive & developmental studies). The source for the reference dose and the uncertainty factor allocation is EPA (EPA 2007). The point of departure BMDL₁₀ is 2155 mg/kg-d and the BMD₁₀ is 5064.4 mg/kg-d from NTP (2000), based on decreased body weight observed in a 13-week dietary study in mice. Co-critical effects include decreased relative liver weight and decreased epididymal spermatozoal concentration.

Chronic duration.

The reference dose is 2 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability, 3 for subchronic to chronic extrapolation and 3 for database insufficiencies due to inadequate evaluation of neurological effect, which is identified as a sensitive endpoint in inhalation studies, and lack of a LOAEL from oral reproductive & developmental studies). EPA is the source of the reference dose and the uncertainty factor allocation. The point of departure BMDL₁₀ is 2155 mg/kg-d and the BMD₁₀ is 5064.4 mg/kg-d from NTP (2000), based on decreased body weight observed in a 13-week dietary study in mice. Co-critical effects include decreased relative liver weight and decreased epididymal spermatozoal concentration.

Cancer.

1,1,1-TCA is classified as Group D, "not classifiable as to carcinogenicity to humans" (EPA 2007). The existing oral studies are considered inadequate for evaluation of carcinogenic potential to humans. Inhalation studies reported no treatment-related increase in tumor incidence in rats and mice at an exposure concentration below the maximum tolerated dose.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	20,000	9,000	NA
RfD (mg/kg-d)	-	-	7	2	-
RSC	-	-	0.2	0.2	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-d)	-	-	0.077	0.043	-

Endpoint(s)	-	-	hepatic (liver) system, Male reproductive system	hepatic (liver) system, male reproductive system	-
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Subpart 21. **1,1,2-Trichloroethylene (TCE).**

CAS Number: 79-01-6
Year Established: 2008
Volatility: High
MCL-based HRL: 5µg/L

Maximum Contaminant Level-based HRL value of 5 µg/L, based on a federal regulatory standard developed by EPA, is adopted for 1,1,2-Trichloroethylene; see definition of MCL-based HRL values in 4717.7820, Subpart 16. This limit will apply until MDH derives and promulgates a HRL value.

Subpart 22. **2 (2,4,5-Trichlorophenoxy)propionic acid (2,4,5-TP or Silvex).**

CAS Number: 93-72-1
Year Established: 2008
Volatility: Nonvolatile
MCL-based HRL: 50 µg/L

A Maximum Contaminant Level-based HRL value of 50 µg/L, based on a federal regulatory standard developed by EPA, is adopted for 2,4,5-TP; see definition of MCL-based HRL values in 4717.7820, Subpart 16. This limit will apply until MDH derives and promulgates a HRL value.

Subpart 23. **1,3,5-Trimethylbenzene.**

CAS number: 108-67-8
Year Established: 2008
Volatility: High

Acute duration. Not derived due to insufficient data.

Short-term duration.

The reference dose is 0.14 mg/kg-d and the total uncertainty factor is 1000 (10 for interspecies extrapolation, 10 for intraspecies variability and 10 for database insufficiencies for lack of several types of studies, including oral reproductive/developmental, neurological, and immunological studies, which were reported as sensitive endpoints in inhalation studies). The source for the reference dose and the uncertainty factor allocation is MDH. The point of departure NOAEL is 143 mg/kg-d and the LOAEL is 600 mg/kg-d from IIT Research Inst (1995b), based on hepatic (liver) effects observed at 30 days in a 90-day oral study in rats.

Subchronic duration.

The intake rate used to calculate the subchronic HRL is lower (0.077 L/kg-day) than the short-term (0.289 L/kg-day) intake rate and results in a higher calculated subchronic HRL despite identical RfD values (0.143 mg/kg-day). The subchronic HRL must be protective of the short-term exposures that occur within the subchronic period, so the subchronic nHRL was set equal to the short-term non-cancer HRL. Hepatic and renal effects observed in the 90-day study were listed as health endpoints.

Chronic duration.

The intake rate used to calculate the chronic HRL is lower (0.043 L/kg-day) than the short-term (0.289 L/kg-day) intake rate and produces a higher calculated chronic HRL despite a 3-fold lower RfD value (0.048 mg/kg-day versus 0.143 mg/kg-day). The chronic HRL must be protective of the short-term exposures that occur within the chronic period, so the chronic nHRL was set equal to the short-term non-cancer HRL.

Cancer.

There are no cancer bioassay data for 1,3,5-trimethylbenzene. Data collected from studies on another trimethylbenzene (1,2,4-) indicate that the compounds are similarly metabolized and have similar health endpoints, therefore the two isomers may be considered surrogates for one another. No significant incidence of tumor formation were reported in the chronic study of 1,2,4-trimethylbenzene in Sprague-Dawley rats (Maltoni et al. 1977).

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	100	100 (2)	100 (2)	NA
RfD (mg/kg-d)	ND	0.14	(2)	(2)	-
RSC	-	0.2	(2)	(2)	-
SF (per mg/kg-d)	-	-	-	-	-
ADAF or AF _{lifetime}	-	-	-	-	-
Intake Rate (L/kg-d)	-	0.289	(2)	(2)	-
Endpoint(s)	-	hepatic (liver) system	hepatic (liver) system, renal (kidney) system	hepatic (liver) system, renal (kidney) system	-

Subpart 24. Vinyl Chloride.

CAS number: 75-01-4

Year Established: 2008

Volatility: High

Acute duration. Not derived due to insufficient data.

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

Subchronic duration.

The reference dose is 0.03 mg/kg-d and the total uncertainty factor is 30 (3 for toxicodynamic interspecies extrapolation and 10 for intraspecies variability). An EPA route-to-route PBPK analysis was used to address interspecies toxicokinetic differences. The source for the reference dose and the uncertainty factor allocation is MDH. The point of departure NOAEL is 10 ppm, the corresponding Human Equivalent Dose (HED) is 1 mg/kg-d and the LOAEL is 100 ppm from EPA (2000) based on hepatic (liver) effects observed in a 2-generation reproductive inhalation study in rats.

Chronic duration.

The reference dose is 0.003 mg/kg-d and the total uncertainty factor is 30 (3 for toxicodynamic interspecies extrapolation and 10 for intraspecies variability). An EPA route-to-route PBPK analysis was used to address interspecies toxicokinetic differences. The source for the reference dose and the uncertainty factor allocation is MDH. The point of departure NOAEL is 0.13 mg/kg-d and the corresponding HED is 0.09 mg/kg-d; the LOAEL is 1.3 mg/kg-d and the corresponding HED is 0.9 mg/kg-d (EPA-IRIS 2000), based on hepatic (liver) effects observed in a 149-week dietary study in rats.

Cancer.

EPA has classified vinyl chloride as Group A, "a known human carcinogen," based on evidence in humans and laboratory animals. Vinyl chloride is a linear carcinogen and is considered to be a mutagen. EPA calculated an oral slope factor of $7.2E-1$ (mg/kg-d)⁻¹, based on liver tumors in adult rats, for continuous exposure during adulthood. For continuous lifetime exposure from birth, EPA multiplied the adult-based slope factor by a factor of two, resulting in a lifetime slope factor of 1.4 (mg/kg-d)⁻¹. MDH used the lifetime slope factor of 1.4 (mg/kg-d)⁻¹ from EPA (2000) with a time-weighted average lifetime intake rate. Since the lifetime slope factor already incorporated an adjustment for lifetime exposure, a value of 1 was used for the AF_{lifetime}.

	Acute	Short-term	Subchronic	Chronic	Cancer
HRL (µg/L)	ND	ND	80	10	0.2
RfD (mg/kg-d)	-	-	0.03	0.003	-
RSC	-	-	0.2	0.2	-
SF (per mg/kg-d)	-	-	-	-	1.4
AF _{lifetime}	-	-	-	-	1
Intake Rate (L/kg-d)	-	-	0.077	0.043	0.043
Endpoint(s)	-	-	hepatic (liver) system	hepatic (liver) system	cancer

4717.7870. EVALUATING CONCURRENT EXPOSURES TO MULTIPLE CHEMICALS.

This part and parts 4717.7880 and 4717.7890 include recommended procedures for risk assessment in the presence of multiple chemicals in groundwater. If the multiple chemical health risk index calculated according to the methods described herein exceeds one, the allowable limit has been exceeded.

In addition, if a chemical has both cancer and noncancer effects, then it should be included in each of the endpoint-specific, multiple-chemical health risk limit calculations.

The default approach for assessing risk from multiple chemicals is an additive model, where effects from individual chemicals are assumed to be independent of one another, as opposed to a synergistic or antagonistic model, in which chemicals are assumed to interact with one another to either magnify or mitigate their combined effect. While models that adopt an assumption of synergism or antagonism might be possible, the additive model is used by the EPA and is a reasonable compromise given what is unknown about how chemicals interact in the body.

4717.7880 MULTIPLE CHEMICAL HEALTH RISK LIMITS: NONCANCER.

This part describes the method for determining whether concurrent exposures to multiple chemicals exceed the multiple chemical health risk limit for any noncancer effect. This method calls for calculation of a health risk index to determine whether the multiple chemical health risk limit has been exceeded. In any assessment of risk from multiple chemicals, if the health risk index is greater than one (1), the applicable multiple chemical health risk limit has been exceeded.

The health risk index for effects other than cancer is calculated by adding the hazard quotients of assortments of chemicals that share the same toxicological effect, i.e., the same health endpoint. A separate health risk index for each duration should be generated for each health endpoint, using all chemicals that share that endpoint. Because many chemicals have more than one endpoint, a single chemical may contribute to health risk indices for several endpoints. In the absence of information to the contrary, it is reasonable to assume that chemicals with the same noncancer health endpoint have similar toxicological characteristics. Therefore, it is reasonable to group chemicals by noncancer health endpoints.

Subpart 1. **Scope.** This Subpart specifies that the procedures contained in this part are applicable when assessing the risk of noncancer endpoints from multiple chemicals present in groundwater.

Subpart 2. **Grouping of chemicals.** This Subpart specifies the first step for performing a risk assessment for noncancer endpoints when multiple chemicals are present in groundwater. In this first step, chemicals are grouped according to the health endpoints, other than cancer, listed in part 4717.7850 for each duration. The EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* acknowledges that grouping chemicals by common mechanism of action may be preferable: "The assumption of dose addition is most clearly justified when the mechanisms of action of the compounds under consideration are known to be the same." However, the *Supplementary Guidance* goes on to state "since the mechanisms of action for most compounds are not well understood, the justification of the assumption of dose addition will often be limited to similarities in pharmacokinetic and toxicological characteristics." The *Supplementary Guidance* does not recommend any single approach but gives guidance for the use of several approaches depending on the nature and quality of the data. It also explicitly states, referring to the 1986 guidelines, that "the principles and concepts put forth in the Guidelines remain in effect." Therefore, the additive model remains an accepted practice (EPA 2000c).

Item A. states that chemicals for which no health endpoint is specified will not be included in any group. There are three situations in which no health endpoint might be listed for a chemical: (i) no dose tested in the critical study resulted in an adverse effect; however, adverse effects were observed in other studies available to MDH; (ii) the health effect observed at the lowest level was body weight

alterations in adults; and (iii) general clinical signs of toxicity could not be associated with a particular organ.

Item B. specifies that a chemical must be included in as many multiple chemical risk calculations as it has health endpoints. This is consistent with EPA practice:

Since the assumption of dose addition is most properly applied to compounds that induce the same effect by similar modes of action, a separate hazard index should be generated for each endpoint of concern. (EPA 1987; EPA 2000c)

Subpart 3. **Equation.** This Subpart sets forth the equation for the additive risk model for noncancer effects. For each chemical within a health endpoint grouping, a hazard quotient for each duration is calculated by dividing the measured concentration by the HRL. Hazard quotients for all chemicals within a health endpoint grouping are added to arrive at the health risk index for each duration.

Item A specifies the values and units of the numerators in the hazard quotients. If the number of chemicals in the group is expressed as N , the concentrations appear in the equation as C_1, C_2, \dots, C_N . Generally, these values represent the concentration of a chemical that has been measured in groundwater. If testing reveals that a chemical is present, but it cannot be quantified, Item A specifies that a surrogate can be used in lieu of a measured concentration.

Every procedure to quantify chemicals present in a sample has a lower limit. Below this limit, a test may reveal that a chemical is present, but the test cannot accurately quantify that chemical. When this occurs, testing laboratories report that the chemical is present, but is below the level at which it can be accurately quantified. Several statistical methods have evolved so that these situations can be included in data analyses. These methods use surrogates for the actual concentration, including zero, half the detection limit, the log of the detection limit, and the detection limit.

Item B specifies the denominators, including units, for the hazard quotients in the hazard index equation. $nHRL_{\text{duration}}$ represents the noncancer HRL for a given duration of the N^{th} chemical in the sequence of chemicals in the endpoint group.

Part 4717.7860 specifies that when the multiple chemical health risk index generated by this equation is greater than one, the multiple chemical health risk limit has been exceeded.

4717.7890. MULTIPLE CHEMICAL HEALTH RISK LIMITS: CANCER.

This part describes the method for determining whether concurrent exposures to multiple carcinogens exceed the multiple chemical health risk limit for cancer. This method calls for the calculation of a cancer health risk index to determine whether the multiple chemical health risk limit has been exceeded. In any assessment of risk from multiple chemicals, if the health risk index is greater than one (1), the applicable multiple chemical health risk limit has been exceeded.

For each carcinogen, a cancer quotient is calculated by dividing the measured concentration by the HRL. (For the purpose of this part, carcinogenic chemicals are those for which part 4717.7850 provides a cancer HRL.) The cancer health risk index is calculated by adding the cancer quotients of each carcinogen determined to be present in the groundwater. Quotients for all carcinogens are added to arrive at the cancer health risk index.

Subpart 1. **Scope.** This Subpart specifies that the procedures contained in this part are applicable when assessing the risk of cancer from multiple chemicals present in groundwater.

Subpart 2. **Equation.** This Subpart sets forth the equation for the additive risk model for cancer effects. For each carcinogen, a cancer quotient is calculated by dividing the measured concentration by the HRL. Cancer quotients for all carcinogens are added to arrive at the multiple chemical health risk index.

This equation is consistent with the EPA's *Guidelines for Health Risk Assessment of Chemical Mixtures and Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*. (EPA 1986b, 2000c).

Items A and B are exactly the same as the directions for calculating a health risk index for noncancer effects.

4717.7900 CHEMICAL BREAKDOWN PRODUCTS.

This part provides guidance for evaluating chemical breakdown products. At varying time intervals after application, chemicals break down into degradates. Pesticide degradates, in particular, are of increasing concern.

To date, toxicity data have not been available for most degradates. Furthermore, such data as may be available often do not meet peer review standards that are deemed necessary for the derivation of scientifically sound HRLs and that are required by the Health Standards Statute (*Minnesota Statutes*, section 144.0751).¹⁰ Products of degradation can be more or less toxic than their parent compound. In the absence of convincing data to the contrary, it is prudent public health practice to assume that breakdown products of chemicals are at least as toxic as their parent. Therefore, it is reasonable that, in the absence of toxicity data specific to a chemical degradate, toxicity information and analyses for the parent chemical be applied to evaluate the toxicity of the degradate. Therefore, the health endpoint(s) determined for the parent and the HRL(s) derived for the parent should be used to evaluate the degradates.

Because a chemical generally has several breakdown paths, it is unlikely that only one degradate of a given chemical will be present. Therefore, it is reasonable to apply the procedures stated in 4717.7880 and 4717.7890 for evaluating health risks posed by multiple chemicals when multiple degradates of a parent chemical or degradates of more than one parent chemical that share a common mechanism of toxicity or the same health endpoint are present.

¹⁰ *Minnesota Statutes*, section 144.0751 (a)(1) provides, in relevant part, a safe drinking water or air quality standards established or revised by the commissioner of health must: (1) be based on scientifically acceptable, peer-reviewed information.

GLOSSARY

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

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

Cancer Slope Factor: See *Slope Factor*.

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

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

OR,

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

See also: *Linear carcinogen*, *Nonlinear 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 noncancer 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 prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) function deficiency.

