DEPARTMENT OF HEALTH

Air Guidance Values Technical Support Document

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Minnesota Department of Health
Site Assessment and Consultation Unit
625 N. Robert St.
St. Paul, MN 55164-0975
651-201-4897
health.hazard@state.mn.us
www.health.state.mn.us

To obtain this information in a different format, call: 651-201-4897.

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Acronyms

ADAF – Age-Dependent Adjustment Factor

BMC – Benchmark Concentration

BMCL – Benchmark Concentration Lower Bound

DAF – Dosimetric Adjustment Factor

EPA – United States Environmental Protection Agency

ET – Extrathoracic

HBV – Health-Based Value

HEC – Human Equivalent Concentration

HI – Hazard Index

HQ – Hazard Quotient

IUR – Inhalation Unit Risk

LOAEL – Lowest Observed Adverse Effect Level

MDH – Minnesota Department of Health

MOA – Mode of Action

NOAEL – No Observed Adverse Effect Level

PBPK/PBTK – Physiologically-Based Pharmacokinetic/Toxicokinetic

POD – Point of Departure

PU – Pulmonary

RAA – Risk Assessment Advice

RDDR – Regional Deposited Dose Ratio

RGDR – Regional Gas Dose Ratio

TB – Tracheobronchial

TD – Toxicodynamic

TK – Toxicokinetic

UF – Uncertainty Factor

I. Introduction

Minnesota Department of Health (MDH) develops health-based guidance values to evaluate potential human health risks from exposures to chemicals in air. An air guidance value is a concentration of a chemical that is likely to pose little or no risk to human health. Air values are developed to be protective of susceptible portions of the population, including but not limited to children, pregnant women and their fetuses, people compromised by pre-existing diseases, and the elderly. Air values are developed to protect human health for a defined length of exposure and are expressed as micrograms of chemical per cubic meter of air ($\mu g/m^3$).

Air guidance values may be used by the public, industry, state and local risk managers, and other stakeholders to assist in evaluating potential health risks to people from exposures to a chemical in air. These values can be used for assessing risks in the environmental review process, developing air pollution permits, health risk assessments and other site-specific assessments. MDH does not enforce air guidance values and develops them in a nonregulatory capacity. Because MDH air guidance values are concentrations intended to produce no adverse health effects, they are not appropriate to use in emergency response applications (e.g., for making evacuation decisions, etc.).

II. Health-Based Values (HBVs) and Risk Assessment Advice (RAA)

There are two categories of air guidance values: Health-Based Values (HBVs) and Risk Assessment Advice (RAA).

HBVs are developed after undergoing a comprehensive chemical review and evaluation of toxicity studies. If sufficient toxicological information is available, HBVs are derived for multiple exposure durations as discussed below. Typically, RAA is based on more limited information than HBVs or uses an alternative risk assessment method. RAA may be developed on a case-by-case basis because of the need for a timely response to a public health question. It may be derived for only one duration or may be qualitative. Steps are taken to ensure HBV and RAA values are developed using the best available science and that both air guidance value types are set at levels that are protective of the general population, including sensitive subpopulations.

MDH conducts periodic reviews of the air guidance values and monitors state, federal, and international agency content for new toxicological assessment releases that might warrant an MDH evaluation or reevaluation of an existing air guidance value.

Additional technical assistance may be provided on the air guidance value table. For example, a review of inhalation toxicity values for volatile organic compounds is done to support the development of the Intrusion Screening Values for vapor intrusion evaluation.

III. Air Guidance Values Toxicological Basis and Calculations

Air guidance values are based on the most sensitive adverse health effect relevant to humans reported in the scientific literature. When the data is available, noncancer values are calculated

based on different durations of exposure (see Air Durations subheading below). If the chemical is a carcinogen, a cancer value is also derived if data is available. Air values represent concentrations that are likely to be without health impacts, and exceeding a value does not indicate that an adverse health effect would occur. However, the risk of health effects increases as the amount and duration of the chemical exposure increases above the air guidance value.

A. Data Review and Analysis

A chemical review begins with a literature search and evaluation process, including a search of other reputable institutions that may have also derived an air guidance value for the chemical. The amount and quality of data available (both human and animal studies) for different toxic endpoints can vary greatly by chemical.

B. Air Value Durations

Understanding the relationship between timing, duration, and magnitude of exposure is essential in deriving health-based values that are protective of sensitive life stages (e.g., early life-stages or critical developmental windows) and short periods of high exposure. If sufficient toxicological information is available, the U.S. Environmental Protection Agency (EPA) recommends evaluation of multiple exposure durations for use in risk assessment (U.S. EPA, 2002). MDH evaluated different exposure durations and their utility for public health protection and application, and selected the durations as indicated in the table below.

