E = experimental exposure level
D = number of hours exposed/24 hours
W = number of days of exposure/7 days

Adjustments for differences in anatomy and physiology of the respiratory tract

Several types of dosimetric adjustments to a NOAEL, LOAEL, or BMC may be necessary depending on the physical nature of the inhaled substance and the classification of the gas inhaled.

Adjustment for exposures to insoluble particles.

If the critical effect is in the respiratory tract, the default approach for dosimetric adjustment is to calculate a $NOAEL_{[HEC]}$ using a regional deposited dose ratio (RDDR)[2] as follows:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR$$

The RDDR will vary with the species and body weight of experimental animals, as well as with the region(s) in the respiratory tract (extrathoracic, tracheobronchial, pulmonary or total respiratory tract) where the toxic effect is elicited.

If the critical effect is extrarespiratory, the default is to calculate a $NOAEL_{[HEC]}$ using a extrarespiratory regional deposited dose ratio ($RDDR_{ER}$) as follows:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RDDR_{ER}$$

The $RDDR_{ER}$ will vary with species and body weight of experimental animals.

Adjustment for exposure to gases

The potential for an inhaled gas to cause a health effect on the respiratory system and on the extrarespiratory systems is dependent on the reactivity and solubility characteristics of the gas. The two categories of gases with the greatest potential for respiratory tract effects are:

Category 1 gases are very water soluble and/or irreversibly reactive in the respiratory tract. Examples of category 1 gases are chlorine, formaldehyde, organic acids and esters. These gases generally express their critical effects on the respiratory system.

Category 2 gases such as ozone, sulfur dioxide, and xylene are moderately water soluble. These gases may accumulate in blood and have the potential for both respiratory and extrarespiratory critical effects. For category 1 and 2 gases the default approach for dosimetric adjustment is to calculate a $NOAEL_{[HEC]}$ using a ratio (RGDR)[3] of the regional gas dose in an experimental animal to the regional gas dose in humans as follows:

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[2] The regional deposited dose (RDDR) is the ratio of the deposited dose (mg/cm2 of respiratory tract region) for the laboratory animal species of interest to that of humans (U.S. EPA, 1994a).

[3] The Regional gas dose ratio (RGDR) is the ratio of the deposited gas dose (mg/cm^2 of respiratory tract surface area per minute) in a respiratory tract region for the laboratory animal species of interest to that of humans (U.S. EPA, 1994a).

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times RGDR$$

The RGRD will vary with the species and body weight of the experimental animals, as well as the region(s) of the respiratory tract (extrathoracic, bronchial or total respiratory tract) that is the site of the toxicant's insult.

Category 3 gases are relatively water insoluble and are generally extrarespiratory toxicants. Styrene is an example of a category 3 gas. The default approach for dosimetric adjustment of category 3 gases is to calculate a $NOAEL_{[HEC]}$ using the ratio of the blood:gas (air) partition coefficient of the chemical for the experimental animal to the value in humans $[(H_{b/g})_A/(H_{b/g})_H]$ as follows:

$$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times (H_{b/g})_A/(H_{b/g})_H$$

If the ratio of $(H_{b/g})_A/(H_{b/g})_H$ is greater than or equal to1.0, or if the ratio is unknown, the default ratio of 1.0 is used. Analysis of the available data on rats for blood:air partition coefficients shows that $(H_{b/g})_A$ is greater than the $(H_{b/g})_H$ in most cases (U.S. EPA 1994a).

USE OF HRVS AND MHRVS FOR MIXTURES

Despite the fact that HRVs 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 and the development of risk assessment tools to handle complex mixtures has been slow. MDH recommends that, for the few cases where toxicity data for mixtures are available (e.g. diesel exhaust), these data be evaluated and used when appropriate. In those cases where there are no data MDH recommends the use of the additivity model outlined by the U.S. EPA (U.S. EPA, 1986b) to estimate the health risks of exposures to mixtures. This model assesses the health impact of exposures to mixtures by grouping chemicals that either have similar toxicologic effects or exert their effects on the same organ or organ system to create a hazard index as follows:

$$\text{Hazard Index} = HI = \frac{E1}{HRV_1} + \ldots + \frac{Ex}{HRV_x}$$

where:

E_1 = exposure level of chemical or compound 1
E_x = exposure level of the x^{th} chemical or compound
HRV_1 = health risk value of chemical or compound 1
HRV_x = health risk value of x^{th} chemical or compound

As the hazard index approaches 1, the level of concern increases. A hazard index greater than 1 is analogous to finding a level of an individual chemical or compound greater than its HRV, and indicates the potential for adverse effects despite the fact that assessing the health risk by addressing chemical or compound doses separately would not raise a health concern.

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

Studies where the exposure duration is less than 30 minutes will not be used as the single basis for any one-hour acute HRV. On occasion, a study with an exposure duration less than 30 minutes may be of sufficient quality to warrant its use in setting an HRV when there is strong supportive evidence available.

When several studies or data sets are used to develop a BMC for use in calculating an acute HRV, studies where the exposure duration is less than 30 minutes may be used provided that the short exposure duration studies (less than 30 minutes) do not unduly influence or drive the outcome of the modeling.

- Studies where the exposure duration is greater than 8 hours will not be used as the single basis for any one-hour acute HRV.

- If the exposure duration of the study to be used falls within the range of 0.5-1 hour, Haber's Law is used to do a simple time adjustment for deriving the acute HRV.

- If the exposure time ranges from 1 hour up to 2 hours, the study will be used without adjustment for time.

- For non-developmental/non-reproductive toxins, studies where the exposure duration is between 2 to 8 hours are considered suitable for developing acute HRVs. For such studies MDH will use the ten Berge modification of Haber's Law to extrapolate the experimental exposure duration to a 1 hour level. A default value of 2 will be used for the exponent in this equation because it represents a whole number near the midpoint of the range of empirically derived values (Cal EPA, 1999).

ADVERSE EFFECTS AND SEVERITY OF EFFECTS

An adverse health effect may be any effect resulting in functional impairment and/or pathological lesions that may affect the performance of the whole organism, or that reduces the ability of the organism to respond to an additional challenge. For purposes of rule;

- as discussed in Part I (What HRVs are not) by itself odor is not considered an adverse health effect.

- developmental and reproductive effects will be considered separately from other chemicals which are considered to have acute toxicity.

- perception of a contaminant, as reported in laboratory exposure chamber studies, will not be used as an adverse health effect. However, this is not meant to exclude self reported mild mucous membrane irritation (see below).

- acute HRVs will be based on the defined toxicological effects found in the table below under mild adverse effects. Protection from mild adverse effects that occur at lower reported exposure concentrations is assumed to be protective of more severe effects that generally occur at higher exposure levels.

- when mild effects have not been reported for a chemical, an exposure level resulting in a moderate/severe response may be used to develop an acute HRV.

Acute Exposure Level to Toxicants in Air	Symptoms	Signs/ Laboratory Findings
Mild Adverse	Mild subjective complaints with few to no objective findings: •Mild mucous membrane irritation (eye, nose, throat) •Mild skin irritation •Mild headache, dizziness, nausea	•Statistically significant findings of preclinical significance: •Mild conjunctivitis •Mild lung function changes
Moderate-Severe Adverse	Potentially disabling effects that affect one's judgment and ability to take protective actions; prolonged exposure may result in irreversible effects: • Severe mucous membrane irritation • Blurry vision • Shortness of breath, wheezing • Severe nausea • Severe headache • Incoordination • Drowsiness • Panic, confusion	•Clinically significant findings: •Findings consistent with central or peripheral nervous system toxicity • Loss of consciousness • Hemolysis • Asthma exacerbation •"Mild" pulmonary edema • Clinically significant lung function changes • Cardiac ischemia • Some cardiac arrhythmias e.g., atrial fibrillation • Renal insufficiency • Hepatitis • Abnormal immunotoxicity test results • Mild decreases in hemoglobin concentration
•Developmental/ Reproductive	Altered survival, growth, and morphological development Significantly reduced *fetal* body weight, reduced weight gain or specific organ toxicity Alterations of the male and female reproductive functions including gonadal function, the estrous cycle, mating behavior, conception, gestation, parturition, lactation, and weaning.	Potentially lethal effects including: •Death of the developing organism •Structural abnormality •Altered growth •Functional deficiency •organ weights •histopathological changes •sexual behavior •changes in hormone levels

SENSITIZERS

Public health agencies do not purport to protect everyone all of the time. By using the most sensitive endpoint in an experimental study and uncertainty factors, MDH intends that the HRV rule will be protective

of the general public and for certain sensitive sub-populations such as young children and aging populations. However, MDH can not ensure that the HRVs 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 relatively very low doses of chemicals, and therefore population-based dose response curves for allergic reactions can not typically be derived.

To address the issue of chemical hypersensitivity, MDH will attempt to inform the public about chemicals that are known sensitizers by specifically identifying in the rule those chemicals that have been shown either to cause sensitization or to elicit the physiological responses associated with sensitization.

Avoidance of Cumulative Insults for Acute HRVs

Depending on the severity of the critical effect, repeated exposures to chemicals at levels above an HRV may not allow sufficient time for recovery and repair, and depending on their timing, could cause cumulative damage. Based on currently available information, and in agreement with the U.S. EPA and Cal EPA's OEHHA, MDH suggests that:

- When an acute HRV for a chemical is based on its ability to cause mild adverse effects, exposures to that chemical at concentrations above the HRV occurring no more than once every two weeks are unlikely to result in cumulative damage.

- When an acute HRV for a chemical is based on its ability to cause moderate/severe effects, exposures to that chemical at concentrations above the HRV occurring no more than once a month are unlikely to result in cumulative damage.

- When a chemical that has an acute HRV is also a sensitizer, exposures to that chemical at concentrations above the HRV occurring no more than once per year are unlikely to cause adversely effect health.

- When an acute HRV for a chemical is based on its ability to cause developmental effects, which are serious and irreversible, multiple exposures to that chemical to concentrations above the HRV will increase the likelihood of damage.

- For chemicals where bioaccumulation is known to occur and body burden is associated with an adverse effect, longer periods between exposures will decrease the likelihood of cumulative damage.

USE OF UNCERTAINTY FACTORS

MDH intends to minimize the use of order-of-magnitude uncertainty factors in the development of acute HRVs. However, MDH is committed to using uncertainty factors in accordance with principles and practices of the U.S. EPA. This includes using uncertainty factors in a consistent manner and using partial uncertainty factors when appropriate.

In the development of HRVs based on **mild** acute effects:

- only human data will be considered; and

- in general, when a benchmark concentration approach is used:
  - an uncertainty factor of 1 will be used if sensitive individuals have been used in the study population; or
  - an uncertainty factor of 3 will be used if non-sensitive individuals have been used in the study population. If the data indicate a wide variability in response in the population an uncertainty factor of 10 may be used.
- in general, when a NOAEL or LOAEL approach is used:
  - an uncertainty factor of 3 will be used if sensitive individuals have been used as the study population;
  - an uncertainty factor of 10 will be used if non-sensitive individuals have been used as the study population; and
  - if necessary, an additional uncertainty factor of 6 will be used if a LOAEL is used rather than a NOAEL.

In the development of HRVs based on **moderate/severe** acute effects:

- human data will be considered over animal data when available; and
- in general, when a benchmark concentration approach is used:
  - an uncertainty factor of 1 will be used if the study population is composed of sensitive individuals; or
  - an uncertainty factor of 3 will be used if the study population is composed of non-sensitive individuals.
- in general, when a NOAEL or LOAEL approach has been used:
  - an uncertainty factor of 3 will be used if the study population is composed of sensitive individuals;
  - an uncertainty factor of 10 will be used if the study population is composed of non-sensitive individuals;
  - an uncertainty factor of 6 (mild effect) or 10 will also be used if a LOAEL is used in place of a NOAEL; and
  - if an adequate human study is not available and an animal study has to be used, an uncertainty factor of 10 may be used to account for interspecies variability. This factor may be reduced to 3 if toxicokinetic or toxicodynamic information is available for the chemical.

For development of HRVs based on **reproductive/developmental** effects:

- human and animal data will be considered; in general,
- an uncertainty factor of 10 will be used for intraspecies variation;
- an uncertainty factor of 10 will be used for interspecies variation; and
- an uncertainty factor of 10 will be used if a LOAEL is used in place of a NOAEL.

REPRODUCTIVE/DEVELOPMENTAL EFFECTS

The procedures available to establish air toxics criteria for reproductive/developmental effects remain controversial and the MDH recognizes that the study of developmental and reproductive effects is far from complete. However, it is clear that a short exposure could have severe adverse effects on a developing fetus or newborn if the exposure occurs during a critical period of development. Unfortunately, because the critical periods of vulnerability are not known, longer periods of exposure are required for the study of reproductive/developmental effects. MDH will therefore use studies where exposures occur over many days

of gestation to develop acute HRVs for developmental/reproductive toxicants and no time extrapolations will be done.

Historically, reproductive and developmental endpoints have been considered separately, however, recent studies have indicated the potential for profound effects of chemicals on reproductive ability that occur as a result of developmental damage. For the purposes of this rule reproductive/developmental refers to the changes that take place *in utero* or post-natally following an acute exposure. The reproductive/developmental endpoint is distinct from the reproductive endpoint that is a result of chronic or subchronic exposures and the two should not be considered to be equivalent for calculation of hazard indexes.