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

Dosimetric Adjustment Factor (DAF): A 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 noncancer 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," United States Environmental Protection Agency, Risk Assessment Forum (December 2002, <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55365>).

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," United States Environmental Protection Agency, Risk Assessment Forum (March 2005, <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=160003>). 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 noncancer 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 HRLs; however, they have not been promulgated as rules, have not undergone peer review, and may be based on less data and/or subject to greater uncertainty than HRLs. There are several reasons why a chemical might have an HBV rather than a HRL: the chemical may not have been found in groundwater until after the HRL rules were promulgated, toxicological data may not have been available until after rulemaking, or the level of uncertainty in the value may be greater than accepted in the rules. HBVs are re-evaluated when the HRL rules are updated. An HBV is expressed as a concentration in micrograms per liter ($\mu\text{g/L}$).

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 promulgated under rule. A HRL is expressed as a concentration in micrograms per liter ($\mu\text{g/L}$).

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 noncancer and cancer HRLs, 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 was 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. See Section II.C.

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 are 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 ($\mu\text{g/L}$): 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.

Nonlinear 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.

Nonlinear 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, nonlinear methods for determining risk at low dose may be justified.

No observed adverse effect level (NOAEL): An exposure level at which there was 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 percentage (or fraction) of an individual's total permissible exposure to a substance or chemical that is "allocated" to ingestion of water. Application of 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 the Minnesota Department of Health use a relative source contribution in deriving health risk limits for systemic toxicants. MDH relied upon EPA's Exposure Decision Tree approach (<http://www.epa.gov/waterscience/criteria/humanhealth/method/method.html>) to determine appropriate RSC values.

HRLs 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-m³/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 site-specific situations where the Exposure Decision Tree along with site-specific information could be used to derive a site-specific RSC.

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 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 Effect(s): Generally a health effect or health effects observed in any of a number of studies that occurred within three-fold of the exposure level in the critical study associated with the critical effect(s).

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-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:

- the uncertainty in extrapolating from mammalian laboratory animal data to humans, i.e., interspecies uncertainty factor;
- the variation in sensitivity among the members of the human population, i.e., intraspecies variability factor;
- the uncertainty in extrapolating from effects observed in a short-term study to potential effects from a longer exposure, i.e., subchronic-to-chronic uncertainty factor;
- the uncertainty associated with using a study in which health effects were found at all doses tested, i.e., LOAEL-to-NOAEL uncertainty factor; and
- the uncertainty associated with deficiencies in available data, i.e., database uncertainty factor.

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

Uncertainty and variability factors are typically values of three or ten and are multiplied together. The Department has not developed a HRL if the product of all uncertainty factors exceeds 3,000.

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-m³/mol. Chemicals are characterized as being nonvolatile, or being of low, medium, or high volatility as follows:

- Henry's Law constant $< 3 \times 10^{-7}$ atm-m³/mol = nonvolatile
- Henry's Law constant $> 3 \times 10^{-7}$ to 1×10^{-5} atm-m³/mol = low volatility
- Henry's Law constant $> 1 \times 10^{-5}$ to 1×10^{-3} atm-m³/mol = moderate volatility
- Henry's Law constant $> 1 \times 10^{-3}$ atm-m³/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.

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APPENDICES

APPENDIX A. *Food Quality Protection Act*

The *Food Quality Protection Act* (21 U.S.C. § 346a) provides, in part:

Exposure of infants and children. In establishing, modifying, leaving in effect, or revoking a tolerance or exemption for a pesticide chemical residue, the Administrator –

- (i) shall assess the risk of the pesticide chemical residue based on –
 - (I) available information about consumption patterns among infants and children that are likely to result in disproportionately high consumption of foods containing or bearing such residue among infants and children in comparison to the general population;
 - (II) available information concerning the special susceptibility of infants and children to the pesticide chemical residues, including neurological differences among infants and children and adults, and effects of *in utero* exposure to pesticide chemicals; and
 - (III) available information concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity; and
- (ii) shall –
 - (I) ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue; and
 - (II) publish a specific determination regarding the safety of the pesticide chemical residue for infants and children.

The Secretary of Health and Human Services and the Secretary of Agriculture, in consultation with the Administrator, shall conduct surveys to document dietary exposure to pesticides among infants and children. In the case of threshold effects, for purposes of clause (ii)(I) an additional ten-fold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such a margin will be safe for infants and children.

APPENDIX B. Health Effects Listed in the Health Standards Statute

The Health Standards Statute (*Minnesota Statutes*, section 144.0751) directs MDH to consider certain health outcomes in establishing or revising safe drinking water standards: "reproductive development and function, respiratory function, immunologic suppression or hypersensitization, development of the brain and nervous system, endocrine (hormonal) function, cancer, general infant and child development, and any other important health outcomes identified by the commissioner." Some of these outcomes require little if any further explication. Respiratory function and the brain and nervous system, for example, are associated with discrete organs and their roles are easily defined. Cancer, while it can affect virtually any organ, results from the same type of malfunction: unchecked cellular proliferation. Routine toxicological testing would be expected to reveal these outcomes, although, more refined testing might be necessary to characterize the precise nature of the pathology.

The other outcomes listed in the statute may be more difficult to detect or to accurately characterize. They may involve a wide variety of organs and malfunctions; timing of the insult or manifestation of the injury may be crucial. In preparing for this revision, MDH documented and analyzed available toxicity data specific to effects bearing on development, reproduction, immunity, endocrines, the nervous system, and cancer. Lack of testing specific for these effects is not necessarily an indication that the database is incomplete. Basic toxicity tests and other relevant information (for example, effects of chemicals of the same class or structure-activity relationships) may have indicated that a specific type of effect is not likely to be a concern for that chemical (See Appendix J on Toxicity Testing). Because some of these effects are interconnected, testing for one of these types of effects frequently reveals some information about one or more of the others. MDH also documented whether an uncertainty factor for an incomplete database was applied as a result of lack of data.

Since some health endpoints listed are not necessarily directly associated with a single organ or system, some explanation of how MDH interpreted and implemented this mandate is warranted.

Developmental Effects. EPA's *Guidelines for Developmental Toxicity Risk Assessment* (EPA 1991a) define and describe developmental effects. The major manifestations of developmental effects include death of the developing organism, including resorption, fetal death, and stillbirth; structural abnormality, such as extra ribs or cleft palate; growth alteration; and/or functional deficit, such as alterations in neuromotor development, learning, memory, and reproductive behavior. As documented by EPA, developmental effects may be manifested in essentially any organ, system, and functional aspect of an organism. And developmental effects may be expressed at any point during the lifetime of an animal. In fact, effects of exposure to some chemicals may only appear in subsequent generations. Thalidomide and diethylstilbestrol (DES) are examples of chemicals that result in effects in the offspring of the exposed generation. While the disruption of development caused by thalidomide is apparent at birth, the effects of DES are not revealed until much later.

Typically, standard teratology tests document only gross physiological malformations and death. These were the only two types of effects generally considered "developmental effects" in many reports on toxicity published prior to the 1991 EPA guidelines. The 1993/1994 HRL rules are based on this earlier, more limited definition of developmental effects.

In the absence of data, risk assessment practice assumes that an agent that produces an adverse developmental effect in experimental animals will pose a developmental hazard in humans. However, because of species-specific differences in critical periods, timing of exposure, metabolism,

developmental patterns, or mechanism of action, it cannot be assumed that the types of developmental effects seen in animal studies are the same as those that may occur in humans.

For the purpose of this HRL revision, the term "development" is used to refer to the broad range of effects that occur as a result of exposure during periods when cells or tissues undergo differentiation, rapid replication, and maturation. Thus, adverse developmental effects can result from exposure of either parent prior to conception, exposure of the mother during gestation, exposure of the breast-feeding mother or infant, or exposure during childhood through the time of sexual maturation. For chemicals that cause developmental effects, the revised HRLs provide information about the organ or system affected, for example, "development (skeletal)" or "development (cardiovascular)." Developmental effects may be expressed and detected long after the damage was initiated and long after the damaging exposure occurred.

Often, toxicity to the fetus or offspring is concurrent with maternal toxicity. In such instances, it is difficult to distinguish whether toxicity to a fetus or to offspring is a result of direct toxic action upon the developing organism or the result of toxic action affecting the mother's ability to carry a healthy fetus to term. When exposure during gestation results in the same toxic response in both the mother and the fetus or offspring, MDH has treated effects on the fetus or offspring as separately induced toxicity rather than as a result of maternal toxicity (EPA 1998c). This approach ensures that protection of the developing offspring will be equivalent to protection of the mother, because developmental effects often occur at a level that only produces mild or reversible effects in the mother (EPA 1998c). In cases where the mother is reasonably affected by exposure, any toxicity to the fetus is thought to be the result of equal sensitivities to exposure in the fetus and the mother rather than fetal toxicity being the direct result of maternal toxicity.

Endocrine Effects. Hormones, or endocrines, are natural secretions that are transported at very low concentrations in the blood, either in the free state or attached to carrier proteins, and that exert regulatory effects on virtually all physiological processes, including development, growth, metabolism, immune suppression, behavior, and reproductive function. Endocrine glands include the hypothalamus, pituitary, thyroid, parathyroid, pancreas, adrenal, ovary, and testis. Other endocrine tissues include the placenta, liver, kidney, lung, cells throughout the gastrointestinal tract, mammary glands, bone, muscle, and the nervous system. The endocrine system regulates a wide range of biological processes, including: "control of blood sugar (through the hormone insulin from the pancreas); growth and function of reproductive systems (through the hormones testosterone and estrogen and related components from the testes and ovaries); regulation of metabolism (through the hormones cortisol from the adrenal glands, and thyroxin from the thyroid gland); development of the brain and the rest of the nervous system (estrogen and thyroid hormones); and development of an organism from conception through adulthood and old age. Normal functioning of the endocrine system, therefore, contributes to homeostasis (the body's ability to maintain itself in the presence of external and internal changes), and to the body's ability to control and regulate reproduction, development, and/or behavior" (EPA 2003c).

Some substances disrupt the endocrine system by mimicking or blocking hormone action or by directly stimulating or inhibiting the production of hormones. EPA identifies an environmental endocrine disruptor as "an exogenous agent that interferes with the synthesis, secretion, transport, binding action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior" (Crisp *et al.* 1998). Because the endocrine system plays a role in virtually all of the important functions of an organism, including sexual

differentiation and maturation, reproduction, cardiovascular function, metabolism, digestion, and excretion, subtle changes in hormonal action can induce a variety of responses – some with drastic consequences. For example, reproductive and thyroid hormones direct the course of prenatal and postnatal development; an increase or decrease in hormone levels can prevent or alter normal events during development. There is also evidence that hormones are involved in the development of certain cancers. DES is a synthetic estrogen once extensively administered to both humans and livestock to prevent miscarriage. *In utero* exposure was subsequently linked to the development of vaginal and cervical clear cell adenocarcinomas in female offspring.

Some chemicals that upset endocrine balance are well-known; others are merely suspected. MDH carefully scrutinized toxicity data on suspected endocrine disruptors. Even if a chemical is known to affect endocrine balance, questions remain about whether and how disruption affects normal processes. A change in hormone levels may not be accompanied by any observed adverse effect, but may be a normal compensatory response. Measurement of hormone levels and evaluation of the effects is a particularly challenging area for risk assessment.

As mandated by recent amendments to food safety and drinking water laws, EPA has established a task force to develop screening and testing methods for use in evaluating chemicals for endocrine effects (EPA 1998b).

While the potential failure to adequately account for effects on the endocrine system is a serious concern, the process by which toxicity values are derived should alleviate some of that concern. Toxicity testing and knowledge about chemical structure and mechanisms of action provide a basis for refining further testing to focus on effects of concern and the dose at which those effects may arise. Iterative testing identifies the effect (or effects) that appear at the lowest dose. By protecting against this most-sensitive endpoint, the toxicity value resulting from this process is assumed to be protective of effects that occur at higher doses.

Even though testing may not directly assess endocrine levels, data typically available for a chemical will detect many of the functional changes or health endpoints that may result from endocrine disruption. For example, because of the critical role that hormones play in reproduction and development, testing for these effects is likely to provide evidence about disruption of hormone functioning. MDH reviewed toxicological research results to determine and document which HRL chemicals have been tested for effects on reproduction or development and whether the results of any such tests have been positive or negative.

Because of the many organs and tissues that secrete and/or are affected by hormones, the endocrine system is not a discrete classification of toxicity, but rather a means through which toxicity is caused or manifested. In this revision of the HRLs, endocrine effects are indicated with the designation "(E)"; for example, "thyroid (E)." An effect will only be considered an endocrine effect if there is evidence of altered hormone production or degradation or altered receptor binding; that is, if a change in endocrine levels has been measured. The endpoint may be either an organ that produces the hormone measured or an organ that is affected by the hormone measured. If a functional endpoint has been observed, that endpoint is given preference. For example, a chemical may have a direct toxic effect on the thyroid gland resulting in altered thyroid hormone (T3/T4) ratios. If no further changes have been noted, the health endpoint would be "thyroid (E)." However, if the altered ratios result in altered cardiovascular function, the health endpoint would be "cardiovascular system (E)."

Reproductive Effects. Chemicals that affect the ability of an organism to successfully reproduce are considered reproductive toxicants. Reproductive effects include effects on the germ cells, that is, the sperm and the egg, and effects on structures specific to reproduction, including the testes, the ovaries, and the uterus. Reproductive effects also include changes in mating or rearing behaviors that interfere with successful reproduction. Gross manifestations of an inability to successfully reproduce and developmental effects may be identical. Resorption, for example, may be the result of a disturbance of development, or it may be the result of some alteration in the mother that makes her unable to successfully carry a fetus to term. This same etiological ambiguity exists for fetal death, stillbirth, and litter size. As another example, the developing reproductive system of a fetus may be affected by the mother's exposure to a toxicant during pregnancy. In this case, reproductive effects are an outcome of developmental toxicity. While overt manifestations of toxicity are the same, the etiology of these manifestations is different.

The 1991 EPA *Guidelines for Developmental Toxicity Risk Assessment* state that developmental toxicity can be considered a component of reproductive toxicity and note that it is often difficult "to distinguish between effects mediated through the parents versus direct interaction with developmental processes." (EPA 1991a). The more recent *Guidelines for Reproductive Toxicity Risk Assessment* (EPA 1996a) describe developmental effects as a potential subset of reproductive toxicity. The guidelines state that disorders of the male or female reproductive systems in the parents may be manifested as adverse pregnancy outcomes, and specifically list low birth weight, congenital malformations at birth, and serious developmental deficits as examples of such outcomes.

Both female and male reproductive organs are targets for toxicity. The endpoint listed for HRLs is "male reproduction" or "female reproduction." If it is known, the specific organ or structure will be specified in MDH documentation. Summary sheets for individual chemicals, indicating the more specific organ or structure, are available on the MDH HRL Rules Revision web page; sample summary sheets for selected chemicals are provided in Appendix P.

If toxicity testing shows that a chemical is causally associated with the disturbance of hormone levels, the effect will be noted as an endocrine effect, even if the hormones involved are classically considered "reproductive" hormones. Conversely, if an effect on reproduction is thought to be the result of an alteration in hormone levels, but this has not been proven, the effect will be noted as a reproductive effect.

Immune Effects. Like the endocrine system, the immune system is not confined to a single site within the body. Numerous organs and cell populations throughout the body play a role in distinguishing foreign matter from self and responding to eliminate or incapacitate foreign matter. Some organs with significant immune function include the bone marrow, the thymus, the spleen, and the lymph nodes. Cells involved in immune function include T cells, B cells, leukocytes, macrophages, and fibroblasts, to name just a few. Existing toxicological knowledge and the iterative nature of toxicity testing can provide some indication of whether testing specific to immune effects is necessary.

Standard toxicological studies generally evaluate the overall health of the animal, body weight, the weight of certain organs, general observations, selected serum chemistries and hematological parameters, and bone marrow status. The results of these standard tests provide a base from which to determine what, if any, further testing is advisable. If immunotoxic effects are detected or suspected, further testing specifically designed to define the immunotoxic response can be undertaken. Such tests include tests for cell-mediated immunity, secondary antibody responses, enumeration of lymphocyte

populations, and host resistance models (Burns *et al.* 1996). Thus, iterative testing may reveal and characterize specific immune system effects. A HRL based on a general endpoint observed as a result of basic toxicological testing, such as reduced body weight gain, may provide protection from immunological effects that would be detected at higher doses or with specific testing.