Air Guidance Value	Exposure Duration	Toxicological Study Duration Example
Acute 1-hour	1 hour	Acute human or animal toxicity studies where the exposure duration is typically less than 24 hours and time adjustment is defensible for the critical effect.
Acute 24-hour	24 hours	Acute human or animal toxicity studies where the exposure duration is 6 to 24 hours, or for a multi-day study where the critical effects may occur in 24 hours or less.
Intermediate	>24 hours to 1 year	Intermediate human study durations include exposures ranging from greater than 24 hours up to approximately 10% of a lifetime; animal studies would include exposure durations greater than 1 day and up to 90 days. The most protective value is chosen for the intermediate duration.

Air Guidance Value	Exposure Duration	Toxicological Study Duration Example
Chronic	> 1 year to a lifetime	Long-term human study durations include exposures ranging from greater than approximately 10% of a lifetime; animal studies would include an exposure duration of 90 days or longer.
Cancer	Lifetime (70 years)	Human epidemiological studies will generally cover a range of years individuals are working in an industry or living near a site with known levels of chemical contamination; lifetime animal studies are used.

In general, shorter-duration values will be higher than longer-duration air guidance values for a given chemical. The human body can usually tolerate a higher dose when the exposure duration is short, even though that dose may be harmful when it occurs over a longer duration. It is possible, however, that the guidance for a shorter duration is the same as, or in some cases, lower than the guidance value for longer durations. This could happen if a short duration was sufficient to elicit an adverse effect – such as if a more sensitive endpoint was assessed in the shorter-duration study (e.g., respiratory irritation, developmental, and immune toxicological studies generally involve short exposure durations) – or if a different species or life stage was assessed. When this occurs, the longer-duration guidance value is set equal to the lower, shorter-duration value as recommended by EPA (U.S. EPA, 2002). This ensures that the guidance value for a longer duration is also protective of sensitive shorter exposures.

For more information on the development of acute duration values, including time adjustment and considerations of reproductive / developmental effects, see section D below.

C. Steps for Derivation of Noncancer Values

Steps taken to derive noncancer air guidance values include:

1. **Review chemical data and identify key studies.** Review physical and chemical properties, determine how the chemical enters and moves through the body, and how it affects the body. Identify toxicological and epidemiological studies that evaluate the relationship between a dose of a chemical and the animal or human's response.
2. **Determine the Point of Departure (POD) for each key study.** The POD can be the lower bound on dose for an estimated incidence of change in response level from a dose-response model (Benchmark Dose), or a No or Lowest Observed Adverse Effect Level (NOAEL / LOAEL) for an observed incidence or change in the level of response. Exposure duration adjustments are made if needed.
3. **Adjust to a Human Equivalent Concentration (HEC).** If data is from experimental animals, conduct appropriate dosimetric modeling, or apply a dosimetric adjustment factor to convert from animal to a human concentration.

4. **Apply Appropriate Uncertainty Factors (UFs).** UFs are applied to account for what is not known about a chemical's toxicity to a human population. This helps ensure air guidance values are protective.
5. **Select Most Sensitive Critical Effect(s).** After applying UFs to multiple studies, select the lowest value as the air guidance value, in order to be protective of all potential adverse effects.

C.1 Review Chemical Data and Identify Key Studies

The first step is to review all relevant data to identify credible health hazards associated with exposure to a chemical. Human studies of sufficient quality are generally preferred over animal models. Epidemiological studies, or human studies, may include occupational or clinical studies. Laboratory animal studies are used to derive air guidance values when human studies are not available or appropriate. Adverse effects reported in animal studies must be relevant to humans and it is assumed that the adverse effect will act similarly in humans.

The review records all relevant toxicokinetic and toxicodynamic factors as well as any appropriate mode of action (the sequence of major biochemical events that lead to an adverse response; MOA). Toxicokinetics (TK) refers to how the body responds to a chemical exposure, including the chemical's absorption, distribution, metabolism, and excretion. Toxicodynamics (TD) describes how the chemical and its metabolites affect the body. This includes how the chemical effects target tissue(s), how the toxicant damages tissue and cells and how long it takes for the body to repair itself, if possible. A strong understanding of the chemical's effects on animals and humans helps identify key studies for deriving air guidance values across exposure timeframes, as well as pinpoint sensitive subpopulations or data gaps. The review uses a weight of evidence approach (using multiple studies and sources of information) to determine whether there is potential for a human health effect and to understand the dose-response relationship. Key studies are identified to carry through the air guidance value derivation process.

C.1.2 Dose-Response Study Evaluation

The dose-response or toxicity evaluation describes the quantitative relationship between the amount of exposure to a substance (dose) and the extent of adverse effects (response). The EPA defines 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." For the purposes of deriving air guidance values, an adverse effect is identified as the organ, tissue, or system where the effect manifests or as the occurrence of cancer. The Air Guidance Value table lists these health endpoints. MDH conducts a thorough evaluation of available toxicological studies and their methods in order to select reliable studies showing a true response. Data from selected studies are carried forward in the process for each of the air toxicity study durations listed above, if available.

