Air Toxics Hot Spots Program Risk Assessment Guidelines

Part I

The Determination of Acute Reference Exposure Levels for Airborne Toxicants

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Secretary for Environmental Protection
California Environmental Protection Agency
Winston H. Hickox

Director
Office of Environmental Health Hazard Assessment
Joan E. Denton, Ph.D.

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CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

AIR TOXICOLOGY AND EPIDEMIOLOGY SECTION

Prepared by:

George V. Alexeeff, Ph.D.
John D. Budroe, Ph.D.
James F. Collins, Ph.D.
Richard H.F. Lam, Ph.D.
David C. Lewis, Ph.D.
Michael J. Lipsett, M.D., J.D.
Melanie A. Marty, Ph.D.
Thomas R. Parker, M.S.

Air Toxicology and Epidemiology Section
Office of Environmental Health Hazard Assessment

OEHHA also acknowledges the following contributors:

Sharan Campleman, M.S., M.P.H.
Rupali Das, M.D., M.P.H.
Jefferson R. Fowles, Ph.D.
Richard J. Jackson, M.D., M.P.H.
Peggy Lopipero, M.P.H.
Lee Moore, M.P.H.
Renee Paige, B.S.

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1. Introduction

Hazardous substances are routinely released into the environment as a result of predictable continuous or short-term emissions from facilities and predictable process upsets or leaks. As a result, the public living or working in communities surrounding industrial facilities is at risk of being exposed to airborne toxicants.

Local air pollution control officers, industrial facility operators, and others have a need for clear guidance regarding the acute health effects of hazardous substances. Currently there are numerous sources of acute exposure levels developed by various committees for application primarily to occupational and military settings. However, values for acute exposure of the general public are of limited number and uneven quality, and focus on industrial accidents instead of predictable, routine, short-term emissions. While some methods relate toxicological information from human data and animal experiments to acute chemical exposure, they may be based upon flawed or inconsistent algorithms or are not designed for the special case of predictable exposure of the public to airborne toxicants (Robinson and Paxman, 1992). Furthermore, there often exist several different acute exposure levels for a single compound, each developed by a different organization. These values may differ by more than 100-fold, which confounds prudent decisions. Consequently, there are few existing guidelines that reflect sound science, clearly take into account issues such as appropriate endpoints and uncertainties about toxicity, and focus on routine or predictable acute air releases.

The National Academy of Sciences (NAS)[1] recommends that the United States Environmental Protection Agency (U.S.EPA) more clearly define, and in some cases change, the methods and assumptions used to estimate the risk of cancer and other health problems from hazardous air pollutants (NRC, 1994). Specifically, NAS has endorsed the development of biologically based quantitative methods for assessing the effects of exposure to a chemical. This includes incorporating information on mechanisms of action and variability among populations and between individuals that might affect susceptibility to toxic insults, such as age, lifestyle, genetic background, sex, and ethnicity. NAS recognized the continued need to use default options to address the uncertainties of underlying mechanisms in risk assessment for populations. NAS has recommended that U.S.EPA (1) explicitly identify each use of a default option in risk assessment; (2) clearly state the scientific and policy basis for each default option; and (3) articulate criteria for allowing departure from default options. NAS has also recommended that U.S.EPA screen the hazardous air pollutants identified in the 1990 Clean Air Act Amendments to establish priorities for setting standards, identifying data gaps, and developing incentives to expedite the generation of data by other governmental agencies.

The Office of Environmental Health Hazard Assessment (OEHHA) has followed the NAS recommendations by establishing uniform, science-based guidelines to be used in the derivation of acute severity levels applicable to the general public exposed routinely to hazardous substances released into the environment. By investigating existing exposure values developed by other organizations (described below), OEHHA has been able to identify some of the data gaps and

[1] Appendix E contains a glossary of the principal acronyms used in this document.

inconsistencies contained in the existing guidelines. The results of this investigation have allowed the development of a more rigorous and resource-intensive scientific methodology which has been used to calculate acute exposure levels for prioritized chemicals. The use of benchmark dose methodology, described later in this document, is an example of departure from default options as recommended by NAS. Better human dose-response data, for example, from improved workplace monitoring correlated with symptoms and more extensive epidemiologic studies, are needed before the departure from default approaches can be expanded to more substances.

1.1 Objective

The objective of this document is to present a method for deriving acute (one-hour) inhalation Reference Exposure Levels (RELs) for hazardous airborne substances. The acute REL is an exposure that is not likely to cause adverse effects in a human population, including sensitive subgroups, exposed to that concentration for one hour on an intermittent basis. These health-based acute RELs are applicable to risk characterization of air releases, defined in Health and Safety Code Section 44303, as:

> "including actual or potential spilling, leaking, pumping, pouring, emitting, emptying, discharging, injecting, escaping, leaching, dumping, or disposing of a substance into the ambient air and that results from routine operation of a facility or that is predictable, including, but not limited to continuous and intermittent releases and predictable process upsets or leaks."

1.1.1 Definition of Reference Exposure Level (REL)

The concentration level at or below which no adverse health effects are anticipated for a specified exposure duration is termed the reference exposure level (REL). RELs are based on the most sensitive, relevant, adverse health effect reported in the medical and toxicological literature. RELs are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety. Since margins of safety are incorporated to address data gaps and uncertainties, exceeding the REL does not automatically indicate an adverse health impact. Figure 1 depicts the steps involved in developing RELs. While we conduct a complete literature search for each chemical, in the chemical summaries in Appendix C we only describe the key studies used in the acute REL development.

1.1.2 Legislative Mandate

As defined under the Air Toxics "Hot Spots" Information and Assessment Act of 1987 ("AB 2588" [Chapter 1252, Statutes of 1987], California Health and Safety Code Section 44300 *et seq*., as amended), a risk assessment includes a comprehensive analysis of the dispersion of hazardous substances in the environment, and the potential for human exposure and a quantitative assessment of both individual and population-wide health risks associated with those levels of exposure. This document establishes a standardized procedure for generating the health based values (acute reference exposure levels) used for assessing acute, noncancer risks within the risk assessment process.

In preparing this document, OEHHA is responding to state legislation enacted in 1992. Senate Bill (SB) 1731 (Stats. 1992, Ch. 1162) requires OEHHA to develop risk assessment guidelines for implementing the "Hot Spots" Act. Assembly Bill (AB) 2728 (Statutes of 1992, Chapter 1161; California Health and Safety Code Section 39660) added a mandate to the Toxic Air Contaminants Program that all Federal Hazardous Air Pollutants be identified as Toxic Air Contaminants. The Health and Safety Code also requires OEHHA to use a margin of safety when estimating levels of exposure that may cause adverse health effects. This margin of safety must account for heterogeneity within human populations and uncertainty related to the applicability and completeness of the available data. To help meet the requirements of AB 2728 and SB 1731, OEHHA described and evaluated methodology to estimate acute RELs and derived such levels for specific chemicals. The acute RELs are designed for use in the Air Toxics "Hot Spots" Program.