Prior testing of chemicals of a similar class or with a similar mechanism may indicate whether that chemical could have immunological effects. Chemical classes that are represented in the HRL rules and that have been implicated in immunological suppression include the polycyclic aromatic hydrocarbons (PAHs); organochlorines (e.g., DDD, DDE, and DDT); and organic solvents such as benzene. Chromium and pesticides have been implicated in hypersensitivity reactions (Burns *et al.* 1996). Even if a chemical has been associated with effects on immune response, this may not be the "most sensitive" effect; that is, the chemical may cause other effects at lower doses.

Characterizing immunological effects associated with a chemical is further complicated by the apparent bimodal dose-response that some chemicals exhibit. Some metals, for example, are immunosuppressant at high doses, but may act to enhance immune responses at lower concentrations (Burns 1996).

Appendix C. Criteria Relevant to Causality in Toxicological Evaluation

Scientists have developed a number of criteria to be considered in determining whether an association is consistent with a cause and effect relationship, or is merely coincidental. A set of guidelines for evaluating epidemiological associations (Hill 1965) was developed in conjunction with the 1964 Surgeon General's Report on Smoking. In the 2005 Final Guidelines for Carcinogen Risk Assessment (EPA 2005a), EPA adapted those criteria as follows:

- (a) Consistency of the observed association. An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
- (b) Strength of the observed association. The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. A modest risk, however, does not preclude a causal association and may reflect a lower level of exposure, an agent of lower potency, or a common disease with a high background level.
- (c) Specificity of the observed association. As originally intended, this refers to increased inference of causality if one cause is associated with a single effect or disease. Based on our current understanding that many agents cause cancer at multiple sites, and many cancers have multiple causes, this is now considered one of the weaker guidelines for causality. Thus, although the presence of specificity may support causality, its absence does not exclude it.
- (d) Temporal relationship of the observed association. A causal interpretation is strengthened when exposure is known to precede development of the disease. Because a latent period of up to 20 years or longer is associated with cancer development, the study should consider whether exposures occurred sufficiently long ago to produce an effect at the time the cancer is assessed. This is among the strongest criteria for an inference of causality.
- (e) Biological gradient (exposure-response relationship). A clear exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times). Because there are many possible reasons that an epidemiologic study may fail to detect an exposure-response relationship (for example, a small range of observed exposure levels or exposure misclassification), the absence of an exposure-response relationship does not exclude a causal relationship.
- (f) Biological plausibility. An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A lack of mechanistic data, however, is not a reason to reject causality.
- (g) Coherence. An inference of causality may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. Information is considered from

animal bioassays, toxicokinetic studies, and short-term studies. The absence of other lines of evidence, however, is not a reason to reject causality.

- (h) Experimental evidence (from human populations). Experimental evidence is seldom available from human populations and exists only when conditions of human exposure are altered to create a "natural experiment" at different levels of exposure. Strong evidence for causality can be provided when a change in exposure brings about a change in disease frequency, for example, the decrease in the risk of lung cancer that follows cessation of smoking.
- (i) Analogy. Structure-activity relationships (SARs) and information on the agent's structural analogues can provide insight into whether an association is causal.

Appendix D. Chemicals Considered in the Revision of the Health Risk Limits Rules

1,1,1,2-Tetrachloroethane	2-Chlorophenol	Bromobenzene
1,1,1-Trichloroethane	2-Methyl-4-chlorophenoxyacetic acid (MCPA)	Bromodichloromethane
1,1,2,2-Tetrachloroethane	4-(2-Methyl-4-chlorophenoxy) butyric acid (MCPB)	Bromoform
1,1,2-Trichloro-1,2,2-trifluoroethane	2-Methylnaphthalene	Bromomethane
1,1,2-Trichloroethane	2-Methylphenol (o-Cresol)	Bromoxynil
1,1-Biphenyl	2-Nitrophenol	n-Butanol
1,1-Dichloroethane	3,3'-Dichlorobenzidine	Butyl benzyl phthalate
1,1-Dichloroethylene	3,4-Dichlorophenol	Butylate
1,2,3-Trichloropropane	3,5-Dichlorophenol	Butylbenzene, n
1,2,4-Trimethylbenzene	3-Methylphenol(m-Cresol)	Butylbenzene, sec
1,2-Dibromoethane	4-(2,4-Dichlorophenoxy) butyric acid	Butylphthalyl butylglycolate
1,2-Dichlorobenzene	4-Isopropyltoluene	Cadmium
1,2-Dichloroethane (EDC)	4-Methylphenol (p-Cresol)	Carbaryl
1,2-Dichloroethylene, cis	Acenaphthene	Carbazole
1,2-Dichloroethylene, trans	Acenaphthylene	Carbon Disulfide
1,2-Dichloropropane	Acetochlor	Carbon tetrachloride
1,2-Diphenylhydrazine	Acetochlor ESA (Acetochlor degradate)	carcinogenic Polycyclic aromatic Hydrocarbons
1,3,5-Trimethylbenzene	Acetochlor OA (Acetochlor degradate)	Chloramben
1,3,5-Trinitrobenzene	Acetone	Chlorimuron-ethyl
1,3-Dichloropropene	Acetonitrile	Chlorobenzene
1,4-Dichlorobenzene	Alachlor	Chloroethane
1,4-Dioxane	Alachlor ESA (Alachlor degradate)	Chloroform
1-Butanol	Alachlor OXA (Alachlor degradate)	Chloromethane
1-Methylnaphthalene	Aldicarb	Chlorothalonil
1-Methylphenol	Aldrin	Chlorpropham
2-(2,4,5-Trichlorophenoxy) propionic acid	Allyl Chloride	Chlorpyrifos
2-(2-Methyl-4-chlorophenoxy) propionic acid (MCPB)	Aluminum	Chlorsulfuron
2,2-Dichloropropane	Aniline	Chromium III
2,3,4,5-Tetrachlorophenol	Anthracene	Chromium VI
2,3,4,6-Tetrachlorophenol	Antimony	Chrysene
2,3,5,6-Tetrachloroterephthalic acid	Arsenic	Clomazone
2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dioxin)	Asbestos (fibers/L > 10 mm length)	Clopyralid (and salts)
2,3,5-Trichlorophenol	Atrazine	Cobalt
2,3,6-Trichlorophenol	Barium	Copper
2,4,5-Trichlorophenol	Bentazon	Cumene
2,4,5-Trichlorophenoxyacetic acid	Benzene	Cyanazine
2,4,6-Trichlorophenol	Benzo(g,h,i)perylene	Cyanazine amide (Cyanazine degradate)
2,4-Dichlorophenol	Benzoic Acid	Cyanazine acid (Cyanazine degradate)
2,4-Dichlorophenoxyacetic acid	Beryllium	Cyanide, free
2,4-Dimethylphenol	Bis(2-chloroethyl) ether	Dacthal
2,4-Dinitrophenol	Bis(2-chloromethyl) ether	Dalapon
2,4-Dinitrotoluene	Bisphenol A	DDD
2,6-Dinitrotoluene	Boron	DDE
2,6-Diethylaniline (Alachlor degradate)		DDT
		Deaminated diketometribuzin (Metribuzin degradate)
		Deaminated metribuzin (Metribuzin degradate)

Deethylatrazine (Atrazine and/or Propazine degradate)	Hexachlorocyclohexane, beta isomer	Phenanthrene
Deisopropylatrazine (Atrazine, Cyanazine and/or Simazine degradate)	Hexachlorocyclohexane, gamma isomer	Phenol
Dethylcyanazine acid (Cyanazine degradate)	Hexahydro-1,3,5-Trinitro-1,3,5-Triazine (RDX)	Phorate
Di(2-ethylhexyl)phthalate	n-Hexane	Picloram
Diallate	Hexazinone	Polychlorinated biphenyls (PCBs)
Diazinon	Hydroxyatrazine	Primisulfuron-methyl (Beacon)
Dibenzofuran	Indeno(1,2,3-c,d) pyrene	Prometon
Dibromochloromethane	Iron	Propachlor
Dibutyl phthalate	Isophorone	Propazine
Dicamba	Isopropyl ether	Propiconazole
Dichlorodifluoromethane	Isoxaflutole	Pyrene
Dichlorofluoromethane	Lead	Radionuclides (all)
Dichloromethane	Linuron	Selenium
Dieldrin	Lithium	Silver
Diethyl phthalate	Malathion	Simazine
Diketometribuzin (Metribuzin degradate)	Manganese	Sodium
Dimethenamid and s-Dimethenamid	Mercury, inorganic	Strontium, stable (non-radioactive, not 90Sr)
Dimethenamid ESA (Dimethenamid degradate)	Methamidophos	Styrene
Dimethenamid OXA (Dimethenamid degredate)	Methanol	Sulfate
Dimethoate	Methyl ethyl ketone	Terbacil
Dimethyl phthalate	Methyl isobutyl ketone	Terbufos
Dinitrotoluene mixture	Methyl parathion	Tebuthiuron
Dinoseb	Methyl tertiary butyl ether	Tetrachloroethylene
Disulfoton	Metolachlor and s-Metolachlor	Tetrahydrofuran
Diuron	Metolachlor ESA (Metolachlor degradate)	Thallium
d-Limonene	Metolachlor OA (Metolachlor degradate)	Thifensulfuron methyl
Endosulfan	Metribuzin	Tin
Endrin	Metsulfuron-methyl(Ally)	Toluene
EPTC	Molinate	Total Petroleum Hydrocarbons (TPH)
Ethafuralin	Molybdenum	Toxaphene
Ethyl ether	Monomethyl tetrachloroterephthalic acid	Triallate
Ethylbenzene	Naphthalene	Triasulfuron(Amber)
Ethylene glycol	Nickel	Tribenuron-methyl
Express (Tribenuron methyl)	Nicosulfuron	Tributyltin oxide
Fenvalerate (Pydrin)	Nitrate (as N)	Trichloroethylene
Fluoranthene	Nitrobenzene	Trichlorofluoromethane
Fluorene	n-Nitrosodiphenylamine	Triclopyr
Fonofos	Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX)	Trifluralin
Formaldehyde	n-Propylbenzene	Trinitro-phenylmethylnitramine
Heptachlor	Pendimethalin	Triphenyltin hydroxide
Heptachlor epoxide	Pentachloronitrobenzene	Vanadium
Hexachlorobenzene	Pentachlorophenol	Vinyl chloride
Hexachlorobutadiene	Perchlorate	Xylene
Hexachlorocyclohexane, alpha isomer	Perfluorooctane sulfonate and salts	Zinc
	Perfluorooctanoic acid and salts	Total = 270 chemicals

Appendix E. EPA's 1986 Carcinogenicity Classifications

Pursuant to the classification scheme set forth in EPA's Risk Assessment Guidelines of 1986, EPA uses a weight of the evidence approach to evaluate whether a chemical is a human carcinogen. In the first step of this three-step procedure, evidence is characterized separately for human studies and for mammalian animal studies. In the second step, human and animal evidence are combined into a presumptive overall classification. Finally, supporting evidence is used to determine whether the provisional classification should be adjusted upward or downward (EPA 1986a, 1992a). The 1986 guidelines divide chemicals into six groups:

Group A. Human carcinogens. Sufficient evidence from epidemiological studies supports a causal relationship between exposure to a chemical and cancer.

Group B1. Probable human carcinogens. Limited evidence of human carcinogenicity.

Group B2. Probable human carcinogens. Sufficient evidence of carcinogenicity in animals; inadequate or no evidence of carcinogenicity in humans.

Group C. Possible human carcinogens. Evidence of carcinogenicity in animals is limited and there is no evidence of carcinogenicity in humans.

Group D. Not classifiable as to human carcinogenicity. Evidence of carcinogenicity in animals and humans is inadequate or nonexistent.

Group E. Evidence of non-carcinogenicity for humans. At least two adequate tests in different species have shown no evidence of carcinogenicity.

Appendix F. EPA's 2005 Carcinogenicity Classifications

In 2005, EPA published the final Guidelines for Carcinogen Risk Assessment. This document reflects significant changes first proposed in 1996, and uses descriptors within the context of a weight-of-evidence narrative to summarize biological evidence of carcinogenicity. In contrast to the three-step process described in the 1986 guidance, these guidelines reflect the weighing of evidence in one step (EPA 2005a). The result of this evaluation is a narrative rather than a letter classification. According to this 2005 guidance, the weight-of-evidence narrative should include:

- ◆ a summary of the key evidence supporting these conclusions (for each descriptor used), including information on the type(s) of data (human and/or animal, *in vivo* and/or *in vitro*) used to support the conclusion(s),
- ◆ available information on the epidemiologic or experimental conditions that characterize expression of carcinogenicity (e.g., if carcinogenicity is possible only by one exposure route or only above a certain human exposure level),
- ◆ a summary of potential modes of action and how they reinforce the conclusions,
- ◆ indications of any susceptible populations or life stages, when available, and
- ◆ a summary of the key default options invoked when the available information is inconclusive, and
- ◆ conclusions about human carcinogenic potential (choice of descriptor(s), described below).

The carcinogenic potential descriptors are as follows:

- ◆ *Carcinogenic To Humans.* There is convincing epidemiologic evidence demonstrating causality between human exposure and cancer or there is compelling evidence of carcinogenicity in animals and mechanistic information demonstrates that a similar mode(s) of carcinogenic action in animals and in humans.
- ◆ *Likely to be Carcinogenic To Humans.* Data demonstrate carcinogenic potential to humans but do not meet the weight of evidence standard for classification as "Carcinogenic to Humans."
- ◆ *Suggestive Evidence of Carcinogenic Potential.* Evidence from human or animal data is suggestive of carcinogenicity but is judged not sufficient for a conclusion as to human carcinogenic potential.
- ◆ *Inadequate Information to Assess Carcinogenic Potential.* Available data are judged inadequate to perform an assessment.
- ◆ *Not Likely To Be Carcinogenic To Humans.* Available data are considered robust for deciding that there is no basis for human hazard concern.

Appendix G. MDH HRL Carcinogen Review Committee Guidelines

In order to address the list of HRL candidate chemicals classified according to the 1986 EPA criteria (Appendix E) as "*Group C. Possible human carcinogens*" that have as yet not been re-classified by EPA according to the 2005 EPA criteria (Appendix F), MDH formed a carcinogen review committee. This group consists of three staff members who used a weight-of-evidence approach to consider all of the available information regarding the carcinogenic potential for a chemical, including available human epidemiological and experimental animal studies, structure activity relationship comparisons with other carcinogens, and *in vivo* and *in vitro* mechanism of action experiments. Based on this process, a narrative was prepared for each chemical reviewed summarizing the applicable information including the evidence supporting or refuting concern for carcinogenicity. This evaluation and narrative was based on the following criteria:

- ◆ Adequacy of the experimental design:
 - ◇ sufficient numbers of animals, multiple strains or species, and both sexes used,
 - ◇ consistently controlled environment for the animals used during treatment,
 - ◇ accurate and consistent dosing,
 - ◇ adequate dose selection for a response,
 - ◇ acceptable survival rates (i.e., maximum tolerated dose not exceeded),
 - ◇ acceptable purity of the test chemical(s),
 - ◇ adequate treatment and observation durations,
 - ◇ protocol included randomized group assignments, and
 - ◇ proper statistical analysis conducted.
- ◆ Presence of common versus uncommon neoplasms,
- ◆ Progression (or lack thereof) from benign to malignant neoplasia as well as from pre-neoplastic to neoplastic lesions and whether or not it is appropriate to combine benign and malignant tumor incidence (they should be combined if they are known or thought to represent stages of progression in the same organ or tissue),
- ◆ Latency in tumor induction,
- ◆ Multiplicity in site-specific neoplasia,
- ◆ Metastases as added evidence of malignancy,
- ◆ Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species),
- ◆ Presence or absence of dose-response relationships,
- ◆ Statistical significance of the observed tumor increases,
- ◆ Concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm,

- ◆ Survival-adjusted analyses and false positive or false negative concerns,
- ◆ Structure-activity correlations,
- ◆ Genetic toxicology data, and
- ◆ Evaluations/Classifications from other agencies (e.g., NTP, see Appendix H; IARC, see Appendix I; etc.)

