

**Health-Based Water Guidance
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 compared to background. The BMD approach uses mathematical models to statistically determine a dose associated with a predefined benchmark response.

Benchmark Dose Lower Confidence Level (BMDL): The 95th percentile lower confidence interval on the benchmark dose (BMD).

Benchmark Response (BMR): An adverse or biologically meaningful effect, used to define a benchmark dose (BMD) from which an RfD can be derived. The BMR may be a percent change over control, or some number of standard deviations from control.

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 bodyweight.

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), $10^{0.5}$ ($\sqrt{3}$), 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.