Figure 1. REL development process

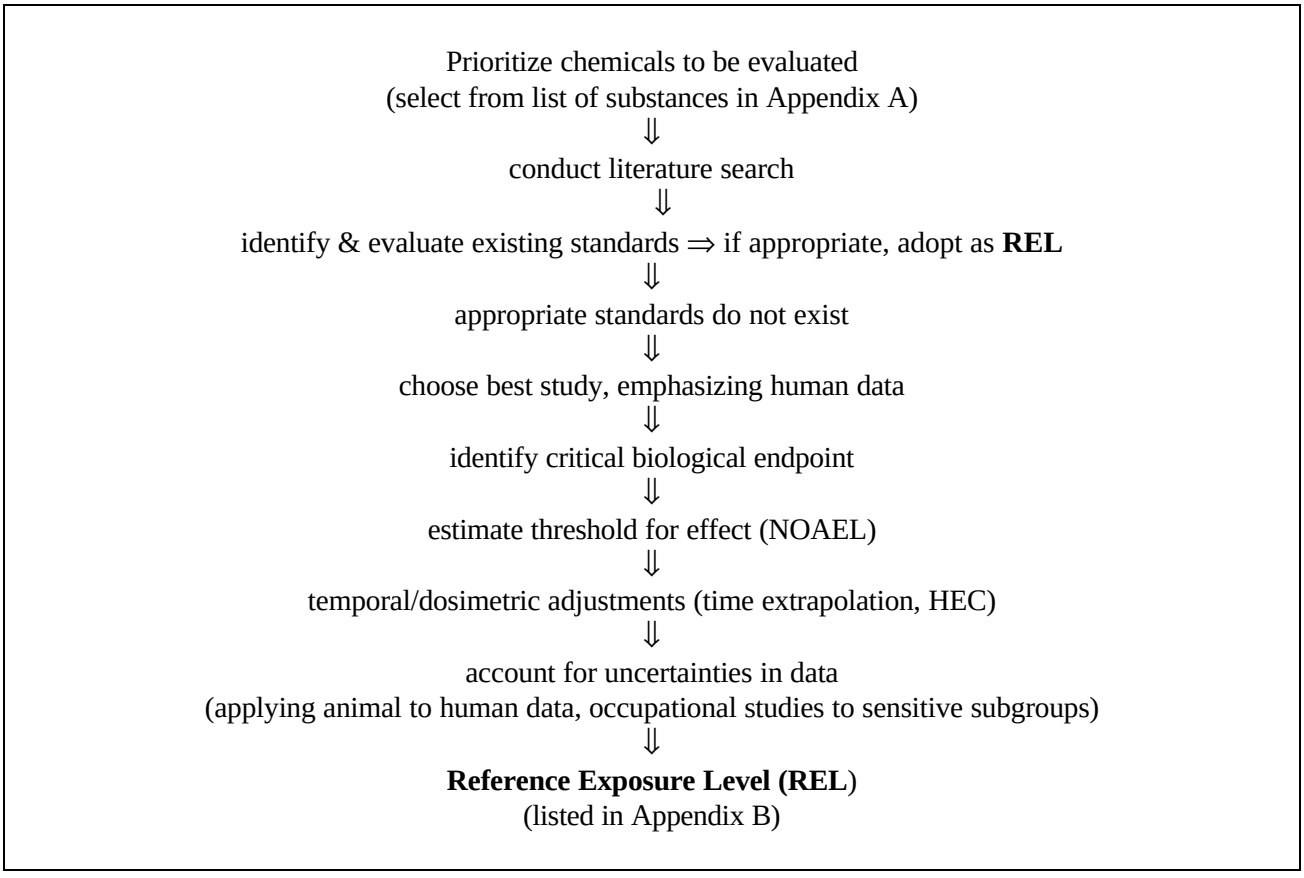
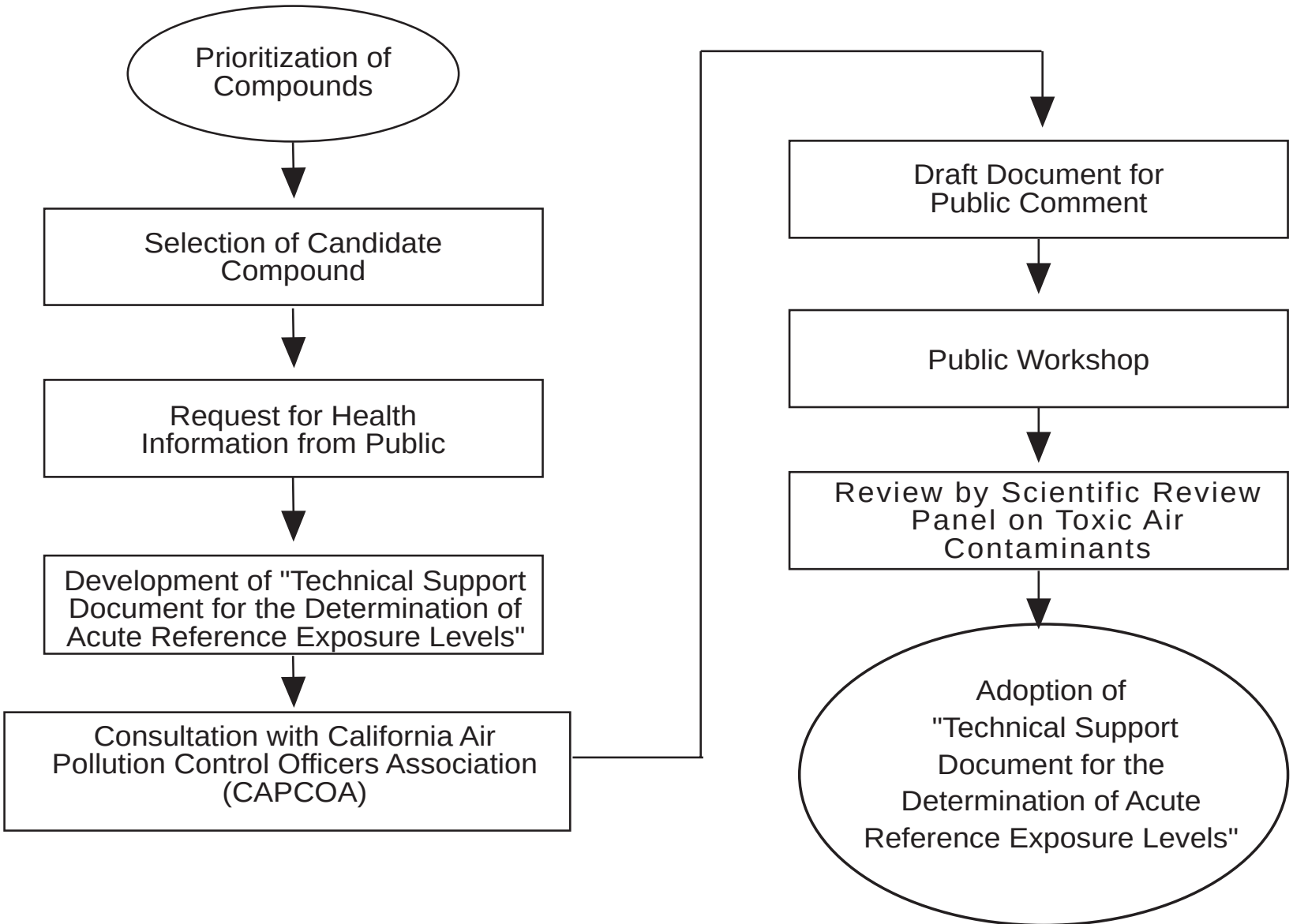