Appendix H. National Toxicology Program's Carcinogenicity Classifications

The National Toxicology Program (NTP) classifies chemicals according to their carcinogenicity using two categories: "Known To Be Human Carcinogen" and "Reasonably Anticipated to be Human Carcinogen" (NTP 2002). These are defined as follows:

Known To Be Human Carcinogen: "There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer."

Reasonably Anticipated To Be Human Carcinogen: "There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, or

"there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, or

"there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans."

Appendix I. International Agency for Research on Cancer's Carcinogenicity Classifications

The International Agency for Research on Cancer (IARC) classified chemicals into five groups based on carcinogenic potential (IARC 2004). These groups are described as follows:

Group 1: The agent (mixture) is carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

Group 2A: The agent (mixture) is probably carcinogenic to humans. This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans.

Group 2B: The agent (mixture) is possibly carcinogenic to humans. This category is used for agents, mixtures and exposure circumstances for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is inadequate evidence of carcinogenicity in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3: The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans. This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals. Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Group 4: The agent (mixture) is probably not carcinogenic to humans. This category is used for agents or mixtures for which there is evidence suggesting lack of carcinogenicity in humans and in experimental animals. In some instances, agents or mixtures for which there is inadequate evidence of carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

APPENDIX J. Toxicity Testing

Toxicity data underlie every HRL. Usually these data are from an animal study; occasionally, the data are from an epidemiological study. Toxicity data may emerge from basic research but, more often, it emerges from applied research – that is, research with the goal of a practical application. Because of governmental restrictions, companies that produce chemicals are often required to provide data about chemical safety and/or efficacy. Consequently, parties with a vested interest produce a great deal of data that are used in derivation of HRLs. Governmental testing protocols and peer review of the studies add assurance to the validity of the process. This section discusses, very generally, some of the regulatory requirements for certain classes of chemicals.

Three primary federal acts authorize testing of chemicals that may pose a general or specific risk to human health through contamination of water resources and food: (1) the *Federal Insecticide, Fungicide, and Rodenticide Act* (FIFRA), 7 U.S.C. 136 *et seq.*; (2) the *Food Quality Protection Act* (FQPA) (amending the *Food, Drug, and Cosmetic Act*, 21 U.S.C. 301 *et seq.*); and (3) the *Toxic Substances Control Act* (TSCA), 15 U.S.C. 2601 *et seq.* Testing may be required by the Acts themselves or by agencies authorized to establish regulations under the auspices of the Acts. Elements of these and other laws address other specific human health or environmental concerns such as worker protection, occupational exposure, and non-target plant and animal health effects. For purposes of establishing HRLs, MDH focuses primarily on testing that provides data relevant to potential human health risks associated with exposure to contaminants in drinking water.

All pesticides are subject to regulatory testing under the authority of FIFRA. FIFRA mandates that pesticides undergo a registration process prior to distribution or sale, and authorizes the establishment of requirements for toxicity testing. The FQPA requires a general re-evaluation of pesticide toxicity and pesticide residues on food, with an emphasis on the health of infants and children. The FQPA also requires that EPA develop and implement a comprehensive screening program for endocrine disruption (21 U.S.C. § 346a(p)). The FQPA leaves the selection of chemicals for priority testing to EPA.

Under FIFRA, basic toxicology data requirements for pesticides are determined by the chemical type (structure and pesticidal action) of the pesticide and its intended use. Basic, or “core” toxicity testing required for food crops includes, at a minimum:

- ◆ a battery of acute studies (acute oral, acute dermal, acute inhalation, primary eye irritation, primary dermal irritation, dermal sensitization, and delayed neurotoxicity);
- ◆ 90-day (subchronic) feeding studies in rodents and nonrodents;
- ◆ chronic feeding studies in rodents and nonrodents;
- ◆ oncogenicity (cancer) studies in two species of rodents (rats and mice preferred);
- ◆ teratogenicity (fetal viability, structure, and growth) toxicity studies in rodents and nonrodents (rats and rabbits preferred);
- ◆ a two-generation reproduction study in rodents;
- ◆ a general metabolism study in rodents; and
- ◆ mutagenicity studies (*in vivo* and *in vitro* assays of gene mutation, structural chromosomal aberration, and other genomic effects).

Subchronic (90-day) studies of dermal or inhalation exposure or of neurotoxicity, may be included as core requirements. (See 40 CFR § 158.340.) Biochemical pesticides (e.g., those made up of insect

pheromones, insect growth hormones, natural plant and insect regulators, and enzymes) are routinely tested for immunotoxicity and may be subject to testing for hypersensitivity, while microbial pesticides (e.g., those made up of bacteria, fungi, viruses, and protozoans) may be tested for immunotoxicity and virulence enhancement (40 CFR §§ 158.690, 158.740).

Testing is an iterative process. Further testing requirements are determined individually for each pesticide active ingredient. At each step, the outcome of previous testing informs the need for additional testing (40 CFR § 158.75). Pursuant to the FQPA, a determination by EPA that testing conducted does not adequately address all concerns regarding reproductive, developmental, or neurotoxicity, will result in lowering of exposure limits.

TSCA authorizes EPA to regulate manufacturing, processing, use, distribution in commerce, and disposal of chemical substances. Pesticides and certain other substances addressed by other acts are exempt from TSCA. Under TSCA, EPA has broad authority to issue regulations designed to gather health/safety and exposure information on, and control exposure to, chemical substances and mixtures (15 U.S.C. § 2603). However, EPA may only require testing of a commercial chemical if it finds that the chemical may "present an unreasonable risk of injury to health or the environment" or is produced in substantial quantities that could result in significant or substantial human or environmental exposures.

Health effects testing under the TSCA findings of hazard ("an unreasonable risk of injury to health or the environment") and/or exposure is regulated under 40 CFR Parts 790 to 799. Guidelines relevant to groundwater exposures include:

- ◆ oral toxicity;
- ◆ chronic toxicity;
- ◆ oncogenicity (cancer);
- ◆ combined chronic toxicity and oncogenicity;
- ◆ reproduction and fertility effects;
- ◆ developmental toxicity; functional observational battery;
- ◆ motor activity;
- ◆ neuropathology;
- ◆ schedule-controlled operant behavior; and
- ◆ subchronic delayed neurotoxicity.

However, under TSCA, EPA cannot require that data from any test be submitted without a formal rule-making process. Since formal rule-making can be time consuming and tends to cast EPA and industry as adversaries, the Agency has developed some alternatives to testing pursuant to agency rules in order to expedite chemical testing and reduce the adversarial atmosphere around testing. Enforceable Consent Agreements (ECAs) encourage members of the chemical industry to submit offers to conduct needed testing on chemicals for which the Agency has not yet issued final test rules. Voluntary Testing Agreements (VTAs) require industry to come forward with a voluntary testing program before EPA considers final test rules for a chemical. In addition, a voluntary cooperative international testing program, the Screening Information Data Set (SIDS), focuses on developing base level test information on poorly characterized international high production volume (HPV) chemicals.

These are the types of toxicity data that may be available for HRL chemicals as a result of regulatory efforts. While regulatory requirements tend to promote at least temporal uniformity in toxicity testing between chemicals of the same or similar types, the data generated in compliance with regulatory

requirements will depend on factors such as the type or use of the particular chemical, the date it first came into use, the date of any recent review, and concerns raised by existing toxicity testing.

Appendix K. Relative Source Contribution

As discussed in Section IV.E.1. of this SONAR, MDH has developed default Relative Source Contribution (RSC) values for use in calculating HRLs. The use of these RSCs ensures that each HRL value will be protective of human health even when other routes of exposure, such as inhalation and food ingestion, may be present. To develop RSCs, MDH made use of the Exposure Decision Tree (EDT) approach developed by EPA in its Ambient Water Quality Criteria document (EPA, 2000c). The EDT, shown in Figure 1, consists of a series of decision points at which the availability and quality of chemical and exposure data are evaluated. In general, a lack of statistically significant exposure data will tend to steer the process towards a lower, i.e., more protective, RSC value. Higher RSC values may result if situation-specific data indicate that alternate exposures may not be as significant as in the generic case. EPA (2000) recommends that RSC values stay within the range of 0.2 to 0.8; the lower end of the range protects against other routes of exposure when uncertainty is high, and the upper end of the range allows for unknown exposures when uncertainty is low.

The first two boxes of the EDT (Figure 1) are simply a definition of the problem. In the case of HRL development, the population of concern is the general public, with a particular interest in subpopulations that may have higher exposure, such as children or individuals who consume more water than a "typical" person. The exposure pathway of primary concern is water ingestion, but other exposure routes such as food consumption, inhalation, and dermal exposure are of interest in apportioning the overall risk across all potential pathways.

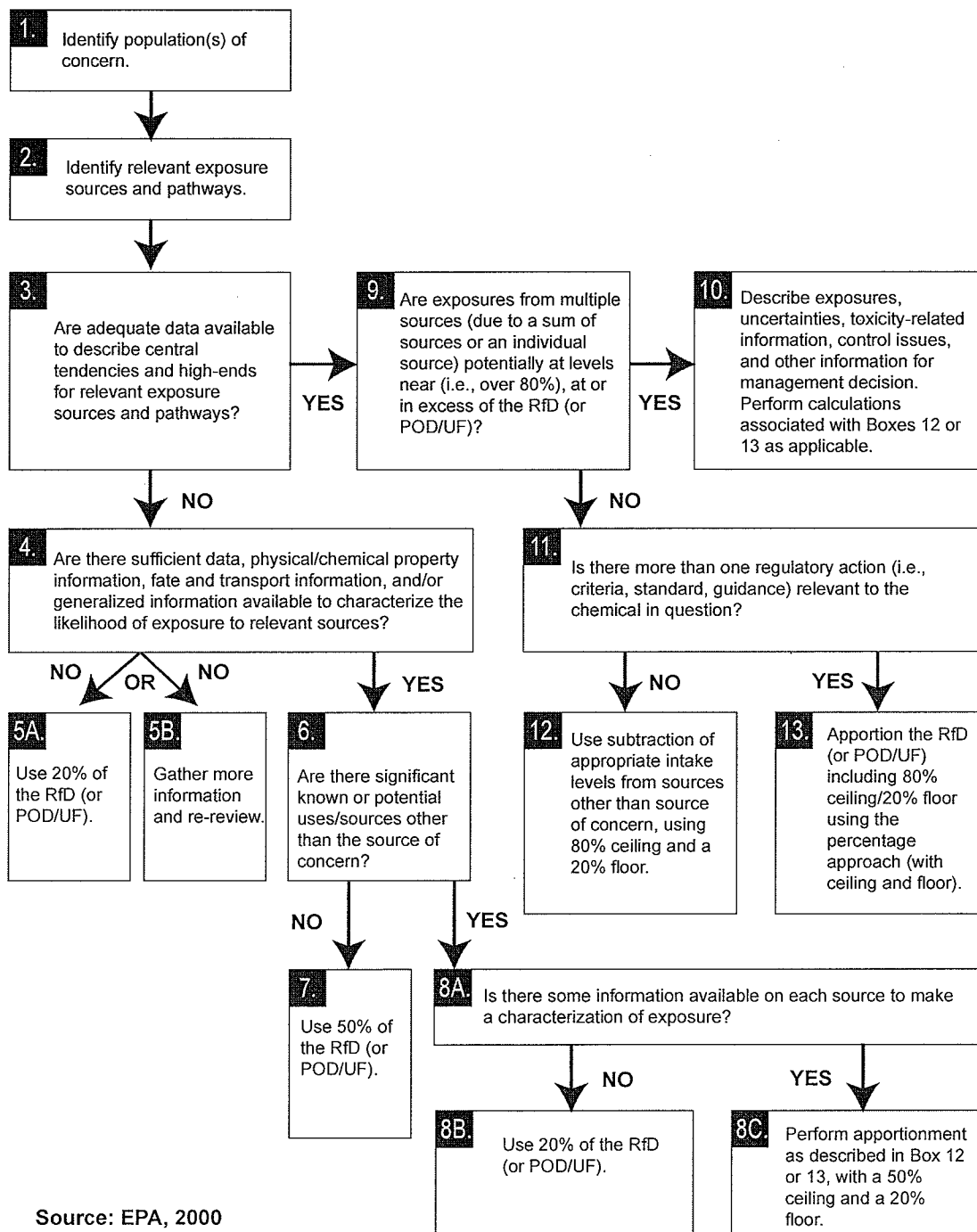
Box 3 contains the first decision point. The criterion of "adequate data" is met if there are sufficient data to calculate exposure in a statistically meaningful way. Because the HRL development process is applied to a generic case, the response for Box 3 is "no." The next decision point, Box 4, asks a similar question, but with a lower threshold for a positive response; rather than requiring statistically significant numerical data, "generalized" information on the likelihood of exposure is sufficient for a positive response. Because there may be qualitative information on alternative pathways of exposure, the response for Box 4 is "yes."

The next decision point, Box 6, asks if there are significant known or potential sources and uses other than the one under consideration, i.e., groundwater. If no other sources or uses exist, the RSC is set at 0.5 (Box 7), and if other sources and uses do exist, the RSC is either 0.2 or a value between 0.2 and 0.5, depending on the availability of information on those alternate sources (Boxes 8A, 8B, and 8C.) For the HRL process, the response to Box 6 depends on chemical volatility. The volatilization of chemical compounds from water to air results in a potential for inhalation exposure that may be as significant as exposure via ingestion. Therefore, for highly volatile chemicals, MDH decided that the response for Box 6 is "yes," and the response for Box 8A is "no," resulting in an RSC of 0.2. Likewise, food consumption and dermal contact with contaminated media are significant potential sources of exposure for most of the population, resulting in the same responses and an RSC of 0.2. The exception to this conclusion for alternate exposures *other than inhalation* applies to infants from birth to three months of age. These individuals have an extremely limited potential for dietary and environmental exposure (other than inhalation) because of the very limited range of environments and foods they encounter. For this reason, the response to Box 6 is "no" for infants less than three months old, but only for chemicals that do not carry a significant risk of inhalation exposure, e.g., those that are not highly volatile.

In summary, the RSC values adopted by MDH in the revised HRL rules are as follows:

	Infants (0 to 3 months old)	All other children and adults
Highly volatile chemicals (Henry's Law Constant > 1×10^{-3})	0.2	0.2
All other chemicals	0.5	0.2

Figure 1. Flowchart for Exposure Decision Tree Model.



Source: EPA, 2000

Appendix L. Volatilization

Showering, bathing, washing clothes and dishes, and other uses of household water allow chemicals to evaporate, or volatilize. Thereafter, these chemicals are present in air. Consequently, in a residential setting, an individual may be exposed to chemicals from groundwater both through ingestion (drinking) and through inhalation (breathing).

The magnitude of an individual's exposure to chemicals volatilized during household water use is dependent on a number of factors: the physical characteristics of the specific chemical; the quantity of water used; the temperature of the water; characteristics of the house, such as size and air exchange rate; and the behavior patterns of an individual. Several models have been proposed to estimate exposures to volatilized chemicals (Andelman 1990; McKone 1987; Schaum 1994; Wilkes 1996). Researchers differ as to how an individual's exposure to volatilized chemicals compares to the individual's exposure to the same chemicals through ingestion. One estimate is that exposure from volatilization of drinking water could range from three to ten times that from ingestion; another researcher suggests a differential of 1.6 to six fold for adults (EPA 1991b; McKone 1987). While the contribution of volatilized chemicals to total exposure will vary, all sources agree that showering is the primary source for this type of exposure.

Because volatilization of chemicals under the conditions of household water use can contribute significantly to total exposure, MDH has indicated whether each HRL chemical is volatile. MDH has also indicated the extent of volatility: high, moderate, or low. While a nonvolatile chemical may still be present in air, concentrations will generally not be high enough to contribute significantly to total exposure from domestic use of groundwater. This information will permit the risk manager to determine whether additional protections beyond those in the HRL are advisable to protect the health of potentially exposed individuals.