4717.8000 PURPOSE AND SCOPE.

Subpart 1. **Purpose.**

Subp. 2. **Scope.**

The purpose and scope provide the reader with introductory information about the Department's HRV Rule. A definition of HRVs, including what HRVs are and are not, is presented in the introduction of this document. The scope is limited to providing HRVs for chemicals or defined mixtures of chemicals emitted to the ambient air. The methods and factors used in calculating the HRV are also provided in rule to provide transparency with regard to the Department's process in determining the HRV. The rule is not comprehensive in its listing of chemicals.

By intent, the rule does not specify how HRVs must or even should be used. The Department cannot accurately predict all situations where HRVs might be used. Providing an HRV based on a stated methodology provides a single criteria for inclusion into health risk assessment applications conducted outside of the scope of this rulemaking. This rule was conceived and is structured like the Department's Health Risk Limits Rule for ground water (Minnesota Rules, parts 4717.7100 to 4717.7800), which also provides the numbers and methods but not the applications.

4717.8050 DEFINITIONS.

Subpart 1. **Scope**. The terms defined are limited in their applicability to specified rule parts, in this case the sequence of parts that constitute the HRV rules. This is standard procedure in administrative rulemaking. The terms defined are limited to those terms that are not used in their ordinary usage – a commonly understood usage that can be confirmed by consulting a standard dictionary. Because the definition is not of common usage, it is necessary to limit the scope of its applicability so as not to have unintended consequences in other law.

Subp. 2. **Acute health risk value or acute HRV.** Subpart 2 is necessary to establish that the time period for an acute exposure is approximately one hour. It is also necessary to provide the units in which the acute HRVs are expressed.

Many of the acute HRVs are based on mild adverse effects such as irritation; however, several chemicals for which acute HRVs have been calculated are reproductive/developmental toxicants. The impact of exposure to such chemicals can be profound. Some developmental effects are immediately obvious, but for some exposures it may take years before developmental effects become apparent; some may result in the premature

onset of senescence and /or organ failure later in life. Unfortunately, the potential occurrence of such effects has not been systematically studied.

It is essential that the concept of critical periods of sensitivity, based on the stage of development, be considered. Because the sensitivity of the fetus to chemicals varies during development, the timing of an exposure may be critical. A chemical exposure during a critical period may have devastating effects, but exposure to a similar dose of the same chemical at another time might be harmless. Because both the timing and length of exposure to a chemical or mixture of chemicals are critical in producing effects and typically have not been characterized experimentally, a shorter exposure time provides a conservative default. An hour is a convenient sampling period and provides protection to the developing organism.

The critical effect of a chemical does not have to be a long-term, irreversible effect for an HRV to be developed. Short term, acute exposures that can stress an organism can exacerbate preexisting illnesses.

Subp. 3. **Additional lifetime risk level.** This term is necessary because it is a concept used to calculate the exposure level allowed for carcinogenic chemicals. The additional lifetime risk level is 1×10^{-5}.[1]

The additional lifetime risk level is a policy of the MDH and refers to the additional risk of developing cancer over background levels of cancer. The lifetime risk level is the probability that exposure to the carcinogen for a lifetime will cause cancer. Thus, a person exposed to a concentration of a carcinogen corresponding to the proposed increased lifetime risk level of 1×10^{-5} for a lifetime would have an increased risk of 1 in 100,000 for developing cancer from this exposure. Because of the conservative techniques used to develop these numbers they are upper bound risks; the true risk from exposures ranges from zero to 1×10^{-5}.

An additional lifetime risk of 1×10^{-5} is well within the range of additional lifetime risk levels (1×10^{-4} to 1×10^{-6}) recommended by the U.S. EPA (U.S. EPA, 1990). While the U.S. EPA recommends using a lifetime risk level between 10^{-4} and 10^{-6}, the choice of a specific lifetime risk level is left to the discretion of the regulatory agency. A risk level of 1×10^{-5} has previously been adopted in three Minnesota rules: the MDH Rules for Health Risk Limits [Minnesota Rules, parts 4717.7100 to 4717.7800], the MPCA's Solid Waste Rules [Minnesota Rules, part 7035.2815, subpart 4, item H, subitem (5), subsubitem (b)] and MPCA Surface Water Rules [Minnesota Rules, part 7050.0218, subpart 6, item C]. Additional rationale for choosing a lifetime risk level of 1×10^{-5} is provided in a MDH Briefing Paper (MDH, 1996a).

The use of a lifetime risk level factor to calculate exposure limits for carcinogens results from the U.S. EPA assumption that carcinogens are non-threshold agents, i.e. exposure to any level of a carcinogen above zero presents some additional risk of causing cancer. Under these assumptions the only risk-free dose of a carcinogen is zero. The MDH recognizes that setting the HRVs for carcinogens at zero ignores the possible benefits of some chemicals or the processes that produce them. These benefits can be economic, technological and also health related. For example, from the view of public health, the benefit of chlorinating water to prevent the spread of infectious disease far outweighs the small potential risk of developing cancer from the resulting chlorinated compounds. The MDH justifies setting a cancer risk level above zero by weighing large benefits against small additional risks, and by recognizing that the presence of a low level of increased risk does not preclude safety.

Subp. 4. **Benchmark concentration or BMC.** The benchmark concentration (BMC) approach was used to develop several of the HRVs for chemicals or mixtures of chemicals in this rule. The BMC approach uses a specific mathematical model (e.g., Weibull, logistic, polynomial) to determine chemical concentrations and the statistical lower confidence limit (usually 95%) associated with a predefined effect level (e.g., 10%

response of a dichotomous outcome is often used as the benchmark response) as the BMC. The development of a RfC from a BMC involves an evaluation of the entire data base and the selection of studies and endpoints for the risk assessment, calculation of a BMC based on the lower confidence limit of a population response selected from a range of 1-10%, and application of uncertainty factors. The BMC approach has quickly gained support as an alternative for the NOAEL in noncancer risk assessment because it uses all of the available data and provides a risk manager with more information on which a decision may be based. The U.S. EPA has promoted the development of the BMC approach where sufficiently robust data bases are available and several of the RfCs listed on IRIS have been calculated using the BMC approach.

Subp. 5. **Benchmark dose or BMD.** The benchmark dose (BMD) approach was used to develop several of the MHRVs for chemicals or mixtures of chemicals in this rule. The BMD approach uses a specific mathematical model (e.g., Weibull, logistic, polynomial) to determine the statistical lower confidence limit of a dose of chemical that is associated with a predefined effect level (e.g., 10% response of a dichotomous outcome is often used as the benchmark response) as the BMD. The development of a RfD from a BMD involves an evaluation of the entire data base and selection of studies and endpoints for the risk assessment, calculation of a BMD based on the lower confidence limit of a population response selected from a range of 1-10%, and the application of uncertainty factors. The BMD approach has quickly gained support as an alternative for the NOAEL in noncancer risk assessment because it uses all of the available data, thus providing a risk manager with more information on which a decision may be based. The U.S. EPA has promoted the development of the BMD approach where sufficiently robust data bases are available and a number of the RfDs listed on IRIS have been calculated using the BMD approach.

Subp. 6. **Carcinogen.** The term carcinogen is used throughout the proposed rule in reference to chemicals, compounds, or defined mixtures of chemicals that cause cancer. The U.S. EPA categorizes chemicals as A, Human carcinogen; B, Probable human carcinogen; C, Possible human carcinogen; D, Not classifiable as to human carcinogenicity; and E, Evidence of noncarcinogenicity for humans (U.S. EPA, 1986a). The rule's definition of carcinogen includes chemicals or mixtures of chemicals classified by the U.S. EPA as human carcinogens (A) and probable carcinogens (B). For purposes of the rule possible human carcinogens (C) are not considered to be carcinogens because there is limited or equivocal evidence that they are capable of causing cancer in humans (U.S. EPA, 1986a; Federal Register, 1991a; U.S. EPA, 1990). The rule does not consider chemicals or mixtures of chemicals to be carcinogenic if they have been assigned to group D or group E by the U.S. EPA.

In 1996 the U.S. EPA issued a document entitled *Proposed Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1996) which would replace the A to E grouping of carcinogens with descriptors to classify human carcinogenic potential. The three descriptors proposed are; known/likely, cannot be determined, and not likely. Although there have been no new revisions to IRIS using the updated descriptors, in this rule only those chemicals classified as known/likely carcinogens by the proposed guidelines would be considered carcinogenic. Although these guidelines were released in 1996 they have not been issued in a final form and are not currently being used to develop IRIS values. When the 1996 guidelines are finalized and the U.S. EPA begins using them to develop risk estimates the values developed will be incorporated into the HRV rule.

The U.S. EPA periodically reevaluates the available experimental evidence for the carcinogenicity of individual chemicals and, while the evaluation is underway, withdraws the IRIS file for those chemicals. For the purposes of these rules the carcinogen classification in effect at the time of withdrawal or review will be used until a new classification is available.

When the basis for classification of a chemical or substance as a carcinogen is a study where the substance or chemical has been administered orally, and subsequent inhalation studies of the substance or chemical are

negative for carcinogenicity, the Commissioner may determine that the substance or chemical is not carcinogenic by the inhalation route of administration.

Although the current rules use only cancer information from the IRIS data base, MDH will consider using data from the National Toxicology Program (NTP) and the International Agency for the Research on Cancer (IARC) in revisions to include additional carcinogenic HRVs.

Subp. 7. **Chemical abstracts service registry number or CAS RN.** "Chemical abstracts service registry number" or "CAS RN" is the unique identifier established and maintained by the American Chemical Society. It is reasonable to use this identification system because it is the standard identifier used by chemists and by chemical industries.

Subp. 8. **Chronic health risk value or chronic HRV.** "Chronic health risk value" or "chronic HRV" or is used throughout the rule to indicate a HRV where the risk is associated with an inhalation exposure. The HRVs in this category are calculated with the assumption that exposure is occurring daily over a 70 year lifetime. Chronic HRVs include both carcinogenic and noncarcinogenic toxicants. The chronic HRVs are derived from long term human epidemiology studies or from chronic animal studies. A chronic study in rats is generally two years; however, in the case of some highly potent carcinogens, a study conducted over a shorter time may be adequate.

Subp. 9. **Defined mixture of chemicals.** The term "defined mixture of chemicals" refers to those cases where the toxicity of a mixture has been determined by testing a specific combination of chemicals. Coke oven emissions, diesel particulate and nickel refinery dust are examples of defined mixtures. In other cases where the toxicity of a mixture has only been characterized by examining the toxicity individual components of that mixture, e.g., gasoline, the mixture is dealt with by using the rule of additivity and calculating either a hazard index or a total value for cancer risk.

Subp. 10. **Endpoint of concern or endpoint .** "Endpoint of concern or endpoint" is necessary to clarify the endpoints used in parts 4717.8100 to 4717.8250. These endpoints provide a basis to calculate the hazard index and cancer indexes.

Subp. 11. **Extrarespiratory effect**. "Extrarespiratory effect" is necessary to specify those endpoints that differ from the endpoints listed in subp. 36.

Subp. 12. **Extrarespiratory regional dose deposition or RDD_{ER}.**[5]

Subp. 13. **Extrarespiratory regional dose deposition ratio or $RDDR_{ER}$.**[5]

Subp. 14. **$(H_{b/g})_A$.**[5]

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[5] This definition has the same meaning as the U.S. EPA definition provided in the Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994a). It is reasonable to use definitions consistent with the U.S. EPA's methods because the HRV rule and the EPA methods document address the same subject matter, i.e., development of health based values for inhaled chemicals or defined mixtures of chemicals. Also, users of the HRVs are familiar with the terminology used in the U.S. EPA's methods document. A copy of this document is available at the state law library.

Subp. 15. **$(H_{b/g})_H$** [5]

Subp. 16. **Health effects assessment summary tables or HEAST**. "Health effects assessment summary tables or HEAST" is a document, prepared and periodically published by the U.S. EPA's Environmental Criteria and Assessment Office that lists provisional risk assessment values that have been reviewed and accepted by individual U.S. EPA program offices, but are not recognized agency-wide. If cancer and non-cancer criteria are not available through IRIS, MDH will use certain HEAST values to develop HRVs and MHRVs.

Subp. 17. **Health Risk Value or HRV.** This term is necessary to define those HRVs where the risk of exposure is through an inhalation route. The HRV is directly contrasted with the MHRV in that the HRV is a concentration of chemical in air expressed in micrograms per cubic meter of air, while the MHRV is based on oral or dermal exposures expressed in micrograms of chemical per kilogram body weight per day. HRVs are subdivided into three exposure categories; acute HRVs, subchronic HRVs, and chronic HRVs.

Subp. 18. **Human equivalent concentration or HEC**.[6]

Subp. 19. **Integrated risk information system or IRIS.** [6]

Subp. 20. **Lowest observed adverse effect level or LOAEL**.[6]

Subp. 21. **Lowest observed adverse effect level adjusted or $LOAEL_{[ADJ]}$.**[5]

Subp. 22. **µg/m^3**. "µg/m^3" is necessary to define the units for HRVs used throughout the rule.