Figure 2

Public and Peer Review Process for Establishing Reference Exposure Levels



OEHHA and the Air Resources Board (ARB) have set up a procedure to facilitate the extensive public comment and peer review necessary for implementation of AB 2728 and SB 1731 (Figure 2). This process includes internal OEHHA and Cal/EPA review, consultation with the California Air Pollution Control Officers Association (CAPCOA), a public comment period, and public workshops. In addition, this document has been reviewed by the Scientific Review Panel onToxic Air Contaminants administered by the ARB. A draft of this document was released for public comment in January 1995. We have responded to public comment and updated and revised the chemical-specific information. The State's Scientific Review Panel on Toxic Air Contaminants reviewed this document and provided comments which were incorporated into this final draft.

1.1.3 Implementation of Risk Assessment Advisory Committee (RAAC) Recommendations

The California Environmental Protection Agency (Cal/EPA) Risk Assessment Advisory Committee (RAAC) was a panel of scientists convened under Chapter 418, Statutes of 1993, Health and Safety Code, Section 57004, to review the health risk assessment practices within Cal/EPA. The RAAC issued a report on its findings (Risk Assessment Advisory Committee, 1996). In the completion of the acute REL document, the RAAC recommendations were carefully considered (Table 1).

Table 1. Implementation of RAAC Recommendations

RAAC Recommendation	Implementation
Formalized peer review program	This document was reviewed by an advisory committee of non-governmental scientists: the Scientific Review Panel on Toxic Air Contaminants, prior to adoption.
Input from risk managers and from external stakeholders	This document has been reviewed by risk assessors and managers of the Cal/EPA Boards and Departments. The document has also been reviewed by representatives of the Air Quality Management and Air Pollution Control Districts, as part of the California Air Pollution Control Officers Association review. The early draft of this document was distributed for comment to others, including external stakeholders. Two public workshops were held, one in Northern California and one in Southern California to solicit stakeholder input. Many changes were made in response to the input.
Balance level of effort with importance	The selection of chemicals for intensive review in this document was based in part on the importance of the chemical within California. Emphasis was placed on developing health levels for those substances with high emissions or of concern to risk managers. The project incorporated all available risk assessment information from U.S.EPA, NAS, and other authoritative bodies.
Coordinate effort with U.S.EPA	The project made use of all available risk assessment information. At the time of preparation of this document, no final U.S.EPA documents were available. A draft U.S.EPA report for consideration of accidental exposures to 12 chemicals was released in 1997 (CFR 62 No. 210; Oct 30, 1997). These were reviewed, but since they are subject to change, were not incorporated into the OEHHA document. The draft was sent to U.S.EPA's ORD for review and technical issues were discussed with U.S.EPA staff.

RAAC Recommendation	Implementation
Incorporate consideration of effect severity	Concerns that severely adverse and high incidence effects should be addressed differently from mild and/or rarely encountered effects were addressed by incorporation of intermediate LOAEL uncertainty factors. In addition, the data are presented based on a classification scheme of severity. Adverse effects were classified as mild, severe, and life-threatening. Information was also provided, when available, on the effects that could result from doses above the REL. Additional research will be needed to use more sophisticated approaches to this problem.

In general, the committee recommendations were well addressed. Complete implementation of all committee recommendations will require additional efforts and research beyond the scope of the current project. In particular, developing alternative approaches to some areas of uncertainty now addressed with default assumptions will require extensive data collection and analyses.

1.2 List of Substances Considered

All substances compiled by the ARB for the Air Toxics "Hot Spots" list of substances were considered for evaluation and inclusion in this guidance. The substances included on the Air Toxics "Hot Spots" Program List are those substances found on lists developed by the International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency (U.S.EPA), the U.S. National Toxicology Program, the ARB (list used in the Toxic Air Contaminant Program), the Hazard Evaluation System and Information Service (State of California), or on the Proposition 65 list of carcinogens and reproductive toxicants (State of California). The complete list of substances whose emissions must be quantified is contained in Appendix B.

Several exposure guidelines as well as published toxicological and epidemiologic literature serve as sources of information for chemicals for which acute RELs are being developed. These are: California Ambient Air Quality Standards (CAAQS) developed by the State of California; Emergency Exposure Guidance Levels (EEGLs) and Short-term Public Emergency Guidance Levels (SPEGLs) developed by the NAS; Emergency Response Planning Guidelines (ERPGs) developed by the American Industrial Hygiene Association (AIHA); and Immediately Dangerous to Life and Health (IDLH) levels developed by the National Institute of Occupational Safety and Health (NIOSH).

1.2.1 Priority For Evaluation Of Chemicals

Substances were prioritized for the development of acute RELs on the basis of several criteria (Table 2). All 32 chemicals for which acute noncancer RELs appeared in the *Air Toxics "Hot Spots" Program Revised 1992 Risk Assessment Guidelines* (California Air Pollution Control Officers Association, 1993) were considered for evaluation. This was done to maintain consistency in the Hot Spots program and, by using existing information as much as possible, to conserve resources. Additional substances were chosen from the ARB's Air Toxics "Hot Spots"

emissions inventory based on: (1) the availability of California ambient air quality standards, (2) the magnitude of emissions in California, or (3) known toxic properties. The list of 51 substances that have been evaluated with the methods delineated in this Technical Support Document is contained in Appendix A.