MDH has adopted the general definition of the term *volatile* commonly used by the Agency for Toxic Substances and Disease Registry (ATSDR). The 2001 ATSDR Public Health Assessment Guidance Manual (ATSDR 2001) used the Henry's Law Constant, a measure of the tendency for a chemical to pass from an aqueous solution to the vapor phase, to classify the volatility potential of chemicals. Henry's Law Constant is a function of molecular weight, solubility, and vapor pressure. Henry's Law Constant can be predicted fairly accurately by the ratio of a chemical's vapor pressure to its solubility in water. A high Henry's Law Constant corresponds to a greater tendency for a chemical to volatilize to air.

Chemicals are classified as follows:

- Henry's Law constant $< 3 \times 10^{-7}$ atm-m³/mol = nonvolatile
- Henry's Law constant $> 3 \times 10^{-7}$ to 1×10^{-5} atm-m³/mol = low volatility
- Henry's Law constant $> 1 \times 10^{-5}$ to 1×10^{-3} atm-m³/mol = moderate volatility
- Henry's Law constant $> 1 \times 10^{-3}$ atm-m³/mol = high volatility

APPENDIX M. Cancer Incidence for Lifetime and Early-life Exposure

Several types of studies examine whether the timing and duration of an exposure to a carcinogen makes a difference in the development of cancer. Relevant studies are of several types:

- ◆ Standard chronic cancer bioassay – Current standardized chronic carcinogenesis studies generally begin dosing animals at 6 – 8 weeks of age and continue dosing for the remaining lifespan of the animal (18 – 24 months).
- ◆ “Stop-exposure” studies – In the “stop-exposure” study, a subgroup of animals in the standard chronic cancer bioassay is dosed for a short period of time and is then maintained and until the end of the study. The tumor incidence rates from the short period of time are compared to tumor incidence rates resulting from the standard chronic cancer bioassay. “Stop-exposure” studies evaluate the assumption that exposures of limited duration are associated with a proportional reduction in risk.
- ◆ “Single dose” studies, or acute exposure during early life stages – The rates of tumor incidence resulting from single doses administered at different life stages are compared. Doses may be administered during early life, including gestation; the growth of tumors is typically evaluated late in life. Dosing test animals at different times of life allows a comparison of cancer potency (incidence per mg/kg/day) at different stages of life.
- ◆ “Short-term repeated” studies, or exposure during early life stages – The tumor incidence resulting from short-term repeated dosing during the early postnatal to juvenile period is compared to the tumor incidence resulting from the standard chronic adult-only cancer bioassay. The objective of this comparison is to estimate the incidence attributable to early-life exposures.
- ◆ “Lifetime exposure” studies – The tumor incidence resulting from animals dosed for a “lifetime” (beginning at or before birth and continuing through adulthood) is compared to the tumor incidence resulting from the standard chronic adult-only cancer bioassay. The objective of this comparison is to evaluate whether dosing during early life contributes disproportionately to the lifetime incidence of cancer.

Only adult animals were exposed in the standard chronic cancer studies and “stop-exposure” studies, whereas, the “single-dose,” “short-term repeated” and “lifetime” exposure studies included exposure during early life. MDH has summarized evaluations of these studies below.

“Stop-Exposure” Studies. In 2000, Halmes, Roberts, Tolson, and Portier tested the cumulative dose assumption by comparing observations from short-term adult exposure versus chronic adult exposure cancer studies (Halmes *et al.* 2000). They analyzed data from eleven stop-exposure studies conducted by the NTP. The NTP’s stop-exposure studies followed the standard cancer bioassay study design, but included a subset of animals exposed for less-than-lifetime durations. The objective of the study was to test the hypothesis that short-term adult exposure to carcinogens, when compared to the standard chronic adult exposure, results in a proportional decrease in cancer risk.

The authors tested this hypothesis in a number of ways. First, each dose of each chemical used in the stop-exposure study was converted to a 2-year average dose. This “averaged dose” was used to

determine whether the tumor response fell on the dose-response line generated by the standard 2-year bioassay. The stop-exposure responses were significantly higher than expected compared to the standard 2-year bioassay for at least one cancer site for 6 of the 11 chemicals. On a site-by-site basis, 33 of the 59 sites with increased cancer displayed a statistically significant difference.

The authors also evaluated dose averaging by determining the length of time one should average the stop-exposure dose so that the observed response fell on the dose-response line generated by the standard 2-year bioassay. An averaging time equivalent to the 2-year bioassay (104 weeks) would indicate that the stop-exposures produced results consistent with the 2-year bioassay. Most of the averaging times were less than 104 weeks. For some tumor sites, the equivalent averaging time was quite comparable with the actual exposure duration. There were also cases where the equivalent averaging time was less than the actual exposure time. For most tumor sites, however, the equivalent averaging times for the stop-exposure studies were longer than the actual exposure duration, but less than 2 years, suggesting that short-term exposures are generally more effective in producing tumors than 2 year standard bioassays would predict. The median equivalent averaging time for all stop-exposure groups was 62 weeks.

To evaluate the effect of these differences identified above, the estimated doses yielding a 1 percent tumor response (ED01) from the standard 2-year bioassay data only were compared with the ED01 from the standard 2-year bioassay and the stop-exposure data combined. Inclusion of responses from the stop-exposure groups decreased the ED01 by greater than a factor of 2 for tumors at 1 or more sites for 6 of the 11 chemicals. Twenty-four of the 47 chemical/tumor site combinations had ED01 values that were at least two-fold smaller when the stop-exposure groups were included.

For the majority of the chemicals evaluated, short-term exposures were generally more effective in producing tumors than the standard 2-year bioassays would predict. The authors also noted that no obvious relationship could be deduced between genotoxicity and the influence of exposure duration on tumor response for the eleven chemicals tested.

The analyses by Halmes *et al.* indicate that while cancer risk may increase with cumulative carcinogen dose, that increase is not necessarily linear; that is, the increase per unit dose may decrease with increasing doses. Alternatively, at some point, further dosing may simply be "wasted;" dosing for a longer period may not give rise to further cases of cancer. In either case, calculating cancer risk using a lifetime average daily dose (LADD) may underestimate risk from short-term exposures. This result is not obvious from the two-year animal cancer bioassays, since cancer status is typically assessed at the termination of the study.

With the Halmes *et al.* analysis in mind, as well as the information gaps left by the standard two-year cancer bioassay, MDH believes that the approach that best protects public health is to calculate cancer risk using methodology that considers early-life sensitivity.

Early-Life-Stage Exposure Studies. A limited set of studies allows an evaluation of the second corollary of LADD; i.e., that no period of life is considered any more sensitive than any other period of life. These studies generally allow a comparison of cancer risks from exposures early in life with cancer risks from exposures later in life. EPA (EPA 2003f), an EPA Science Advisory Board (EPA 2004b), Dr.

Gary Ginsberg,¹¹ and Dr. Dale Hattis¹² have recently examined these studies in detail. Their approaches varied, as did their attempts to summarize conclusions quantitatively. However, all researchers agreed that, at least for some carcinogens, exposure during early life leads to a higher incidence of cancer than exposure in later life.

In the final *Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens*, released in March of 2005, EPA scientists performed a quantitative evaluation of studies that administered similar dose levels across various age groups (EPA 2005a). Two types of studies were evaluated: acute ("single-dose") exposure and repeated exposures. The acute exposure analysis evaluated studies that used a single dose administered either during early postnatal, juvenile, or adult periods. The repeated exposure analyses examined studies with short-term repeated exposures during the early postnatal to juvenile period and repeated chronic adult exposures. The objective was to estimate increased incidence attributable to early-life exposure. To do this, EPA normalized data for the exposure duration.

The acute exposure studies generally compared a single exposure during the first weeks of life with an identical or similar dose in young adult animals. Studies were available for eight mutagenic chemicals: benzo(a)pyrene (BaP), dibenzanthracene (DBA), diethylnitrosamine (DEN), dimethylbenz(a)anthracene (DMBA), dimethylnitrosamine (DMN), ethylnitrosourea (ENU), methylnitrosourea (MNU), and urethane. The doses were administered largely by subcutaneous or intraperitoneal (IP) injection.

An analysis of repeat exposure studies compared tumor incidence rates from short-term early-life-stage exposures to tumor incidence rates from chronic adult-only exposures was also conducted. Studies were available for four mutagens: benzidine, 3-methylcholanthrene (3-MU), safrole, and vinyl chloride. EPA also evaluated repeat exposure studies for six nonmutagenic carcinogens: amitrole, dichlorodiphenyltrichlorethane (DDT), dieldrin, 5,5'-diphenylhydantoin (DPH), ethylene thiourea (ETU), and polybrominated biphenyls (PBB). Ratios of tumor incidence in juvenile animals with short-term exposure to the tumor incidence in adult animals with chronic exposure were calculated.

EPA also calculated ratios of early-life to adult cancer potencies for studies with lifetime exposures starting with juvenile and adult animals to carcinogens with mutagenic (DEN, safrole and urethane) or nonmutagenic (DDT, dieldrin, DPH, ETU, and PBB) modes of action.

A summary of the early-life cancer susceptibility evaluation conducted by EPA is presented below.

¹¹ Dr. Gary Ginsberg is associated with the Connecticut Department of Public Health, Division of Environmental Epidemiology & Occupational Medicine.

¹² Dr. Dale Hattis is with Clark University.

Table M-1. Summary of early-life to adult cancer potency ratios

Study Type	Tissue	No. of Chemicals	Inverse-weighted Geometric mean ratio	Unweighted Minimum	Unweighted Maximum	No. of ratios	Percent > 1
<i>Chemicals with mutagenic mode of action</i>							
Acute	Combined	11	1.5	0.01	178	268	55
Repeated		4	10.5	0.12	111	45	42
Lifetime		3	8.7	0.18	79	6	67
<i>Chemicals with nonmutagenic mode of action</i>							
Repeated		6	2.2	0.06	13	22	27
Lifetime		5	3.4	0.15	36	38	21

Data taken from Table 8 of the EPA Supplemental Guidance (EPA 2005a).

Based on its analysis of studies for mutagenic carcinogens, EPA proposed the following approach for assessing cancer risks from mutagenic carcinogens. First, use the cancer slope factor based on linear extrapolation of data from standard 2-year (adult) bioassays. Second, adjust the slope factor for the life stage of exposure. For exposures before two years of age, use a ten-fold potency adjustment; for exposures between two and sixteen years of age, use a three-fold potency adjustment; and for exposures at or after sixteen years of age no adjustment is necessary. Application of the life stage-specific adjustment factors account for differences in sensitivity only (i.e., when life stage-specific intake rate differences are not incorporated in the calculations) results in roughly a doubling of the cancer potency over a lifetime of exposure: $\{[(10 \times (2/70))] + [(3 \times (13/70))] + [1 \times (55/70)] = 1.6.\}$. The final Supplemental Guidance recommends using age-specific exposure data when available.

The ten-fold adjustment factor recommended for the 0 - 2 year age group represents a combination of the geometric mean ratio for repeat exposures (10.5) and lifetime exposures (8.7). As discussed above, in its analysis of short-term repeated exposure studies, EPA normalized the tumor incidence rates by exposure duration (e.g., the incidence was divided by the number of weeks of exposure). This approach is consistent with the cumulative dose assumption (i.e., cancer risks are proportional to exposure duration). However, EPA acknowledged that exposure occurring near the end of adult chronic exposure period may have had little effect on the lifetime cancer risk. At some point further dosing may simply be "wasted", dosing for a longer period may not give rise to further cases of cancer. If this is true, normalization over the entire adult exposure period would result in inflating the magnitude of the early-life to adult ratio.

A Science Advisory Board (SAB) reviewed and commented on the draft supplemental guidance (EPA 2004b). The SAB agreed that the studies evaluated provide evidence of increased susceptibility during early life stages and felt that a broader look at the scientific literature (beyond the selected studies) would further strengthen this conclusion. The SAB supported the use of a slope factor adjustment in developing default assumptions, but requested an expanded discussion of recommended default adjustment factors. The SAB suggested use of a separate age group to represent puberty. The SAB also noted that the quantity and quality of data for the nonmutagenic carcinogens did not differ appreciably from the mutagen data. Finally, the SAB requested that EPA consider development and application of default adjustment factors for nonmutagenic chemicals, with unknown modes of action

(i.e., nonmutagenic chemicals for which EPA has decided to implement a linear approach), as well as mutagenic chemicals.

Dr. Hattis and his colleagues conducted a more formal statistically-weighted evaluation of the database assembled by EPA, augmented by some additional studies (Hattis *et al.* 2004a). This more formal analysis quantified the relative cancer potency in terms of cancer transformations per animal per unit dose for animals of three different age groups (fetal, birth-to-weaning, and weaning-to-60 days). In their analysis, the doses expressed in terms of environmental media concentrations were left unchanged, but the doses expressed as $\mu\text{g}/\text{kg}/\text{day}$ weight were transformed into $\mu\text{g}/(\text{kg body weight}^{0.75} \cdot \text{day})$. The objective of this dose transformation was to express dosage for mammalian animals of different weights on a metabolically consistent basis. The continuous dosing ("short-term" repeated exposure) dataset contains data for 9 chemicals: 5 mutagens (benzidine, benzo(a)pyrene, diethylnitrosamine, safrole, and vinyl chloride) and 4 nonmutagens (amitrole, diphenylhydantoin, ethylene thiourea and polybrominated biphenyls). The discrete dosing ("single dose" exposure) dataset contains 6 chemicals, all of which are considered mutagenic (benzo(a)pyrene, diethylnitrosamine, dimethylbenzanthracene, ethylnitrosourea, methylnitrosourea, and urethane).

Hattis *et al.* (2004a) presented the results as maximum likelihood estimates (central estimates) and confidence limits. A summary of the key findings is presented in Table M-2.

Table M-2. Maximum likelihood estimate of cancer induction per dose/(body weight^{0.75}- day) relative to comparably dosed adults^a

	Fetal	Birth-to-weaning	Weaning-to-60 days
All Continuous Dosing vs. All Discrete			
Continuous Dosing Experiments (9 chemicals, 151 observations)	4.9 (0.5 – 9.3) [1.9]	8.7 (6.5 – 10.8) [5.4]	0.0 (0.0 – 0.24) [0]
Discrete Dosing Experiments (6 chemicals, 274 observations)	5.1 (3.6 – 8.5) [2]	10.5 (7.2 – 16.2) [6.6]	1.51 (1.03 – 2.31) [1.4]
Continuous Dosing – Mutagenic vs. Nonmutagenic			
Mutagenic Chemicals^b (5 chemicals, 43 observations)	8.4 (3.5 – 15.5) [3.2]	24 (17.1 – 34) [15]	3.7 (0.0 – 9.1) [3.4]
Nonmutagenic chemicals^b (4 chemicals, 108 observations)	0.0 (0.0 – 17.4) [0]	3.0 (0.0 – 4.7) [1.9]	0.0 (0.0 – 2.0) [0]
Continuous + Discrete Combined, Mutagenic Chemicals^b - Lactational vs. Direct Administration (9 mutagenic chemicals, 317 observations)			
	6.0 (5.5 – 8.8) [2.3]	Lactational: 21.4 (15.3 – 30) [13] Direct: 11.6 (8.5 – 16.1) [7]	1.7 (0.77 – 2.4) [1.5]

^aMaximum Likelihood Estimate (MLE) (95 % LCL – 95% UCL). MLE ratio converted to **approximate** dose/kg body weight – day shown in brackets []

^bAs classified by EPA

This analysis suggests: 1) the sensitivity results for continuous (repeated) dosing and discrete ("acute") dosing are similar; 2) in contrast with mutagenic carcinogens, nonmutagenic carcinogens did not

manifest a significantly greater sensitivity than adults; 3) for mutagens (and nonmutagens to a much lesser degree), birth to weaning is the most sensitive period, followed by the fetal period and the weaning to 60 day period; and 4) that lactational exposures appear somewhat more potent than direct administration. One possible explanation of this last observation is that some of the direct bolus doses may have partially saturated metabolic activation pathways, leading to a less effective dose than when dosing is administered more slowly via milk.