Subp. 23. **mg/m^3**. "mg/m3" is necessary to define the units of RfCs used throughout the rule

Subp. 24. **Modifying factor**.[6]

Subp. 25. **Multimedia health risk value or MHRV.** This definition is necessary because the rule refers to MHRVs. MHRVs are actual doses where the units are provided in micrograms of the substance per kilogram of body weight per day. MHRVs were developed because, for certain chemicals or defined mixtures of chemicals emitted to air, the greatest risk for toxicity occurs with exposure through routes other than inhalation. Generally, the more environmentally persistent, bioaccumulative chemicals and mixtures of chemicals fall into this category.

Subp. 26. **No observed adverse effect level or NOAEL**.[6]

Subp. 27. **No observed adverse effect level adjusted or $NOAEL_{[ADJ]}$.** [5]

Subp. 28. **Potency slope or slope factor.**[6] "Potency slope" or "slope factor" is necessary to define because it provides the denominator in the equation used to calculate HRVs and MHRVs for carcinogens in parts

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[6] This definition has the same meaning as the U.S. EPA definition provided in the *Glossary of IRIS Terms* (U.S. EPA, 1999d) available at http://www.epa.gov/ngispgm3/iris/gloss8.htm. It is reasonable to use definitions consistent with the U.S. EPA IRIS database because the HRV rule and the IRIS database address the same subject matter, i.e., toxicologic information on chemicals). Also, users of the HRVs are familiar with the terminology used in U.S. EPA's IRIS database.

4717.8100 and 4717.8250. A "potency slope" or "slope factor" is a key risk assessment parameter derived by the U.S. EPA.

Subp. 29. **Reference concentration or RfC**.[6]

Subp. 30. **Reference dose or RfD**.[6]

Subp. 31. **Reference exposure level or REL**. The definition has the same meaning as provided by the Office of Environmental Health Hazard Assessment, California EPA, and may be found at http://www.oehha.org/air/acute_rels/acuterel.html.

Subp. 32. **Regional deposited dose or RDD**.[6]

Subp. 33. **Regional deposited dose ratio or RDDR**.[6]

Subp. 34. **Regional gas dose or RGD**.[6]

Subp. 35. **Regional gas dose ratio or RGDR**.[6]

Subp. 36. **Respiratory effect.** This definition is necessary to specify the portions of the respiratory system that comprise the respiratory system regions used in rule parts 4717.8100 to 4717.8250.

Subp. 37. **Respiratory system.** It is necessary to define the portions of the respiratory system because these portions may be listed or cited in rule part 4717.8050, subparts 32 and 34, and also in rule parts 4717.8100 to 4717.8250.

Subp. 38. **Statistical significance.**[6]

Subp. 39. **Subchronic health risk value or subchronic HRV.** "Subchronic HRV" is used throughout the rule to indicate a HRV where the risk occurs through the route of inhalation. The HRVs in this category are calculated with the assumption that exposure is occurring over a period of 1 day to 13 weeks. All of the subchronic HRVs are for noncarcinogenic toxicants and are based on short term human epidemiology studies, or animal studies lasting from 10 weeks to one year. The U.S. EPA defines a subchronic exposure as multiple or continuous exposures occurring for approximately 10% of an experimental species lifetime, usually over 3 months.

Subp. 40. **Uncertainty factor**.[6]

Subp. 41. **Unit Risk.**[6]

4717.8100 TABLE OF CHRONIC HRVs.

For each substance or chemical listed in the table, the variables required to calculate the Chronic HRV using the formulas provided in parts 4717.8300 for noncarcinogenic toxicants and part 4717.8400 for carcinogens are provided. The variables for noncarcinogens are the $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$,or $BMC_{[HEC]}$, and the uncertainty/modifying factor. The variable for carcinogens is the unit risk. The endpoint of concern is provided for use in evaluating simultaneous exposure under parts 4717.8550 and 4717.8600.

This part of the SONAR will identify the source of the variables which is, in most cases, the U.S. EP A's IRIS database. It is reasonable to use scientific data available from the federal agency responsible for environmental standards. Where MDH has diverged from U.S. EPA data, additional justification is provided. The individual Chronic HRVs are not justified in this section of the SONAR because they are mathematically derived from the equations in parts 4717.8300 and 4717.8400. See those parts for an explanation on the reasonableness of the formulas.

Since the variables used to calculate the HRVs are generally only accurate to one significant digit, the resulting HRVs are usually rounded to one significant digit. All digits less than 5 are rounded down. All digits 5 and over are rounded up.

Unless otherwise noted, information regarding each of the chemicals that follow is from the U.S. EPA IRIS database (U.S. EPA, 2001).

A. **Acetaldehyde.** The portion of the U.S. EPA IRIS database dealing with acetaldehyde:
- classifies acetaldehyde as a class B2 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 2.2×10^{-6} per $\mu g/m^3$. [7]

B. **Acetonitrile.** The portion of the U.S. EPA IRIS database dealing with acetonitrile:
- classifies acetonitrile as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $NOAEL_{[HEC]}$ for acetonitrile as 6.0×10^{1} mg/m^3; and
- lists an uncertainty/modifying factor of 1,000.

C. **Acrylonitrile.** The portion of the U.S. EPA IRIS database dealing with acrylonitrile:
- classifies acrylonitrile as a class B1 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 6.8×10^{-5} per $\mu g/m^3$.

D. **Ammonia.** The portion of the U.S. EPA IRIS database dealing with ammonia:
- classifies ammonia as a gas having a respiratory effect (formula from part 4717.8300, subpart 5);
- lists the $NOAEL_{[HEC]}$ for ammonia as 2.3 mg/m^3; and
- lists an uncertainty/modifying factor of 30.

[7] In this document and the HRV rule exponents are expressed in one of two formats; numeric or alphanumeric. As used here 2.2×10^{-6} is equivalent to 2.2E-6.

E. **Antimony trioxide.** The portion of the U.S. EPA IRIS database dealing with antimony trioxide:

- classifies antimony trioxide as a particle with a respiratory effect (formula from part 4717.8300, subpart 3);
- lists the $BMC_{[HEC]}$ for antimony trioxide as 7.4×10^{-2} mg/m^3; and
- lists an uncertainty/modifying factor of 300.

F. **Arsenic.** The portion of the U.S. EPA IRIS database dealing with arsenic:

- classifies arsenic as a class A or known human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 4.3×10^{-3} per µg/m^3.

G. **Benzene.** The portion of the U.S. EPA IRIS database dealing with benzene:

- classifies benzene as a class A or known human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as a range from 2.2×10^{-6} to 7.8×10^{-6} per µg/m^3.

H. **Benzidene.** The portion of the U.S. EPA IRIS database dealing with benzidene:

- classifies benzidene as a class A or known human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 6.7×10^{-2} per µg/m^3.

I. **Beryllium.** The portion of the U.S. EPA IRIS database dealing with beryllium:

- classifies beryllium as a class B2 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 2.4×10^{-3} per µg/m^3.

J. **Bis(chloromethyl)ether.** The portion of the U.S. EPA IRIS database dealing with bis (chloromethyl) ether:

- classifies bis (chloromethyl) ether as a class A or known human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 6.2×10^{-2} per µg/m^3.

K. **Bromomethane.** The portion of the U.S. EPA IRIS database dealing with bromomethane:

- classifies bromomethane as a gas with a respiratory effect (formula from part 4717.8300, subpart 5);
- lists the $LOAEL_{[HEC]}$ for bromomethane as 4.8×10^{-1} mg/m^3; and
- lists an uncertainty/modifying factor of 100.

L. **1,3-Butadiene.** The portion of the U.S. EPA IRIS database dealing with 1,3-butadiene:

- classifies 1,3-butadiene as a class B2 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 2.8×10^{-4} per µg/m^3.

M. **Cadmium.** The portion of the U.S. EPA IRIS database dealing with cadmium:

- classifies cadmium as a class B1 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 1.8×10^{-3} per µg/m^3.

N. **Carbon disulfide.** The portion of the U.S. EPA IRIS database dealing with carbon disulfide:

- classifies carbon disulfide as a gas with an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $BMC_{[HEC]}$ for carbon disulfide as 1.97×10^{1} mg/m3; and
- lists an uncertainty/modifying factor of 30.

O. **2-Chloroacetophenone.** The portion of the U.S. EPA IRIS database dealing with 2-chloroacetophenone:

- classifies 2-chloroacetophenone as a gas with a respiratory effect (formula from part 4717.8300, subpart 5);
- lists the $LOAEL_{[HEC]}$ for 2-chloroacetophenone as 3.0×10^{-2} mg/m^3; and
- lists an uncertainty/modifying factor of 1,000.

P. **Chromium VI.** The portion of the U.S. EPA IRIS database dealing with chromium VI:

- classifies chromium VI as a class A or known human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 1.2×10^{-2} per µg/m^3.

Q. **Coke oven emissions.** The portion of the U.S. EPA IRIS database dealing with coke oven emissions:

- classifies coke oven emissions as a class A or known human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 6.2×10^{-4} per µg/m^3.

R. **1,2-Dibromoethane.** The portion of the U.S. EPA IRIS database dealing with 1,2-dibromoethane:

- classifies 1,2-dibromoethane as a class B2 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 2.2×10^{-4} per µg/m^3.

S. **Dichloromethane.** The portion of the U.S. EPA IRIS database dealing with dichloromethane:

- classifies dichloromethane as a class B2 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 4.7×10^{-7} per µg/m^3.

T. **1,3-Dichloropropene.** The portion of the U.S. EPA IRIS database dealing with 1,3-dichloropropene:

- classifies 1,3-dichloropropene as a gas with a respiratory effect (formula from part 4717.8300, subpart 5); and
- lists the $BMC_{[HEC]}$ for 1,3-dichloropropene as 7.2×10^{-1} mg/m^3; and
- lists an uncertainty/modifying factor of 30.

The U.S. EPA, in a recent reevaluation of the noncarcinogenic toxicity of 1,3-dichloropropene, derived a RfC of 0.02 mg/m^3 using a benchmark concentration (BMC) for upper respiratory system effects (hypertrophy/hyperplasia of the nasal epithelium). The $BMC_{[HEC]}$ also takes into account extrarespiratory, reproductive and developmental effects. The U.S. EPA has a high level of confidence in this value. The U.S. EPA considers 1,3-dichloropropene to be a B2 carcinogen and has developed a unit risk of 4×10^{-6} per µg/m3 which would equate to an additional lifetime risk of 1 in 100,000 at a 1,3-dichloropropene level of 3 µg/m^3. However, because the U.S. EPA has a lower level of confidence with the cancer number MDH has used the RfC for the HRV for 1,3-dichloropropene. It is recommended that the cancer endpoint also be considered when calculating a cancer index.

U. **Dichlorvos.** The portion of the U.S. EPA IRIS database dealing with dichlorvos:

- classifies dichlorvos as a gas with an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $NOAEL_{[HEC]}$ for dichlorvos as 5.0×10^{-2} mg/m^3; and
- lists an uncertainty/modifying factor of 100.

V. **Diesel particulates.** The portion of the U.S. EPA IRIS database dealing with diesel particulates:

- classifies diesel engine emissions as particles with a respiratory effect (formula from part 4717.8300, subpart 3);
- lists the $NOAEL_{[HEC]}$ as 1.55×10^{-1} mg/m^3; and
- lists an uncertainty/modifying factor of 30.

Diesel emissions were extensively discussed with the HRV workgroup during the HRV workgroup meeting on May 21, 1997. Controversial issues regarding the derivation for a toxicity value for diesel engine emissions include whether or not diesel emissions should be considered to be carcinogenic, and whether adverse health effects are due to hazardous air pollutants attached to the particulate or from other gaseous components of diesel emissions. While some of the questions remain unanswered because of a lack of scientific knowledge, exposure to high levels of diesel emissions are recognized to be a potential chronic health hazard.

As a result of workgroup discussion, MDH has used the term "diesel particulate" rather than EPA's "diesel emissions" because it has been hypothesized that the particle fraction is the most important from a disease causation standpoint (U.S. EPA, 1994b). MDH has chosen not to propose a cancer-based HRV for diesel particulate at this time.

W. **N, N-dimethylformamide.** The portion of the U.S. EPA IRIS database dealing with N, N-dimethylformamide:

- classifies N, N-dimethylformamide as a soluble vapor or gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $LOAEL_{[HEC]}$ as 7.9 mg/m^3; and
- lists an uncertainty/modifying factor of 300.

X. **Epichlorohydrin.** The portion of the U.S. EPA IRIS database dealing with epichlorohydrin:

- classifies epichlorohydrin as a class B2 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 1.2×10^{-6} per µg/m^3.

Y. **1, 2-Epoxybutane.** The portion of the U.S. EPA IRIS database dealing with 1, 2-epoxybutane:

- classifies 1, 2-epoxybutane as a gas with a respiratory effect (formula from part 4717.8300, subpart 5);
- lists the $LOAEL_{[HEC]}$ as 4.8 mg/m^3; and
- lists an uncertainty/modifying factor of 300.

Z. **Ethylene glycol monobutyl ether (EGBE).** The portion of the U.S. EPA IRIS database dealing with ethylene glycol monobutyl ether (EGBE):

- classifies ethylene glycol monobutyl ether as a gas with an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $BMC_{[HEC]}$ as 3.8×10^{2} mg/m^3; and

- lists an uncertainty/modifying factor of 30.