C.2 Determine Point of Departure

The point of departure (POD) is the point on a dose-response curve that marks the initial impact for a critical effect. The lowest POD, which is generally the most sensitive critical effect(s), is selected for noncancer or cancer endpoints (as applicable) and serves to be protective of other

less sensitive endpoints. Generally, human studies are preferred if they are of sufficient quality; however, MDH often relies on animal studies, which are generally more available and may have better dosimetry data than human studies.

Toxicants exert their effect either by causing cancer or by damaging organs or organ systems to varying degrees of severity depending on TKTD properties. Because noncarcinogens and carcinogens exert their effects through different mechanisms, the techniques used to derive respective PODs and health protective values are based on fundamentally different approaches. The non-cancer-causing chemical approach assumes that a threshold, or no effect level, exists and exposures to chemicals at or below their threshold value present an insignificant threat to health. Non-carcinogenic toxicants are set at levels that are expected to cause little to no risk for a given exposure duration.

C.2.1 Benchmark Concentration Lower Bound, Lowest Observed Adverse Effect Level, No Observed Adverse Effect Level

A toxicant's POD is determined based on study-specific data resulting in the development of a Benchmark Concentration Lower Bound (BMCL), No Observed Adverse Effect Level (NOAEL), or Lowest Observed Adverse Effect Level (LOAEL) for each study's critical effect. Preferable human or animal studies are those that provide a dose-response relationship suitable for analysis using quantal or continuous data, resulting in a BMCL, which represents the lower 95% confidence interval limit for a specific response level. The BMCL approach uses all the available dose-response data and is generally superior to the traditional approach of identifying a NOAEL or LOAEL, which is more influenced by dose selection.

MDH generally follows EPA's Benchmark Dose Technical Guidance (U.S. EPA, 2012a) and EPA Benchmark Dose Software (U.S. EPA, 2024). When a benchmark dose analysis is not possible, the NOAEL or LOAEL approach is used. The LOAEL is the lowest dose at which a response is determined to be statistically different from the response observed in the control group. The NOAEL is the highest experimental dose that does not produce a response statistically different from background or the response observed in the control group. By definition, a LOAEL or NOAEL must be an experimental data point. The most sensitive effect in the most sensitive sex and species is then selected. The dose resulting from the dose-response evaluation – the POD – serves as the starting point for deriving health-based guidance values.

C.2.2 Time Adjustments for Continuous Intermediate or Chronic Exposures

Most human data are from occupational exposure studies where the exposure takes place for 8-10 hours a day for 5 days a week. The default approach for adjusting an occupational exposure timeframe to a general population exposure estimate is to correct for the occupational ventilation rate and for the discontinuous work schedule as follows:

Equation 1:

$$POD_{ADJ} = POD\ (mg/m^3) * \frac{VE_{ho}}{VE_h} * \frac{5\ days}{7\ days}$$

Where:

POD = occupational time-weighted average (mg/m^3)

VE_{ho} = occupational (8-hour day) ventilation rate default value = 10 m^3/day

VE_h = non-occupational (24-hour day) default ventilation rate default value = 20 m^3/day

Experimental exposures are also usually discontinuous (e.g., 6 hours a day for 5 days a week). The default approach is calculated an adjusted POD as follows:

Equation 2:

$$POD_{ADJ} = POD\ (mg/m^3) * D\left(\frac{h}{24\ h}\right) * W\left(\frac{days}{7\ days}\right)$$

Where:

D = number of hours exposed over a 24-hour day

W = number of days of exposure over a 7-day week

C.3 Adjust to a Human Equivalent Concentration

After appropriately adjusting a POD for time, researchers must make further adjustments if the data come from experimental animals. The analysis requires these adjustments because of anatomic, physiologic, and metabolic differences between humans and experimental animals. The adjustments result in a number called a human equivalent concentration (HEC). An HEC is the human concentration of a contaminant that is believed to induce the same magnitude of toxic effect as the experimental animal species concentration.

Physiologically-based toxicokinetic (PBTK) modeling – sometimes called physiologically-based pharmacokinetic (PBPK) modeling – is a mathematical modeling technique for predicting the absorption, distribution, metabolism, and excretion of a toxic chemical in humans and other animal species. PBTK models reduce uncertainty and increase scientific understanding of the dose-response relationship. Ideally, when PBTK models are available, they are a preferred method to best predict animal toxicity data in humans. This model estimates the human dose needed to achieve the same internal dose that caused the observed toxicity in an animal (U.S. EPA, 2006). This prediction of an internal dose at target organs is then used to derive a point of departure. However, validated published PBTK models are rarely available and risk assessors must use default dosimetry adjustments from animal to human.