The authors concluded: "On a qualitative level, this analysis provides more detailed understanding and confidence in the fact that there is an increased early-life sensitivity for mutagenic carcinogens – reinforcing the conclusions drawn by EPA . . ." (Hattis *et al.* 2004a). In a related publication, Hattis and his colleagues estimated that the population arithmetic mean risk from lifetime exposures to a generic mutagenic carcinogen is about 3.5 fold higher (5 – 95% confidence limit 1.7 – 7.4) than for exposure during the adult period alone (Hattis *et al.* 2004b).

In 2003, Dr. Gary Ginsberg of the Connecticut Department of Public Health also conducted a literature-based review of early life stage exposure data (Ginsberg 2003). Dr. Ginsberg compared the results of acute exposures during early life stages to the results of acute exposures in adults and compared short-term repeated exposure during early life to chronic repeated exposure in adults.

A comparison of acute exposures during early life versus acute exposure during adulthood was conducted for eight carcinogens: benzo(a)pyrene (BaP), dibenzanthracene (DBA), diethylnitrosamine (DEN), dimethylbenz(a)anthracene (DMBA), ethylnitrosourea (ENU), 3-methylchloanthrene (3-MC), urethane, and X-rays. This comparison of acute exposure data showed at least a two-fold increase in sensitivity in juvenile animals. However, not all tissues were equally responsive to timing of exposure. The direct sensitivity differences between juvenile and adult animals were commonly between three and ten-fold, but with evidence that for certain carcinogens and tissues, the differential can be greater than one order of magnitude.

Dr. Ginsberg also compared the results of short-term repeated exposure during early life stages to the results of chronic repeated exposures in adults. This comparison allowed an evaluation of whether exposure during early life would result in additional tumors and/or higher potency than adult-only exposure. For ten carcinogens (3'azido-3'-deoxythymidine (AZT), benzidine, benzo(a)pyrene (BaP), dichlorodiphenyltrichloroethane (DDT), diethylnitrosamine (DEN), diethylstilbestrol (DES), dieldrin, safrole, tamoxifen, and vinyl chloride), studies with similar rates of administered doses (mg/kg-day during the dosing period) across different life stages facilitated a direct comparison of tumor response. The early-life versus adult-only chronic exposure comparisons did not show the large response differences noted in the acute comparison above, in part because the adult exposures are chronic, while the early-life exposures are short-term. With the exception of DEN, each example provided evidence of similar tumor response per unit of administered dose for short-term juvenile exposure as compared to chronic adult-only exposure. This supports the hypothesis that brief exposures early in life are just as important as long-term exposures that begin later in life.

Dr. Ginsberg suggested a step-wise approach for incorporating children's exposure and sensitivity into cancer risk assessment. First, calculate exposures that are specific to children. Second, calculate children's cancer risk by applying the cancer slope factor from adult animal or human epidemiology studies to the children's exposure dose. Third, apply the same cancer slope factor to the average exposure during later life stages to calculate cancer risk for these age groups. Finally, add the cancer risk from young children to the older age groups to yield a lifetime cancer risk estimate. Focusing on

differences in life stage sensitivity only (i.e., not adjusting for life stage-specific exposure differences) the application of the Ginsberg approach would result in doubling the lifetime cancer risk (risk from exposure during childhood plus risk from exposures later in life).

Based on Dr. Ginsberg's recommendations, the Connecticut Department of Environmental Protection (DEP) has proposed an approach that accounts for early-life exposures in its Remediation Standard Regulations' Volatilization Criteria for Target Indoor Air Concentrations (TACs) (Connecticut DEP 2003). TACs based on standard adult exposure and toxicity values are adjusted by using child-based factors. Inhalation exposure is adjusted upward by a factor of two and toxicity of genotoxic carcinogens is adjusted upward by a factor of two. The net result is a four-fold reduction in the TACs. Currently, the TACs are being used as guidance, pending approval.

Evidence from these early-life-stage exposure studies indicates that, at least for some chemicals, the standard practice in risk assessment may not be adequately protective. Studies that allow a comparison of short-term dosing relatively early in life to continuous dosing later in life (using the same dose of mg/kg - day) suggest that, for some chemicals, the cancer potency from short-term dosing can be similar to that of a longer-term exposure. Although these studies do not allow a quantitative analysis of exposure duration and cancer potency, they do suggest that averaging exposures over a lifetime may result in an underestimation of risk.

The California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) has also evaluated the effects of carcinogenic exposures early in life (Sandy *et al.* 2006). Age Sensitivity Factors (ASFs) were derived for the following age windows: prenatal (*in utero*), postnatal (birth to weaning), juvenile (weaning to sexual maturity), and adult (sexual maturity onwards).

For the prenatal age window the ASF distributions ranged from less than 0.1 up to greater than 100, with a weighted median value of 2.38. For the postnatal age window the ASF distributions, based on 18 carcinogens, ranged from greater than 1 up to greater than 100, with a weighted median value of 7.66 (mean of the trimmed distribution (1st-99th percentile range) was 15.95). For the juvenile age window the ASF distributions, based on 5 carcinogens, ranged from less than 0.1 up to greater than 10, with a weighted median value of 3.03 (mean of the trimmed distribution (1st-99th percentile range) was 3.88).

OEHHA is also in the process of determining how best to incorporate concerns about children's exposures and children's sensitivity into environmental standards. The evaluation of increased sensitivity, discussed above, has been completed. OEHHA will be integrating information regarding sensitivity as well as exposure differences into risk assessment guidance. This guidance is available as a draft document that is being publically reviewed at this time (OEHHA 2008).

Summary. The standard risk assessment methods that have evolved for evaluating cancer risk use lifetime dose averaging. Results from short-term early-life exposure studies indicate that cancer incidence from short exposures early in life can be as great as, and in some cases higher than, cancer incidence from longer exposures during adult life. "Stop-exposure" studies in adult animals also indicate that a lifetime of exposure is not necessary to give rise to cancer, and that averaging short-term exposures over a lifetime can underestimate risk.

The standard methods for evaluating cancer risk typically use cancer slope factors based on chronic, adult-only exposure. Available early-life and "lifetime" studies indicate that exposure to some

carcinogens during early life may result in increased cancer rates compared to chronic adult-only exposure. The comparison of tumor incidence rates resulting from early-life exposure to chronic adult exposure is highly variable across chemicals, gender, and tumor site. However, the ratios exceed 1 for the majority of the chemicals studied. Unfortunately, the dataset is limited in quantity (e.g., only a small number of chemicals have been evaluated) and quality (e.g., largely older studies which were not designed to address the question of early-life-stage sensitivity). In addition, the design of the early-life exposure studies do not allow for a determination of whether the increased tumor rates are the result of increased susceptibility (e.g., rapid cell division and differentiation during early life), differences in dosing (e.g., many of the "short-term" and "lifetime" studies were dietary and the actual dose early in life was not measured), a longer time for tumors to develop (e.g., dosing began earlier in life), a higher cumulative dose in the case of "lifetime" studies, or a combination of these factors.

MDH has concluded that while the available data are not amenable to rigorous quantitative analysis, their import cannot be ignored. As a matter of public health policy, MDH is therefore applying the EPA early-life sensitivity default algorithm (EPA 2005a) to account for increased sensitivity as the result of exposure during early life. If data for an individual chemical show that there is no increased potency as a result of exposure during early life, MDH would not apply this algorithm. Conversely, if data for an individual chemical show that the potency is different than the age-dependent adjustment factors (ADAFs) in the EPA default approach, MDH would apply the chemical-specific adjustment factor.

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

Where:

- cHRL = the cancer health risk limit expressed in units of micrograms of chemical per liter of water ($\mu\text{g}/\text{L}$).
- (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 ($[1 \text{ per mg/kg-day}]$ or $[1 / \text{mg/kg/day}]$ or $[\text{mg/kg-day}]^{-1}$).
- ADAF = the age-dependent adjustment factor for each age group: 10, for up to 2 years of age ($\text{ADAF}_{<2}$); 3, for 2 up to 16 years of age ($\text{ADAF}_{2<16}$); and 1, for 16 years of age and older (ADAF_{16+}).
- IR = the intake rate for each age group: 0.137 L/kg-day, for up to 2 years of age ($\text{IR}_{<2}$); 0.047 L/kg-day, for 2 up to 16 years of age ($\text{IR}_{2<16}$); 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 EPA in the characterization of lifetime cancer risk.

EPA has recommended that the supplemental approach be applied to mutagenic mode of action carcinogens. However, the EPA Science Advisory Board suggested that EPA reconsider limiting the application of adjustment factors only to mutagenic agents and instead apply a default approach to

both mutagenic and to non-mutagenic chemicals for which mechanism of action remains unknown or insufficiently characterized (EPA 2004b). EPA acknowledged that the nonmutagenic studies provided evidence that early life stages can be more susceptible to exposures to chemicals causing cancer through a variety of modes of action other than mutagenicity. However, a major factor that complicated the interpretation of the results was that most of these studies involved dietary feeding initially to the mother, resulting in uncertainty regarding dose received during early life. EPA chose to continue to limit application of the ADAFs to only carcinogens acting through a mutagenic mode of action based in part on the analysis of available data but also on EPA's long-standing science policy decision regarding the conservativeness of low-dose linear extrapolation. It is interesting to note that OEHHA did not separate carcinogens based on mode of action in their analysis and the weighted median value for the postnatal and juvenile age windows (i.e., 7.66 and 3.03) are very similar to the EPA ADAFs (i.e., 10 and 3).

The use of mechanism of action in selecting the appropriate low-dose extrapolation model (e.g., linear non-threshold versus nonlinear threshold) is an area of active discussion. There is a wide array of scientific opinion making it evident that additional research is needed. The MDH external Expert Advisory Panel (ERG 2005) had a far-ranging discussion, expressing a diversity of opinion that reflected the ongoing debate on this topic. Unlike mutagens, the case for nonmutagens is less data-rich and less supported by a consistent mechanistic framework. Ideally, data regarding early-life sensitivity would be available to inform the decision; however, in most cases, such data will not be available. Some panelists noted that several nonmutagens appear to exhibit early-life sensitivity and that it would be premature to conclude that for any particular nonmutagenic carcinogen, there are no sensitivity issues for early life. In the face of such limited data they felt it is prudent to take the more health-protective approach as the default and be flexible to move from the default if data are submitted that indicate the specific nonmutagenic mechanism is not a vulnerability issue for early life.

Panelists also expressed concern that many carcinogens have a mixed mechanisms of action involving nongenotoxic (e.g., nonmutagenic) as well as genetic actions. Thus, it may be difficult to place carcinogens in a mutagen or nonmutagen category. One panel member advised that it might be more productive to think about whether the cancer assessment is based on a linear or nonlinear dose extrapolation approach. A cancer assessment based on linear dose extrapolation may warrant use of the early-life sensitivity factor (regardless of the mechanism of action), as the linear low dose extrapolation is used in cases of receptor-mediated mechanisms, for mutagens, or for where the mechanism is too uncertain to document a threshold. If a nonlinear approach had been used, data documenting a threshold mechanism would already exist.

The EPA RfD/RfC Technical Panel (EPA 2002c) recommended that the dose-response relationship (e.g., linear or nonlinear) as well as the underlying mode of action (e.g., mutagenic) should be taken into consideration when selecting a low-dose extrapolation model. This approach recognizes that some mutagenic carcinogenic agents may work through nonlinear mechanisms and some chemicals that produce effects other than cancer may work through linear mechanisms.

Given the significance of early-life sensitivity and the uncertainties surrounding mechanism of action MDH has chosen to apply the EPA approach as a default approach for linear carcinogens, regardless of the mechanism of action. The application of the EPA algorithm as a default approach for linear carcinogens is a policy decision. Chemical-specific information regarding early-life sensitivity will be used in place of the default approach whenever possible. When available, the chemical-specific information would be used in the following cancer HRL algorithm:

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

Where:

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

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

SF = adult-exposure based cancer slope factor ($[mg/kg-day]^{-1}$).

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

IR = water intake rate representative of a lifetime period (L/kg-day)

An example of a chemical-specific adjustment is EPA's derivation of oral slope factors for vinyl chloride. The angiosarcoma incidence after short-term, early-life exposure to vinyl chloride was approximately equal to that of long-term exposure starting after maturity. Hepatoma incidences also differed. Based on these observations, EPA determined that continuous lifetime exposure from birth would about double cancer risk. EPA derived two oral slope factors: 0.72 per mg/kg-day for continuous lifetime exposure during adulthood and 1.4 per mg/kg-day for continuous lifetime exposure from birth.

For non-linear carcinogens, current theories propose that these compounds exhibit a mode of action that requires precursor events to occur (e.g., cytotoxicity with regenerative hyperplasia), and that a dose threshold exists below which there is essentially no risk of developing cancer. The MDH approach for evaluation of non-linear carcinogens will be to use a margin of exposure (MOE) and that a reference dose, for which the endpoint will be some precursor to cancer, will be derived in a manner consistent with deriving any other reference dose.

The MDH methodology reflects an approach that is protective of public health in light of indicative but inadequate scientific information. MDH will revisit this policy when additional data and/or generally accepted methods become available.

The cancer HRLs are based on lifetime consumption and represent a concentration in water that if consumed over a lifetime will not result in an additional lifetime cancer risk of greater than 1×10^5 (i.e., 1 in 100,000). The stop-exposure studies in adults and early-life short-term exposure studies have indicated that lifetime averaging of less-than-lifetime exposures may underestimate cancer risk. MDH cautions risk managers that prorating the cancer HRL for less-than-lifetime exposures may underestimate the risk and may not be protective of health.

APPENDIX N. Alternatives for Assessing Risk from Multiple Chemicals

The 1986 *Guidelines for the Health Risk Assessment of Chemical Mixtures* (EPA 1986b) recommend three approaches to quantitative health risk assessment of a chemical mixture, depending upon the type of available data:

1. If toxicity data on the mixture of concern are available, the quantitative risk assessment is done directly from these preferred data.
2. If toxicity data are not available for the mixture of concern, but toxicity data on a "sufficiently similar" mixture are available, and if the mixture of concern and the proposed surrogate mixture are judged to be similar, then the quantitative risk assessment for the mixture of concern may be derived from health effects data on the similar mixture.
3. If toxicity data on the mixture of concern or a similar mixture are not available, the mixture is evaluated through an analysis of its individual components. The evaluation of components of a mixture can be one of several approaches, depending on whether the mixture components act by the same mode of action or are functionally independent, or whether the data may be grouped by chemical structure, or biologic activity.

In 2000, EPA issued supplemental guidance on assessing risks from mixtures of chemicals (EPA 2000b). The supplemental guidance provides a decision flowchart to assist in the selection of a chemical mixture risk assessment method.

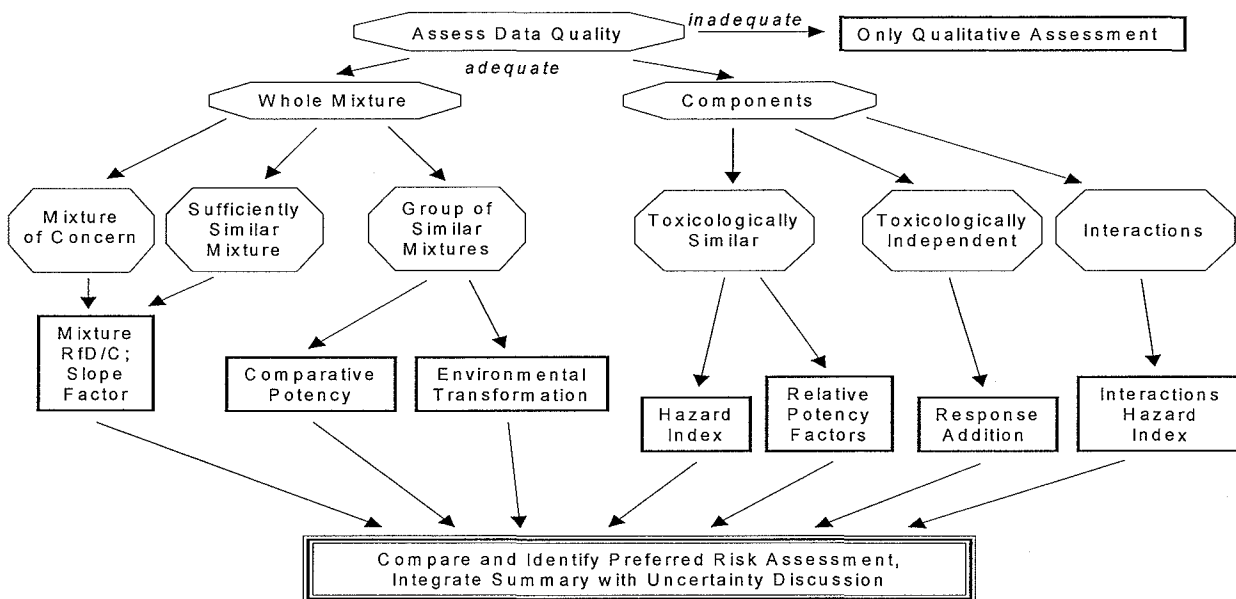


FIGURE 2-1

The different types of mixtures assessments based on the availability and quality of the data. All possible assessment paths should be performed.