Table 2. Prioritization Process for Acute Toxicity Exposure Levels

Listed in CAPCOA (1993) Document	**California Ambient Air Quality Standard (not already listed by CAPCOA)**
1. Acrolein	1. Carbon monoxide
2. Ammonia	
3. Arsine	
4. Benzyl chloride	**High Emissions (High on ATEDS emissions inventory)**
5. Carbon tetrachloride	1. Arsenic and compounds
6. Chlorine	2. Benzene
7. Copper and compounds	3. Chloroform
8. 1,4-Dioxane	4. Chloropicrin
9. Ethylene glycol monobutyl ether	5. Copper and compounds
10. Ethylene glycol monoethyl ether acetate	6. Epichlorohydrin
11. Ethylene glycol ethyl ether	7. Isopropyl alcohol
12. Ethylene glycol methyl ether	8. Methanol
13. Formaldehyde	9. Methyl bromide
14. Hydrochloric acid	10. Nitric acid
15. Hydrogen cyanide	11. Phenol
16. Hydrogen fluoride	12. Styrene
17. Hydrogen sulfide	13. Sulfuric acid
18. Mercury (inorganic)	14. Toluene
19. Methyl chloroform	15. Vanadium pentoxide
20. Methylene chloride	16. Vinyl chloride
21. Nickel and compounds	
22. Nitrogen dioxide	
23. Ozone	**Other known toxic compounds**
24. Perchloroethylene	
25. Phosgene	1. Acrylic acid
26. Propylene oxide	2. Carbon disulfide (CEPRC list)
27. Selenium and compounds	3. Triethylamine
28. Sodium hydroxide	
29. Sulfates	
30. Sulfur dioxide	
31. Xylenes	

1.3 Time Frame of Interest

In the Air Toxics Hot Spots program, routine industrial emissions are evaluated for potential public health impacts. Chronic exposure is evaluated using ambient air concentrations of emitted chemicals averaged over a year. The annualized average air concentration forms the basis for both chronic noncancer and cancer risk evaluation. In reality, exposure over a 24-hour period does not occur at a continuous level. Facility emissions may fluctuate considerably, with daily and

hourly maximum and minimum concentrations. The commonly used air dispersion models account for only some of this variation as they can only accommodate emissions data entered as a single value in pounds emitted per hour or per year. However, the models can calculate concentrations hour by hour throughout a year, giving an indication of the one-hour maximum exposure concentrations. The hourly fluctuations are a reflection of the changing meteorological conditions that are included in the model.

In general, the one-hour modeled maximum concentrations in the Air Toxics Hot Spots program are used in a hazard index approach in order to evaluate "acute" exposures and potential public health impacts from such exposure. Modeled concentrations of several hours are used for some reproductive/developmental toxicants (see section 1.6.1). The hazard index is the ratio of the modeled concentration to the acute reference exposure level. If the ratio exceeds one, then the risk manager needs to consider whether risk reduction is appropriate. An exceedance of one does not mean adverse effects will occur. Rather, it is an indication of the erosion of the margin of safety for exposure to that chemical.

1.4 Criteria for Development of Acute Severity Levels

Acute severity levels are concentration levels at or below which specified health effects are not expected to occur. Toxicological responses to acute exposures follow a graded response, dependent on the exposure dose (determined by concentration and time). Dividing this graded response into several categories facilitates the development of graded acute severity levels for each chemical, based on the severity of effect. OEHHA has chosen to follow the NAS guidelines (NRC, 1993) to divide these responses into three severity levels, as detailed below.

The Air Toxics Hot Spots Program uses the reference exposure levels, derived from the most sensitive endpoint of toxicity, for the risk assessment process. Designation of the effects of exposure to increasing doses into severity categories will likely be helpful to risk assessors evaluating exceedances by helping them to better understand the practical implications of the endpoint of concern. Furthermore, the proximity of the REL to the next severity level may help risk managers in making decisions on appropriate actions. In a brief review of approximately 300 risk assessments submitted by facilities complying with the Air Toxics Hot Spots Program, OEHHA found 20% of the facilities with exceedances of the acute reference exposure levels, ranging from 2-fold to as high as 500-fold.

1.4.1 Definition of Acute Severity Levels

This methods document is focused on the development of three categories of acute severity levels in accordance with criteria established by NRC (1993): the level protective against mild adverse effects, the level protective against severe adverse effects, and the level protective against life-threatening effects (see Figure 3). Each of these three acute exposure levels is determined for a one-hour exposure duration. While NAS established these categories for the evaluation of accidental chemical releases, the toxicological principles validating the three severity levels are applicable to any acute exposures. However, the major focus of this document is in developing acute RELs for the preparation of risk assessments for non-emergency routine releases. Thus, the

RELs used in the risk assessment are generally levels protective against mild adverse effects; a few are based on severe effects (e.g., reproductive/developmental).

A central assumption in the development of acute noncancer toxicity levels is that all toxicologic endpoints included under these levels are considered to have a threshold for adverse effects. However, the threshold may not be observable and, in some cases, may only be estimated. Areas of uncertainty in estimating effects among a diverse human population are addressed using extrapolation and uncertainty factors (UFs).

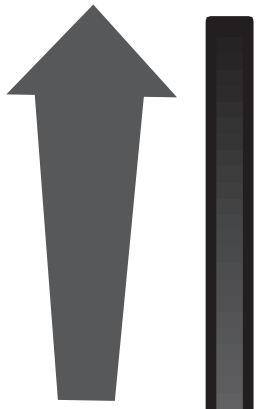
Protection against carcinogenicity and against the adverse health effects of chronic exposures are not considered in these guidelines. For this reason, chemicals should be evaluated separately for their carcinogenicity and for any additional chronic health effects that may occur. Methods for these evaluations are provided in the related OEHHA documents entitled *Technical Support Document for Describing Available Cancer Potency Factors* and *Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels*.

1.4.2 Hazard Index Approach

RELs are used by the Air Toxics "Hot Spots" Program as indicators of the potential adverse health effects of chemicals. A "hazard index" approach is used to estimate potential health effects resulting from hazardous substances by comparing measured exposure levels to calculated RELs. This approach assumes that multiple sub-threshold exposures to chemicals acting on the same target organ could result in an overall risk of developing an adverse health effect.

For many facilities a large number of chemicals may be emitted or may be present in the air at the location of the receptor or exposed population. To assess the cumulative impact of several chemicals present at the same time, it is important to consider the interaction of effects of the toxicants. Unless specific information is available to the contrary, the interaction of two or more chemicals is assumed to be additive for a given toxicological endpoint. This may underestimate the effect in the cases in which interactions are synergistic or overestimate it if the effects are not additive or are antagonistic.
An underlying issue in chemical interactions and additivity is the concept of a threshold. Exposure to a single chemical in the air may not result in a toxic response if it is below the threshold necessary to elicit a response. However, simultaneous exposure to two similar chemicals at sub-threshold levels may result in a toxic response. This is taken into account by adding the individual ratios of modeled concentrations to acute RELs for chemicals that impact

Figure 3. Acute Severity Exposure Levels for 1-hour Durations



Level protective against life-threatening effects: Any exposure above this level is potentially lethal to sensitive individuals, and as exposure duration increases, death becomes a high probability for all exposed persons. Exposure for specified time duration can lead to complete incapacitation. Depending on the chemical, severe, irreversible injury can occur to any organ system.

Level protective against severe adverse effects: Exposure above this level and time duration may lead individuals to seek assistance. Effects may be disabling by causing impaired judgement or by adversely affecting one's ability to take protective actions or to escape. Effects of exposure may be long-lasting or permanent and may include effects on the outcome of an existing or subsequent pregnancy. This level is sometimes used as the Reference Exposure Level (REL) (e.g., for reproductive/developmental effects).