AA. **Formaldehyde.** The portion of the U.S. EPA IRIS database dealing with formaldehyde:
- classifies formaldehyde as a class B1 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 1.3×10^{-5} per $\mu g/m^3$.

BB. **1, 6-Hexamethylene diisocyanate.** The portion of the U.S. EPA IRIS database dealing with 1,6-hexamethylene diisocyanate:
- classifies 1,6-hexamethylene diisocyanate as a gas with a respiratory effect (formula from part 4717.8300, subpart 5);
- lists the $NOAEL_{[HEC]}$ as 1.0×10^{-3} mg/m3; and
- lists an uncertainty/modifying factor of 100.

CC. **n-Hexane.** The portion of the U.S. EPA IRIS database dealing with n-hexane:
- classifies n-hexane as a soluble vapor having an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $LOAEL_{[HEC]}$ as 7.3×10^{1} mg/m^3; and
- lists an uncertainty/modifying factor of 300.

In developing the HRV for hexane MDH considered new information regarding hexane's toxicity and chose to reduce the overall uncertainty factor to 30. MDH considered the LOAEL to be a mild effect and reduced the uncertainty factor for extrapolation from a LOAEL rather than a NOAEL from 10 to 3. MDH also considered information not available to EPA when the IRIS number was developed and felt it was appropriate to remove an uncertainty factor of 3 that EPA had applied for data deficiencies. These decisions resulted in a 10-fold reduction in the original IRIS uncertainty factor.

DD. **Hydrazine / Hydrazine sulfate.** The portion of the U.S. EPA IRIS database dealing with hydrazine/ hydrazine sulfate:
- classifies hydrazine/ hydrazine sulfate as a class B2 or probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 4.9×10^{-3} per $\mu g/m^3$.

EE. **Hydrogen chloride.** The portion of the U.S. EPA IRIS database dealing with hydrogen chloride:
- classifies hydrogen chloride as a gas having a respiratory effect (formula from part 4717.8300, subpart 5);
- lists the $LOAEL_{[HEC]}$ as 6.1 mg/m^3; and
- lists an uncertainty/modifying factor of 300.

FF. **Hydrogen cyanide.** The portion of the U.S. EPA IRIS database dealing with hydrogen cyanide:
- classifies hydrogen cyanide as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $LOAEL_{[HEC]}$ as 2.5 mg/m^3; and
- lists an uncertainty/modifying factor of 1,000.

GG. **Manganese.** The portion of the U.S. EPA IRIS database dealing with manganese classifies manganese as a particle with an extrarespiratory effect (formula from part 4717.8300, subpart 4);

MDH used information obtained from the IRIS database and calculated the HRV using:

- a $BMC_{[HEC]}$ of 1.9×10^{-2} mg/m^3; and
- an uncertainty/modifying factor of 100.

MDH used the same study as the U.S. EPA to develop a RfC, however, MDH incorporated more recent U.S. EPA methodology in determination of the HRV for manganese. Enough information was provided in the Roels et al. (1992) study to enable MDH to calculate an HRV based on the logistic regression equation provided in that study. Because the Roels et al. (1992) study provides adequate information to determine the response at the lower end of the dose response curve, MDH used this logistic regression equation as the starting point for calculation of the chronic HRV.

According to Roels et al. (1992), a lifetime integrated exposure to manganese (Mn) dust above 3,575 µg per year (total Mn dust) or 730 $\mu g/m^3$ per year (respirable Mn dust), causes slight neurofunctional changes in a significant proportion of exposed subjects. MDH calculated the integrated exposure corresponding to a 5% response or 287 $\mu g/m^3$.

Using the same adjustments as used by the U.S. EPA:

287 $\mu g/m^3$ * years/ 5.3 years ave. exposure duration = 54.15 $\mu g/m^3$

and

54.15 $\mu g/m^3$ * 10 m^3/day / 20 m^3/day * 5 days/ 7 days = 19.3 $\mu g/m^3$.

Because MDH uses the logistic regression curve to determine a 5% response, the uncertainty factor for extrapolation from a LOAEL to a NOAEL is unnecessary. The overall uncertainty factor is therefore 100: 10 to account for sensitive individuals; 3 for database deficiencies including the lack of developmental toxicity and chemical speciation data; and 3 for extrapolation to lifetime exposure duration using a less than lifetime study.

The chronic HRV based on logistic regression is:

19.3 $\mu g/m^3$ / 100 = 0.193 $\mu g/m^3$ (0.2 $\mu g/m^3$ when rounded to one significant figure)

HH. **Methyl methacrylate.** The portion of the U.S. EPA IRIS database dealing with methyl methacrylate:
- classifies methyl methacrylate as a gas having a respiratory effect (formula from part 4717.8300, subpart 5);
- lists a $BMC_{[HEC]}$ of 7.2 mg/m^3; and
- lists an uncertainty/modifying factor of 10.

II. **Methylene diphenyl diisocyanate and polymeric methylene diphenyl diisocyanate.** The portion of the U.S. EPA IRIS database dealing with methylene diphenyl diisocyanate (MDI) and polymeric methylene diphenyl diisocyanate (PMDI):
- classifies methylene diphenyl diisocyanate (MDI) and polymeric methylene diphenyl diisocyanate (PMDI) as particles having a respiratory effect (formula from part 4717.8300, subpart 3);
- lists a $BMC_{[HEC]}$ of 6.0×10^{-2} mg/m^3; and
- lists an uncertainty/modifying factor of 100.

JJ. **Naphthalene.** The portion of the U.S. EPA IRIS database dealing with naphthalene:
- classifies naphthalene as a gas having both respiratory and extrarespiratory effect (formula from part 4717.8300, subpart 6);

- lists the $LOAEL_{[HEC]}$ as 9.3 mg/m^3; and
- lists an uncertainty/modifying factor of 3,000.

Although the toxicologic endpoint of concern for naphthalene is the upper respiratory system, the U.S. EPA's RfC and MDH's HRV for naphthalene were calculated using the equation for a gas having an extrarespiratory effect. This approach was necessary because naphthalene's respiratory effect on the nasal epithelium is not due to direct contact, but occurs following the absorption and subsequent metabolism of naphthalene to reactive products that are responsible for the toxic effects .

KK. **Nickel refinery dust.** The portion of the U.S. EPA IRIS database dealing with nickel refinery dust:
- classifies nickel refinery dust as a class A or known human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 2.4×10^{-4} per $\mu g/m^3$.

LL. **Nickel subsulfide.** The portion of the U.S. EPA IRIS database dealing with nickel subsulfide:
- classifies nickel subsulfide as a class A or known human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 4.8×10^{-4} per $\mu g/m^3$.

MM. **2-Nitropropane.** The portion of the U.S. EPA IRIS database dealing with 2-nitropropane:
- classifies 2-nitropropane as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $LOAEL_{[HEC]}$ as 1.6×10^{1} mg/m^3; and
- lists an uncertainty/modifying factor of 1,000.

NN. **Propylene oxide.** The portion of the U.S. EPA IRIS database dealing with propylene oxide:
- classifies propylene oxide as a class B2 or a probable human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 3.7×10^{-6} per $\mu g/m^3$.

OO. **Styrene.** The portion of the U.S. EPA IRIS database dealing with styrene:
- classifies styrene as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $NOAEL_{[HEC]}$ as 3.4×10^{1} mg/m^3; and
- lists an uncertainty/modifying factor of 30.

PP. **Toluene.** The portion of the U.S. EPA IRIS database dealing with toluene:
- classifies toluene as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $LOAEL_{[HEC]}$ as 1.19×10^{2} mg/m^3; and
- lists an uncertainty/modifying factor of 300.

QQ. **2,4-/2,6-Toluene diisocyanate (TDI).** The portion of the U.S. EPA IRIS database dealing with toluene diisocyanate:
- classifies toluene diisocyanate as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6);
- lists the $NOAEL_{[HEC]}$ as 2.3×10^{-3} mg/m^3; and
- lists an uncertainty/modifying factor of 30.

Although the toxicologic endpoint of concern for TDI is the lower respiratory system, the U.S. EPA's RfC and MDH's HRV for TDI were calculated using the equation for a gas having an extrarespiratory effect. TDI is a sensitizer that can cause an immune system response (an extrarespiratory effect) in an individual exposed to TCI. Because this immune response can impact the lower respiratory system and cause breathing difficulties, the endpoint of concern is the lower respiratory system.

RR. **Vinyl acetate.** The portion of the U.S. EPA IRIS database dealing with vinyl acetate:

- classifies vinyl acetate as a gas having a respiratory effect (formula from part 4717.8300, subpart 5);
- lists the $NOAEL_{[HEC]}$ as 5 mg/m^3; and
- lists an uncertainty/modifying factor of 30.

SS. **Vinyl chloride.** The portion of the U.S. EPA IRIS database dealing with vinyl chloride:

- classifies vinyl chloride as a class A or known human carcinogen (formula from part 4717.8400, subpart 2); and
- lists the unit risk as 8.8×10^{-6} per $\mu g/m^3$.

4717.8150 TABLE OF SUBCHRONIC HRVs.

For each substance or chemical listed in the table, the variables required to calculate the subchronic HRV using the formulas provided in parts 4717.8300 for noncarcinogenic toxicants are provided. RfCs and RfDs are derived by dividing the selected NOAEL, LOAEL, BMD, or BMC The variables for noncarcinogens are the $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$,or $BMC_{[HEC]}$, and the uncertainty factor. The $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$,or $BMC_{[HEC]}$ are divided by the uncertainty factor to account for the scientific uncertainty inherent in the dose response assessment process. The endpoint of concern is provided for use in evaluating simultaneous exposure under part 4717.8600.

This part of the SONAR will identify the source of the variables that, unless otherwise noted, is the U.S. EPA's IRIS database (U.S. EPA, 2001). It is reasonable to use scientific data available from the federal agency responsible for environmental standards. Where MDH has diverged from U.S. EPA data, additional justification is provided. The individual subchronic HRVs are not justified in this section of the SONAR because they are mathematically derived from the equations in parts 4717.8300 and 4717.8400. See those parts for an explanation on the reasonableness of the formulas.

A. **Acrolein.** The portion of the U.S. EPA IRIS database dealing with acrolein:

- classifies acrolein as a gas having an respiratory effect (formula from part 4717.8300, subpart 5); and
- lists the $LOAEL_{[HEC]}$ as 2.0×10^{-2} mg/m^3.

MDH derived a subchronic HRV for acrolein, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 100.

B. **Acrylic acid.** The portion of the U.S. EPA IRIS database dealing with acrylic acid:

- classifies acrylic acid as a gas having an respiratory effect (formula from part 4717.8300, subpart 5); and
- lists the $LOAEL_{[HEC]}$ as 3.3×10^{-1} mg/m^3.

MDH derived a subchronic HRV for acrylic acid, therefore, the factor of 3 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses an uncertainty factor of 100.

C. **Allyl chloride.** The portion of the U.S. EPA IRIS database dealing with allyl chloride:

- classifies allyl chloride as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $NOAEL_{[HEC]}$ as 3.6 mg/m^3.

MDH derived a subchronic HRV for allyl chloride, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 300.

D. **Arsine.** The portion of the U.S. EPA IRIS database dealing with arsine:

- classifies arsine as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $NOAEL_{[HEC]}$ as 1.4×10^{-2} mg/m^3.

MDH derived a subchronic HRV for arsine, therefore, the factor of 3 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 100.

E. **Chlordane.** The portion of the U.S. EPA IRIS database dealing with chlordane:

- classifies chlordane as a particle having an extrarespiratory effect (formula from part 4717.8300, subpart 4); and
- lists the $NOAEL_{[HEC]}$ as 6.5×10^{-1} mg/m^3.

MDH derived a subchronic HRV for chlordane, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 100.

F. **Chlorine dioxide.** The portion of the U.S. EPA IRIS database dealing with chlorine dioxide:

- classifies chlorine dioxide as a gas having a respiratory effect (formula from part 4717.8300, subpart 5); and
- lists the $LOAEL_{[HEC]}$ as 6.4×10^{-1} mg/m^3.

MDH derived a subchronic HRV for chlorine dioxide, therefore, the factor of 3 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 1,000.

G. **Chromic acid mists and dissolved Cr (VI) aerosols.** The portion of the U.S. EPA IRIS database dealing with chromic acid mist and dissolved Cr (VI) aerosols:

- classifies chromic acid mist and dissolved Cr (VI) aerosols as gases having a respiratory effect (formula from part 4717.8300, subpart 5); and
- lists the $LOAEL_{[HEC]}$ as 7.1×10^{-4} mg/m^3.

MDH derived a subchronic HRV for chromic acid mist and dissolved Cr (VI) aerosols, therefore, the factor of 3 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 30.

H. **Cr (VI) particulates.** The portion of the U.S. EPA IRIS database dealing with chrome (VI) particulate:

- classifies chrome (VI) particulate as particles having a respiratory effect (formula from part 4717.8300, subpart 3); and
- lists the $BMC_{[HEC]}$ as 3.5×10^{-2} mg/m3.

MDH derived a subchronic HRV for chrome (VI) particulate, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 30.

I. **Cumene.** The portion of the U.S. EPA IRIS database dealing with cumene:

- classifies cumene as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $NOAEL_{[HEC]}$ as 4.35×10^{2} mg/m^3.