The HEC is typically calculated from the point of departure in the selected animal studies by applying default dosimetric adjustment factors (DAF). MDH follows EPA methodology as described originally in EPA 1994 and updated in EPA 2009, 2011, and 2012. DAFs are determined by the area of the respiratory tract affected by the chemical. The three regions of the respiratory tract include the extrathoracic, tracheobronchial, and pulmonary regions. If no critical effect is specific to one part of the respiratory tract, that effect is simply considered a systemic effect.

DAFs used by MDH follow this guidance for chemicals that are gases, as described in EPA, 2012b:

- When the critical effect occurs in the extrathoracic (ET) respiratory tract region – which includes the nasal and oral passages, pharynx, and larynx – the default DAF is 1. This is because the internal dose equivalency in the ET region is achieved across laboratory animal species and humans through similar external air exposure concentrations, without the need to adjust for differences in ventilation-to-surface-area ratios.
- When the critical effect occurs in the tracheobronchial (TB) and pulmonary (PU) regions, a DAF is calculated as a Regional Gas Dose Ratio (RGDR). The RGDR is the ratio of the regional gas dose calculated for a given exposure in the animal subject to the regional gas dose of the same exposure in humans. This ratio is dependent on the ventilation rate (L / min) and respiratory region surface area (m^2) between animal species and human. Equation 3 is used to achieve an internal dose equivalency in the TB and PU regions across lab animal models and humans by the ventilation-to-surface-area ratio adjustment.

Equation 3:

$$RGDR_r = \frac{(V_E/SA_r)_A}{(V_E/SA_r)_H}$$

Where:

$RGDR_r$ = Regional Gas Dose Ratio region (TB, PU)

V_E = ventilation rate (L/min)

SA_r = surface area of the exposed respiratory tract region (cm^2)

A = animal

H= human

- For systemic effects, the default DAF is 1, although it may be conservative.

For particulate and non-gaseous aerosol chemical exposures, the Regional Deposited Dose Ratio (RDDR) is used to derive DAFs for the different regions of the respiratory tract (EPA, 1994). The RDDR is the ratio of the deposited dose in a respiratory tract region (ET, TB, PU) for the laboratory animal species of interest (RDD_A) to that of humans (RDD_H). The particulate's (or droplet's) physicochemical and aerodynamic properties will largely determine where it will deposit in the respiratory tract. This DAF will include scaled surface area factors to account for the particle's ability to enter the body (soluble, small) or to be cleared (insoluble, large).

For these particulate DAF calculations, a publicly available software program called the Multi-path Particle Dosimetry (MPPD) model is used to characterize the species-specific inhalation dosimetry to predict the deposited dose to various regions in the respiratory tract (https://www.ara.com/mppd/). The MPPD model accounts for differences in inhaled particle deposition between animals and humans, incorporating the particle size, distribution and density of different particle exposures. Additionally, because ventilation rate and breathing mode (nose and / or oral) vary with age and activity pattern, like resting or exercise, the use of the MPPD model provides a means for characterizing variabilities in populations, such as occupational versus ambient activities and differences among various child and adult age groups.

C.4 Apply Appropriate Uncertainty Factors

To account for what is not known about a chemical's toxicity to a human population, uncertainty factors (UF) are applied when deriving an HBV / RAA for noncancer and non-linear carcinogens. Once the dose level (e.g., NOAEL, LOAEL or BMCL) has been selected as the POD, it is then divided by uncertainty factors to derive the HBV / RAA.

MDH considers the application of five uncertainty factors:

- Interspecies extrapolation
- Intraspecies variability
- Subchronic-to-chronic extrapolation
- LOAEL to NOAEL extrapolation
- Database uncertainty

In the absence of chemical-specific information, each of the five factors is typically assigned a value between 1 and 10. Uncertainty factors are normally expressed as full or half powers of ten, such as 10^0 (=1), $10^{0.5}$ (=3.16), and 10^1 (=10). All applicable uncertainty factors are multiplied together to yield a composite uncertainty factor for the air guidance value. 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 (U.S. EPA, 2002). Therefore, a composite UF using values of 3 and 10 would be expressed as 30 (3×10^1), whereas a composite UF using values of 3 and 3 would be expressed as 10 ($10^{0.5} \times 10^{0.5} = 10^1$). The maximum total uncertainty factors used to derive an air guidance value is 3,000. If the uncertainty associated with a chemical's toxicity warrants application of uncertainty factors where the product exceeds 3,000, MDH believes there is insufficient chemical information to derive a value.

The toxicological summary for each air guidance value lists and explains the UFs used to derive the value.

C.5 Select Most Sensitive Critical Effect(s)

There may be a number of toxicology or epidemiology studies that are carried through the process above. The goal is to derive an air guidance value using the most sensitive health endpoint, which would then be protective for all other health endpoints. The most sensitive critical effects (the studies that result in the lowest air guidance value), are selected as the basis for the final HBV or RAA.

C.5.1 Noncancer Equation

If data is available and appropriate, air guidance values are developed for all noncancer durations. Each duration will have a unique POD. The POD variables for noncarcinogens are the $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$, or $BMCL_{[HEC]}$ (already time adjusted as needed), and uncertainty factors (unitless).