Level protective against mild adverse effects: The level at or below which no adverse effects are expected. Exposure above this level may produce mild irritation of the eyes, nose, or throat, or may result in other mild adverse physiological changes (see text or Table 5). For most individuals, the irritation and other adverse physiological changes do not persist after exposure ceases. As exposure concentration and duration increases, however, adverse health effects of short duration may be observed in an increasing number of persons. This level is generally used as the Reference Exposure Level (REL).

Persons may detect exposure by odors, sights, taste, or smell. There are no adverse effects of exposure on health.

the same target organ or system (Appendix A lists RELs and toxicologic endpoints). For a particular target organ or system, the HI is calculated as follows:

$$HI = C_1 / REL_1 + C_2 / REL_2 + \ldots + C_i / REL_i$$

where for *i* substances with the same toxicological endpoint,

HI = hazard index

C_i = 1-hour maximum concentration for the i^{th} substance

REL_i = acute REL for the i^{th} substance

Target organs or systems considered for hazard index calculations are general categories that may include varied effects (Table 3). For example, the target system, "Respiratory System," includes upper airway irritation as well as lower airway effects, such as bronchoconstriction. This approach assumes additive interactions, as explained above. Because the precise relative contributions of exposure to multiple substances that principally affect different areas of the same physiologic system (in the previous example, the respiratory system) are unknown, this approach may under- or over-estimate the effects of chemical interactions in certain cases. However, in most cases this approach provides an appropriate health protective assumption. We have indicated in Appendix A, Table A-1 which toxicological endpoints are relevant to the specific REL for each chemical. While the REL is based on the most sensitive endpoint, some toxicological endpoints are manifested at exposures close to that which induces the toxicological endpoint that serves as the basis for the REL. Therefore, some chemicals should be evaluated for impacts on multiple target organs or systems. In addition, predisposing conditions are known to increase susceptibility to some chemicals. The target organs for those predisposing conditions should also be included in the hazard index approach. The target organs to be evaluated for hazard index are presented in Table A-2 in Appendix A, and in each chemical summary in Appendix C.

Table 3. Target organs or systems used in acute hazard index calculations

Hazard Index Targets	Health Effects Included Among the 51 RELs
Hematologic System	Hemolysis; anemia; platelet abnormalities; effects on hematopoietic stem cells
Cardiovascular System	Aggravation of angina
Nervous System	Electroencephalograph (EEG) results; performance on neurobehavioral or neuropsychological tests; clinical neurological exam; headache, lightheadedness, dizziness
Eyes	Irritation of eyes; histological changes to eye tissue

Alimentary Tract	Hepatotoxicity; nausea, vomiting
Immune System	Lymphocyte proliferation; host resistance to infection
Reproductive/Developmental	Fetotoxicity; teratogenicity; intrauterine growth retardation; preimplantation loss; altered behavior in offspring
Respiratory System	Irritation of nose and throat; increased mucus production; histological changes in nasal epithelium; histologic changes in lung tissue; lung function following inhalation challenge (see Table 8)
Skin	Irritation of skin
Physiological Response to Odors	Headache; nausea

1.4.3 Relationship of RELs to Severity Levels

OEHHA has defined the lowest available acute severity level as the REL. It is important to note that the level protective against the lowest severity level for a given chemical may be associated with a severe, rather than a mild, toxic effect for the following reason. Adverse health effects that are minor and reversible are classified as mild effects (U.S.EPA effect severity level 5 or less, see Table 5). However, the most sensitive detectable adverse effect of a chemical may be a severe effect (U.S.EPA effect severity level 5-9, see Table 5). For chemicals with three severity levels, the level protective against mild adverse effects is considered the REL; for chemicals for which such a level is not appropriate (i.e., does not exist), the level protective against severe adverse effects is the REL. For example, the most sensitive endpoint found in the literature for arsenic and related compounds was reproductive toxicity, a severe effect (Acute Toxicity Summary for Arsenic, Appendix C); thus, for arsenic, the REL is a level protective against severe adverse effects.

For most compounds there are three identifiable severity levels. However, as stated above, there are some chemicals for which all severity level criteria do not apply. Those chemicals for which a severe toxicologic effect may occur below the level at which mild adverse effects occur will have fewer severity levels described. For example, there would be no level protective against mild adverse effects for a chemical if reproductive toxicity, considered a severe adverse effect, was the most sensitive endpoint, as is the case for carbon disulfide. Additionally, the toxicology data for some chemicals may be lacking and thereby not permit the establishment of a particular level. The amount of data and the quality of the information will ultimately determine which acute exposure levels are identified. As more data become available, either in the toxicologic literature or from guideline committees, such as U.S.EPA or the NAS, the acute exposure levels may be updated.

1.5 Populations of Concern

Acute RELs are intended to protect the individuals who live or work in the vicinity of emissions of these substances. The general population consists of individuals with a wide range of susceptibility. The susceptibility may be transitory or chronic. Individuals in the general population who may be at greater risk for developing adverse effects following chemical exposure include those with increased exposure (e.g., children, adults engaged in physical activity), those undergoing physiological change (e.g., children, pregnant women and their fetuses), individuals with impaired physiological conditions (e.g., elderly persons, persons with existing diseases such as lung, heart or liver disease), and individuals with lower levels of protective biological mechanisms due to genetic variability within the population (U.S.EPA, 1994a). Less susceptible individuals are healthy adults without any genetic or biological predisposition that may increase sensitivity to the chemical of concern.

Acute RELs are intended to protect both individuals at low risk for chemical injury as well as identifiable sensitive subpopulations (highly susceptible or sensitive individuals) from adverse health effects in the event of exposure. However, they may not protect hypersensitive individuals (those exhibiting idiosyncratic responses that cannot be predicted from studying the health effects of the substance).

While OEHHA has attempted to identify specific sensitive subgroups for each substance from the literature, it has not been possible to identify all conditions predisposing toward adverse health effects following exposure to toxic substances. Because RELs pertain to inhalation exposures, the lungs are often the major target organ of toxicity, and asthmatics are frequently identified as a sensitive group. For most compounds, the range of intraindividual variability is poorly characterized. An exception is sulfur dioxide, which has been extensively studied in both normal as well as asthmatic individuals. In a study of asthmatic subjects, Horstman *et al.* (1986) found that there was a 7-fold distribution in the range of sulfur dioxide concentrations required to produce bronchoconstriction. Thus, it is reasonable to conclude that asthmatics may be at least seven times as sensitive to the effects of sulfur dioxide as normal individuals.

An analysis of human variability in threshold responses in pharmacodynamic and toxicologic studies by Hattis (1996) has shown that human variability in response can often be well modeled by a log-normal distribution and that the magnitude of the variability depends greatly on the endpoint and slope of the dose-response curve. In their analysis, some human threshold responses ranged over more than 3 orders of magnitude. Because the range of variability within the human population for most responses is unknown, there may be a proportion of the population for whom the acute RELs will not be protective. It is OEHHA's intent that, to the maximal extent possible, the levels will protect nearly all individuals. As more susceptible groups are defined, it is our intent to adjust the levels as necessary to protect such individuals.

