MINNESOTA DEPARTMENT OF HEALTH

STATEMENT OF NEED AND REASONABLENESS

Proposed Permanent Rules Relating to Health Risk Values
Minnesota Rules, Parts 4717.8000 to 4717.8600

INTRODUCTION

The Minnesota Department of Health (MDH) Health Risk Values (HRVs) rule is designed to achieve, to the extent possible, the Department's goal of developing health protective values for chemicals or substances emitted to the air that have the potential to pose a human health hazard. The initial list of HRVs is not inclusive, and the absence of a chemical from the HRV list does not imply that there are no health risks associated with the emission of that chemical to air.

Reliable technical and scientific information is essential for making the sound risk-related decisions that are necessary for protection of public health. With this in mind, MDH has developed its HRV rule using techniques and approaches that staff and the agency's external work group have determined are the best currently available. The HRV rule is not static and should not be perceived to be a completed product. Indeed, MDH intends to add HRVs for other chemicals to the rule as additional information is analyzed. Periodic review and revision of HRVs and multimedia HRVs (MHRVs) will be done to assure that new data of acceptable quality and applicable methodologies are incorporated into the rule.

The HRV rule provides publicly reviewed, consistent health-based estimates of specific chemical exposures that are likely to be without appreciable risk of harmful effects on humans. HRVs and MHRVs are intended for use by state agency programs that manage air pollutants; however, because they are guidelines and their application will be a function of risk management, the rule does not specify applications. HRVs and MHRVs are designed to protect the most sensitive individuals in a population (including but not limited to children, pregnant women and their fetuses, individuals compromised by pre-existing diseases, and elderly persons), but are not necessarily protective of hypersensitive individuals who may respond in an idiosyncratic fashion to an exposure. HRVs and MHRVs are based only on the best peer-reviewed health information available and are not adjusted for such technological considerations as limits of detection or ease of removal. Recently there has been some concern that current risk assessment techniques are not adequately protective of children. Although MDH currently understands that HRVs are protective of all sensitive portions of the population, including children, MDH will continue to monitor new research and make changes in the rule as appropriate to assure that HRVs continue to be protective for children.

The Minnesota Pollution Control Agency (MPCA) has authority to permit facilities that contribute to air pollution. Historically the MPCA has issued permits estimating potential human health risks of chemical emissions to air by using non-promulgated values. The MDH and the MPCA, along with many of the regulated industries, are advocating, via this proposed rule, for standards for development of consistent techniques to be used to derive scientifically defensible health-based numbers which will in turn be used in the regulatory process. In July 1994, the MDH developed a Memorandum of Agreement (MOA) with the MPCA that assigned the MDH responsibility for the development of human HRVs and MHRVs for toxic substances emitted to the air. The MOA has undergone several revisions, the most recent of which was signed in February, 2001.

What are HRVs?

HRVs are concentrations of chemicals emitted to air that are unlikely to pose a significant risk of harmful effects when humans are exposed to those concentrations over a specified time. HRVs provide uniform, science-based public health policy guidelines to be used as aids in protecting people from exposure to potentially harmful substances released into the environment. HRVs are publicly reviewed, health-based criteria that may be used by state agency programs to manage the emissions of air pollutants. For risk managers in these agencies, HRVs may be used as one set of criteria to evaluate health risk posed by specific chemicals emitted to air.

HRVs include both HRVs for chemicals or defined mixtures of chemicals emitted to the ambient air where the risk for exposure is via inhalation (expressed as a concentration of micrograms of chemical per cubic meter of air, or $\mu g/m^3$), and MHRVs for those chemicals or defined mixtures of chemicals that are emitted to the air but where non-inhalation routes of exposure are important to human health. The MHRVs proposed here are all for oral exposure and expressed as micrograms of chemical per kilogram body weight per day of exposure (µg/kg-day).

Each of the proposed HRVs and MHRVs were derived using the best peer-reviewed science and public health policies available at the time of their development. There are, however, uncertainties that limit the accuracy of HRVs and MHRVs. These include limited toxicological information, exposure assumptions, and other uncertainties inherent in the HRV process. However, because the approaches used to develop HRVs and MHRVs are conservative (i.e., by design they err in the direction of protecting public health), MDH is confident that exposures to chemicals in concentrations at or below the HRVs and MHRVs present minimal risk to human health. In addition, because of MDH's conservative approach, exposures to chemical concentrations above HRVs and MHRVs do not necessarily pose a public health risk. The potential for exposures to chemical concentrations that exceed HRVs and MHRVs is not an absolute indicator of the need for additional analysis. HRVs and MHRVs are one set of multiple criteria to be used for deciding if ambient concentrations of chemicals are acceptable.

HRVs and MHRVs are developed using public health protection practices that advocate the protection of the most sensitive portion of the population. However, HRVs may not be protective of every individual. Certain people are hypersensitized by exposures to high concentrations of particular chemicals during occupational chemical use or in other situations. Because ranges of exposures that result in such hypersensitivities are highly variable and poorly studied, MDH is unable to derive HRVs that would be protective of all sensitized individuals. Chemicals that are known to cause sensitization are noted in the chemical lists found in rule parts 4717.8100 - 4717.8250.

HRVs are similar to Health Risk Limits (HRLs), health-based concentrations for contaminants found in groundwater (*Minnesota Rules*, parts 4717.7100 - 4717.7800). HRLs were originally placed into rule in 1993 and have served the Department and other state agencies well since that time. The HRL rule does not specify how the HRLs should be used. HRLs provide one set of criteria to be used by risk managers in evaluating potential health risks posed by chemicals in groundwater. The proposed HRV rule specifies the methods and factors for calculating the HRVs but, like the department's HRL rule for ground water, do not specify applications for HRVs. MDH cannot anticipate or accurately predict all situations where HRVs might be used. To maintain flexibility in the application of HRVs, the MDH has chosen not to specify applications.

What HRVs are not.

MDH has developed the HRVs to gauge the risk of exposures to chemicals or mixtures of chemicals in ambient air. Ambient air is not workplace air, therefore, HRVs do not apply to workplace exposures. Workplace air is regulated by the Occupational Safety and Health Administration (OSHA). MDH does not use workplace guidelines or standards to develop health-based values for protection of the general population. OSHA standards are often based on human studies that are conducted with healthy working individuals using the intermittent exposures normally found in the work place. More sensitive segments of the population such as the young, the old, and individuals with a preexisting health condition or disease typically are not tested because they are not normally part of the working population. In addition, typical occupational exposures occur on an eight to ten hours per day, five days a week schedule. These intermittent exposures allow time for elimination of chemicals from the body. Because the exposure of the general population to chemicals in ambient air may be continuous, there are no recovery periods for the exposed individual. For these reasons HRVs are lower concentrations than those allowable as workplace standards. For workers covered under OSHA, the OSHA workplace standards apply.

HRVs are not intended to address the risk management concerns of chemical impacts on quality of life issues such as odors. Odor perception need not be directly related to adverse health effects. In some cases, chemicals may produce odors without causing adverse health effects, and in other instances adverse health effects may result from an exposure to a chemical that produces no detectable odor. For example, the odor of chemicals such as acetone or hydrogen sulfide can be detected at levels far below concentrations associated with adverse health effects. Conversely, carbon monoxide has no odor but can cause headaches, nausea, dizziness and in high enough concentrations death. The presence or absence of an odor, therefore, cannot be directly correlated with health effects.

The Technical Advisory Group and public participation

A "Notice of Solicitation of Outside Information or Opinions" was published on September 5, 1995 (State Register, 1995). The notice was also mailed to the MPCA's *Air Mail* newsletter mailing list (more than 2,500 subscribers). More than 400 individuals responded and were placed on a mailing list (provided as an attachment) to receive information on HRV rulemaking. During rule development (November 1995 to November 1999), the MDH mailed nine HRV rulemaking newsletters to persons on the HRV interested parties mailing list.

A "Request for Comments" was published on September 13, 1999 (State Register, 1999). The "Request for Comments" served the same function as the September 5, 1995, "Notice of Solicitation" for this rulemaking. Republication was required to meet the revised noticing requirements of the Administrative Procedures Act.

A technical advisory group was assembled with representatives from industry, consulting firms, environmental advocacy groups, public health organizations, academia, state agencies and local governments. The charge to the work group was to identify, discuss, and provide advice on technical and policy issues; provide expert opinion related to risk assessment methods used to develop HRVs; review documentation supporting proposed HRVs; and exchange data and information related to the development of HRVs. The work group met more than two dozen times between May 1995 and the publication of the "Notice of Intent to Adopt." In addition, a subcommittee on acute values met three times in 1999.

MDH also received comments from experts in the field of risk assessment and met with representatives from four industry groups. In addition to examining and collecting peer-reviewed data, MDH staff used available resources to both increase the database supporting the HRVs and identify policy related issues in risk

assessment (see bibliography). For instance, the California Environmental Protection Agency's (Cal EPA) acute (1-hour) health-based standards provided an important aid in the HRV development process.