Equation 4: Noncancer Air Guidance Value ($\mu g/m^3$) =

$$\frac{NOAEL_{[HEC]} \text{ or } LOAEL_{[HEC]} \text{ or } BMCL_{[HEC]}}{UF}$$

D. Development of Acute Values

Acute (1-hour and 24-hour) values are calculated as described above in section C, often with time adjustments as described below in D.1. Because study data is of various durations, professional judgment is needed to determine the appropriateness of the data to adjust and derive 1-hr and / or 24-hr values. One consideration is the reasonableness of the study effect to occur from a single exposure, particularly a single 1-hr exposure. For example, it is likely more defensible to adjust 6-hour study data showing an effect to a 24-hr guidance value than to adjust to 1-hr, since the effect may not occur from a single 1-hr exposure.

It is expected that most 1-hr guidance values derived will be based on irritation effects, likely mild and reversible. In this case, it is possible that a 1-hr value and a 24-hr value could be the same. For other chemicals, the 1-hr and 24-hr values may be derived from different study data and health endpoints, or the data may only be available to derive one of the acute durations.

Certain study health endpoints may not be considered acute effects, but it is possible that a chemical's mode of action could indicate that an acute exposure could cause an adverse effect later in life; therefore, an acute value is derived.

D.1 Acute Time Adjustment

The critical study chosen for an acute air guidance value has an exposure timeframe that can range from minutes to hours, depending on the experimental protocol. It may also be a multi-day reproductive / developmental study producing an adverse effect during the first day of exposure. Before implementing time adjustment calculations, it is important to look at the mechanistic data for the chemical and determine the appropriate duration adjustment on a case-by-case basis. Mode of action information is considered to ensure both concentration and time impact toxicity (NRC, 2001). For example, if concentration alone drives the adverse health effect, which is the case for some airway surface irritants, time adjustment of POD concentration would not be warranted. Time adjustment may also not be performed for reproductive / developmental endpoints (see Reproductive / Developmental Effects section below for details).

In cases where the toxicant's MOA is not well understood, time adjustment is applied as a protective measure. Using a robust and validated PBTK model would be a preferred approach, but these models are often not available. Duration adjustments for chemicals with limited available toxicological information are typically completed by applying Haber's Law as modified by ten Berge (1986).

Equation 5 Haber's Law as modified by ten Berge:

$$C^n * T = K$$

Where:

C^n = C represents the concentration of the chemical; n is a chemical-specific value greater than zero

T = time

K = constant (toxic) effect

This can be arranged (Equation 6) in order to perform exposure time adjustment calculations.

Equation 6:

$$C_1^n * T_1 = C_2^n * T_2$$

Where:

C_1= key study's concentration resulting in observed toxicological effect (POD)

T_1= timepoint at which the key study toxicological effect occurred

C_2 = time adjusted concentration estimate

T_2 = desired adjusted timepoint (1-hour or 24-hour)

n = experimentally determined chemical factor (ten Berge et al., 1986)

The value of n for 20 structurally diverse chemicals was studied and found to range from 0.8 to 3.5. Additionally, values of n from 1 to 3 were found to encompass approximately 90% of the chemicals examined (ten Berge et al., 1986). In selecting a value for n when the empirical derivation of n is not feasible, the upper or the lower boundary value of n (1 or 3) is used within the context of other supporting data to determine the reasonableness of the extrapolated value (NRC, 2001).

When adjusting from a study's POD concentration (C_1) using their reported exposure duration (T_1) to determine the concentration (C_2) at a longer (e.g., 24 hour) desired exposure duration (T_2), the factor n = 1 is used as a conservative estimate that results in less rapid rates of increase in estimated effect concentrations when extrapolated to longer exposure periods (NRC, 2001).

Conversely, when adjusting from a study's POD concentration (C_1) using their reported exposure duration (T_1) to determine the concentration (C_2) at a shorter (e.g., 1 hour) desired exposure duration (T_2), the factor n = 3 is used as a conservative estimate that results in less rapid rates of increase in estimated effect concentrations when extrapolated to shorter exposure periods (NRC, 2001; OEHHA, 2008).

D.2 Sensitizers

By selecting the most sensitive critical effects, the air guidance values developed by MDH are considered protective of the public, including sensitive sub-populations such as young children and aging populations. However, MDH cannot ensure that the air guidance values will provide protection for chemically hypersensitive individuals. Chemical hypersensitivity is an immunologically mediated, adverse reaction to a chemical resulting from previous exposure to that chemical or to a structurally similar one. Sensitization reactions are sometimes very severe and may be fatal. Once sensitization has occurred, allergic reactions may result from exposure to very low doses of chemicals, and therefore population-based dose-response curves for allergic reactions cannot typically be derived. As a result, chemicals that are found to have sensitizing properties are noted in the air guidance values table.