1.6 Exposure Duration and Patterns

As indicated in Section 1.3, the focus of acute RELs is generally a one-hour exposure. While shorter and longer durations may also provide useful information, the one-hour increment is

consistent with hour-by-hour monitoring or modeling that is generally conducted for facilities under the Hot Spots program. The exceptions in this document include RELs based on several hours exposure for reproductive/developmental endpoints (see Section 1.6.1). The acute REL may be adjustable to other exposure durations. Sometimes it is necessary to extrapolate from other experimental exposure durations to a one-hour exposure duration. This is described in Section 3.4.

The distribution and concentration of a chemical following predictable continuous or intermittent emissions will be influenced by meteorological conditions and topography. The most useful descriptors of exposure are the duration and the concentration to which people were exposed during the time period involved. Several acute exposure guidelines, for example, EEGLs and ERPGs, are expressed in terms of a 1-hour duration. In order to maintain a practical and standard time frame, a 1-hour exposure duration was chosen for the determination of the acute RELs. However, as mentioned previously, health effects of concern may occur hours to days after exposure ceases. For example, the onset of pulmonary edema may be delayed for up to 24 hours following exposure to phosgene at doses several fold higher than the REL.

1.6.1 Exposure Concentration Averaging Period

The acute REL is a concentration that is not likely to cause adverse effects in a human population, including sensitive subgroups, exposed on an intermittent basis to that concentration for one hour (or in the case of reproductive/developmental endpoints several hours as indicated in individual toxicity summaries). Intermittent exposure is difficult to define. U.S.EPA views intermittent exposure as that lasting less than 24 hours and occurring no more frequently than monthly (U.S.EPA, 1994b). This is in part based on an assumption that an acute exposure concentration is at least 10-fold higher than the monthly average, and the presumption that individual exposures are independent of one another. U.S.EPA (1994b) points out that very few chemicals will have sufficient data to determine safe "periodicity" of an acute exposure. Thus, U.S.EPA (1994b) has identified three issues to be addressed: length of acute exposure, periodicity of exposures, and the relationship between the acute exposure and the chronic background. These will be discussed below.

In acute toxicology experiments, the study design usually involves exposures of short duration to an otherwise unexposed animal. However, real world "acute" exposures occur intermittently, rather than as rare events in a lifetime. Thus, the typical ambient exposure scenario is not reflected in the standard acute toxicology experimental design. The possibility of cumulative effects from intermittent ambient exposure cannot be addressed in acute REL development. Hence, acute environmental exposures are considered by U.S.EPA to occur no more frequently than monthly. U.S.EPA also recommends that longer interexposure periods be established for chemicals with long clearance times or with evidence of cumulative or sensitizing effects.[2]

[2] In April 1998 U.S.EPA updated its planned approach to the Acute Reference Exposure (U.S.EPA, 1998, an external review draft). U.S.EPA defines the Acute Reference Exposure (ARE) as "the exposure (concentration and duration), with an uncertainty spanning an order of magnitude, that is not likely to cause adverse effects in a human population, including sensitive

A related exposure issue is the fact that peak exposures are superimposed on lower long-term exposures to the same compound. This is also not reflected in the standard acute toxicology design. For some compounds this will result in an increased body burden relative to the typical toxicology experimental design and in a potential lowering of the acute exposure needed to produce an adverse effect. U.S.EPA's approach is to assume that the peak exposures are at least 10 times the monthly average so that the acute exposure can be considered relatively independent of the longer-term chronic exposure to the same substance (U.S.EPA, 1994b).

Despite the inability to mimic typical human exposures in the laboratory, it is imperative to examine whether short-term exposures to peak concentrations might result in adverse public health impacts. OEHHA's RELs are intended to be compared to the modeled one-hour maximum (or multi-hour as noted for specific reproductive/developmental toxicants) concentrations used in the hazard index approach to risk assessment (described earlier). OEHHA recommends that these acute RELs be used to evaluate exposures that occur no more frequently than every two weeks in a given year. The two-week interval was chosen because in most acute toxicology experiments two weeks is the duration of time an animal is observed for signs of adverse outcome following exposure (U.S.EPA, 1996).

An assumption in making this recommendation is that the REL is protective of adverse health effects that are not cumulative; thus, the effects of each peak exposure are independent of previous or subsequent peak exposures that occur as often as every two weeks. This recommendation is only valid for substances that do not bioaccumulate. When bioaccumulation is known to occur and body burden is associated with an adverse effect, longer interexposure periods should be specified.

The modeled one-hour peak concentrations are typically much greater than the maximum average annualized concentrations used for determining chronic exposure and risk. Thus, it is assumed that acute exposures are independent of the long-term average exposure based on the modeled annualized maximum average concentration. However, under certain meteorological conditions (poor mixing, persistent calm winds), it is conceivable that there are many hours in a day or within a few days where exposures are close to the peak one-hour in any given year. Concentrations close to the maximum one-hour exposure may occur many times during the year including on consecutive days. In addition, it is conceivable that exposure concentrations close to the maximum may occur in consecutive hours. Currently, OEHHA does not ascertain how often exposures close to the one-hour maximum occur in a given day, week, month or year. This contributes to the uncertainty in evaluating the adverse health effects of peak one-hour exposures.

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subgroups, exposed to that scenario on an intermittent basis." Three methods for deriving AREs are described in the draft report: a NOAEL/UF approach, a benchmark approach, and a categorical regression approach (see Appendix D of this report). An example of the derivation of the Acute Reference Exposure (ARE) for one chemical is given for each approach. The NOAEL/UF and benchmark approaches are similar to those described in this document. However, we define acute exposure as a 1 hour exposure.

In evaluating chemicals with reproductive/developmental toxicity, we found that the standard experimental paradigm of repeated exposure over several days did not lend itself easily to extrapolation to a one-hour Reference Exposure Level (REL). Since reproductive/developmental endpoints are frequently manifested in a small window of time during gestation, the standard protocol is to expose pregnant animals for several hours per day over several days during gestation in order to increase the power of the study to detect an effect. The Scientific Review Panel discussed this point during their February 10, 1999 meeting. Issues that affect the extrapolation to one hour include not only when the sensitive gestational period is, but also toxicokinetic issues. For example, the animals are exposed for 6 hours per day but unexposed the remaining 18 hours in that day. A rapidly metabolized toxicant capable of inducing a reproductive or developmental toxic response may not build up in the animal's system to the point where it would induce a response. A slowly metabolized chemical would build up in the animal despite the intermittent exposure. Whether or not a single one-hour exposure could produce a reproductive or developmental adverse outcome depends on the toxicokinetics governing the concentration of the chemical in maternal and fetal tissues, timing of exposure, mechanism of action, and other factors. These issues are not easily taken into account in extrapolating to a one-hour Reference Exposure Level. As such, after public review and review by the Scientific Review Panel, OEHHA chose to use a single day's exposure from the key study (usually 4 to 7 hours) as the basis of the REL calculation, without time extrapolation to an equivalent one-hour concentration. Thus, for those RELs addressing a reproductive/developmental endpoint in this document, the REL is for whatever exposure duration was chosen for a single day in the experimental protocol. For example, for arsenic, the experimental paradigm involved exposing pregnant animals for 4 hours per day over several days of gestation. Thus the REL for arsenic is for a 4 hour exposure rather than a one-hour exposure. This will require those assessing risks to calculate a 4-hour maximum for arsenic rather than a one-hour maximum to use in the hazard index approach.