When determining whether exposures need to be reduced, risk managers must consider, along with risk assessment information, other factors including social, economic, technological feasibility, and other environmental concerns. Logically, the MDH work group raised questions about how the MPCA would use or apply HRVs. Following much discussion, the HRV work group decided on July 10, 1996, that an MPCA applications work group, operating in parallel with MDH's work group, was necessary. MPCA assembled an applications work group that met a number of times to discuss the possible uses or application of HRVs in MPCA programs. MPCA's application work group has suspended meetings pending promulgation of the HRV rule.

ALTERNATIVE FORMAT

Upon request, this Statement of Need and Reasonableness (SONAR) can be made available in an alternative format, such as large print, Braille, or cassette tape. To make a request, contact Kathleen Norlien at the Minnesota Department of Health, Environmental Surveillance and Assessment Section, 121 East Seventh Place, Suite 220, PO Box 64975, St. Paul, Minnesota 55164-0975, phone (651) 215-0876, fax (651) 215-0975, e-mail kathleen.norlien@health.state.mn.us. TTY users may call the Department of Health at (651) 215-0699.

STATUTORY AUTHORITY

The Department's statutory authority to adopt the rules is set forth in *Minnesota Statutes*, section 144.12, subd. 1, item 14, which provides:

> **144.12 Regulation, enforcement, licenses, fees.**
>
> Subdivision 1. **Rules**. The commissioner may adopt reasonable rules pursuant to chapter 14 for the preservation of the public health. The rules shall not conflict with the charter or ordinance of a city of the first class upon the same subject. The commissioner may control, by rule, by requiring the taking out of licenses or permits, or by other appropriate means, any of the following matters:
>
> (14) Atmospheric pollution which may be injurious or detrimental to public health;

Under this statute, the Department has the necessary statutory authority to adopt the proposed rules.

REGULATORY ANALYSIS

Minnesota Statutes, section 14.131, sets out six factors for a regulatory analysis that must be included in the SONAR. Paragraphs (1) through (6) below quote these factors and then give the agency's response.

"(1) a description of the classes of persons who probably will be affected by the proposed rule, including classes that will bear the costs of the proposed rule and classes that will benefit from the proposed rule"

All persons living in Minnesota could potentially be affected by the proposed rule. The proposed rule may affect permitting of facilities or operations which could emit pollutants into the air, particularly when a facility is in an area considered to be polluted. For example, in a recent press release, the MPCA used United States Environmental Protection Agency (U.S. EPA) air estimates for a comparison with proposed draft HRVs for specific chemicals. They found that about 45 percent of the state's 1,230 census tracts, many in the seven-county Twin Cities area, had six or seven air pollutants that exceeded proposed state guidelines for long-term exposures to chemicals.

Potentially, there are benefits for the entire state from the proposed rule, but the rule will particularly impact individuals living in areas where air pollution concerns or problems already exist. The HRVs will assist the state and others in identifying areas where there may be health risks associated with breathing the air. Subsequent steps might include an identification of air pollution problems which would allow the social and economic issues that may have been responsible for them to be addressed.

"(2) the probable costs to the agency and to any other agency of the implementation and enforcement of the proposed rule and any anticipated effect on state revenues"

The proposed rules do not require the expenditure of public monies by state or local public bodies. MDH will not directly apply the proposed HRVs to any public programs, services or public party in these proceedings. When state agencies apply the proposed HRVs, the impact of each application will have to be determined by the agencies using the HRVs. This rulemaking has no impact on state revenues.

"(3) a determination of whether there are less costly methods or less intrusive methods for achieving the purpose of the proposed rule" and **"(4) a description of any alternative methods for achieving the purpose of the proposed rule that were seriously considered by the agency and the reasons why they were rejected in favor of the proposed rule"**

Prudent public health policy dictates that the HRVs protect the very young, the elderly, and the sick and infirm. MDH considered using workplace ambient air guidelines or standards to develop HRVs, but rejected the use of such occupational standards as Threshold Limit Values (TLVs) for development of the HRVs because occupational exposure limits have generally been based on research that used healthy subjects between the ages of 18 and 35. The very young, the very old, and individuals with preexisting disease have not been routinely tested. For convenience, many human studies used to develop occupational exposure limits were conducted with healthy college-age adults as their subjects because they have been a readily available population. In addition, intermittent workplace exposures allow for periods of elimination or detoxification whereas sustained exposures to chemicals in ambient air do not allow time for the removal of chemicals from the body. For these reasons, MDH decided not to use existing workplace standards in developing the HRVs.

The HRVs provide uniform, science-based rules that can be applied to the protection of the health of the general public routinely exposed to potentially harmful substances released into the environment. The HRVs

provide a set of numbers that have been developed with full comment from a diverse workgroup and publicly reviewed through the rulemaking process, and available to anyone interested in using the HRVs.

"(5) the probable costs of complying with the proposed rule"

Because the HRV rule does not specify how the health-protective numbers are to be applied, the probable cost of complying with the proposed rule cannot be estimated. HRVs are intended to be only one set of criteria used for deciding if an ambient air concentration is acceptable, but they are not intended to be a bright line between "good" and "bad". As previously stated, the HRVs were developed using conservative methods so that exposures below a HRV would be expected to present minimal if any risk to human health. Similarly, ambient air concentrations above HRVs without consideration of other information do not necessarily indicate a public health problem.

"(6) an assessment of any differences between the proposed rule and existing federal regulations and a specific analysis of the need for and reasonableness of each difference"

There is no comparable set of human health based numbers for hazardous air pollutants issued by the federal government.

COMMISSIONER OF FINANCE REVIEW OF CHARGES

Minnesota Statutes, section 16A.1285, does not apply because the rules do not set or adjust fees or charges.

PERFORMANCE-BASED RULES

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

The proposed HRV rule is a performance-based standard because the rule focuses on outcomes and not on processes. Risk managers and stakeholders are allowed flexibility in the determination of how best to protect public from potentially harmful substances. The HRVs will provide a scientific context with which the risks from a particular situation may be analyzed. After the analysis of risk the stakeholders examine options, make decisions about options they may want to implement, take action, and evaluate the results of those actions taken. Other performance-based programs, such as the flexible permitting done at MPCA, could then use the HRVs in the manner consistent with the protection of public health and the environment.

ADDITIONAL NOTICE

Our Notice Plan includes giving notice required by statute. The Department will mail the rules and Notice of Intent to Adopt to everyone on the Department's rulemaking mailing list under Minnesota Statutes, section 14.14, subdivision 1a. We will also give notice to the Legislature per Minnesota Statutes, section 14.116. The Department's additional notice includes mailing the Notice to individuals on the Department's HRV mailing list.

LIST OF WITNESSES

The Department does not anticipate these rule amendments will go to a public hearing. If these rules do go to a public hearing, the Department anticipates having the following witnesses testify in support of the need for and reasonableness of the rules:

1. Kathleen Norlien, Hillary Carpenter, and Larry Gust of the Department will testify about the development and content of the rule amendments in general.

1. David Aafedt, Assistant Attorney General, will address the statutory authority and other legal aspects of the rule amendments.

1. Jeanne Eggleston of the Department will address procedural issues.

RULE-BY-RULE ANALYSIS

The core outcome of this rulemaking is four tables of chemicals and defined mixtures of chemicals that designate each chemical's HRV: Chronic Health Risk Values, Subchronic Health Risk Values, Multimedia Health Risk Values, and Acute Health Risk Values. The accounting of the process the agency followed in developing the HRVs is separated into two parts. Part I includes chronic, subchronic, and multimedia HRVs, addressed together because the same process was used for all three categories. Acute HRVs are addressed separately in part II because they were developed using a different process.

PART I
CHRONIC, SUBCHRONIC, AND MULTIMEDIA HEALTH RISK VALUES

DEVELOPMENT

HRVs or MHRVs have been developed within this rulemaking and will continue to be developed in future rule makings for chemicals listed on either the Minnesota Superfund Amendments and Reauthorization Act Title III Toxic Release Inventory or the 1990 Clean Air Act Hazardous Pollutants (HAPs), and those chemicals whose emissions have been documented in an environmental or air toxics review. The list of potential HRVs and MHRVs includes industrial and agricultural chemicals and petroleum constituents. HRVs and MHRVs have been and will be generated only when there is sufficient information regarding the toxicity of a chemical available on the U.S. EPA's Integrated Risk Information System (IRIS) database (U.S. EPA, 1999a; 2001), the Cal EPA's Office of Environmental Health Hazard Assessment (OEHHA) Reference Exposure Levels (REL) (Cal EPA, 1999), the U.S. EPA's Health Effects Assessment Summary Table (HEAST) database (U.S. EPA, 1995), the U.S. Public Health Services Agency for Toxic Substances and Disease Registry's (ATSDR) Toxicological Profiles, or in the primary peer reviewed scientific literature.

The list of HRVs is not inclusive. The absence of a HRV or MHRV for a chemical does not imply that there are no health risks associated with the emission of that chemical to air. Periodic revisions of the HRVs and MHRVs will be conducted to both add additional chemicals and to review, and modify where necessary, existing HRVs and MHRVs as more information becomes available.

Potential Data Sources

- **U.S. EPA's IRIS data base** (U.S. EPA, 2001). IRIS is the primary data source for the development of HRVs and MHRVs. IRIS is an electronic data base that contains health risk and regulatory information for a large number of chemicals. Documentation for the development of values is available on the Internet at http://www.epa.gov/ngispgm3/iris.