MDH derived a subchronic HRV for cumene, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 100.

J. **1, 2-Dibromo-3-chloropropane.** The portion of the U.S. EPA IRIS database dealing with 1,2-dibromo-3-chloropropane:

- classifies 1,2-dibromo-3-chloropropane as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $NOAEL_{[HEC]}$ as 1.7×10^{-1} mg/m^3.

MDH derived a subchronic HRV for 1,2-dibromo-3-chloropropane, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 100.

K. **1, 4-Dichlorobenzene.** The portion of the U.S. EPA IRIS database dealing with 1,4-dichlorobenzene:

- classifies 1,4-dichlorobenzene as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $NOAEL_{[HEC]}$ as 7.5×10^{1} mg/m^3.

Since 1,4-dichlorobenzene is classified as a subchronic HRV, the factor of 3 to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. However, MDH uses an additional uncertainty factor of 3 to account for database deficiencies, primarily the lack of respiratory system data which, based on data presented by Hollingsworth et al.(1956) and Weller and Crellin (1953), MDH considers to be an inadequately investigated endpoint.

MDH uses an uncertainty/modifying factor of 100.

L. **1, 2-Dichloropropane.** The portion of the U.S. EPA IRIS database dealing with 1,2-dichloropropane:

- classifies 1,2-dichloropropane as a gas having a respiratory effect (formula from part 4717.8300, subpart 5); and
- lists the $NOAEL_{[HEC]}$ as 1.3 mg/m^3.

MDH derived a subchronic HRV for 1,2-dichloropropane, therefore, the factor of 3 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 100.

M. **Dicyclopentadiene.** For dicyclopentadiene, MDH derived a subchronic HRV using the same study on which EPA used to develop an RfC for HEAST. The RfC is based on a 13 week inhalation toxicity study conducted with rats and mice (Dodd et al., 1982). MDH:

- classifies dicyclopentadiene as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $LOAEL_{[HEC]}$ as 9.6×10^{-1} mg/m^3;
- used a total uncertainty/modifying factor of 300.

N. **2-Dimethylamino ethanol.** MDH based the subchronic HRV for 2-dimethylamino ethanol (DMAE) on a 13-week inhalation rat study by Klonne et al. (1987). MDH:

- classifies 2-dimethylamino ethanol as a gas having a respiratory effect (formula from part 4717.8300, subpart 5); and
- lists the $NOAEL_{[HEC]}$ as 1.96 mg/m^3; and
- used an uncertainty factor of 30.

O. **Ethylene glycol monoethyl ether (EGEE) or 2-ethoxyethanol.** The portion of the U.S. EPA IRIS database dealing with ethylene glycol monoethyl ether (EGEE) or 2-ethoxyethanol:

- classifies EGEE or 2-ethoxyethanol as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $NOAEL_{[HEC]}$ as 6.8×10^{1} mg/m^3.

MDH derived a subchronic HRV for EGEE or 2-ethoxyethanol, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 30.

P. **Ethylene glycol monomethyl ether (EGME) or 2-Methoxyethanol.** The portion of the U.S. EPA IRIS database dealing with ethylene glycol monomethyl ether (EGME) or 2-methoxyethanol:

- classifies EGME or 2-methoxyethanol as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $NOAEL_{[HEC]}$ as 1.7×10^{1} mg/m^3. However, because Miller et al. (1983) showed that exposure of male rabbits to 30 ppm EGME results in testicular effects in a small percentage of animals, MDH uses the 1.7×10^{1} mg/m^3 as a $NOAEL_{[HEC]}$.

MDH derived a subchronic HRV for EGME or 2-methoxyethanol, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses an additional uncertainty factor of 3 to account for the extrapolation of a NOAEL from a LOAEL resulting in a total uncertainty factor of 300.

Q. **Hydrogen sulfide.** The portion of the U.S. EPA IRIS database dealing with hydrogen sulfide:

- classifies hydrogen sulfide as a gas having a respiratory effect (formula from part 4717.8300, subpart 5); and
- lists the $NOAEL_{[HEC]}$ as 1.01 mg/m^3.

MDH derived a subchronic HRV for hydrogen sulfide, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 100.

R. **Phosphine.** The portion of the U.S. EPA IRIS database dealing with phosphine:

- classifies phosphine as a gas having an extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $NOAEL_{[HEC]}$ as 2.5×10^{-1} mg/m^3.

MDH derived a subchronic HRV for phosphine, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 100.

S. **Propylene glycol monomethyl ether.** The portion of the U.S. EPA IRIS database dealing with propylene glycol monomethyl ether:

- classifies propylene glycol monomethyl ether as a gas having a extrarespiratory effect (formula from part 4717.8300, subpart 6); and
- lists the $NOAEL_{[HEC]}$ as 6.58×10^{2} mg/m^3.

MDH derived a subchronic HRV for propylene glycol monomethyl ether, therefore, the factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 30.

T. **Triethylamine.** The portion of the U.S. EPA IRIS database dealing with triethylamine:

- classifies triethylamine as a gas having a respiratory effect (formula from part 4717.8300, subpart 5); and
- lists the $NOAEL_{[HEC]}$ as 1.95×10^{1} mg/m^3

MDH derived a subchronic HRV for triethylamine, therefore, a factor of 10 that IRIS uses to account for extrapolation of a subchronic study to a chronic scenario is unnecessary. MDH uses a total uncertainty factor of 300.

4717.8200 TABLE OF ACUTE HRVs.

For each substance or chemical listed in the table, the variables required to calculate the acute HRV using the formulas provided in parts 4717.8500 for acute toxicity are provided. The endpoint of concern is provided for use in evaluating simultaneous exposure under part 4717.8600.

This part of the SONAR will identify the source of the variables that, in most cases, is Cal EPA's OEHHA REL database. Because the U.S. EPA does not yet have acute toxicity values available on IRIS, MDH relied on other sources for acute values.

Cal RELs were developed in response to state mandates and, because of their availability on the internet (http://www.oehha.org/air/acute_rels/acuterel.html), have received substantial review.

In those cases where MDH diverged from the Cal REL approach for a given chemical, additional justification is provided. The individual acute HRVs are not justified in this section of the SONAR because they are mathematically derived from the equation in part 4717.8500. See those parts for an explanation on the reasonableness of the formulas.

For the acute HRVs, the HRVs are rounded to two significant figures if the uncertainty factor used in the development of that HRV was 10 or less, or 1 significant figure if the uncertainty factor was greater than 10. Digits under 5 are rounded down, while digits 5 and over are rounded up. Where necessary, MDH has converted the units of parts per million (ppm) and parts per billion (ppb) into units of $\mu g/m^3$.

A. **Ammonia.** The portion of the Cal REL database dealing with ammonia:

- classifies ammonia as an eye irritant and a respiratory system toxicant;
- lists the $BMC_{[ADJ]}$ as 13.6 ppm (9.5 mg/m^3); (formula from part 4717.8500, subpart 3 used to calculate a BMC); and
- lists an uncertainty factor of 3.

The HRV is the same as the Cal REL. Ammonia has been more extensively studied more than most chemicals and as a result of this there is a relatively rich data base for this chemical. MDH agrees with the Cal EPA approach of using a BMC analysis to incorporate information from multiple studies to derive a health protection value for ammonia. Concern has been raised regarding the HRV for ammonia because the data set used for the BMC analysis includes some data points that do not fall into the HRV workgroup's preferred exposure time frame of 30 minutes to 8 hours. As stated in part II (Acute Health Risk Values) "Studies where the exposure duration is less than 30 minutes will not be used as the single basis for any one-hour acute HRV." Removal of the studies in question from the analysis results in a loss of statistical power in the modeling and makes a BMC approach impossible. MDH feels that when such data are part of a larger data base, and do not significantly impact the results that would be obtained using an alternative approach, including these data to strengthen the analysis and remove uncertainty is appropriate.

B. **Arsine.** The portion of the Cal REL database dealing with arsine:

- classifies arsine as hematologic or blood toxicant;
- lists the $NOAEL_{[ADJ]}$ as 5 ppm (1.6×10^1 mg/m^3); (formula from part 4717.8500, subpart 4); and
- lists an uncertainty factor of 100.

The HRV differs from the Cal REL because the final value was rounded to one significant figure.

C. **Benzene.** The portion of the Cal REL database dealing with benzene:

- classifies benzene as a reproductive/developmental toxicant;
- lists the NOAEL as 40 ppm (1.3×10^2 mg/m^3); (formula from part 4717.8500, subpart 6); and
- lists an uncertainty factor of 100.

The HRV differs from the Cal REL because the final value was rounded to one significant figure.

D. **Carbon disulfide.** The portion of the Cal REL database dealing with carbon disulfide:

- classifies carbon disulfide as a reproductive/developmental toxicant;
- lists the NOAEL as 200 ppm; (6.2×10^2 mg/m^3); (formula from part 4717.8500, subpart 6); and
- lists an uncertainty factor of 100.

The HRV differs from the Cal REL because the final value was rounded to one significant figure.

E. **Chlorine.** For chlorine, the supporting chemical information was taken from the Cal REL database and an HRV was derived using MDH protocols for developing an acute HRV:

- The Cal REL database classifies Chlorine as an irritant of the eye and the respiratory system; and
- lists the NOAEL as 1 ppm (2.9 mg/m^3). This value was extrapolated to 1.5 mg/m^3 in accordance with MDH guidelines (4717.8500, subpart 3).
- The Cal REL database lists an uncertainty factor of 10.

The HRV differs from the Cal REL because MDH guidelines require a different method for adjustment of the NOAEL or LOAEL when the experimental exposure time ranges from 30 minutes up to, but not including, one hour.

F. **Chloroform.** The portion of the Cal REL database dealing with chloroform:

- classifies chloroform as a reproductive/developmental toxicant;
- lists the LOAEL as 30 ppm (1.5×10^2 mg/m^3); (formula from part 4717.8500, subpart 6); and
- lists an uncertainty factor of 1,000.

The HRV is the same as the Cal REL

G. **Dichloromethane.** For dichloromethane, the supporting chemical information was taken from the Cal REL database for methylene chloride and an HRV was derived using MDH protocols for deriving an acute HRV:

- Dichloromethane is classified as a central nervous system toxicant.
- The Cal REL database lists the LOAEL as 195 ppm (6.8×10^2 mg/m^3); in accordance with MDH acute guidelines (part 4717.8500, subpart 4) no time adjustment was needed.
- An uncertainty factor of 60 was used.

The HRV differs from the Cal REL because the Cal REL was developed using a $LOAEL_{[ADJ]}$ that had been extrapolated from a 90 minute exposure to a one hour concentration using an exponent of 2. In accordance with MDH acute guidelines (part 4717.8500, subpart 4) no time adjustment was needed to develop the HRV.

H **1,4-Dioxane.** The portion of the Cal REL database dealing with 1,4-dioxane:

- classifies 1,4-dioxane as a nasal and eye irritant;
- lists the $LOAEL_{[ADJ]}$ as 50 ppm (1.8×10^2 $mg/m^{3)}$); (formula from part 4717.8500, subpart 4); and
- lists an uncertainty factor of 60.

The HRV is the same as the Cal REL.

I. **Ethyl benzene.** For ethyl benzene, the supporting chemical information was taken from the U.S. EPA IRIS database and an HRV was derived using MDH protocols for deriving an acute HRV. IRIS:

- classifies ethyl benzene as a reproductive/developmental toxicant;
- lists the $NOAEL_{[HEC]}$ as 4.3×10^2 mg/m^3 (formula from part 4717.8500, subpart 6); and
- lists an uncertainty factor of 30.

The acute HRV for ethyl benzene is calculated according to MDH acute protocols for reproductive/developmental toxicity. Developmental toxicity is considered as acute toxicity because even a short exposure could have a severe adverse effect on a developing fetus or newborn if the exposure occurs during a critical period of development. Because the window of vulnerability is unknown, MDH has developed an acute HRV for ethyl benzene.

J. **Ethyl chloride.** For ethyl chloride, the supporting chemical information was taken from the U.S. EPA IRIS database and an HRV was derived using MDH protocols for deriving an acute HRV. IRIS:

- classifies ethyl chloride as a reproductive/developmental toxicant;
- lists the $NOAEL_{[HEC]}$ as 4.0×10^3 mg/m^3 (formula from part 4717.8500, subpart 6); and
- lists an uncertainty factor of 30.

The acute HRV for ethyl chloride is calculated according to MDH acute protocols for reproductive/developmental toxicity. Developmental toxicity is considered as acute toxicity because even a short exposure could have a severe adverse effect on a developing fetus or newborn if the exposure occurs during a critical period of development. Because the window of vulnerability is unknown, MDH has developed an acute HRV for ethyl chloride.

K. **Ethylene glycol monoethyl ether.** The portion of the Cal REL database dealing with ethylene glycol monoethyl ether:

- classifies ethylene glycol monoethyl ether as a reproductive/developmental toxicant;
- lists the NOAEL as 10 ppm (3.7×10^1 mg/m^3); (formula from part 4717.8500, subpart 6); and
- lists an uncertainty factor of 100.

The HRV differs from the Cal REL because the final value was rounded to one significant figure.