1.7 Cumulative Effects of Multiple Chemical Exposures

Concomitant exposures to more than one chemical may cause effects that are equal to, less than, or greater than predicted from the effects observed with exposures to the individual chemicals (Ikeda, 1988; Jonker *et al.*, 1990). Of the thousands of potential combinations of chemicals in common use, only a small fraction has been tested for the potential that combined exposures could have synergistic or antagonistic properties. Effects of multiple chemical exposures on human health remain an area for future study. As noted earlier, in risk assessment exposures to multiple chemicals that cause similar health effects are treated as additive in the hazard index approach.

1.8 Pre-Existing Exposure Guidelines

Acute exposure levels have been developed by several different organizations. However, there are no inhalation exposure values that were derived using a consistent basis to protect the public from planned industrial emissions. Values designed for protection of the general public exist, but they are intended to address accidental releases and use methodologies that we have not been able to reproduce. Occupational exposure guidelines are available for hundreds of substances, but

have an inconsistent basis, often have not incorporated recently available data, and are not designed to protect sensitive subpopulations. The existing exposure guidelines reviewed for OEHHA's acute severity levels are described below.

1.8.1 Description of Existing Guidelines

1.8.1.1 The **California Ambient Air Quality Standards (CAAQS)**, promulgated by the Air Resources Board based on recommendations from OEHHA, are specified concentrations and durations of air pollutants which reflect the relationship between the intensity and composition of air pollution to undesirable effects. When a CAAQS existed for a criteria air pollutant, it was adopted as the acute REL. If necessary, a one-hour value was derived using time extrapolation (described below).

1.8.1.2 An **Emergency Exposure Guidance Level (EEGL)** is defined by the National Academy of Sciences (NRC, 1986) as the ceiling concentration of a substance in air that may be judged by the Department of Defense to be acceptable for the performance of specific tasks during rare emergency conditions lasting for periods of 1-24 hours. "Emergency" connotes an unexpected situation with potential for loss of life. EEGLs are designed to provide guidelines for military personnel operating under emergency conditions that are peculiar to military operations and for which regulatory agencies have not set standards. The methods used to derive the EEGLs are not always explicitly stated and EEGLS were not derived with the intent to protect the general public. However, the levels derived for sulfuric acid and for xylenes were deemed acceptable for use as levels protective against serious adverse effects.

1.8.1.3 **Emergency Response Planning Guidelines (ERPGs)** are defined by the American Industrial Hygiene Association (1991) as concentration ranges where adverse health effects could be observed. Although ERPGs were evaluated, they were not routinely adopted as acute severity levels because the methods for their derivation were not consistent, the AIHA did not always consider all relevant data, and they have a specific emphasis on responding to accidental releases. Three ERPGs are available for each substance; the AIHA definitions are provided below:

1.8.1.3.1 The **ERPG-1** is the maximum airborne concentration below which nearly all individuals could be exposed for 1 hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odor.

1.8.1.3.2 The **ERPG-2** is the maximum airborne concentration below which nearly all individuals could be exposed for 1 hour without experiencing or developing irreversible or other severe health effects which could impair an individual's ability to take protective action.

1.8.1.3.3 The **ERPG-3** is the maximum airborne concentration below which nearly all individuals could be exposed for 1 hour without experiencing or developing life-threatening health effects.

1.8.1.4 **Immediately Dangerous to Life and Health (IDLH)** values are defined by NIOSH (1994, 1995) as 30-minute concentrations from which a worker could escape without injury or irreversible health effects in the event of respiratory protection equipment failure and above which

only "highly reliable" respirators are required. These levels were designed for healthy workers in an exposure situation that is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment.

1.8.1.5 The **Short-term Public Emergency Guidance Level (SPEGL)** is defined by the National Academy of Sciences (NRC, 1986) as a suitable concentration for unpredicted, single, short-term, emergency exposure of the general public. In contrast to the EEGL, the SPEGL takes into account the wide range of susceptibility of the general public, but it is not designed for repeated or multiple exposures.

1.8.1.6 The **Threshold Limit Value-Time Weighted Average (TLV-TWA)** and **Short-Term Exposure Limit (STEL)** are developed by the American Conference of Governmental Industrial Hygienists (ACGIH, 1991); similar, NIOSH recommended exposure limits also exist (NIOSH, 1994). The TLV-TWA is defined as the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. The STEL is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday.

Occupational exposure limits have been used to derive chemical exposure guidelines for the general public (U.S.EPA, 1994a; National Air Toxics Information Clearinghouse, 1991; Robinson and Paxman, 1992). More than 600 ACGIH TLVs and NIOSH RELs are available. These values have been attractive because of the large number of accessible values and the concept that they are intended to protect a human population from inhalation exposures. However, these values lack a consistent basis for derivation, are not designed for or recommended for protection of the general public, and in many cases may not prevent adverse health effects among workers (Roach and Rappaport, 1990).

1.8.1.7 **U.S.EPA's Acute Emergency Guidance Levels (AEGLs)** are currently being developed. Several draft AEGL values were recently released for public comment (62 CFR, No. 210). However, these values focus on emergency planning and response, not on routine emissions and exposure, which are the focus of this document.

1.8.1.8 **U.S.EPA's Air Pollution Warning Levels** (40 CFR, Subchapter C, Part 51, Appendix L) indicate poor air quality that may endanger the public's health and suggest that additional control actions are necessary to reduce the level of the pollutant. Air Pollution Warning Levels are available for the following criteria air pollutants: sulfur dioxide, particulates 10 μm or less in diameter, carbon monoxide, ozone, and nitrogen dioxide.

1.8.1.9 **U.S.EPA's Levels of Concern** (U.S.EPA, 1987) are defined as the concentrations of substances in air above which there may be severe irreversible health effects or death as a result of a single exposure for a relatively short period of time. For most compounds, the level of concern is derived from the existing guidelines listed above (IDLH, TLV, EEGL or ERPG).

1.8.2 Priority for Adopting Existing Guidelines

Almost all acute RELs were developed *de novo* for these guidelines. However, existing guidelines for acute exposure were first reviewed. If they were found to be appropriate, they were adopted as the relevant acute toxicity exposure level using the following order of preference (also see Table 4). For the six criteria air pollutants carbon monoxide, nitrogen dioxide, sulfates, ozone, hydrogen sulfide, and sulfur dioxide, the CAAQS for short-term (1-hour) exposure is considered equivalent to a mild adverse effect level and is used as the REL, or one-hour values were derived by extrapolation from the 24-hour standard.