- **Cal EPA's OEHHA RELs** (Cal EPA, 1999). Cal EPA's OEHHA has produced a number of health based values for chemicals emitted to air. These values are referred to as RELs and have been developed using methods and techniques consistent with those recommended by the U.S. EPA and the MDH external work group. Cal EPA's RELs are routinely subjected to internal and external peer review and documentation for the development of RELs is available on the Internet at http://www.oehha.org/air.html.

- **HEAST** (U.S. EPA, 1995). If cancer and noncancer criteria are not available through IRIS, the U.S. EPA's Environmental Criteria and Assessment Office (ECAO) recommends using HEAST. This document, prepared by the ECAO and published periodically, lists the health based criteria and references for the studies used to determine HEAST values. These are provisional risk assessment values that have been reviewed and accepted by individual agency program offices, but are not recognized agency-wide. HEAST values are used for chemicals commonly found at Superfund and Resource Conservation and Recovery Sites. Because summaries of the principle and supporting documents for the HEAST values do not accompany the HEAST document, MDH collected and reviewed the studies cited in support of the HEAST values to assure that they were correct and calculated in a manner consistent with both the U.S. EPA and MDH guidelines.

- **ATSDR.** Reference concentrations (RfCs), reference doses (RfDs), and cancer potency estimates not listed in IRIS or HEAST may sometimes be found in the U.S. Public Health Services (U.S. PHS) ATSDR Toxicological Profiles which contain a thorough assessment of a chemical's toxicity (minimal risk levels or MRLs). When an ATSDR value is used, the critical study and supporting literature will be

obtained and reviewed to ensure that the processes used in development of these numbers are consistent with both the U.S. EPA and these guidelines.

- **Primary Literature**. If information is not available from any of the above sources, MDH will conduct a search of the primary scientific literature for inhalation or oral toxicity studies. Only published and/or peer reviewed data will be considered for use. Rule-making in Minnesota is a public process, therefore, any study used in the development of a rule must be available to the public. Unpublished studies completed by governmental agencies or industry that contain proprietary information will not be used by MDH.

- **Occupational Exposure Limits (OELs).** MDH will not use OELs such as those derived by OSHA, the National Institute for Occupational Safety and Health or the American Conference of Industrial Hygienists (ACGIH) to develop HRVs. OELs are neither intended nor recommended for protecting the general population. OELs, although they were developed to protect humans from inhalation exposure, are calculated to be protective of a healthy working male population that is exposed to chemicals on a 5 work day per week basis.

Derivation of HRVs and MHRVs

In the current version of the HRV rule MDH derived HRVs and MHRVs for carcinogenic chemicals using unit risks or potency slopes developed by the U.S. EPA (U.S. EPA 1986a; 1992; 1996). A discussion of the default assumptions MDH used to develop HRVs and MHRVs for carcinogenic chemicals is presented in part I; however, because MDH did not derive any unit risks or potency slopes for the current HRVs and MHRVs, the techniques used to develop unit risks or potency slopes will not be presented in detail here. If in subsequent revisions of the HRV rule it becomes necessary for MDH to independently develop these numbers the techniques used to derive unit risks or potency slopes will be presented at that time.

HRVs and MHRVs developed for noncarcinogenic chemicals were derived using reference dose (RfD) or reference concentration (RfC) approaches (U.S. EPA, 1989; 1994a; 1999b; 1999c). In general the RfDs and RfCs used were obtained from IRIS or HEAST. However, there were occasions when no IRIS or HEAST RfC or RfD values were available and MDH (when sufficient data were available in the primary literature) used U.S. EPA techniques to derive RfDs and RfCs for these chemicals (U.S. EPA, 1989; 1994a; 1999b; 1999c). MDH anticipates that there will be other instances when this situation will arise. Included in part I are the techniques and default assumptions used by the U.S. EPA and that MDH will use to both develop RfDs or RfCs, or to modify or reject RfDs and RfCs that may be available from other sources.

TOXICOLOGICAL BASES

The steps involved in development of HRVs and MHRVs include: hazard identification; determination of the critical study or studies; determination of critical or adverse effects; determination of the dose that causes the lowest observable adverse critical effect (LOAEL), or the dose at which there are no observable adverse effects (NOAEL), a benchmark concentration (BMC) or a benchmark dose (BMD); calculation of human equivalent concentrations for determination of the critical dose when the critical study was an animal bioassay; and the application of uncertainty factors.

Where sufficient data are available, HRVs for chemicals will be developed following consideration of a number of criteria including the length of exposure, route of exposure, and toxic endpoint.

Length of exposure

Acute or short-term exposures are those that take place for one hour or less and typically involve relatively high levels of a chemical. Acute HRVs are derived using data from short-term human exposure studies and animal studies where exposure times are less than eight hours. In addition, HRVs with developmental endpoints are derived using results from developmental toxicity studies done on animals. The techniques and default assumptions used in the derivation of acute HRVs are presented in Part II.

Subchronic exposures are those that occur for approximately 10 percent of lifetime of an organism. Subchronic HRVs are derived from short-term human epidemiological studies or from animal studies with exposure durations of 10 weeks to one year. Chronic exposures are those that occur over the period of several years to a lifetime. Chronic HRVs are derived using long-term epidemiologic studies or from chronic animal studies. The exposure duration for a chronic study in rats is generally two years.

Derivation of HRVs will often be hampered by incomplete inhalation toxicity databases. MDH has therefore established the policy that the type of HRV will be based on data from a study of an appropriate exposure duration. For instance, chronic HRVs will be derived only for chemicals that have been evaluated in a chronic study. This approach will minimize the need for uncertainty factors in extrapolating from a short- term (acute or subchronic) study to a chronic (lifetime) exposure scenario and will ensure that the resulting chronic HRVs are protective for the toxicity that would be expected with a long-term low level exposure.
For example, an acute exposure to a large amount of a chemical may cause sensory irritation while a long-term low level exposure to the same chemical might have a carcinogenic effect.

Route of exposure

- **Multi-media HRVs (MHRVs)**

  Not all chemicals emitted to air present only a potential inhalation hazard. For certain metals, such as mercury, and bioaccumulative compounds such as 2,3,7,8-tetrachlorodibenzo-p-dioxin, the primary exposure route of concern for long-term or chronic toxicity is ingestion or dermal rather than (or in addition to) inhalation. For other compounds dermal exposures may present more of a risk than inhalation exposures. For chemicals such as these, MHRVs will be developed based on the potential for health effects following dermal exposure or ingestion and expressed in terms of doses (µg/kg-day) rather than as concentrations in air (µg/m^3).

- **Route to route extrapolation**

  Situations will undoubtedly arise where there is a need for a HRV but the available toxicology data are from an oral rather than an inhalation exposure study. As a rule, chronic ingestion studies will not be used to develop HRVs; however, route to route extrapolation may be appropriate when sufficient toxicokinetic information about a given chemical is available (NRC, 1986; U.S. EPA, 1994a). If the critical effect of a toxicant is noncarcinogenic, the route of administration would likely result in differences in the amount of toxicant at the target site (and therefore the severity of its effect), but the critical effect would be the same regardless of how the toxicant is administered. In such cases MDH considers it appropriate to correct for differences in absorption by multiplying the RfC or RfD by the ratio of the quantity absorbed via inhalation to the amount absorbed following an oral exposure.

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

higher concentrations of ingested chemicals than other organs. In addition, the unique biochemistry of the hepatocytes can result in the generation of very different metabolic products of a toxicant in the liver than would be produced in other organs. For these reasons an extrapolation approach will not be used if the liver is the target organ for a toxicant following an oral exposure.

Toxic endpoints

Chronic toxicants exert their effect either by causing cancer or by damaging organs or organ systems. Subchronic toxicants have noncarcinogenic endpoints. Because noncarcinogens and carcinogens exert their effects by different mechanisms, the techniques used to derive health protective values are based on fundamentally different approaches. For noncancer causing chemicals a RfD or RfC approach is used. For such chemicals it is assumed that a threshold or no effect level exists and that exposures to chemicals at or below their threshold value present an insignificant threat to health. For noncarcinogenic toxicants, chronic HRVs are set at levels that are expected to cause no harm when exposure occurs on a daily basis for a 70 year lifetime. Subchronic HRVs are set at levels that are expected to cause no harm when exposure occurs on a daily basis for up to 13 weeks.

For carcinogens it is assumed there is no threshold or safe level of exposure and that exposure to any amount of these toxicants results in some increased level of risk. Under these assumptions the only risk-free dose of a carcinogen is zero. Because economic, technological, and health factors make the total elimination of environmental carcinogens an impractical goal, exposure to carcinogens is generally controlled to negligible risk levels. MDH uses 1 in 100,000 (1×10^{-5})[1] as the additional lifetime risk from exposure to carcinogens to calculate HRVs. This increased risk needs to be considered against the background cancer risk. For example, the background cancer incidence in males is about 1 in 2 (or 0.5) in Minnesota. This means that with exposure to a chemical at or above the HRV level, the total estimated lifetime risk of developing cancer is 0.500001 and suggests that in a population of 100,000 people, rather than 50,000 cases of cancer there could be 50,001. An important point to consider with cancer risk estimates is that risk is a mathematical approximation of a likelihood of occurrence - it does not equate to actual increased cases of cancer. The derivation of HRVs that have cancer as an endpoint includes a number of conservative estimates to ensure that these numbers are maximum estimates of risk and that they will overestimate rather than underestimate risk. The true risk of exposure to a chemical at a HRV level actually lies somewhere between a maximum of 1×10^{-5} and zero.