L. **Ethylene glycol monoethyl ether acetate.** The portion of the Cal REL database dealing with ethylene glycol monoethyl ether acetate:

- classifies ethylene glycol monoethyl ether acetate as a reproductive/developmental toxicant;
- lists the LOAEL as 25 ppm (1.4×10^2 mg/m^3); (formula from part 4717.8500, subpart 6); and
- lists an uncertainty factor of 1,000.

The HRV differs from the Cal REL because the final value was rounded to one significant figure.

M. **Ethylene glycol monomethyl ether (EGME or 2-methoxymethanol).** The portion of the Cal REL database dealing with ethylene glycol monomethyl ether:

- classifies ethylene glycol monomethyl ether as a reproductive/developmental toxicant;
- lists the NOAEL as 3 ppm (9.3 mg/m^3); (formula from part 4717.8500, subpart 6); and
- lists an uncertainty factor of 100.

The HRV differs from the Cal REL because the final value was rounded to one significant figure.

N. **Formaldehyde.** The portion of the Cal REL database dealing with formaldehyde:

- classifies formaldehyde as an eye and respiratory system irritant;
- lists the BMC as 7.6×10^{-1} ppm (9.4×10^{-1} mg/m^3); (formula from part 4717.8500, for calculation of the BMC); and
- lists an uncertainty factor of 10.

The HRV is the same as the Cal REL.

O. **Hydrogen chloride.** The portion of the Cal REL database dealing with hydrogen chloride:

- classifies hydrogen chloride as an eye and respiratory system irritant;
- lists the $NOAEL_{[ADJ]}$ as 1.4 ppm (2.1 mg/m^3); (formula from part 4717.8500, subpart 3); and
- lists an uncertainty factor of 1.

The HRV is the same as the Cal REL.

P. **Hydrogen cyanide.** The portion of the Cal REL database dealing with hydrogen cyanide:

- classifies hydrogen cyanide as a central nervous system toxicant;
- lists the $NOAEL_{[ADJ]}$ as 3×10^1 ppm (3.4×10^1 mg/m^3); (formula from part 4717.8500, subpart 3); and
- lists an uncertainty factor of 100.

The HRV differs from the Cal REL because the final value was rounded to one significant figure.

Q. **Hydrogen fluoride.** The portion of the Cal REL database dealing with hydrogen fluoride:

- classifies hydrogen fluoride as a respiratory system irritant;
- lists the $NOAEL_{[ADJ]}$ as 3 ppm (2.4 mg/m^3); (formula from part 4717.8500, subpart 4); and
- lists an uncertainty factor of 10.

The HRV is the same as the Cal REL.

R. **Hydrogen sulfide.** For hydrogen sulfide, the supporting chemical information was taken from a study by Jappinen et al. (1990). Using this data, MDH:

- classifies hydrogen sulfide as a respiratory irritant;
- lists the $LOAEL_{[ADJ]}$ as 1.4 mg/m^3 (formula from part 4717.8500, subpart 3); and
- lists an uncertainty factor of 18.

The Jappinen et al. (1990) study had originally been used by California to develop a REL for hydrogen sulfide, but California changed its number and basis for a REL after receiving a great deal of comment that the REL for hydrogen sulfide was not protective enough for odors produced by hydrogen sulfide. The State of Minnesota already has an ambient air quality standard for hydrogen sulfide to protect Minnesotans from odor due to hydrogen sulfide. A more detailed discussion of hydrogen sulfide and the development of an acute HRV for hydrogen sulfide can be found in a MDH HRV rule briefing paper (MDH, 2000).

S. **Methanol.** For methanol, the supporting chemical information was taken from the Cal REL database and an HRV was derived using MDH protocols for deriving an acute HRV. The Cal REL database:

- classifies methanol as a central nervous system toxicant;
- lists the NOAEL as 1.92×10^2 ppm (2.5×10^2 mg/m^3). MDH used this unadjusted value in accordance with part 4717.8500, subpart 4.
- The Cal REL database lists an uncertainty factor of 10.

The HRV differs from the Cal REL because, in accordance with part 4717.8500 subpart 4, MDH did not extrapolate the NOAEL to a one hour exposure.

T. **Methyl bromide.** For methyl bromide, the supporting chemical information was taken from the Cal REL database and an HRV was derived using MDH protocols for deriving an acute HRV. For methyl bromide, the Cal REL database:

- classifies methyl bromide as a central nervous system toxicant;
- lists the LOAEL as 3.5×10^{1} ppm (1.4×10^{2} mg/m^3). MDH used this unadjusted value in accordance with part 4717.8500, subpart 4.
- The Cal REL database lists an uncertainty factor of 60.

The HRV differs from the Cal REL because, in accordance with part 4717.8500 subpart 4, MDH did not extrapolate the LOAEL to a one hour exposure.

U. **Methyl ethyl ketone.** The portion of the Cal REL database dealing with methyl ethyl ketone:

- classifies methyl ethyl ketone as an eye and respiratory system irritant;
- lists the $LOAEL_{[ADJ]}$ as 2.7×10^{2} ppm (8.0×10^{2} mg/m^3); (formula from part 4717.8500, subpart 4); and
- lists an uncertainty factor of 60.

The HRV differs from the Cal REL because the final value was rounded to one significant figure.

V. **Nickel and nickel compounds.** The portion of the Cal REL database dealing with nickel and nickel compounds:

- classifies nickel and nickel compounds as respiratory system irritants;
- lists the $LOAEL_{[ADJ]}$ as 3.4×10^{-2} mg/m^3 (formula from part 4717.8500, subpart 3); and
- lists an uncertainty factor of 6.

The HRV is the same as the REL.

W. **Nitric acid.** The portion of the Cal REL database dealing with nitric acid:

- classifies nitric acid as a respiratory system irritant;
- lists the $NOAEL_{[ADJ]}$ as 3.3×10^{-2} ppm (8.6×10^{-2} mg/m^3) (formula from part 4717.8500, subpart 3); and
- lists an uncertainty factor of 1.

The HRV is the same as the REL.

X. **Phenol.** The portion of the Cal REL database dealing with phenol:

- classifies phenol as an eye and respiratory system irritant;
- lists the $NOAEL_{[ADJ]}$ as 1.5×10^{1} ppm (5.8×10^{1} mg/m^3) (formula from part 4717.8500, subpart 5); and
- lists an uncertainty factor of 10.

The HRV is the same as the REL.

Y. **Phosgene.** The portion of the Cal REL database dealing with phosgene:

- classifies phosgene as a respiratory system irritant;

- lists the $NOAEL_{[ADJ]}$ as 1×10^{-1} ppm (4.0×10^{-1} mg/m^3) (formula from part 4717.8500, subpart 4); and
- lists an uncertainty factor of 100.

The HRV is the same as the REL.

Z. **Sodium hydroxide.** The portion of the Cal REL database dealing with sodium hydroxide:
- classifies sodium hydroxide as an eye, skin, and respiratory system irritant;
- lists the $LOAEL_{[ADJ]}$ as 5×10^{-1} mg/m^3 (formula from part 4717.8500, subpart 4); and
- lists an uncertainty factor of 60.

The HRV is the same as the REL.

AA. **Styrene.** The portion of the Cal REL database dealing with styrene:
- classifies styrene as an eye and respiratory system irritant;
- lists the $NOAEL_{[ADJ]}$ as 5.1×10^{1} ppm (2.1×10^{2} mg/m^3) (formula from part 4717.8500, subpart 4); and
- lists an uncertainty factor of 10.

The HRV is the same as the REL.

BB. **Tetrachloroethylene or perchloroethylene.** The portion of the Cal REL database dealing with tetrachloroethylene or perchloroethylene:
- classifies tetrachloroethylene or perchloroethylene as an eye and respiratory system irritant, and a central nervous system toxicant;
- lists the $LOAEL_{[ADJ]}$ as 1.2×10^{3} mg/m^3 (formula from part 4717.8500, subpart 5); and
- lists an uncertainty factor of 60.

The HRV is the same as the REL.

CC. **Toluene.** The portion of the Cal REL database dealing with toluene:
- classifies toluene as an eye and respiratory system irritant, and a central nervous system toxicant;
- lists the $NOAEL_{[ADJ]}$ as 9.8×10^{1} ppm (3.7×10^{2} mg/m^3) (formula from part 4717.8500, subpart 5) ; and
- lists an uncertainty factor of 10.

The HRV is the same as the REL.

DD. **1, 1, 1-Trichloroethane or methyl chloroform.** The portion of the Cal REL database dealing with 1,1,1-trichloroethane or methyl chloroform:
- classifies 1,1,1-trichloroethane or methyl chloroform as a central nervous system toxicant;
- lists the $NOAEL_{[ADJ]}$ as 1.25×10^{2} ppm (6.8×10^{2} mg/m^3) (formula from part 4717.8500, subpart 3); and
- lists an uncertainty factor of 10.

The HRV is the same as the REL.

EE. **Trichloroethylene.** For trichloroethylene, MDH used a study by Healy et al. (1982) to develop an acute HRV. MDH:

- classifies trichloroethylene as a reproductive/developmental toxicant;
- lists the LOAEL as 5.4×10^2 mg/m^3 (formula from part 4717.8500, subpart 6); and
- lists an uncertainty factor of 300.

Healy et al. (1982) exposed Wistar rats to 100 ppm trichloroethylene for 4-hours daily from day 8 to day 21 of gestation and found statistically significant decreases in litter size, skeletal abnormalities, and total fetal resorptions. Using its acute procedures, MDH calculated an acute HRV using a total uncertainty factor of 300 (10 for intraspecies variation; 10 for use of a LOAEL rather than a NOAEL; and 3 for interspecies variation).

FF. **Triethylamine.** The portion of the Cal REL database dealing with triethylamine:

- classifies triethylamine as an eye irritant;
- lists the $NOAEL_{[ADJ]}$ as 2.8×10^1 mg/m^3 (formula from part 4717.8500, subpart 5); and
- lists an uncertainty factor of 10.

The HRV is the same as the REL.

GG. **Vanadium pentoxide.** The portion of the Cal REL database dealing with vanadium pentoxide:

- classifies vanadium pentoxide as a respiratory system irritant;
- lists the $LOAEL_{[ADJ]}$ as 3.0×10^{-1} mg/m^3 (formula from part 4717.8500, subpart 5); and
- lists an uncertainty factor of 10.

The HRV is the same as the REL.

HH. **Xylenes.** The portion of the Cal REL database dealing with xylenes:

- classifies xylenes as an eye and respiratory system irritant, and a central nervous system toxicant;
- lists the $NOAEL_{[ADJ]}$ as 5×10^1 ppm (2.2×10^2 mg/m^3) (formula from part 4717.8500, subpart 3) ; and
- lists an uncertainty factor of 10.

The HRV is the same as the REL.

4717.8250 TABLE OF MHRVs FOR MULTIMEDIA EXPOSURE TO AIR TOXICS.

For each substance or chemical listed in the table, the variables required to calculate the MHRV using the formulas provided in parts 4717.8350 for noncarcinogenic toxicants and part 4717.8450 for carcinogens are provided. The endpoint of concern is provided for use in evaluating simultaneous exposure under parts 4717.8550 and 4717.8600.

This part of the SONAR will identify the source of the variables that is, in most cases, the U.S. EPA's IRIS database. It is reasonable to use scientific data available from the federal agency responsible for environmental standards. Where MDH has diverged from U.S. EPA data, additional justification is

provided. The individual MHRVs are not justified in this section of the SONAR because they are mathematically derived from the equations in parts 4717.8350 and 4717.8450. See those parts for an explanation on the reasonableness of the formulas.

A. **Antimony.** The portion of the U.S. EPA IRIS database dealing with antimony:
- classifies antimony as a hematologic system toxicant (formula from part 4717.8350, subpart 2);
- lists the LOAEL as 3.5×10^{-1} milligrams/kilogram-day; and
- lists an uncertainty factor of 1,000.

B. **Arsenic.** The portion of the U.S. EPA IRIS database dealing with arsenic:
- classifies arsenic as a class A or human carcinogen (formula from part 4717.8450, subpart 2); and
- lists the oral slope factor as 1.5 per milligram/(kilogram/day).

C. **Benzo[a]pyrene.** The portion of the U.S. EPA IRIS database dealing with benzo[a]pyrene:
- classifies benzo[a]pyrene as a class B2 or probable human carcinogen (formula from part 4717.8450, subpart 2); and
- lists the oral slope factor as 7.3 per milligram/(kilogram/day).

Benzo[a]pyrene is a member of a large group of chemicals referred to as polyaromatic hydrocarbons or PAHs. There are a number of different PAHs and often toxicity information is lacking for individual compounds within this group. MDH anticipates that this MHRV will provide a value that can be used as a surrogate or an equivalency factor when information about individual PAHs is not available.

D. **Cadmium.** The portion of the U.S. EPA IRIS database dealing with cadmium:
- classifies cadmium as a renal noncarcinogenic toxicant (formula from part 4717.8350, subpart 2);
- lists the NOAEL for cadmium as 5.0×10^{-3} milligrams/kilogram-day; and
- lists an uncertainty factor of 10.