D.3 Reproductive / Developmental Effects

MDH considers critical periods of sensitivity when deriving air guidance values that have reproductive and developmental endpoints to ensure protectiveness for the appropriate

exposure duration. Developmental and reproductive endpoints are highly dependent on timing and duration of exposure. This consideration may result in acute values for these endpoints.

The U.S. EPA describes reproductive toxicology as the study of adverse effects on the structure and function of the male and female reproductive systems, the ability to conceive and reproduce, or related endocrine system issues (U.S. EPA, 1996a). Examples of reproductive effects may include disruptions to puberty timing, sperm or egg maturation / development process, menstruation irregularities, reproductive organ integrity, sex hormones, fertility and fecundity, gestation, and childbirth.

Developmental toxicity refers to adverse effects on the developing organism that may result from exposure prior to conception (maternal or paternal exposure), prenatally, or postnatally until sexual maturity. Examples of developmental toxicity may include fetal death, structural abnormality or malformation, altered growth, or functional deficiencies.

Developmental and / or reproductive effects are often both reported from studies investigating adverse changes that take place in utero or postnatally following a short exposure. Typically, developmental / reproductive studies involve a repeated chemical exposure to an experimental animal over some period of gestation (e.g., 6-8 hours per day during gestational days 6-15). A short exposure could have severe and potentially lifelong adverse effects on a developing fetus or newborn if the exposure occurs during a critical window of development. Because the sensitivity of the fetus to chemicals varies during development, the timing of an exposure may be critical. A 24-hour or less window of exposure may be all that is needed to produce an adverse effect. Because the critical periods of vulnerability are often unknown, MDH will use best professional judgement to decide whether exposures that occur over many days of gestation may be used to develop acute air guidance values for developmental and reproductive toxicants.

E. Cancer Values

For carcinogens it is most often assumed there is no threshold or safe level of exposure and that exposure to any amount of these toxicants results in some increased level of risk. Under these assumptions the only risk-free dose of a carcinogen is zero. Because economic, technological, and health factors make the total elimination of environmental carcinogens an impractical goal, exposure to carcinogens is generally controlled to negligible risk levels.

The chemical review process for determining a cancer value begins similarly to the noncancer methodology with a literature search and evaluation, but the cancer value is calculated differently than a noncancer value. The availability and quality of chronic cancer study data, both human and animal studies, for different cancer endpoints (e.g., tumor type or tumor site) can vary greatly and is chemical dependent. Best efforts are made to understand a chemical's MOA for carcinogenesis. The MOA is a sequence of key events or processes resulting in cancer formation. Examples of carcinogenic MOA often include mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression (U.S. EPA, 2005). Understanding the MOA is critical to identifying if the cancer data can be modeled using a linear extrapolation approach.

For chemicals identified as linear carcinogens – those without a demonstrated threshold below which cancer is not a concern – researchers typically derive an inhalation unit risk (IUR) based

on chronic exposure scenarios. An IUR represents an upper-bound estimate of cancer risk from exposure to 1 µg/m^3 for a lifetime, which is derived from toxicological studies.

Cancer risks are characterized using an excess lifetime cancer risk, representing the incremental probability that an individual will develop cancer over a lifetime due to exposure to a carcinogen. Minnesota's long-standing public health policy is to derive values that limit excess cancer risk to 1 in 100,000 (10^{-5}) as a negligible, or acceptable, additional lifetime risk from exposure to carcinogens.

The IUR can be multiplied by an estimate of lifetime exposure (in µg/m^3) to estimate the lifetime cancer risk. The risk is a mathematical approximation of the likelihood of occurrence of cancer – it does not equate to actual increased cases of cancer. The true risk of cancer due to exposure to a chemical at an HBV or RAA could be zero.

E.1 Incorporating Early-Life Sensitivity for Linear Carcinogens

The EPA recommends combining age-dependent adjustment factors (ADAFs) with the cancer toxicity values to account for early-life susceptibility. EPA developed ADAFs of 10, 3, and 1 for the age groups of 0-2 years, 2-16 years, and 16-70 years, respectively (U.S. EPA, 2005b). MDH agrees that for many carcinogens, toxicity values calculated from adult animal studies or adult epidemiological studies underestimate lifetime exposure cancer risk. MDH applies EPA's ADAFs to linear carcinogens, unless study data sufficiently account for early-life susceptibility, or there is other chemical-specific information to determine that a different numerical adjustment should be made, or that no adjustment is appropriate (MDH, 2020). Most cancer air guidance incorporates ADAFs into the calculation.

E.2 Cancer Equations

Cancer air guidance values are calculated by dividing an excess cancer risk of 1 in 100,000 by the IUR (Equation 7). As indicated above, most air guidance values are adjusted for early-life sensitivity to derive an air guidance value associated with a negligible cancer risk over a lifetime (Equation 8).