Source: EPA 2000b. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures.

The various methods are briefly summarized here. For additional information, the reader is referred to EPA's 2000 Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures.

Methods for Whole-Mixtures Data

If whole-mixture data are available, one approach to the risk evaluation of a chemical mixture is to use health effects and dose-response data on the complex mixture. EPA divided the evaluation of whole-mixtures into three categories depending on data availability: (1) data directly on the mixture of concern; (2) data on a sufficiently similar mixture; or (3) data on a group of similar mixtures.

Health effects and exposure data from the mixture of concern are preferred for evaluating health risk from multiple chemicals. Optimally, data on the precise mixture of concern would be available. That is, the mixture tested would contain all the chemicals in the mixture of concern, only the chemicals in the mixture of concern, and in the same proportion as found in the mixture of concern. Such data is rarely available.

If data on the mixture of concern are not available but health effects and dose-response data are available on a similar mixture(s), a decision should be made whether the mixture(s), on which the data are available, is or is not "sufficiently similar" to the mixture of concern. The determination of "sufficiently similar" should be made on a case-by-case basis. Consideration should be given to any information on the components that differ or are contained in markedly different proportions from the mixture of concern. Information on bioavailability or toxicological effects for either mixture(s) or their components should be considered in selecting a mixture risk assessment approach.

In some cases, chemical mixtures are considered as pre-defined mixtures in which the relative proportions of each individual chemical are widely accepted. An example of such a chemical mixture is xylenes. In 1993, a HRL was promulgated for a mixture of m-, p- and o-xylenes. The RfD for xylenes was based on a toxicity evaluation of a defined mixture comprised of 60% m-xylene, 13.6% p-xylene, and 9.1% o-xylene and 17% ethylbenzene. There are no defined mixtures included in the current rules revision, but HRLs for mixtures may be added in the future.

Methods for Components Data

If data are not available on an identical or "sufficiently similar" mixture(s), the risk assessment may be based on the toxic or carcinogenic properties of the components in the mixture. When quantitative information on toxicological interaction exists, it should be incorporated into the component-based approach. When information on interactions is inadequate, dose or risk-additive models are recommended. Dose-addition and response addition represent the default approaches for toxicologically similar and toxicologically independent chemicals, respectively.

The specific term *toxicological similarity* represents a general knowledge about the action of a chemical or a mixture and can be expressed in broad terms such as at the target organ level in the body. In the EPA Supplementary guidance, assumptions about toxicological similarity are made in order to choose among risk assessment methods. In general, EPA assumes a similar *mode of action* across mixtures or mixture components and, in some cases, this requirement may be relaxed to require that these chemicals act only on the *same target organ*.

Approaches based on the mixture's components are recommended for relatively simple, identified mixtures. For exposures at low doses with low component risks, the likelihood of significant interactions is usually considered to be low. The default component approach at low exposure levels is to use dose addition when the component toxicological processes are assumed to be similar, and response addition

when the component toxicological processes are assumed to act independently. For dose addition, a Hazard Index approach is recommended.

Toxicological Interactions. Types of interactions that can affect toxicological response to a mixture of chemicals include chemical-to-chemical, toxicokinetic, and toxicodynamic interactions. The effect of joint exposure on a toxicological response can be additive, less-than-additive (e.g., dietary zinc can reduce the absorption of cadmium thereby reducing cadmium toxicity), or greater-than-additive (e.g., synergistic interaction). Interaction effects may result from events taking place at many different locations in the body, including the site of toxic action or during the processes of absorption, distribution, metabolism, excretion or repair. Interactions can vary with route of administration, age, sex, health status, nutritional status, etc.

With an almost infinitely large number of possible chemical mixtures in the environment, systematic studies relevant to the toxicity of the various mixtures are impractical. If evidence of toxicological interactions is available, this information should be reflected in the mixture risk assessment. Due to the absence of this information, risk assessments of multiple chemicals typically consider interactions in a qualitative manner only. Predictive and alternative methods are being developed.

Dose-Addition – Toxicologically Similar. Several studies have demonstrated that dose addition is often a reasonably good predictor of the toxicities of mixtures composed of a substantial variety of both similar and dissimilar compounds (EPA 2000b). Dose-additive models may be an adequate default procedure for chemicals affecting the same target organ, but may not be the most biologically plausible approach if the compounds do not have the same mode of toxicological action. Consequently, depending on the nature of the risk assessment and the available information on modes of action, the most reasonable dose-response model should be used.

EPA discusses two component methods that are based on dose addition in the supplementary guidance: the Hazard Index and the Relative Potency Factor (RPF) method. The Toxicity Equivalence Factor method, which is a special case of the RPF method, is also discussed. Each method differs in the required knowledge about toxic mechanism and in the extent over which toxicological similarity is assumed.

The primary method for component-based mixture risk assessment of toxicologically similar chemicals is the Hazard Index. Dose additivity may not hold for all toxic effects. The relative toxicity between chemicals may differ for different types of toxicity or toxicity by different routes. To reflect these potential differences, the Hazard Index is usually developed for each exposure route and for a single and specific toxic effect, or for toxicity to a single target organ. A mixture may then be assessed by several Hazard Indices, each representing a single route of exposure and a toxic effect or target organ. The Hazard Index is defined as a weighted sum of the exposure measures for the mixture component chemicals. The multiple-chemical HRLs are based on the Hazard Index dose addition methodology.

If the toxicity of one component of a mixture of related, toxicologically similar compounds has been well characterized, the mixture may be evaluated using relative potency factors (RPFs). In this approach, the toxicity of each related compound is estimated by scaling it relative to the index compound. The scaling factor is usually determined by a few toxicological assays or even an analysis of structure. For each component of the mixture, a dose equivalent to the index compound is constructed by multiplying the component concentration by the scaling factor. For example, if a component is only one-tenth as toxic as the index compound, the scaling factor is 0.1. Dose equivalents for the individual

components, including the index compound, are summed and compared to the toxicity value for the index compound to determine whether the mixture poses a human health risk.

MDH recommends a relative toxicity approach if the toxicity of at least one component (of a mixture of related, toxicologically similar compounds) has been well characterized, but the toxicity of most of the components has not. MDH has recommended this approach in non-rule guidance for assessing the toxicity of carcinogenic polycyclic aromatic hydrocarbons (PAHs). The index compound for the carcinogenic PAHs is benzo[a]pyrene.

The Toxicity Equivalence Factor method is a specific type of RPF. MDH has recommended this approach in non-rule guidance for assessing the carcinogenicity of dioxin-like compounds. The index compound for the dioxin-like compounds is 2,3,7,8-tetrachloro dibenzo-p-dioxin (2,3,7,8-TCDD).

Response Addition – Toxicologically Independent. Response addition may apply when components act on different systems or produce effects that do not influence each other. Under response addition, the chemicals in the mixture are assumed to behave independently of one another, so that the body's response to the first chemical is the same whether or not the second chemical is present.

APPENDIX O. Risk Management for Drinking Water

Derivation and Application of HRLs

HRLs are derived as health-protective upper limits for contaminants found in groundwater. They are intended to be generally applicable to contaminated groundwater that may be used as a drinking water. Potential human health effects resulting from ingestion of water is the only consideration in derivation of HRLs. HRLs do not consider human exposure resulting from non-ingestion pathways (e.g., dermal, inhalation of volatilized chemicals), aquatic life, animal life, or remote links between these and human health. Additionally, HRLs for individual chemicals do not protect from exposure to multiple chemicals. First, they do not address the potential for synergism, potentiation, antagonism, masking, or inhibition; nor do they allow for the absence of any interaction. Second, in the absence of a multiple-chemical risk assessment, they do not protect a toxic endpoint from multiple chemical insults. Thus, HRLs are not intended as levels generally appropriate for protection of the environment. Use of HRLs as "pollute-up-to levels" is not consistent with the state's nondegradation policy.

MDH does not specify application of HRLs or enforce any application of HRLs. Agencies may adopt HRLs for regulatory purposes. Depending on the circumstances, a risk manager may consider modifying the HRLs. Since economics and technological feasibility are not considered in the derivation of HRLs, the risk manager may need to take these into account in order to establish realistic goals for remediation or protection of groundwater. Other factors to consider include the characteristics of the population likely to be exposed, the source of the pollution, the chemical, and the nature and duration – if known – of the exposure. For example, a risk manager may want to deviate from the HRLs if the chemicals in question are volatile.

Identifying Contaminated Groundwater

Generally, it is assumed that groundwater is pristine – or at least free of man-made chemicals. When groundwater is contaminated, levels of contaminants are usually not high enough to be detected by odor or taste. State groundwater monitoring programs, special studies, and site investigations provide knowledge about contaminants in groundwater.

Mitigation efforts may be effective even for chemicals that are present but that have not been identified. First, laboratories can often perform analyses for suites of related chemicals, or can report unanticipated occurrences of "peaks" or outcomes not typically seen when running specific analytical methods. Such testing may indicate the presence of a chemical not previously suspected to be present. Second, most cleanup strategies effectively remove or reduce the presence of not just the target chemical, but many related chemicals. Thus, once cleanup is implemented, chemicals not known to be present may none-the-less be removed from groundwater.

Federal Drinking Water Standards

EPA's Office of Water (OW) develops several sets of values for contaminants in drinking water. Maximum contaminant levels (MCLs) are regulatory standards that must be met by public drinking water supplies in Minnesota; other values are only advisory, or are goals, such as the maximum contaminant level goals (MCLGs). MCLs incorporate information about technological feasibility and cost, as well as information about human health effects. MCLGs and the Health Advisories (HAs) are based only on considerations of human health. EPA sets the MCL to be as close to the health-based MCLG as is technically feasible.

For noncarcinogens, the MCLG is based on the reference dose. The reference dose is multiplied by typical adult body weight (70 kilograms) and divided by a daily water intake appropriate for an adult (2 liters) to provide a Drinking Water Equivalent Level (DWEL). The DWEL, in units of mg/L, is multiplied by a (unitless) percentage of the total daily exposure allocated to drinking water to arrive at the MCLG. The percentage of the total daily exposure contributed by drinking water is called the relative source contribution (RSC) (EPA 2003d). The default RSC used in deriving DWELs is 0.2.

$$\text{DWEL} = \frac{\text{RfD} \times \text{BW}}{\text{DI}}$$

$$\text{MCLG}_{\text{noncarcinogen}} = \text{DWEL} \times \text{RSC}$$

Where:

RfD = reference dose (mg/kg-day).

BW = body weight (kg).

DI = daily water intake rate (L/day), not to be confused with the water intake rate (IR) used elsewhere in this SONAR, which is in units of L/kg-day).

RSC = Relative Source Contribution factor (unitless).

MCLGs, DWELs, and the RSC are established and explained in the Federal Register, 1991, pp. 3531 – 3536 (EPA 1991b).

MCLGs for carcinogens are set at zero since, according to the standard conservative assumptions about cancer, no exposure to a linear carcinogen is without risk. For carcinogens, EPA OW provides health advisories associated with a 10^{-4} cancer risk. Recall that 10^{-4} is the high end of EPA's risk range for cancer.

Identifying the Population of Concern

It is important for a risk manager to know the exposed population. If factors that tend to increase susceptibility are compounded, a smaller percentage of the exposed population may actually be protected. For example, an elderly population with many concurrent exposures, poor nutritional status, and poor general health might be less protected.

The default intake rates are based on highly exposed populations. EPA generally supports a goal of protecting 90 percent or more of the exposed population (EPA 2004a; EPA 2000a). MDH practice has been consistent with this goal. There may be site-specific situations in which the default intake rate, in particular the age group upon which it is based, is not representative of the population of concern. In these situations the risk manager may choose to use an alternative intake rate. For example, if the population of concern for short-term exposure was limited to adult males, the risk manager may choose to use an intake rate based only on adult consumption rates, rather than the default short-term intake rate of 0.289 L/kg-day (based on infants).

The risk manager must consider that the consumption of the contaminated water may be ongoing (e.g., may have been occurring for some time prior to the discovery of the contamination) and whether the composition of the population is likely to change in the future.

Relative Source Contribution Factor

As stated above, the EPA default RSC for the derivation of DWELs is twenty percent. HRLs are derived for contaminants that have been found in Minnesota's groundwater as the result of human activity. HRLs are often applied at contaminated sites where media other than groundwater may also be contaminated. The type of media contaminated, the level of contamination, and the populations potentially exposed will vary from site to site and from chemical to chemical.

MDH has used the EPA Exposure Decision Tree approach to determine appropriate default RSC values. There may be site-specific situations in which the default RSC is not appropriate. For example, if site-specific data are adequate to describe central tendencies and upper-end estimates for all relevant exposure sources and pathways, the risk manager may choose to use the Exposure Decision Tree procedure to develop a site-specific RSC.

Chemicals Present but Below Quantification Levels

Below certain concentrations for specific chemicals, laboratory procedures can indicate that a chemical is present, but cannot accurately quantify that chemical. When this occurs, testing laboratories report that the chemical is present, but is below the level at which it can be accurately quantified. Several approaches to data analysis have evolved that allow these situations to be included in data reporting and statistical analysis. These methods may use surrogates for the actual (and unquantifiable) concentration, including zero, half the detection limit, the log of the detection limit, and the detection limit. MDH recommends that chemicals that are detected but not quantifiable be accounted for using any method generally accepted in environmental monitoring practice, but does not recommend one method over another.

APPENDIX P. Chemical Summary Sheets

Chemical summary sheets are available on the web at <http://www.health.state.mn.us/divs/eh/groundwater/data/index.cfm>. HRL values in this Appendix are identical to those published on the web as of the date of publication of the SONAR. The web pages may be updated with newly completed chemicals at a later date.

The following pages present chemical summary sheets for selected chemicals.

Chemical Name: Dieldrin**CAS:** 60-57-1**Synonyms:****Draft Acute Non-Cancer Health Risk Limit (nHRL_{acute}) = 0.2 ug/L**

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

$$= \frac{(0.0001 \text{ mg/kg/d}) \times (0.5) \times (1000 \text{ ug/mg})}{(0.289 \text{ L/kg-d})}$$

$$= 0.173 \text{ rounded to } \mathbf{0.2 \text{ ug/L}}$$

Reference Dose:	0.0001 mg/kg-d	(laboratory animal)
Source of Reference Dose:	MDH 2007	
Point of Departure (POD):	0.1 mg/kg-d	(LOAEL, Richardson et al., 2006)
Human Equivalent Dose Adjustment:	None	(inadequate information)
Total uncertainty factor:	1000	
UF allocation:	10 interspecies; 10 intraspecies; 10 LOAEL-to-NOAEL	
Critical effect(s):	increased dopamine transporters and enhanced vulnerability of dopamine neurons to Parkinsonism inducing agent	
Co-critical effect(s):	hepatic lesions in pups; decreased pup viability	
Additivity endpoint(s):	Developmental (hepatic system, nervous system, mortality)	
Secondary effect(s):	None	

Draft Short-term Non-Cancer Health Risk Limit (nHRL_{short-term}) = 0.2 ug/L

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

$$= \frac{(0.0001 \text{ mg/kg/d}) \times (0.5) \times (1000 \text{ ug/mg})}{(0.289 \text{ L/kg-d})}$$

$$= 0.173 \text{ rounded to } \mathbf{0.2 \text{ ug/L}}$$

Reference Dose:	0.0001 mg/kg-d	(laboratory animal)
Source of Reference Dose:	ATSDR 2002	
Point of Departure (POD):	0.01 mg/kg-d	(NOAEL, Smith et a 1976)
Human Equivalent Dose Adjustment:	Not available	(inadequate information)
Total uncertainty factor:	100	
UF allocation:	10 interspecies; 10 intraspecies	

Critical effect(s): impaired learning
 Co-critical effect(s): hepatic lesions in pups; increased dopamine transporters and enhanced vulnerability of dopamine neurons; decreased pup viability; decreased antigen processing and tumor cell killing ability
 Additivity endpoint(s): Nervous system; Developmental (hepatic system, nervous system, mortality); Immune system
 Secondary effect(s): None

Draft Subchronic Non-Cancer Health Risk Limit (nHRL_{subchronic}) = 0.2 ug/L

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

$$= \frac{(0.0001 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.077 \text{ L/kg-d})}$$

$$= 0.260 \text{ rounded to } 0.3 \text{ ug/L}$$

The subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Draft Subchronic nHRL is set equal to the Short-term nHRL of 0.2 ug/L. Additivity endpoints: Developmental, Immune system, Nervous system.