RISK ASSESSMENT MODEL

MDH anticipates that HRVs will be used to evaluate health risks posed by chemicals emitted to air and recommends that they be used in the four-step model for risk assessment developed by the National Academy of Sciences (NAS, 1983, NRC, 1994). Briefly these steps are:

- Hazard identification which is the process of determining whether an agent can cause an increase in the incidence of a health condition such as cancer or birth defects.
- Dose response assessment which is the characterization of the relationship between dose and the incidence and severity of the adverse health effect. Dose response assessments often involve extrapolation from high dose responses to low dose responses and from animal responses to human responses.
- Exposure assessment which is the determination of the intensity, frequency, and duration of the exposures of humans to the substance in question. Concentrations of the substance are estimated at

[1] In this document and the HRV rule exponents are expressed in one of two formats; numeric or alphanumeric. As used here 1×10^{-5} is equivalent to 1E-5.

various points as the substance disperses from its emission source to various receptors in the environment.

- Risk characterization which combines the assessments of dose response and exposure to estimate the probability of a health risk to an exposed individual or population.

HRVs and MHRVs will provide the information necessary to complete the hazard identification and dose response assessment steps in the risk assessment process. The exposure assessment and risk characterization steps of the risk assessment process are application related and will, therefore, vary depending how state programs that use HRVs and MHRVs choose to apply them.

Hazard Identification

The development of HRVs will require that a thorough analysis of the available toxicologic research be conducted and that a weight of evidence approach be used to determine whether there is a potential for human health effects. From this analysis a principal study or studies will be selected for use in the quantitative dose response phase of the risk assessment. Whenever possible, MDH prefers to use human data for the derivation of HRVs and MHRVs; however, for many chemicals adequate studies providing human data are not available. In these cases it will be necessary to select a study that used nonhuman mammals as experimental animals as the principal study.

Human Studies

- Data from three types of human studies have been used to assess the health effects of chemicals: epidemiological studies, controlled exposure experiments, and case reports. Each can provide valuable information for developing HRVs; however, a careful analysis to determine the quality and limitations of the study is necessary.

- Epidemiological studies generally examine exposures to large numbers of people, but typically provide poor estimates of exposure (dose). In order for an epidemiological study to be considered for use in developing a HRV the study population must be specified. Population characteristics such as age, sex, health status, habits and worker versus non-worker status must be specified along with the type or design of the study. Confounding variables should be evaluated as part of the analysis and there should be some discussion of the medical importance or significance of any adverse findings. Study biases should be identified, and issues of objectivity versus subjectivity in the endpoint should be discussed either by the authors or MDH if the authors do not specifically address bias in their paper.

- In a clinical or controlled exposure (chamber) experiment the number of individuals (n) must be identified. As with the epidemiological study, population characteristics such as age, sex, health status, habits and worker versus non-worker status should also be identified. Non-toxicant exposure conditions such as temperature, relative humidity, etc. should be specified. The study must indicate what the individual activity level/breathing pattern is during the study. Because sample sizes are usually small and exposures are typically of short durations, results from controlled human exposure studies will generally by themselves be inadequate for developing subchronic and chronic HRVs.
- Case reports will typically be used on a qualitative basis only. Case reports are often problematic because they only address severe effects, are conducted with a limited number of individuals (small n), and their exposure conditions are typically uncontrolled or unknown because concentrations of chemicals in air are not typically measured.

Animal Studies

- As previously stated, MDH prefers to use human data for the development of HRVs and MHRVs; however, MDH does recognize that for many chemicals the only information available for use in risk assessment will be from experimental studies conducted with animals. When animal data are used to assess human health risk the default assumption is that any adverse effects observed in animals will also be apparent in humans. This default applies unless there are good rationales for physiological or biochemical differences between the test species and humans. A second default assumption is that humans are at least as sensitive as the most sensitive animal species for which there are toxicological data.

- If an animal study must be used, the study must be supported either by human studies wherein similar identified effects were observed or by a biologically plausible justification for each effect that can be extrapolated to humans. The study must describe the number, type and sex of animals used, the age, the weight, etc. Good laboratory practices should be followed and include issues of animal handling, facilities, equipment, and record keeping. Care must be taken to compare the animal model to the human model for applicability (i.e., the same mechanism of action would be available in both species). In general, the most sensitive endpoint (i.e., the critical effect) from a scientifically acceptable study or studies, as reflected in the criteria below, will be used to develop HRVs.

- Derivation of a HRV should be based on key studies where inhalation was the route of exposure. Good documentation of the toxicant should be available including establishment of toxicant purity, analytical techniques used and quality assurance and quality control methods (QA/QC) used. The concentration in the air should be relatively constant throughout the exposure period and monitored throughout the exposure period.

- The effects measured that are to serve as the critical effects should be dose related, reproducible, sensitive, and biologically relevant to humans.

Critical effect or endpoint of concern

The exposure of an organism to a particular chemical can cause a range of effects depending on how much of the chemical is administered. Low dose exposures may cause subtle changes in enzyme levels, while severe gross pathological changes or even death may result from higher doses of the same chemical. After considering all of the available data, generally the effect with the lowest NOAEL is selected for noncarcinogens and the highest slope factor or unit risk is selected for carcinogens. A health based value developed based on a response occurring at a low dose is assumed to be protective of responses that occur at higher administered doses.

Given the fact that there is a potential for multiple endpoints for chemical exposures, it would be prudent to include information regarding multiple endpoints (when available) for use in air toxics reviews when making qualitative estimates of risk. If information concerning multiple endpoints is to be used for additivity calculations for chemicals that have similar endpoints (discussed below), sufficient data must be available to develop an RfC for each endpoint. In either case, when information about multiple endpoints is available, it will be included in guidance documents produced by MDH.

Dose Response Assessment

As mentioned above there is a fundamental difference in the risk assessment process for noncarcinogenic chemicals and that for chemicals which can cause cancer. This results in marked differences dose response assessments.

Carcinogens

For carcinogens the basic assumption used to estimate health risks is that any exposure to a carcinogenic compound imparts an increased risk of developing cancer. Epidemiological data and tumor data from chronic animal bioassays are selected as the primary database. These data are then extrapolated using models that assume a linear relationship at the lower end of the dose response curve. This approach is necessary because, despite the fact that data are frequently lacking, the low dose region of the dose response curve is used by risk assessors and regulators to establish the potency of carcinogenic chemicals. This extrapolative approach is identical to that currently used by the U.S. EPA. These conservative estimates of potency are then used to calculate the risk associated with exposure to a given amount of chemical. MDH uses cancer potency factors and inhalation unit risks to determine how much of a particular chemical would present an increased lifetime risk (70 years) of 1×10^{-5}. An overview of MDH's choice of 1×10^{-5} as an additional lifetime risk level is presented in a MDH HRV rule briefing paper (MDH, 1996a). A detailed presentation of the techniques involved in the risk assessment of carcinogenic exposures is available in a MDH HRV rule briefing paper (MDH, 1996b).

Recent research has provided a good deal of new information about the mechanisms involved in the carcinogenic process, and in turn, this new information led the U.S. EPA to reconsider the approaches traditionally used for assessing cancer risks. In 1996 the agency proposed major changes in its current cancer guidelines (U.S. EPA, 1986a), suggesting that a more complete analysis of the dose response curve (including an evaluation of the possibility of a threshold) should be done (U.S. EPA, 1996). Recognition that some carcinogens may indeed exhibit thresholds would result in a fundamental change in the risk assessment process. Linear low dose extrapolation would no longer be the default approach for assessing the risks of exposure to carcinogens. In addition, the proposed guidelines recommend that endpoints other than total tumors counts be considered for modeling purposes. Alternate endpoints include, but are not limited to, biomarkers and mechanistic data. MDH is monitoring these proposals, however, because the guidelines are still draft and are not currently being routinely used by the U.S. EPA to develop cancer numbers for IRIS, MDH will continue to use the U.S. EPA's current potency estimates and procedures until revised risk assessments are available (U.S. EPA, 1999c).

Classification of carcinogens.

The U.S. EPA currently uses a weight of evidence approach to classify chemicals according to their potential to cause cancer in humans. Their classification system is based primarily on three types of data: human epidemiological studies, animal data from bioassays, and results from supporting in vitro and in vivo experiments.

- Group A chemicals are known human carcinogens, i.e., there are sufficient epidemiological data to establish the fact these chemicals can cause cancer in humans.

- Group B1 chemicals are probable human carcinogens. These are chemicals for which human data are limited and therefore insufficient to establish carcinogenicity in humans but where data are adequate to establish carcinogenicity in animals.

- Group B2 chemicals are probable human carcinogens. These are chemicals where data are inadequate or non-existent for carcinogenicity in humans but animal data are sufficient to establish carcinogenicity.

- Group C chemicals are possible human carcinogens. Data for carcinogenicity of these chemicals in animals are limited and data in humans are either lacking or non-existent.