E. **Manganese.** The portion of the U.S. EPA IRIS database dealing with manganese:
- classifies manganese as a nervous system toxicant (formula from part 4717.8350, subpart 2);
- lists the NOAEL for manganese as 1.4×10^{-1} milligrams/kilogram-day; and
- lists an uncertainty factor of 1;
- when the total uncertainty/modifying factor is less than 10, two significant figures are used.

F. **Methylmercury.** The portion of the U.S. EPA IRIS database dealing with methylmercury:
- classifies mercury as a developmental and nervous system toxicant (formula from part 4717.8350, subpart 2);
- lists the benchmark dose (BMD) for methylmercury as 1×10^{-3} milligrams/kilogram-day; and
- lists an uncertainty/modifying factor of 10.

G. **Nickel.** The portion of the U.S. EPA IRIS database dealing with nickel:
- classifies nickel as having a noncarcinogenic effect causing decreased body and organ weights (formula from part 4717.8350, subpart 2);
- lists the $NOAEL_{[ADJ]}$ for nickel as 5 milligrams/kilogram-day;
- lists an uncertainty/modifying factor of 300.

H. **Polychlorinated biphenyls (PCBs).** MDH previously developed criteria for PCBs for use in issuing fish consumption advice (MDH, 1995). MDH:

- classifies PCBs as developmental toxicants (formula from part 4717.8350, subpart 2);
- lists the LOAEL for PCBs as 5×10^{-4} milligrams/kilogram-day;
- lists an uncertainty/modifying factor of 10.

There are a number of different PCBs and often toxicity information is lacking for individual compounds within this group. MDH anticipates that this MHRV will provide a value that can be used as a surrogate or an equivalency factor when information about individual PCBs is not available.

I. **2, 3, 7, 8-Tetrachlorodibenzo[p]dioxin (TCDD).** The portion of HEAST dealing with TCDD:

- classifies TCDD a class B2 or probable human carcinogen (formula from part 4717.8450, subpart 2);
- lists the oral slope factor as 1.5×10^{5} per milligram/(kilogram/day) (HEAST, 1995).

TCDD is a member of a large class of chemicals, the chlorinated[p]dioxins. The toxicity of TCDD has been extensively characterized, however, much less information is available for other members of this class. MDH anticipates that the MHRV for TCDD will provide a value that can be used as a surrogate or an equivalency factor for the class of chlorinated[p]dioxins when toxicologic information about individual congeners is unavailable.

4717.8300 EQUATIONS FOR CALCULATION OF HRVs FOR NONCARCINOGENIC TOXICANTS.

This part describes the proposed methods for the calculation of an HRV for a noncarcinogenic toxicant. The proposed methods are the same as those used by the U.S. EPA to calculate a RfC for a noncarcinogenic toxicant such as those listed in the IRIS database. Methodology for deriving an RfC or inhalation health-based value is described in *Interim Methods for Development of Inhalation Reference Doses* (U.S. EPA, 1989) and *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994a).

Subpart 1. **Scope.** Subpart 1 is necessary to establish that the equations within this part refer to noncarcinogenic toxicants that are potentially harmful to human health when inhaled. The equations are consistent with U.S. EPA methodology (U.S. EPA, 1989; 1994a).

Subp. 2. **General equation; calculating HRV for noncarcinogenic toxicant.** Subpart 2 is necessary to provide the general equation for calculating an HRV and to define each component of that equation for a direct contact, noncarcinogenic toxicant. Units are provided to display the mathematic steps taken to arrive at the HRV. HRVs are expressed in concentrations of micrograms of chemicals, substances or defined mixtures per cubic meter of air.

Items A to E are necessary to specify each of the units of measurement for the terms used in this equation.

Subp. 3. **Equation for $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$, or $BMC_{[HEC]}$; particles with a respiratory effect.** Subpart 3 is necessary to provide the equation for calculating an HRV for a chemical or substance considered to be a particulate, having the potential to produce adverse health effects in the respiratory system. The use of the equation in this subpart is limited at this time to relatively insoluble and non-hygroscopic particles. To calculate a $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$, or $BMC_{[HEC]}$ the $NOAEL_{[ADJ]}$, $LOAEL_{[ADJ]}$, or $BMC_{[ADJ]}$ from animal studies is multiplied by the regional deposited dose ratio (RDDR). For a chemical or substance that is inhaled as a relatively insoluble particulate, body weight is generally used as the normalizing factor between animals and humans.

The RDDR may take into account one, two or three of the respiratory tract regions. It is frequently desirable to use a normalizing factor when deriving a numerical value for a human exposure based on data obtained from an animal study. Other factors sometimes needed to calculate a RDDR include the chemical concentration, the minute volume, and the fractional deposition in the region of interest in the respiratory tract.

Additional detail on calculating RDDRs for particles are available in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994a).

Items A to C are necessary to specify each of the units of measurement for the terms used in this equation.

Subp. 4. **Equation for calculating $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$ or $BMC_{[HEC]}$; particles with extrarespiratory effect.** This subpart is necessary to provide an equation for calculating a $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$, or $BMC_{[HEC]}$ for particles having an extrarespiratory tract effect, i.e. a health effect outside of the respiratory tract.

The $RDDR_{ER}$ is the regional deposited dose ratio for extrarespiratory effects.

Items A to C are necessary to specify each of the units of measurement for the terms used in this equation.

Subp. 5. **Equation for $NOAEL_{[HEC]}$, $LOAEL_{HEC}$, or $BMC_{[HEC]}$; gas with respiratory tract effect.** This subpart is necessary to provide an equation for calculating a $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$, or $BMC_{[HEC]}$ for a gas or soluble aerosol that has an effect on the respiratory tract. A RDGR is the regional gas dose ratio in a specific region of the respiratory tract. To calculate the RGDR for a human using data from an animal study, a multiplicative factor may be used to convert an observed inhalation gas exposure concentration of an animal (A) to the predicted inhalation gas exposure concentration for a human (H) that is associated with the same dose delivered to the specific target tissue. This equation is expressed as the ratio (RGDR) of the regional gas dose for an animal (RGD_A) over the regional gas dose for a human (RGD_H).

For a chemical or substance that is inhaled as a gas and then exerts effects on the respiratory system, surface areas of each affected lung region are generally used as the normalizing factor between animals and humans. The use of pharmacokinetic and pharmacodynamic data, may require incorporation of default values for additional parameters such as minute volumes, regional surface areas, and estimation of overall mass transport coefficients and penetration fractions. Further detail on calculating RGDRs for category 1 or category 2 gases is available in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994a).

Items A to C are necessary to specify each of the units of measurement for the terms used in this equation.

Subp. 6. **Equation for $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$, or $BMC_{[HEC]}$; gas with extrarespiratory tract effect.** This subpart is necessary to provide an equation for calculating the $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$, or $BMC_{[HEC]}$ for a gas or soluble aerosol that has an extrarespiratory effect or an effect outside of the respiratory tract. This extrarespiratory effect is important for category 3 gases and is often important when calculating the potential for health effects caused by exposures to category 2 gases. Category 3 gases are relatively water insoluble and tend to be unreactive in the extrathoracic and tracheobronchial regions of the respiratory tract. Both category 2 and 3 gases may significantly accumulate in the blood so these gases have the potential to exert their toxicity at target tissues outside the respiratory tract.

This equation is expressed as the $NOAEL_{[HEC]}$, $LOAEL_{[HEC]}$, or the $BMC_{[HEC]}$ times the ratio of the blood:gas partition coefficient for an animal (Hb/g)A over the blood:gas partition coefficient for a human (Hb/g)H.

For a chemical or substance that is inhaled as a gas and exerts an extrarespiratory effect, the uptake of these gases is predominantly in the pulmonary region and is perfusion limited. Further detail on calculating human equivalent concentrations category 2 or category 3 gases is available in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994a).

Items A to C are necessary to specify each of the units of measurement for the terms used in this equation.

4717.8350 EQUATION FOR CALCULATION OF MHRV FOR NONCARCINOGENIC TOXICANTS.

Subpart 1. **Scope.** This part describes the methods for the calculation of a MHRV for a noncarcinogenic toxicant. MHRVs have been developed for those situations where the primary risk of human exposures to chemicals emitted to the air is from a route other than inhalation. Details of this approach are presented in part I (Chronic, Subchronic, and Multimedia Health Risk Values) of this SONAR.

Subp. 2. **General equation for of MHRV for noncarcinogenic toxicant.** This subpart is necessary to present the general equation for calculating a MHRV for a chemical or defined mixture of chemicals. The method for deriving a MHRV is the same as that used by the U.S. EPA to calculate a RfD (U.S. EPA, 1993). MHRVs are health-based exposure concentrations that specify safe levels of daily exposure over a lifetime. The chronic MHRVs are derived from long-term human epidemiology studies or from chronic animal studies.

Items A to E are necessary to specify each of the units of measurement for the terms used in the equations.

4717.8400 EQUATION FOR CALCULATION OF HRVS FOR CARCINOGENS.

This part describes the methods for calculation of a HRV for a carcinogenic toxicant. The methods are the same as those used by the U.S. EPA to calculate carcinogenic risks (U.S. EPA, 1986a). Only carcinogens categorized as group A or group B are considered to be carcinogenic.

Chemicals or mixtures of chemicals are not considered carcinogenic if they are classified by the U.S. EPA as group C, D, or E carcinogens.

Subpart 1. **Scope.** Subpart 1 is necessary to establish that the equations within this part refer to carcinogens that are potentially harmful to health by exposure through the route of inhalation.

Subp. 2. **Equation for carcinogens.** This subpart is necessary to define, by an equation, the general calculation of a carcinogenic HRV.

Items A to C are necessary to specify each of the units of measurement for the terms used in the equations.

4717.8450 EQUATION FOR CALCULATION OF MHRVs FOR CARCINOGENS.

This part describes the methods used for the calculation of a MHRV for a carcinogenic toxicant and establishes that the MHRVs are intended for use when chemicals are emitted to the air but where the primary risk from exposure occurs through routes other than inhalation. Both the MHRVs and the HRVs use additional lifetime risk in the numerator of the equation; however, the terms of the denominator differ. For air, the denominator (unit risk) is expressed as a concentration of a chemical in a specified volume of air. For MHRVs, the denominator (potency slope) is expressed as a dose, or milligrams of a chemical per kilogram of body weight of an individual per day.

The proposed methods are the same methods used by the U.S. EPA to calculate carcinogenic risks for non-inhalation exposures (U.S. EPA, 1986a). Only carcinogens categorized as group A or group B are considered to be carcinogenic. Chemicals or mixtures of chemicals are not considered carcinogenic if they are classified as group C, D, or E carcinogens.

Subpart 1. **Scope.** Subpart 1 describes the methods used to calculate MHRVs for carcinogenic chemicals emitted to air that are primarily toxic by non-inhalation exposure routes.

Subp. 2. **General equation for calculating MHRVs for carcinogens.** This subpart is necessary to present the general equation for calculating a MHRV for a carcinogenic chemical or defined mixture of chemicals.

Items A to D are necessary to specify each of the units of measurement for the terms used in this equation.

4717.8500 EQUATIONS FOR CALCULATION OF HRVs FOR ACUTE TOXICITY.

Subpart 1. **Scope.** This part describes the methods used to calculate acute HRVs for noncarcinogenic toxicants. Details of this approach are presented in part II (Acute Health Risk Values) of this SONAR.

Subp. 2. **General equation for calculating an HRV for an acute irritant.** This subpart is necessary to provide the general equation for the calculation of an acute HRV for chemical irritants. An HRV is expressed as a concentration of micrograms of chemical or substance per cubic meter of air.

Items A to E are necessary to specify each of the units of measurement for the terms used in this equation.

Subp. 3. **Equation acute irritant; study exposure time from 30 minutes to one hour.** Subpart 3 is necessary to provide guidance for calculating an acute HRV when the duration of the study or time to effect ranges from 30 minutes up to, but not including, one hour. Following lengthy discussions with the subgroup and full workgroup, it was decided that studies where the exposure duration is less than 30 minutes would not be used as the sole determinant for a one-hour acute HRV. If the experimental exposure duration of the study was between 30 minutes and one hour, a simple Haber's Law adjustment for time would be made to adjust the exposure to a one-hour concentration. This adjustment is made to estimate the concentration that would have occurred as a result of a one-hour exposure.

Items A to C are necessary to specify each of the units of measurement for the terms used in this equation.

Subp. 4. **Equation for acute irritant; study exposure time from one to two hours.** This subpart is necessary to provide a method for using studies where the exposure duration falls within the one to two hour range. For studies where the exposure duration is one hour up to and including two hours, no adjustment for time or concentration will be made. The NOAEL, LOAEL or BMC from the study will be used, without conversion, as the concentration that is then divided by the uncertainty and/or modifying factors to arrive at an acute HRV.

Items A and B are necessary to specify each of the units of measurement for the terms used in this equation.

Subp. 5. **Equation for acute irritant; study exposure time from than two to eight hours.** This subpart is necessary to provide a method for using data from studies where the exposure duration is greater than 2 hours but less than or equal to 8 hours. For such studies, an adjustment to a one hour scenario is done using the ten Berge equation (ten Berge et al., 1986). MDH's HRV workgroup decided that, in general, studies with exposure durations greater than 8 hours should not be used to derive non-developmental, acute HRVs.