Draft Chronic Non-Cancer Health Risk Limit (nHRL_{chronic}) = 0.2 ug/L

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

$$= \frac{(0.00005 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.043 \text{ L/kg-d})}$$

$$= 0.233 \text{ rounded to } \mathbf{0.2 \text{ ug/L}}$$

Reference Dose: 0.00005 mg/kg-d (laboratory animal)
 Source of Reference Dose: IRIS 1990
 Point of Departure (POD): 0.005 mg/kg-d (NOAEL, Walker et al 1969)
 Human Equivalent Dose Adjustment: None (inadequate information)
 Total uncertainty factor: 100
 UF allocation: 10 interspecies; 10 intraspecies
 Critical effect(s): increased liver weight
 Co-critical effect(s): significantly increase in plasma alkaline phosphatase activity, significant decrease in serum protein (males), increased relative liver weight (female); cerebral edema
 Additivity endpoint(s): Hepatic (liver) system; Nervous system

Secondary effect(s): Developmental (hepatic system, nervous system, mortality) and Immune System; Decreased survival

Draft Cancer Health Risk Limit (cHRL) = 0.006 ug/L

The lifetime versus adult only tumor incidence information from Vesselinovitch et al, 1979 was used to derive a chemical-specific adjustment factor of 2.5:

$$\frac{(Additional\ Lifetime\ Cancer\ Risk,\ 1 \times 10^{-5}) \times (Conversion\ Factor,\ 1000\ ug/mg)}{(Slope\ Factor,\ per\ mg/kg-d) \times (Lifetime\ Adjustment\ Factor) \times (Lifetime\ Intake\ Rate,\ L/kg-d)}$$
$$= \frac{(1E-5) \times (1000\ ug/mg)}{(16\ per\ mg/kg-d) \times (2.5) \times 0.043\ L/kg-d}$$
$$= 0.0058\ rounded\ to\ \mathbf{0.006\ ug/L}$$

Cancer classification: B2, probable human carcinogen
Slope factor: 16 (mg/kg/day)⁻¹ (laboratory animal)
Source of slope factor: IRIS, 1993
Tumor site(s): liver

Volatile: No

Summary of changes since 1993/1994 HRL promulgation:

The draft cancer HRL (0.006 ug/L) is approximately 3 times lower than the 1997 cancer HBV (0.02 ug/L) as the result of: 1) using more recent lifetime intake rates; 2) use of a chemical specific cancer slope factor adjustment factor of 2.5; and 3) rounding to one significant digit. The draft noncancer HRLs (0.2 ug/L) are new.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	A. Yes	Yes	Yes	Yes
Effects?	No ¹	B. 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 effect was found on levels of a limited number of circulating hormones (thyroxin, FSH, LH, TSH, prolactin, or growth hormone). There are some in vivo and in vitro data to suggest that dieldrin has weak estrogenic properties.

² Several studies in mice suggest that exposure may induce immunosuppression at dose levels similar to the short-term and subchronic critical study LOAELs. Immune system has been listed as a short-term and subchronic health endpoint.

³ Several studies have demonstrated that dose levels similar to the acute, short-term and subchronic critical study LOAELs can result in reduced pup survival, increase dopamine transporter levels and increase the incidence of hepatic lesions. Development (hepatic system, nervous system, mortality) has been listed as an acute, short-term and subchronic health endpoint.

⁴ Several reproductive and multigenerational studies have been conducted. At levels slightly higher than the short-term and subchronic critical study LOAEL mothers were not able to adequately nurse their young because both the mother and offspring were too hyperesthetic. Rats appear to be more sensitive than mice. Nervous system is listed as a short-term, subchronic and chronic health endpoint.

⁵ Impaired learning, increases in dopamine transporters, and hyperesthesia were observed at the short-term, subchronic and chronic critical study LOAEL. Nervous system is listed as a short-term, subchronic and chronic critical health endpoint. As dose levels increase irritability, salivation, hyperexcitability, tremors followed by convulsions, loss of body weight, depression, prostrations, and death are observed.

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Chemical Name: Perfluorooctanoic Acid

Synonyms: PFOA

CAS: 335-67-1(free acid)

335-66-0 (acid fluoride)

3825-26-1 (ammonium salt, APFO)

2395-00-8 (potassium salt)

335-93-3(silver salt)

335-95-5 (sodium salt)

1.

The perfluorooctanoate anion does not have a specific CAS number.

Serum concentrations appear to be the best dose-metric for extrapolating to humans. At the present time the information necessary to estimate less than chronic doses (i.e., acute, short-term or subchronic) that would result in a given serum concentration is not available. Additional uncertainty exists regarding toxicokinetics in early life. Therefore, acute, short-term and subchronic HRLs will not be derived at this time.

Draft Acute Non-Cancer Health Risk Limit (nHRL_{acute}) = Not Derived (Insufficient Data)

Draft Short-term Non-Cancer Health Risk Limit (nHRL_{short-term}) = Not Derived (Insufficient Data)

Draft Subchronic Non-Cancer Health Risk Limit (nHRL_{subchronic}) = Not Derived (Insufficient Data)

Draft Chronic Non-Cancer Health Risk Limit (nHRL_{chronic}) = 0.3 ug/L

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

$$= \frac{(0.000077 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.053^* \text{ L/kg-d})}$$

$$= 0.29 \text{ rounded to } \mathbf{0.3 \text{ ug/L}}$$

* Intake rate used corresponds to the time-weighted average 95th intake rate over first 19 years of life. Nineteen years represents the estimated duration to achieve steady-state serum concentration, based on a half-life of 3.8 years.

Reference Dose: 0.000077 mg/kg-d(Cynomolgus monkeys)

Source of toxicity value: MDH
 Point of Departure: 23 mg/L serum concentration (serum BMDL₁₀) (Thomford et al 2001 and Butenhoff et al 2002)
 Human Equivalent Dose Adjustment: 0.0023 mg/kg-d
 [Dose mg/kg-d = (Ln2/1387 day half-life_{human}) x 23 mg/L x 0.2 L/kg (Vd)]
 Total uncertainty factor: 30
 UF allocation: 3 interspecies extrapolation for potential differences in toxicodynamics and 10 intraspecies variability
 Critical effect(s): increased relative liver weight
 Co-critical effect(s): increased liver weight with histopathological changes, decreased total serum cholesterol and triglycerides, developmental delays (e.g., altered body weight gain, delayed physical development, hepatocellular hypertrophy) in offspring, altered immune function
 Additivity endpoint(s): Development (body weight, delayed development), Hepatic (liver) system, Immune system
 Secondary effect(s): Increased incidence of full litter resorption, additional developmental delays (e.g., sexual maturation), increased pup mortality, altered mammary gland development, additional immune system effects, increased kidney weight, hematological effects, decreased thyroid hormone (TT4, T3) serum levels, increased serum estradiol levels, increased incidence of benign hepatocellular adenomas, testicular Leydig-cell tumors and pancreatic acinar-cell adenoma/carcinomas

Proposed Cancer Health Risk Limit (cHRL) = Not Applicable

Volatile: No

Summary of changes since 1993/1994 HRL promulgation:

No 1993/94 HRL value exists for PFOA. The draft chronic HRL (0.3 ug/L) is ~1.7-fold lower than the Good-cause exception HRL (0.5 ug/L) adopted August 1, 2007 as the result of using serum levels as the dose metric rather than administered dose.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Sec. Observations ¹	Yes	Yes	Yes	Yes
Effects?	Yes	Yes ²	Yes ³	Unclear ⁴	Yes ⁵

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect may 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 – comparisons based on HED LOAEL or HED BMDLs are associated with higher uncertainty than comparisons based on serum levels.

¹ Changes in serum thyroid hormone (e.g., decreased thyroxine, T4 and triiodothyronine, T3) and estradiol levels have been observed in some animal studies but not in others. These changes were observed at estimated human equivalent dose (HED) levels higher but within 3-fold of the critical study HED LOAEL and are therefore identified as secondary effects.

² Short-term immunotoxicity studies have shown that PFOA exposure suppresses humoral immunity and may adversely affect cell mediated immunity at HED doses similar to the critical study HED LOAEL. These effects have been identified as co-critical effects.

³ Developmental delays and body weight/weight gain changes in offspring have been observed at serum and HED dose levels similar to the serum and HED LOAEL of the critical study. These effects have been identified as co-critical effects. At HED doses 3- fold higher than the critical study HED LOAEL additional developmental effects (decreased pup viability, delays in eye opening, increased incidence of full-litter resorption, and alterations in mammary gland development) are observed. Effects occurring at doses approximately 3 fold higher have been identified as secondary effects.

⁴ The results of the 2-generational study indicate that fertility is not affected by treatment. Full-litter resorption was observed at HED dose levels 3-fold higher than the critical study HED LOAEL, however, it is unclear whether this resulted from maternal toxicity or a direct effect on the developing organism. Altered mammary gland development during the lactational period was observed in pregnant/lactating mice exposed to dose levels slightly higher than the critical study LOAEL during pregnancy. Increased incidence of full-litter resorption and alterations in mammary gland development have been identified as a secondary effects.

⁵ Hypoactive response to nicotine has been observed in neonatal mice given a single dose at 10 days of age. No serum level information was reported in this study and it is not possible to extrapolate from a single dose to a HED dose. The additional neurological testing has been recommended by the EPA PFOA draft Risk Assessment Science Advisory Review Board.

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Chemical Name: Vinyl Chloride**CAS: 75-01-4****Synonyms:** Chloroethene; chloroethylene; ethylene monochloride; Monochloroethene;
Monochloroethylene**Draft Acute Non-Cancer Health Risk Limit (nHRL_{acute}) = Not Derived (Insufficient data)****Draft Short-term Non-Cancer Health Risk Limit (nHRL_{short-term}) = Not Derived (Insufficient data)****Draft Subchronic Non-Cancer Health Risk Limit (nHRL_{subchronic}) = 80 ug/L**

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

$$= \frac{(0.03 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ ug/mg})}{(0.077 \text{ L/kg-d})}$$

$$= 77.92 \text{ rounded to } 80 \text{ ug/L}$$

Toxicity value: 0.03 (laboratory animal)
 Source of toxicity value: MDH 2007
 Point of Departure: 10 ppm (NOAEL, CMA 1998 as cited by EPA 2000)
 Human Equivalent Dose Adjustment: 1 mg/kg-d
 Total uncertainty factor: 30
 UF allocation: 10 for intraspecies and 3 for interspecies extrapolation because PBPK modeling decreases uncertainty for animal to human extrapolation but does not account for toxicodynamic differences.
 Critical effect(s): increased liver weight, hypertrophy and hepatocellular foci.
 Co-critical effect(s): none
 Additivity endpoint(s): Hepatic (liver) system
 Secondary effect(s): none

Draft Chronic Non-Cancer Health Risk Limit (nHRL_{chronic}) = 10 ug/L

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

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

=13.98 rounded to **10 ug/L**

Toxicity value: 0.003 (laboratory animal)
Source of toxicity value: MDH, 2007
Point of Departure: 0.13 mg/kg-d (NOAEL, Til et al, 1991 as cited by EPA 2000)
Human Equivalent Dose Adjustment: 0.09 mg/kg-d
Total uncertainty factor: 30
UF allocation: 10 for intraspecies and 3 for interspecies extrapolation because PBPK modeling decreases uncertainty for animal to human extrapolation but does not account for toxicodynamic differences
Critical effect(s): liver cell polymorphism and cyst formation
Co-critical effect(s): none
Additivity endpoint(s): Hepatic (liver) system
Secondary effect(s): none

Draft Cancer Health Risk Limit (cHRL) = 0.2 ug/L

The lifetime oral slope factor from IRIS was used as a chemical-specific slope factor:

$$= \frac{\text{(Additional Lifetime Cancer Risk, } 1 \times 10^{-5}\text{)} \times \text{(Conversion Factor, } 1000 \text{ ug/mg)}}{\text{(Slope Factor, per mg/kg-d)} \times \text{(Lifetime Adjustment Factor)} \times \text{(Lifetime Intake Rate, L/kg)}}$$

$$= \frac{(1E-5) \times (1000 \text{ ug/mg})}{(1.4 \text{ (mg/kg-d)}^{-1} \times (1) \times 0.043 \text{ L/kg-d})}$$

= 0.166 rounded to **0.2 ug/L**

Cancer classification: A (a known human carcinogen)
Oral Slope factor: $1.4 \text{ (mg/kg-d)}^{-1}$ (laboratory animal)
Source of slope factor: IRIS 2000
Tumor site(s): Liver, and blood vessels (primary sites);
Kidney, stomach and skin cancers (secondary sites)

Volatile: Yes (highly volatile)

Summary of changes since 1993/1994 HRL promulgation:

Since no non-cancer HRL was previously calculated, the short-term, subchronic, and chronic nHRLs represent new values.

The draft cancer HRL (0.2 ug/L) is the same as the 1993/94 cancer HRL (0.2 ug/L) as the result of: 1) the use of the continuous lifetime exposure from birth cancer slope factor (1.4 per mg/kg/day), 2) the use of a lifetime time-weighted average of water consumption rate of 0.043 L/kg-d 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	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:

Note: Many reported effects occur via the inhalation route of exposure. Vinyl chloride is readily and rapidly absorbed via all routes of exposure and effects via all routes occur systemically.

¹A study of workers exposed to vinyl chloride in PVC manufacturing plants reported that most workers who presented with scleroderma were shown to have thyroid insufficiency. No histopathology effects on the adrenals were reported in guinea pigs exposed to 400,000 ppm for 30 minutes. Rats were found to have colloid goiter and markedly increased numbers of perifollicular cells.

²Stimulation of spontaneous lymphocyte transformation was observed in mice following inhalation exposure. There is some evidence to suggest that an adaptive process may lead to a reduction or elimination of this effect over time. Also, it is not clear from the evidence that a clear adverse effect to the immune system is taking place.

³Developmental toxicity occurred in inhalation experiments at doses that caused maternal toxicity. These effects occurred at exposure levels significantly higher than those producing liver toxicity (i.e., the basis of the RfD)

⁴Testicular histopathological changes and decreased male fertility have been reported in inhalation studies. These effects occur at exposure levels significantly higher than those producing liver toxicity (i.e., the basis of the RfD).

⁵Nervous system toxicity has been observed in inhalation studies at high exposure levels. Vinyl chloride was once considered for use as an inhalation anesthetic. Investigators studying the effects of vinyl chloride exposure frequently report central nervous system symptoms that are consistent with the anesthetic properties of vinyl chloride. The most commonly reported central nervous system effects are ataxia or dizziness, drowsiness or fatigue, loss of consciousness, and/or headache. Other central nervous system effects that have been reported by vinyl chloride workers include euphoria and irritability, visual and/or hearing disturbances, nausea, memory loss, and nervousness and sleep disturbances.

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