- Group D chemicals are not classifiable in regard to human carcinogenicity. Data for the carcinogenicity of these chemicals animals are inadequate or do not exist.

- Group E chemicals are those which have been shown to be noncarcinogenic in adequate studies.

MDH will develop HRVs with a cancer endpoint only for chemicals classified as group A or group B carcinogens. Where sufficient toxicologic data are available, chemicals classified as group C, D and E carcinogens will be treated as noncarcinogenic toxicants and the RfC/RfD approach will be used to develop HRVs. In general, only studies where exposure occurs via inhalation studies will be used to develop HRVs. In contrast, for MHRVs only studies where exposures are oral or dermal will generally be used for MHRVs.

The U.S. EPA draft revised guidelines for estimating risks from exposure to chemical carcinogens (discussed above) will also allow greater flexibility in the information that can be used to assess cancer risks and encourages the use of a weight of evidence approach that would include mechanistic data for hazard identification (U.S. EPA, 1996). The revised approach would also eliminate the use of letters to classify carcinogens and instead use terms such as known, likely, cannot be determined, or not likely. The U.S. EPA's proposed revised cancer guidelines are currently undergoing external scientific review and internal policy review. MDH understands that following adoption the guidelines will be used to re-assess the carcinogenic risk of chemicals where sufficient data are available. As the U.S. EPA re-evaluates cancer potency slopes for carcinogenic chemicals, MDH will re-evaluate its HRVs or MHRVs for these chemicals.

Noncarcinogenic toxicants.

Noncarcinogenic toxicants exert their adverse effects on one or more organs or systems that include; gross alterations in organ function, pathological changes in organs, metabolic and physiological impairment such as changes in the activities of critical metabolic enzymes or nerve impulse conduction, and clinical and blood chemistry abnormalities. Exposure to a chemical, depending on the dose administered, may cause a number of toxic effects.

The reference RfC and RfD methods used to derive HRVs and MHRVs for noncarcinogenic chemicals were initially developed and standardized by the scientific community. Subsequently these techniques were adopted by a number of regulatory agencies, including the U.S. EPA. The basic assumption made about noncarcinogenic toxicants is that they display a threshold, or concentration below which no effects are apparent.

Critical endpoints for noncarcinogens.

The initial step in the process of developing a HRV is an evaluation of the available toxicologic information and selection of a critical study or studies that are most representative of the entire database.

The critical study is then used for the selection of the critical endpoint which will serve as the basis for the development of the HRV or MHRV. Selection of the critical endpoint involves a good deal of scientific judgement in that the endpoint selected should be adverse, but not severe, and should be dose related. The endpoint selected may be; the most sensitive endpoint observed, an effect observed at the lowest dose used in the study, or the first statistically significant response seen in the critical study. This approach is based on the assumption that protection from a relatively mild endpoint will prevent the effects that would occur at higher doses or exposure concentrations of the chemical. From a public health standpoint it is better to base protection on an endpoint such as increased liver size than it is to produce a number designed to protect against lethality. The default assumption is that protecting against a milder toxic endpoint will also protect against more deleterious effects that generally occur at higher exposure doses. In certain cases it may be appropriate to select an early step in the development of the chemical's toxic effect as a critical endpoint. For instance, the neurotoxicity of organophosphate insecticides results from the ability of these compounds to inhibit the activity of the neuronal enzyme acetylcholinesterase (ACHase). When levels of neuronal ACHase are sufficiently reduced a potentially life-threatening neurotoxic response develops. For purposes of deriving a health protective number, the critical endpoint selected is the inhibition of plasma ACHase (as a surrogate for neuronal ACHase) and not the manifestations of neurotoxicity that result from a more intense exposure.

As discussed above, when multiple endpoints have been determined MDH will, in general, select the most representative effect as the critical endpoint. For certain data sets it may be possible to develop RfDs or RfCs for additional endpoints that could be used in the calculation of hazard indexes. In such cases this information will be kept at MDH and shared in guidance documents produced by the Department.

Once a critical endpoint is selected a critical dose such as a LOAEL or NOAEL is selected. The LOAEL is the lowest dose at which a response is determined to be statistically different from the response observed in the control group. The NOAEL is the largest experimental dose which does not produce a response that is statistically different from background or the response observed in the control group. By definition, a LOAEL or NOAEL must be an experimental data point.

In addition to the NOAEL/LOAEL approach, a newer technique called the benchmark dose (BMD - for oral exposures) or benchmark concentration (BMC - for inhalation exposures) approach is being used to determine the critical doses for those chemicals for which more complete toxicologic data sets exist. The BMC/BMD method uses statistically-based models to calculate the lower 95% confidence limit on the dose that produces a predetermined change in the population response rate of an adverse effect (the benchmark response or BMR) compared to background. The BMR is usually in the range of 5-10% depending on the quality of the selected study. The BMC/BMD method is an improvement on the NOAEL/LOAEL approach because, rather than selecting a single experimental point and then ignoring the remainder of the data set, the newer technique utilizes all of the data provided by the critical study or multiple studies and penalizes data sets that contain statistically inferior data. Also, because the BMD/BMC doesn't need to be an actual data point, there is no need for the high to low dose extrapolation that is often required when the NOAEL/LOAEL approach is used. The major factor limiting the use of BMC/BMD approach is that high quality data sets are required for modeling.

Uncertainty and Modifying Factors used to derive RfCs and RfDs.

RfCs and RfDs are derived by dividing the selected NOAEL, LOAEL, BMD, or BMC by uncertainty factors to account for the scientific uncertainty inherent in the dose response assessment process. Uncertainty factors are used to account for:

1) differences in the sensitivity of individuals in the human population (intraspecies variability);
2) the uncertainty inherent in extrapolating from animal data to estimate human risk (interspecies variability);
3) using a LOAEL rather than a NOAEL for the dose response assessment;
4) and the uncertainty inherent in an incomplete toxicologic database.

In certain cases a modifying factor ranging in value from greater than zero to ten may also be applied to account for any residual uncertainty following the use of uncertainty factors. The default value for a modifying factor is one.

To keep the use of uncertainty factors to a minimum, MDH has chosen not to extrapolate from results of studies that utilized subchronic exposures to develop chronic numbers, but rather has created a subchronic category of HRVs. This approach removes the need for using an uncertainty factor to extrapolate from a less-than-lifetime exposure.

Use of Uncertainty factors.

By convention, uncertainty factors that range in value from 1 to 10 and a modifying factor that ranges in value from greater than zero to ten are multiplied together to derive a total or cumulative uncertainty factor. For instance, if the critical study to be used for developing a chronic HRV was done in rats the NOAEL or BMC might be divided by a cumulative uncertainty factor of 100 (10 for intraspecies variability x 10 for intraspecies variability). Although it is theoretically possible to have a cumulative uncertainty factor of up to 1,000,000, MDH has attempted to keep the cumulative uncertainty factor as low as possible when developing HRVs and MHRVs. In general, since a large cumulative uncertainty factor indicates a weak toxicologic data set for a chemical, a subchronic or chronic HRV or MHRV will not be promulgated if it is necessary to use a cumulative uncertainty factor greater than 1,000 for a particular chemical.

Traditionally, the U.S. EPA routinely used full or order of magnitude uncertainty factors and a default modifying factor of 1. However, as the quality and quantity of toxicologic and exposure data increased and the residual uncertainty in the process of developing RfCs and RfDs decreased, the use of uncertainty factors has evolved. The U.S. EPA has chosen to use an uncertainty factor of 3 when an uncertainty factor of 10 is overly conservative. Incorporating this approach MDH chose to use an uncertainty factor of 3 rather than 10 in those cases where a LOAEL was used for the dose response assessment and the critical endpoint was a mild adverse effect. Also, in those situations where dosimetric adjustments were made, a 3 was used rather than a 10 for the interspecies uncertainty factor. Because 3 is the rounded geometric mean of 1 and 10, two intermediate uncertainty factors of 3 are combined as a full uncertainty factor of 10. Using this approach a cumulative uncertainty factor could be 1, 3, 10, 30, 100, 300, or 1,000 for any chemical.

There is a good deal scientific judgement involved in the use of uncertainty factors and the application of these values is often controversial. For the HRVs and MHRVs uncertainty factors will be assigned in a manner consistent with the approaches used by the U.S. EPA and, as these approaches continue to evolve, MDH will incorporate appropriate changes into its policies and rule. A more complete

presentation of uncertainty and modifying factors is available in a MDH HRV rule briefing paper (MDH, 1996c).

Exposure Assessment and Risk Characterization.

As previously stated the HRVs developed by the MDH will provide information necessary for the hazard identification and dose response assessment portions of a risk assessment. The exposure assessment and risk characterization portions of the risk assessment process will be determined by the particular agency that chooses to apply the HRVs.