Equation 7: Cancer Air Guidance Value (µg/m^3) =

$$CR/IUR\ (^{\mu g}/_{m^3})^{-1}$$

Equation 8: Cancer Air Guidance Value with ADAFs (µg/m^3) =

$$\frac{CR}{IUR * [(EF * ED_{(0-2)} * ADAF_{(0-2)}) + (EF * ED_{(2-16)} * ADAF_{(2-16)}) + (EF * ED_{(16-70)} * ADAF_{(16-70)})]}$$

Parameter	Value	Description / Reference
CR – Cancer Risk Level	0.00001 (10^{-5})	MDH guidance for acceptable cancer risk of 1 excess cancer in 100,000 people exposed

Parameter	Value	Description / Reference
IUR – Inhalation Unit Risk	Varies $(\mu g/m^3)^{-1}$	See text above
ED- Exposure Duration	70 years	U.S. EPA, 1989
$ED_{(0\text{-}2)}$ Exposure Duration	2 years	U.S. EPA, 2005b; MDH, 2020
$ED_{(2\text{-}16)}$ Exposure Duration	14 years	U.S. EPA, 2005b; MDH, 2020
$ED_{(16\text{-}70)}$ Exposure Duration	54 years	U.S. EPA, 2005b; MDH, 2020
$ADAF_{(0\text{-}2)}$ Age-Dependent Adjustment Factor	10	U.S. EPA, 2005b; MDH, 2020
$ADAF_{(2\text{-}16)}$ Age-Dependent Adjustment Factor	3	U.S. EPA, 2005b; MDH, 2020
$ADAF_{(16\text{-}70)}$ Age-Dependent Adjustment Factor	1	U.S. EPA, 2005b; MDH, 2020

For nonlinear carcinogens – those with a demonstrated threshold below which cancer is not a concern – a cancer health-based value may or may not be derived based on a threshold response approach or the noncancer value may already be protective of cancer effects.

F. Route to Route Extrapolation

Situations will arise where there is a need for an air guidance value but the available toxicology data are from an oral rather than an inhalation exposure study. Route to route extrapolation may be appropriate on a case-by-case basis when sufficient toxicokinetic information about a given chemical is available.

If the critical effect of a toxicant is noncarcinogenic, the route of administration would likely result in differences in the amount of toxicant at the target site, and therefore the severity of its effect. However, the critical effect would be the same regardless of how the toxicant is administered. In such cases MDH considers it appropriate to correct for differences in the amount absorbed through inhalation. While often not available, appropriately structured PBPK models can be the preferred method for route to-route extrapolation. Models developed for the oral route may be adjusted to estimate the behavior of a chemical following inhalation.

Inhalation toxicity values can be extrapolated from oral values as shown below (U.S. EPA, 1996b).

Equation 9: Extrapolated Air Guidance Value ($\mu g/m^3$) =

$$Oral\ Toxicity\ Value\ (mg/kg/day) * \frac{body\ weight\ (70\ kg)}{inhalation\ rate\ (20\ m^3/day)} * 1000\ \mu g/mg$$

There are, however, situations where this extrapolation technique is inappropriate. Should the critical effect be specific for the respiratory system, or if the toxicity of a chemical is expressed at or near the site of application, data from an oral exposure should not be used to extrapolate to an inhalation exposure. Another case where extrapolation would be inappropriate is when the target organ for the critical effect is the liver. The liver, because of its unique structure and

circulation, is subjected to much higher concentrations of ingested chemicals than other organs.

IV. Interpreting Health Risks

A. Noncancer

A hazard quotient (HQ) is used to describe health risk for noncancer contaminants. An HQ is the ratio of the exposure concentration over a concentration where no adverse health impacts are expected. An HQ of 1 means adverse noncancer effects are unlikely. For HQs greater than 1, the potential for adverse effects increases, although by how much is unknown.

Equation 10: Hazard Quotient (unitless) =

$$\frac{chemical\ air\ concentration\ for\ a\ specific\ duration\ (\mu g/m^3)}{health\ guidance\ value\ for\ a\ specific\ duration\ (\mu g/m^3)}$$

B. Cancer

Excess cancer risk is used to describe health risk for carcinogens. Cancer risk is calculated by dividing the observed air concentration by the cancer air guidance value to get the number of excess cancers in a population per 100,000 exposed people.

Equation 11: Excess Cancer Risk per 100,000 exposed people=

$$\frac{chemical\ air\ concentration\ \ (\mu g/m^3)}{cancer\ health\ guidance\ value\ (\mu g/m^3)}$$

C. Evaluating Concurrent Exposures to Multiple Chemicals

Even though air guidance values are calculated for individual chemicals, MDH recognizes that humans are rarely, if ever, exposed to single contaminants in the air they breathe. Typically, the air that an individual inhales is a complex mixture of many different substances, and the chemicals that make up these mixtures have the potential to interact additively, synergistically, or antagonistically. Unfortunately, there are few data that address the toxicology of mixtures. In the absence of definitive studies, MDH recommends the use of the additivity model outlined by the U.S. EPA (U.S. EPA, 1986) to estimate the health risks of exposures to mixtures.