Item B designates the default value for n as 2 unless otherwise specified. This is the same default value used by the State of California in the development of their acute RELs. Values for n may be determined experimentally; however, different endpoints of concern such as irritation and lethality may have different n

values, raising questions regarding the selection of an appropriate value of n. When a clearly appropriate value for n is available, it will be used in the ten Berge equation.

During an analysis of experimentally derived values for n, Cal EPA's OEHHA found that both published and OEHHA derived values for n range from 0.8 to 4.6 with an average of 2. The inter-quartile range (25%-75%), where most of the n values are found, is from 1 to 2.2 (Cal EPA, 1999). OEHHA therefore, chose a default value of 2 for the exponent n in the ten Berge equation when an empirically derived value for the exponent was unavailable. MDH has chosen to adopt California's decision and will use a default value of 2 for n unless otherwise noted.

Items A to D are necessary to specify each of the units of measurement for the terms used in this equation.

Subp. 6. **Calculation of HRV for chemical causing reproductive/developmental toxicity.** This subpart is necessary to provide the general equation for calculation of an HRV for a chemical that acts as reproductive/developmental toxicant. Primary justification is provided in part II (Acute Health Risk Values, Reproductive/Developmental Effects) of this document.

Items A to E are necessary to specify each of the units of measurement for the terms used in this equation.

CANCER INDEX AND HAZARD INDEX

In general, the RfCs, RfDs, cancer potency slopes, and unit risks used to develop HRVs and MHRVs specified in rule parts 4717.8100, 4717.8150, 4717.8200, and 4717.8250 are calculated for exposure to a single chemical or compound. However, MDH recognizes the fact 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 may cause adverse effects that would not be predicted based on separate exposures to individual chemicals, even if each component of the mixture is present at a concentration below its HRV. Chemicals can cause an additive response where the total effect is the sum of each chemical's individual effect. Mixtures can cause a synergistic response where the total effect is much greater than an additive response, or cause an antagonistic response where the effect is less than the additive response. Because of these potential interactions, it is possible that individual HRVs will not provide an adequate margin of safety for the additive effects that might result from combinations of chemicals or defined mixtures. Unfortunately, there are few data that address the toxicology of mixtures and the development of risk assessment tools to handle complex mixtures has been slow. In those cases where toxicity data for mixtures were available (e.g. diesel exhaust), MDH evaluated and used the information to develop HRVs and MHRVS for those mixtures.

MDH recommends that in those cases where no data are available, the additivity model outlined by the U.S. EPA (U.S. EPA, 1986b) be used to estimate the health risks of exposures to mixtures. The additivity model groups chemicals within a mixture by common endpoints of concern (e.g., a similar mechanism or site of action or a common biological response) and their HRVs or MHRVs are used to calculate a hazard index or cancer index (described below). Minnesota Rules parts 4717.7100 to 4717.7800 for the Health Risk Limits for groundwater contaminants provide a precedent for use of an additivity provision when conducting risk assessments of multiple toxic contaminants and precedence for the use of the hazard index and the cancer index.

Following the U.S. EPA's guidelines for mixtures all carcinogens would be combined into one group and a cancer index would be calculated. Other groups for which a hazard indexes would be calculated would include, but not be limited to, chemicals that cause liver damage, kidney damage, damage to the respiratory system [8], or neurotoxicity. Chemicals or compounds that do not fall into any group are excluded from additivity calculations. As the hazard index or cancer approaches 1, the level of concern increases. A hazard index or cancer index greater than 1 is analogous to finding a level of an individual chemical or compound greater than its HRV or MHRV, and indicates the potential for adverse effects despite the fact that assessing the health risk by addressing chemical or compound doses separately would not raise a health concern. The additivity model does not account for synergistic or antagonistic effects, or for the absence of contaminant interactions; however, the model is a reasonable approach for evaluating the health risk of mixtures.

According to the U.S. EPA guidelines, dose additive models provide reasonable predictions of the toxicities of mixtures composed of a substantial variety of both similar and dissimilar compounds (Pozzani et al, 1959; Smyth et al., 1969; 1970; Murphy, 1980). The U.S. EPA also suggests that based on current information, additivity assumptions are expected to yield generally neutral risk estimates (i.e., neither conservative nor lenient) and are plausible for component compounds that induce similar types of effects at the same sites of action.

As the toxicology of mixtures progresses this model will likely be improved or replaced. MDH will monitor the development of revised or new procedures for assessing the toxicity of mixtures and make recommendations for their use when appropriate.

4717.8550 PROCEDURE FOR DETERMINING CANCER INDEX FOR SIMULTANEOUS EXPOSURE TO MULTIPLE CARCINOGENS.

This part specifies the method for determining whether or not a simultaneous exposure to a mixture of carcinogens exceeds the additional lifetime risk. A cancer index of 1 for a mixture of carcinogenic chemicals is equivalent to an HRV for a single carcinogen.

Subpart 1. **Cancer index.** Specifies that risk of simultaneous exposures to multiple carcinogens must be calculated using the cancer index approach.

Subp. 2. **Carcinogenic HRVs.** This subpart instructs that items A to C apply in determination of the cancer index for multiple carcinogens for any chemical or defined mixture that is considered to be a carcinogen.

Item A specifies the equation for determining a cancer index for carcinogens, i.e., those chemicals or defined mixtures where the endpoint of concern is specified as cancer in part 4717.8100. The cancer index indicates whether the mixture of carcinogens exceeds the additional lifetime risk level. This equation is consistent

[8] Because the chemical effects that occur in the upper respiratory system are often very different from those that occur in the lower respiratory system, MDH has divided the respiratory tract into two areas, the upper and lower respiratory systems. For purposes of the rule the upper respiratory system includes the nose, mouth, nasopharynx, oropharynx, laryngopharynx and larynx and the lower respiratory system includes the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. The tracheobronchial system which includes the trachea, bronchi, bronchioles and terminal bronchioles may be included in either the upper or lower respiratory tract depending on whether upper or the lower parts of the respiratory system are primarily affected.

with the general equation published by the U.S. EPA in the *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b):

Subitem 1 is necessary to specify the numerator in the cancer index equation. This subitem specifies the values and units necessary to calculate the cancer index. E_{Cn}, represents the concentration of a carcinogen detected in air.

Subitem 2 is necessary to specify the denominator in the cancer index equation. This subitem specifies the values and units necessary to calculate the cancer index. HRV_{Cn} represents the HRV for a carcinogen specified in part 4717.8100.

Item B is necessary because each ratio E_{Cn}/HRV_{Cn} represents a fraction of the inhalation concentration of a carcinogen set at an additional lifetime risk level of 1×10^{-5}. If the result of adding the ratios in the equation is 1, then the mixture of carcinogens presents an additional lifetime risk level of 1×10^{-5}, and is equal to an HRV for that combination of carcinogens (i.e., cumulative HRV).

Subp. 3. **Carcinogenic MHRVs.** This subpart instructs that items A to C apply in determination of the cancer index for multiple carcinogens. for any chemical or defined mixture that is considered to be a carcinogen

Item A specifies the equation for determining a cancer index for carcinogens, i.e., those chemicals or defined mixtures where the endpoint of concern is specified as cancer in part 4717.8250. The cancer index indicates whether the mixture of carcinogens exceeds the cumulative MHRV. This equation is consistent with the general equation published by the U.S. EPA in the *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b):

Subitem 1 is necessary to specify the numerator in the cancer index equation. This subitem specifies the values and units necessary to calculate the cancer index. D_{Cn}, represents the dose of a carcinogen in micrograms of chemical per kilogram body weight per day (❍g/kg/day).

Subitem 2 is necessary to specify the denominator in the cancer index equation. This subitem specifies the values and units necessary to calculate the cancer index. $MHRV_{Cn}$ represents the MHRV for a carcinogen specified in part 4717.8250.

Item B is necessary because each ratio D_{Cn}/HRV_{Cn} represents a fraction of the dose of a carcinogen set at an additional lifetime risk level of 1×10^{-5}. If the result of adding the ratios in the equation is 1, the mixture of carcinogens presents an additional lifetime risk level lifetime risk of 1×10^{-5}, and is equal to a MHRV for that combination of carcinogens (i.e., a cumulative MHRV).

4717.8600 PROCEDURE FOR DETERMINING HAZARD INDEX FOR ASSESSING SIMULTANEOUS EXPOSURE TO MULTIPLE NONCARCINOGENIC TOXICANTS

This part specifies the method for determining whether or not a mixture of noncarcinogenic toxicants exceeds the cumulative HRV or the cumulative MHRV. A hazard index of 1 for a mixture of toxicants is equivalent to an HRV for a single chemical.

Subpart 1. **Hazard index.** Specifies that evaluations of simultaneous exposures to multiple toxicants with similar endpoints must be calculated using the hazard index approach.

Subp. 2. **HRVs with noncarcinogenic effects.** This subpart instructs that items A to D apply in determination of the hazard index for multiple noncarcinogenic toxicants through inhalation for any chemical or defined mixture that is considered a noncarcinogenic toxicant

Item A specifies that the first step in the method for determining if a mixture of noncarcinogenic toxicants exceeds a cumulative HRV is to group the substances or chemicals according to the common endpoint of concern specified in part 4717.8100 (chronic HRVs), 4717.8150 (subchronic HRVs), 4717.8200 (acute HRVs). Separate calculations are made for chronic HRVs, subchronic HRVs, MHRVs, and acute HRVs. This is consistent with the U.S. EPA's *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b).

The additivity model is reasonable when a hazard index is calculated for substances or chemicals that have the same mode of toxicological action or same endpoint of concern. A separate hazard index should be generated for each endpoint of concern. In the absence of information to the contrary, it is reasonable to assume that noncarcinogenic toxicants that have a similar endpoint of concern also have similar toxicologic characteristics. Therefore it is reasonable to group the noncarcinogenic toxicants by endpoint of concern.

Item B specifies the second step in the method for determining if a mixture of noncarcinogenic toxicants exceeds the HRV. Step 2 calculates a hazard index for each group of substances or chemicals that share the same endpoint of concern as determined in item A.

Item C specifies the equation for determining a hazard index for noncarcinogenic toxicants, i.e., those chemicals or defined mixtures with a noncarcinogenic endpoint of concern as specified in parts 4717.8100, 4717.8150, and 4717.8200. The hazard index indicates whether the mixture of noncarcinogenic toxicants exceeds the cumulative HRV. The hazard index equation is consistent with the general equation published by the U.S. EPA in the *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b).

Subitem 1 is necessary to specify the numerator in the hazard index equation. This subitem specifies the values and units necessary to calculate the hazard index. E_{STn}, represents the concentration of a noncarcinogenic toxicant detected in air.

Subitem 2 is necessary to specify the denominator in the hazard index equation. This subitem specifies the values and units necessary to calculate the hazard index. HRV_{STn} represents the HRV for a sytemic toxicant specified in parts 4717.8100, 4717.8150, or 4717.8200.

Items D and E are necessary to indicate that the final hazard index calculated from the addition of the proportions having the same toxicological endpoint is comparable to an HRV. A hazard index of 1 is equivalent to a cumulative HRV, and a hazard index greater than 1 exceeds the cumulative HRV.

Subp. 3. **MHRVs with noncarcinogenic effects.** This subpart instructs that items A to C apply in determination of the hazard index for multiple noncarcinogenic toxicants through pathways in addition to inhalation for any chemical or defined mixture that is considered to be a noncarcinogenic toxicant.

Item A specifies the first step in the method for determining if a mixture of noncarcinogenic toxicants exceeds the cumulative MHRV. The first step is to group the substances or chemicals according to the common endpoint of concern specified in part 4717.8250. This is consistent with the U.S. EPA's *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b).

The additivity model is reasonable when a hazard index is calculated for substances or chemicals that have the same mode of toxicological action or same endpoint of concern. A separate hazard index should be generated for each endpoint of concern. In the absence of information to the contrary, it is reasonable to assume that noncarcinogenic toxicants that have a similar endpoint of concern also have similar toxicologic characteristics. Therefore it is reasonable to group the noncarcinogenic toxicants by endpoint of concern.

Item B specifies the second step in the method for determining if a mixture of noncarcinogenic toxicants exceeds the MHRV. This item defines the methods for calculating a hazard index for each group of substances or chemicals that share the same endpoint of concern as determined in item A and specifies the equation for determining a hazard index for noncarcinogenic chemicals or defined mixtures as specified in part 4717.8250. The hazard index equation is consistent with the general equation published by the U.S. EPA in the *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b).

Subitem 1 is necessary to specify the numerator in the hazard index equation. This subitem specifies the values and units necessary to calculate the hazard index. D_{STn}, represents the dose of noncarcinogenic toxicants measured in micrograms of chemical per kilogram body weight per day (❍g/kg/d).

Subitem 2 is necessary to specify the denominator in the hazard index equation. This subitem specifies the values and units necessary to calculate the hazard index. $MHRV_{STn}$ represents the MHRV for a noncarcinogenic toxicant specified in part 4717.8250.

Items C and D are necessary to instruct that the final hazard index calculated from the addition of the proportions having the same toxicological endpoint is comparable to an HRV. A hazard index of 1 is equivalent to a cumulative HRV, and a hazard index greater than 1 exceeds the cumulative HRV.

CONCLUSION

Based on the foregoing, the proposed rules are both needed and reasonable.

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Date Julie Brunner, Deputy Commissioner

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