DOSIMETRIC ADJUSTMENTS

When developing MHRVs, the NOAELs , LOAELs, or BMDs selected or derived from a critical study are used without additional manipulation. For development of HRVs, however, NOAELs, LOAELs, or BMCs may need to be adjusted because experimental exposures are generally discontinuous and HRVs are meant to protect the general public from continuous exposures. For human data which are typically obtained from occupational studies, a simple adjustment of a discontinuous exposure is the only manipulation necessary. Additional adjustments using default assumptions are required when using data from animals because there are well documented anatomic, physiologic, and metabolic differences between humans and experimental animals. The adjustments result in a number referred to as a human equivalent concentration (HEC). The processes for developing HECs for NOAELs, LOAELs, and BMCs were developed by the U.S. EPA (U.S. EPA, 1994a), and their use has been endorsed by the National Research Council (NRC, 1994). A more detailed presentation of these types of adjustments is available in a MDH HRV rule briefing paper (MDH, 1996d).

Adjustments to correct for discontinuous exposure

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

$NOAEL_{[HEC]}$ = NOAEL (mg/m^3) (VEho/VEh) x 5 days/7days.

where:

NOAEL = no observable adverse effect level, occupational time-weighted average
$NOAEL_{[HEC]}$ = NOAEL human equivalent concentration
VEho = occupational (8 hour day) ventilation rate default value = 10 m^3/day
VEh = non-occupational (24 hour day) default ventilation rate default value = 20 m^3/day

Experimental exposures of animals are also usually discontinuous (e.g., six hours per day for five days a week). The default approach is calculate an adjusted NOAEL as follows:

$NOAEL_{[ADJ]}$ = E (mg/m^3) x D (h/24h) x W (days/7 days)

where:

$NOAEL_{[ADJ]}$ = adjusted NOAEL

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

unknown, a hazard index would be calculated for each group of chemicals or compounds that induce a common biological response. Following these guidelines all carcinogens would be combined into one group. Other groups would include, but not be limited to, liver damage, kidney damage, and neurotoxicity. Chemicals or compounds that do not fall into any group are excluded from additivity calculations.

This additivity model does not account for synergistic or antagonistic effects, or for the absence of contaminant interactions. Concern for underestimating the risk of synergistic effects is usually greater than for overprotection in the case of antagonistic or independent action. MDH endorses the use of the additivity model and, in doing so, recognizes and accepts the inherent risk of underestimating or overestimating the true health risk.

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 dealing with mixtures and make recommendations for their use when appropriate. A more complete presentation of the mixture issue is available in a MDH HRV rule briefing paper (MDH 1996e).

As risk assessment continues to evolve as a discipline, methods used to generate health protective values will undoubtedly change. MDH routinely monitors the science and policy aspects of risk assessment to ensure that the techniques and default assumptions remain consistent with those used by the U.S. EPA.

PART II
ACUTE HEALTH RISK VALUES

DEVELOPMENT OF ACUTE VALUES

MDH has also derived acute HRVs or concentrations of specific chemicals that are unlikely to pose a significant risk of harmful effects in a human population, including sensitive subgroups, exposed to those chemicals on an hourly basis. Acute HRVs have been calculated in an analogous manner to the chronic and subchronic HRVs (as presented in Part I) where a selected LOAEL, NOAEL or BMC is dose adjusted and divided by uncertainty factors .

Since the U.S. EPA IRIS database does not currently include acute toxicity values, MDH staff independently developed and presented a set of acute HRVs to the technical advisory work group. This effort was critically reviewed in documents prepared by ChemRisk Services of McLaren-Hart and sent to MDH in June and September, 1998. The ChemRisk review was particularly critical of the fact that MDH had not accounted for concentration vs. time in the extrapolation of hourly values and had not separated the critical effects into different categories based on their severity.

In response to those written comments, MDH agreed to review and, if need be, revise the draft acute HRVs prior to proposing them in rule. Between the workgroup meetings held on January 27, 1999 and April 28, 1999, MDH met twice with a subgroup of its larger technical workgroup to specifically address the possible revision of the proposed acute HRVs and to develop a reasonable set of criteria for use in the development of acceptable acute HRVs. During the course of this effort the subgroup relied in part on a technical support document, *The Determination of Acute Reference Exposure Levels for Airborne Toxicants*, developed by the Cal EPA's OEHHA (Cal EPA, 1999). Letters of critical review and California's responses to these letters were also reviewed.

A number of issues raised by MDH's acute subgroup provided the basis for the development of guidelines for acute HRVs and the subsequent development of the currently proposed acute HRVs. The issues were:

1. Preference in data selection
2. Time adjustment
3. Adverse effects and severity of effects
4. Sensitizers
5. Use of uncertainty factors
6. Developmental effects
7. Voluntary vs. involuntary exposure

PREFERENCE IN DATA SELECTION

Published and Peer Reviewed Data

Only published and/or peer reviewed data will be used to develop acute HRVs. Rule-making in Minnesota is a public process, and any study used during rule development must be available for public review. Unpublished studies completed by governmental agencies or industry that contain proprietary information, and not accessible for public review, will not be used by MDH.

Human vs Animal Studies

Whenever possible, MDH will use data from studies conducted with humans rather than data from animal studies. For chemicals which are primary irritants, human studies are generally available. On the other hand, there are few human studies available for chemicals acting as reproductive or developmental toxicants. For these latter endpoints, animal studies must be used.

In general, the most sensitive endpoint from a scientifically acceptable study or studies, as reflected in the criteria below, will be used to develop HRVs.

Any critical study used to derive an acute HRV should be based on inhalation as the route of exposure. Good documentation of the toxicant should be available and should include an establishment of toxicant purity, a description of the analytical techniques used, and the quality assurance and quality control methods (QA/QC) used. The concentration of the chemical in air should monitored and held relatively constant throughout the exposure period. The effects measured should be reproducible, sensitive, and biologically relevant to humans.

Three types of human studies are common: epidemiological studies, controlled exposure experiments, and case reports. Requirements for these types of studies were discussed in Part I (Chronic, Subchronic, and Multimedia Health Risk Values) of this document.

If an animal study must be used, it should either be supported by human studies where similar effects are observed, or be a case where there is a biologically plausible justification for extrapolation to humans. The study population must be characterized as to the type of animals used, the age, sex, weight, etc. Good laboratory practices, including animal handling, facilities management, equipment maintenance, and record-keeping, should be followed.

Judgement of Causality

A number of formal criteria need to be evaluated when attempting to determine whether or not there is a cause and effect relationship for a particular chemical and an adverse response. Among the questions that need to be asked are:

What is the strength of association? Estimates of the strength of association can be provided by calculating a relative risk, or the ratio of effects observed following exposure to the hypothesized causative factor to those seen without an exposure.

Is there a dose-response relationship? Increasing the dose or exposure should cause an increase in the severity and/or incidence of the effect.

Is there a consistency of association? The adverse response should be consistently observed in studies of other populations and under the various test situations and conditions that occur with different researchers. Ideally, there should be data for each toxicant from a variety of the study types listed above (epidemiological studies, clinical or controlled exposure experiments, case reports, and laboratory animal experiments).

Is there a temporal relationship? The effect should occur at a reasonable time after the exposure.

What is the specificity of association? To prevent undue confounding of results that can occur with mixtures, studies examining one chemical at a time will be used.

Is there a biological plausibility? Is there a reason to assume that results in one species can be extrapolated to another, i.e., is the biological pathway that is responsible for the effect found in both species.

TIME ADJUSTMENT[4]

Acute HRVs have been designed to protect against one hour exposures to chemicals; however, studies used to develop acute HRVs frequently use experimental exposure times different than one hour. For instance, many human studies use exposures that are several hours long while animal studies typically use exposure periods of up to 8 hours per day for multiple days. Rather than only developing HRVs for chemicals where there are studies using one hour exposures, or creating acute HRVs to protect against different exposure lengths, MDH has chosen to use an established time extrapolation technique, the ten Berge modification of Haber's Law, to adjust the experimental durations to one hour.

This technique is based on **Haber's Law** which states that a given biological response is related to the length of exposure and the concentration of chemical as follows:

$$C \times t = k$$

where C represents the concentration of the chemical, t is the time, and k is the constant (toxic) effect. Haber's Law predicts that the magnitude of a given toxic effect is equally dependent on the length of exposure and the concentration of the chemical. However, because it has been noted that the time-dose-effect relationship depends on the chemical being examined, the time-frame considered, and the endpoint being measured, Haber's Law was modified by ten Berge et al. (1986) to include a chemical specific parameter to correct for these factors.

The **ten Berge equation** states that:

$$C^n \times t = k$$

where n is a chemical specific parameter greater than zero (ten Berge et al.,1986). Experimentally derived values for n range from 0.5 - 4.6 (Cal EPA, 1999).

The ten Berge modification of Haber's Law is applicable at low dose ranges where toxicokinetic processes are not saturated and is also valid for certain groups of compounds, including: 1) agents with direct local irreversible toxicity; 2) agents with direct irreversible noncarcinogenic toxicity which equilibrate rapidly with the blood; 3) agents with indirect irreversible toxicity where the toxic metabolites do not undergo appreciable detoxification and evoke a rapid toxic response.

Acute HRV timing issues

Based on work group discussions MDH developed and will continue to develop acute HRVs according to the following procedures.

- For one-hour acute HRVs, priority will be given to studies where exposure durations range from 0.5 to 2 hours. MDH believes that the best information for use in deriving acute 1-hour HRVs is available in studies where exposures are within a factor of 2 times the hour, i.e., studies where the timing of the exposure ranged from 0.5 or one-half hour up to two hours.