U.S. EPA guidelines recommend generating a separate hazard index for each group of chemicals defined by a common endpoint of concern. Therefore, for each mixture, a hazard index is determined for all chemicals or compounds with a similar mechanism of action or site of action. Where the mechanism or site of action is unknown, a hazard index is calculated for each group of chemicals or compounds that induce a common biological response.

Following these guidelines, all carcinogens are combined into one group. Other groups include, but are not limited to, liver damage, kidney damage, and neurotoxicity. Chemicals or compounds that do not fall into any group are excluded from additivity calculations. This additivity model does not account for synergistic or antagonistic effects, or for the absence of contaminant interactions. MDH endorses the use of the additivity model and, in doing so,

recognizes and accepts the inherent risk of underestimating or overestimating the true health risk.

To determine whether the sum exceeds the multiple-chemical hazard index of 1 for noncancer, the chemicals are grouped according to their health endpoints. Equation 12 calculates a ratio of the measured concentration of each chemical in the air to the corresponding air guidance value for each exposure duration.

Equation 12: Noncancer HI =

$$\frac{C_1}{noncancer\ air\ value_1} + \frac{C_2}{noncancer\ air\ value_2} + \cdots \frac{C_N}{noncancer\ air\ value_N}$$

Where:

HI = Hazard Index. An HI over 1 indicates a possible exceedance and an increased risk of adverse health effects associated with the evaluated endpoint / organ system.

C_1, C_2, …C_N = the concentration of the first, second, …Nth chemical in air that causes a specific noncancer effect (µg/m^3)

Noncancer air value$_{1, 2, N}$ = the duration-specific noncancer air guidance value of the first, second, …Nth chemical with the same health endpoint in air (µg/m^3)

This calculation treats all carcinogens as having the same health endpoint, meaning some type of cancer. It calculates a ratio of the measured concentration of each individual carcinogen in air to the air guidance value for that carcinogen. Ratios are added and compared to the multiple-chemical cancer risk level of 1 in 100,000.

Equation 13: Combined Cancer Risk =

$$\frac{C_1}{cancer\ air\ value_1} + \frac{C_2}{cancer\ air\ value_2} + \cdots \frac{C_N}{cancer\ air\ value_N}$$

Where:

C_1, C_2, …C_N = the concentration of the first, second, …Nth carcinogen in air (µg/m^3)

Cancer air value$_{1, 2, N}$ = the cancer air guidance value for first, second, …Nth chemical

Combined cancer risk is an estimated number of excess cancer cases in 100,000 exposed people. Greater than 1 in 100,000 is considered a possible exceedance.

V. Children's Health Risks

Children's environmental health is an important concern because children may be more exposed and more vulnerable to hazards in the environment.

Children are considered in the derivation of air guidance values through use of uncertainty factors. Risk assessors typically use a full intraspecies uncertainty factor of ten in noncancer assessments. This factor allows for differences between people, including additional susceptibility of infants and children.

According to the 2001 Health Standards Statute 144.0751 (https://www.revisor.mn.gov/statutes/cite/144.0751) air quality standards established or revised by the commissioner of health must:

> "…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."

Each air guidance value's toxicological summary addresses the availability of data for the health outcomes identified above and describes the extent of testing or effects. When there is a lack of data that addresses the protection of early life, an increased database uncertainty factor is used to derive the air guidance value that is protective of childhood exposures.

To protect children from cancer risks, age-dependent adjustment factors are applied to linear carcinogens as described in section E.1.

VII. Expedited Review Process

Occasionally, an air guidance value is needed within weeks of the request (e.g., for an ongoing Minnesota Pollution Control Agency site investigation or facility evaluation). To be able to respond and provide health protective guidance in a timely manner, an alternative review process is available.

MDH takes a preliminary look at available data (e.g., federal / state agency assessments, brief literature search since the most recent assessment). Considerations in determining whether an expedited review is appropriate and possible include the urgency of the request, planned use of the value, availability of toxicity assessments and years published, and results of the brief literature search. Using professional judgment, MDH will determine if the situation and available data are amenable to an expedited review.

Expedited reviews are not likely to address all durations. Less time will be spent for detailed chemical evaluation and review of potential key studies. MDH is more likely to use data that is readily available by choosing an existing key study and applying MDH methods; less likely to derive a value from the literature. Following the expedited review, MDH may conduct a full review if it is determined that additional durations are needed or a more rigorous review is warranted based on the use for the values.

These more promptly derived values are called RAA. Documentation on the air guidance table discusses why the expedited review process was conducted and the resulting uncertainties or limitations. It should also be noted that an air guidance value may also be listed as RAA after a comprehensive toxicity review when the data available for a chemical is limited.

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