[4] This section does not apply to developmental/reproductive toxicity. In response to comment provided by McClaren/Hart, MDH considers developmental toxicity separately from the non-developmental acute HRVs.

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

BIBLIOGRAPHY

The following material is available for review at the Minnesota Department of Health or available through the Minitex Interlibrary Loan System.

References Cited

ACGIH (1998). *Threshold Limit Values for Chemical Substances and Physical Agents.* American Conference of Governmental Industrial Hygienists. Cincinnati, Ohio.

Cal EPA (1999). The Determination of Acute Reference Exposure Levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment. Berkeley, CA.

Dodd, D.E., Longo, L.C., and Eisler, D.L. (1982). Dicyclopentadiene vapor ninety-day inhalation study on rats and mice. Bushy Run Research Center Export, PA. TSCA 8e submission by Exxon Chem. Amer. Doc. I.D. 88-8300464, Odd Doc. I.D. 8EHQ-0283-0364. Microfiche No. OTS 204864.

Federal Register (1991a). National Primary Drinking Water Regulations; Final Rule. Vol. 56, No. 97, Monday, May 22, 1989, Pages: 22074-22075.

Federal Register (1991b). Guidelines for Developmental Toxicity Risk Assessment; Notice. Vol. 56, No. 234.

Healy, T.E.J., Poole, T.R., and Hopper, A. (1982). Rat fetal development and maternal exposure to trichloroethylene 100 ppm. *Brit. J. Anaesth.* **54,** 337-341.

Hollingsworth, R.L., Rowe, V.K., Oyen, F., Hoyle, H.R., and Spencer, H.C. (1956). Toxicity of paradichlorobenzene: Determinations of experimental animals and human subjects. *AMA Arch. Ind. Health* **14,** 138-147.

Jappinen, P., Vilka, V., Marttila, O., and Haahtela, T. (1990). Exposure to hydrogen sulfide and respiratory function. *Brit. J. Ind. Med.* **47,** 824-828.

Klonne, D.R., Dodd, D.E., Pritts, I.M., Nachreiner, D.J., Fowler, E.H., Troup, C.M., Homan, E.R., and Ballantyne, B. (1987). Dimethylethanolamine: Acute, 2-week, and 13-week inhalation toxicity studies in rats. *Fund. Applied Toxicology* **9,** 512-521.

Miller, R.R., Hermann, E.A., Largvardt, P.W., McKenna, M.J., and Schwetz, B.A. (1983). Comparative metabolism and disposition of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in male rats. *Toxicol. Appl. Pharmacol* **67,** 229-237.

MDH (1995). MDH/HRA Criteria used to issue fish consumption advice: 1995 Minnesota Fish Consumption Advisory. HRA Series FSH-95-001, Minnesota Department of Health.

MDH (1996a). MDH/HRA Briefing paper #5: Carcinogen Lifetime Risk Level.

MDH (1996b). MDH/HRA Briefing paper #6: Risk Assessment Methods for Carcinogenic Exposures.

MDH (1996c). MDH/HRA. Briefing paper #8: Use of uncertainty and Modifying Factors.

MDH (1996d). MDH/HRA. Briefing paper #9: Dosimetric Adjustments.

MDH (1996e). MDH/HRA. Briefing paper #10: Exposures to Multiple Contaminants and Pathways.

MDH (2000). MDH/HRA. Briefing paper #12: The Development and Application of a Draft Acute HRV for Hydrogen Sulfide.

Minnesota Rules 4717.7100 to 4717.7800, revised as of 11/94 and the accompanying statement of need and reasonableness (SONAR).

Murphy, S.D. (1980). Assessment of the potential for toxic interactions among environmental pollutants. In: Galli, C.L, Murphy, S.D. and Paoletti, R.(eds.). The principles and methods in modern toxicology. Amsterdam, The Netherlands: Elsevier/North Holland Biomedical Press.

NAS (1983). National Academy of Science. *Risk assessment in the federal government: Managing the process.* National Academy Press, Washington, D.C.

NRC (1986). National Research Council. Dose route extrapolations: Using inhalation toxicity data to set drinking water limits. In *Drinking Water and Health, Volume 6.* National Academy Press, Washington D.C.

NRC (1994). National Research Council. *Science and Judgment in Risk Assessment*. National Academy Press, Washington, D.C.

NTP (1992). National Toxicology Program. Toxicology and carcinogenesis studies of naphthalene. NTP TR 410, NIH publication No. 92-3141.

Pozanni, U. C., Weil, C. S., and Carpenter, C.P. (1959). The toxicological basis of threshold values 5: The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. *Am. Ind. Hyg. Assoc. J.* **20,** 364-369.

Ghyselen, P., Buchet, J.P., Ceulemans, E., and Lauwerys, R.R. (1992). Assessment of the permissible exposure level to manganese in workers exposed to manganese dioxide dust. *Brit. J. Industrial Med.* **49,** 25-34.

Smyth, H.F., Weil, C.S., West, J.S., and Carpenter, C. P. (1969). An exploration of joint toxic action I. Twenty-seven industrial chemicals intubated in rats in all possible pairs. *Toxicol. Appl. Pharmacol.* **14,** 340-347.

Smyth, H.F., Weil, C. S., West, J. S., and Carpenter, C. P. (1970). An exploration of joint toxic action II. Equitoxic versus equivolume mixtures. *Toxicol. Appl. Pharmacol.* **17,** 498-503.

State Register (1995). Notices of Solicitation of Outside Opinion. Published in the *State Register,* S.R.443, September 5, 1995.

State Register (1999). Request for comments. Published in the *State Register*, 24S.R.372, September 13, 1999.

ten Berge, W.F., Zwart, A., and Appelman, L.M. (1986) Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *J. Hazardous Materials* **13,** 301-309.

U.S. EPA (1986a). Guidelines for carcinogenic risk assessment. Federal Register 51 (185):33992-34003.

U.S. EPA (1986b). Guidelines for the health risk assessment of chemical mixtures. Fed. Register. 51(185):34014-34025.

U.S. EPA (1989). Interim Methods for Development of Inhalation Reference Doses. (EPA/600/8-88/066F). Office of Health and Environmental Assessment, Washington D.C. 20460.

U.S. EPA (1990). Reducing Risk: Setting Priorities and Strategies for Environmental Protection. SAB-EC-90-021. Washington D.C. 20460.

U.S. EPA (1992). EPA's Approach for Assessing the Risks Associated with Chronic Exposures to Carcinogens. IRIS online Background Document 2.

U.S. EPA (1993). Reference Dose (RfD): Description and use in Health Risk Assessments. IRIS online background document 1a.

U.S. EPA (1994a). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. (EPA/600/8-90/066F). Office of Research and Development, Washington D.C. 20460.

U.S. EPA (1994b). Health Assessment Document for Diesel Emissions. (EPA/600/8-90/057Bb Volume 2). Office of Research and Development, Washington, D.C. 20460.

U.S. EPA (1995). Health Effects Assessment Summary Tables. (EPA 540/R-95-036). Office of Research and Development, Washington DC 20460.

U.S. EPA (1996). Proposed Guidelines for Carcinogen Risk Assessment. (EPA/600/P-92/003C). Office of Research and Development, Washington DC.

U.S. EPA (1997). Exposure Factors Handbook. (EPA/600/P-95/002Fc) Exposure Assessment Group, Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC 20460.

U.S. EPA (1999a). Overview of IRIS in Introduction to IRIS.

U.S. EPA (1999b). Reference Concentration (RfC): Description and Use in Health Risk Assessments. IRIS Background Document.

U.S. EPA (1999c). The U.S. EPA Approach for Assessing the Risks Associated with Chronic Exposure to Carcinogens. IRIS Background Document.

U.S. EPA (1999d). Glossary of IRIS terms. IRIS Background Document.

U.S. EPA (2001). IRIS Database. http://www.epa.gov/ngispgm3/iris

Weller, R.W. and Crellin, A.J. (1953). Pulmonary granulomatosis following extensive use of paradichlorobenzene. *Arch. Int. Med.* **91**, 408-413.

Available Documentation and materials

MDH/HRA (1985). Tolerable risk. Section of Health Risk Assessment, Minnesota Department of Health.

MDH/HRA (1999). Support Document for Acute HRVs. Acute Sub-Work Group.

MDH (1995). Health Risk Values Discretionary Mailing List.

MDH (1999). Health Risk Values Discretionary Mailing List.

MDH/HRA (1996). Health Risk Values Technical Advisory Work Group members.

MDH/HRA. (1996-2000) Minnesota Department of Health, Health Risk Assessment unit (MDH/HRA) set of Briefing papers, numbers 1 to 12:

MDH/HRA. Briefing paper #1: Selection of Chemicals for Health Risk Values, May 1996.
MDH/HRA. Briefing paper #2: Exposure Categories for Health Risk Values, May 1996.
MDH/HRA. Briefing paper #3: Data Sources for Health Risk Values, May 1996.
MDH/HRA. Briefing paper #4: Application of Health Risk Values, June 1996.
MDH/HRA. Briefing paper #5: Carcinogen Lifetime Risk Level, August 1996.
MDH/HRA. Briefing paper #6: Risk Assessment Methods for Carcinogenic Exposures, August 1996.
MDH/HRA. Briefing paper #7: Risk Assessment Methods for Noncarcinogenic Exposures, October 1996.
MDH/HRA. Briefing paper #8: Use of uncertainty and Modifying Factors, October 1996.
MDH/HRA. Briefing paper #9: Dosimetric Adjustments, October 1996.
MDH/HRA. Briefing paper #10: Exposures to Multiple Contaminants and Pathways, October 1996.
MDH/HRA. Briefing paper #11: Use of Lifetime Exposure, April 1997.
MDH/HRA. Briefing paper #12: The Development and Application of a Draft Acute HRV for Hydrogen Sulfide, April 2000.

MDH/HRA (1997). Health Risk Values Technical Advisory Work Group members.
MDH/HRA (1999). Health Risk Values Technical Advisory Work Group members.

MDH/HRA. Health Risk Values Chemical Reviews:
MDH/HRA review for acrolein.
MDH/HRA review for acrylic acid.
MDH/HRA review for allyl chloride.
MDH/HRA review for arsine.
MDH/HRA review for chlordane.
MDH/HRA review for chlorine dioxide.
MDH/HRA review for chromic acid mists and issolved Cr (VI) aerosols.
MDH/HRA review for Cr (VI) particulates.
MDH/HRA review for cumene.
MDH/HRA review for 1,2-dibromo 3-chloropropane.
MDH/HRA review for 1,4-dichlorobenzene.
MDH/HRA review for 1,2-dichloropropane.

MDH/HRA review for dicyclopentadiene.
MDH/HRA review for 2-dimethylamino ethanol.
MDH/HRA review for ethylene glycol monoethyl ether or 2-ethoxyethanol.
MDH/HRA review for ethylene glycol monomethyl ether (EGME) or 2-methoxyethanol.
MDH/HRA review for hydrogen sulfide.
MDH/HRA review for phosphine.
MDH/HRA review for propylene glycol monomethyl ether.
MDH/HRA review for manganese.
MDH/HRA review for triethylamine.

MDH/HRA, MinutesfromTechnicalAdvisoryWorkGroupMeetings:
May 29, 1996
July 10, 1996
August 21, 1996
October 9, 1996
November 20, 1996
December 18, 1996
January 29, 1997
February 19, 1997
April 16, 1997
May 21, 1997
September 24, 1997
November 19, 1997
January 28, 1998
March 12, 1998
December 22, 1998
January 27, 1999
April 28, 1999
July 21, 1999
September 29, 1999
October 28, 1999
December 8, 1999
January 26, 2000
April 5, 2000
December 7, 2000

MDH/HRA (2001). DraftListofSubstancesforHealthRiskValues.

Reference Exposure Level Files: Cal EPA (1999). TheDeterminationofAcuteReferenceExposure LevelsforAirborneToxicants, Office of Environmental Health Hazard Assessment. Berkeley, CA.

Cal EPA (1999). REL file for ammonia.
Cal EPA (1999). REL file for arsine.
Cal EPA (1999). REL file for benzene.
Cal EPA (1999). REL file for carbon disulfide.
Cal EPA (1999). REL file for chlorine.
Cal EPA (1999). REL file for chloroform.
Cal EPA (1999). REL file for dichloromethane.
Cal EPA (1999). REL file for 1,4-dioxane.

Cal EPA (1999). REL file for ethylene glycol monoethyl ether.
Cal EPA (1999). REL file for ethylene glycol monoethyl ether acetate.
Cal EPA (1999). REL file for ethylene glycol monomethyl ether.
Cal EPA (1999). REL file for formaldehyde.
Cal EPA (1999). REL file for hydrogen chloride.
Cal EPA (1999). REL file for hydrogen cyanide.
Cal EPA (1999). REL file for hydrogen fluoride.
Cal EPA (1999). REL file for hydrogen sulfide.
Cal EPA (1999). REL file for methanol.
Cal EPA (1999). REL file for methyl bromide.
Cal EPA (1999). REL file for methyl ethyl ketone.
Cal EPA (1999). REL file for nickel and nickel compounds.
Cal EPA (1999). REL file for nitric acid.
Cal EPA (1999). REL file for phenol.
Cal EPA (1999). REL file for phosgene.
Cal EPA (1999). REL file for sodium hydroxide.
Cal EPA (1999). REL file for styrene.
Cal EPA (1999). REL file for tetrachloroethylene.
Cal EPA (1999). REL file for toluene.
Cal EPA (1999). REL file for 1, 1, 1-trichloroethane.
Cal EPA (1999). REL file for triethylamine.
Cal EPA (1999). REL file for vanadium pentoxide.
Cal EPA (1999). REL file for xylenes.

U.S. EPA IRIS FILES

U.S. EPA (2001). IRIS file for acetaldehyde.
U.S. EPA (2001). IRIS file for acetonitrile.
U.S. EPA (2001). IRIS file for acrolein.
U.S. EPA (2001). IRIS file for acrylic acid.
U.S. EPA (2001). IRIS file for acrylonitrile.
U.S. EPA (2001). IRIS file for allyl chloride.
U.S. EPA (2001). IRIS file for ammonia.
U.S. EPA (2001). IRIS file for antimony.
U.S. EPA (2001). IRIS file for antimony trioxide.
U.S. EPA (2001). IRIS file for arsenic.
U.S. EPA (2001). IRIS file for arsine.
U.S. EPA (2001). IRIS file for benzene.
U.S. EPA (2001). IRIS file for benzidine.
U.S. EPA (2001). IRIS file for benzo[a]pyrene.
U.S. EPA (2001). IRIS file for beryllium.
U.S. EPA (2001). IRIS file for bis (chloromethyl) ether.
U.S. EPA (2001). IRIS file for bromomethane.
U.S. EPA (2001). IRIS file for 1,3-butadiene.
U.S. EPA (2001). IRIS file for cadmium.
U.S. EPA (2001). IRIS file for carbon disulfide.
U.S. EPA (2001). IRIS file for chlordane.
U.S. EPA (2001). IRIS file for chlorine.

U.S. EPA (2001). IRIS file for chlorine dioxide.
U.S. EPA (2001). IRIS file for 2-chloroacetophenone.
U.S. EPA (2001). IRIS file for chromic acid mists and dissolved Cr (VI) aerosols.
U.S. EPA (2001). IRIS file for chromium VI.
U.S. EPA (2001). IRIS file for Cr (VI) particulate.
U.S. EPA (2001). IRIS file for coke oven emissions.
U.S. EPA (2001). IRIS file for cumene.
U.S. EPA (2001). IRIS file for 1,2-dibromo 3-chloropropane.
U.S. EPA (2001). IRIS file for 1,2-dibromoethane.
U.S. EPA (2001). IRIS file for 1,4-dichlorobenzene.
U.S. EPA (2001). IRIS file for dichloromethane.
U.S. EPA (2001). IRIS file for 1,2-dichloropropane.
U.S. EPA (2001). IRIS file for 1,3-dichloropropene.
U.S. EPA (2001). IRIS file for dichlorvos.
U.S. EPA (2001). IRIS file for diesel engine emissions.
U.S. EPA (2001). IRIS file for N, N-dimethylformamide.
U.S. EPA (2001). IRIS file for epichlorohydrin.
U.S. EPA (2001). IRIS file for 1, 2-epoxybutane.
U.S. EPA (2001). IRIS file for 2-ethoxyethanol.
U.S. EPA (2001). IRIS file for ethyl benzene.
U.S. EPA (2001). IRIS file for ethylene glycol monobutyl ether.
U.S. EPA (2001). IRIS file for formaldehyde.
U.S. EPA (2001). IRIS file for 1, 6-hexamethylene diisocyanate.
U.S. EPA (2001). IRIS file for n-hexane.
U.S. EPA (2001). IRIS file for hydrazine and hydrazine sulfate.
U.S. EPA (2001). IRIS file for hydrogen chloride.
U.S. EPA (2001). IRIS file for hydrogen cyanide.
U.S. EPA (2001). IRIS file for hydrogen sulfide.
U.S. EPA (2001). IRIS file for manganese.
U.S. EPA (2001). IRIS file for 2-methoxyethanol.
U.S. EPA (2001). IRIS file for methylmercury.
U.S. EPA (2001). IRIS file for methyl methacrylate.
U.S. EPA (2001). IRIS file for methylene diphenyl diisocyanate and polymeric MDI.
U.S. EPA (2001). IRIS file for naphthalene.
U.S. EPA (2001). IRIS file for nickel.
U.S. EPA (2001). IRIS file for nickel refinery dust.
U.S. EPA (2001). IRIS file for nickel subsulfide.
U.S. EPA (2001). IRIS file for 2-nitropropane.
U.S. EPA (2001). IRIS file for phosphine.
U.S. EPA (2001). IRIS file for propylene glycol monomethyl ether.
U.S. EPA (2001). IRIS file for propylene oxide.
U.S. EPA (2001). IRIS file for styrene.
U.S. EPA (2001). IRIS file for toluene.
U.S. EPA (2001). IRIS file for 2,4- / 2,6-toluene diisocyanate.
U.S. EPA (2001). IRIS file for triethylamine.
U.S. EPA (2001). IRIS file for vinyl acetate.
U.S. EPA (2001). IRIS file for vinyl chloride.