When calculating response severity for levels above the REL, an extensive review was conducted of the existing guidelines described above. Existing guidelines were chosen as a basis for severity levels above the REL when they accurately and completely reflected the scientific literature, considered sensitive populations and included appropriate margins of safety for public health protection. On the basis of these criteria, existing guidelines were chosen in the following order. For the small number of substances for which a SPEGL was available for acute noncancer endpoints, this was the existing value of choice for preventing severe or disabling effects. If no SPEGL existed but an EEGL was available, this was the next existing level of choice. ERPG-2s were chosen for the severe or disabling effect level only if no EEGL existed. ERPG-3s were used as estimates of levels protective against potential lethal effects, if appropriate. In the past, IDLHs were poorly documented and were not deemed to be health-protective (Alexeeff *et al.*, 1989). Since they have been recently revised (NIOSH, 1995), they were considered for adoption for the "life-threatening effect level" based on the adequacy of their documentation and their health protectiveness.

Table 4 . Order of preference for adopting existing guidelines for acute severity exposure levels

Acute severity level	Order of preference[1]
Level Protective Against Mild Adverse Effects [2]	Criteria air pollutant CAAQS appropriate adopt value not appropriate derive value Non criteria air pollutant derive value
Level Protective Against Severe Adverse Effects	U.S.EPA Air Pollution Warning Level SPEGL EEGL ERPG-2 TLV-TWA U.S.EPA Level of Concern Appropriate guidelines do not exist derive value
Level Protective Against Life-threatening Effects	ERPG-3 IDLH Appropriate guidelines do not exist derive value if possible

[1] *See Section 1.8.1 for definition of acronyms.*

[2] *This level would be protective of essentially all adverse effects.*

2. Hazard Identification

2.1 Nature of Adverse Effects

The toxic effects of chemicals are of varying types and degrees of severity. The most important effects following an acute (one hour) exposure to a substance released into the atmosphere are usually respiratory effects. Toxic effects from airborne substances may be due to exposure via the skin, eyes, and upper and lower respiratory tract. Systemic effects, such as hemolysis or central nervous system injury, may result from absorption of material though the lungs, and, to a lesser extent, through the skin. For a toxic endpoint to be considered due to acute exposure, the effects do not have to be observed immediately. Rather, the effects may be observed hours to days following the acute exposure. For example, acute exposure to phosgene may result in pulmonary

edema several hours later. In the case of benzene, death may result from leukopenia days following high-level acute exposure.

Certain chemicals, after a single exposure, have the potential to produce delayed adverse effects. Often acute toxicity tests do not have a sufficient follow up period to allow thorough assessment of the potential for delayed health effects from single exposures. With respect to two kinds of delayed effects, cancer and reproductive or developmental harm, there is more information available. Carcinogens are considered in the *Air Toxics Hot Spots Program Risk Assessment Guidelines Part II: Technical Support Document for Describing Available Cancer Potency Factors*. Reproductive and developmental toxicants are considered in this document because substantial research effort has been devoted toward specifically identifying such delayed effects.

Some substances exert their toxic effects through their metabolites. For example, methylene chloride's acute toxicity is mediated through its metabolite, carbon monoxide. Whenever possible, information on toxic metabolites is provided in the toxicity summaries. When detailed information is available on the relationship of dose of the parent chemical to level of metabolite and the metabolite level to degree of toxic response, this is taken into account in developing the acute severity levels. However, RELs and other acute severity levels are always expressed in terms of the concentration of the parent compound, not the metabolite.

2.2 Definition of Adverse Effect

OEHHA has chosen to adopt U.S.EPA's general definition of adverse effects as "any effects resulting in functional impairment and/or pathological lesions that may affect the performance of the whole organism, or that reduce an organism's ability to respond to an additional challenge" (U.S.EPA, 1994a). All effects reported for a substance were not necessarily considered adverse. For example, the perception of an odor, even if objectionable, was not considered an adverse health effect unless accompanied by other symptoms or signs, such as nausea and vomiting.

OEHHA has chosen to follow the guidance provided by NAS (NRC, 1993) in developing the acute severity levels. Thus, for each compound evaluated for its acute toxicity, multiple effect level thresholds were identified. U.S.EPA's effect severity levels (Table 5) provided some guidance in categorizing adverse effects.

Table 5. U.S.EPA Effect Severity Levels (U.S.EPA, 1994) and Corresponding OEHHA Levels

U.S.EPA Severity Level	Effect Category	Effect	OEHHA Effect Severity Level
0	NOEL	No observed effects.	< Mild
1	NOAEL	Enzyme induction or other biochemical change, consistent with possible mechanism of action, with no pathologic changes and no change in organ weights.	< Mild
2	NOAEL	Enzyme induction and subcellular proliferation or other changes in organelles, consistent with possible mechanism of action, but no other apparent effects.	< Mild
3	NOAEL	Hyperplasia, hypertrophy, or atrophy, but without changes in organ weight.	≤ Mild
4	NOAEL/ LOAEL	Hyperplasia, hypertrophy, or atrophy, with changes in organ weight.	Mild
5	LOAEL	Reversible cellular changes including cloudy swelling, hydropic change, or fatty changes.	Mild / Severe
6	(LO)AEL	Degenerative or necrotic tissue changes with no apparent decrement in organ function.	Severe
7	(LO)AEL/ FEL	Reversible slight changes in organ function.	Severe
8	FEL	Pathological changes with definite organ dysfunction that are unlikely to be fully reversible.	Severe
9	FEL	Pronounced pathological change with severe organ dysfunction and long-term sequelae.	Severe
10	FEL	Life-shortening or death.	Life-threatening

NOEL - no observed effect level; *NOAEL* - no observed adverse effect level; *LOAEL* - lowest observed adverse effect level; *AEL* - adverse effect level; *FEL* - frank effect level.

In addition to the histochemical and pathological effects in Table 5, OEHHA's system for categorizing clinical symptoms and signs into severity levels is presented in Table 6.

Table 6. OEHHA Categorization of Adverse Health Effects into Severity Levels[1]

Acute Exposure Level	Symptoms	Signs/Laboratory Findings
Mild Adverse	Mild subjective complaints with few to no objective findings: Mild mucous membrane (eye, nose, throat) irritation Mild skin irritation Mild headache, dizziness, nausea	Statistically significant findings of pre-clinical significance: Mild conjunctivitis Mild lung function changes[2] Abnormal immunotoxicity test results Mild decreases in hemoglobin concentration
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[2] Cardiac ischemia Some cardiac arrhythmias e.g., atrial fibrillation Renal insufficiency Hepatitis Reproductive/developmental endpoints e.g., infertility, spontaneous abortion, congenital anomalies
Life-threatening		Potentially lethal effects: Severe pulmonary edema Respiratory arrest Ventricular arrhythmias Cardiac arrest

[1] This table is intended to provide examples of health effects commonly considered for each level. It is not meant to be a comprehensive list of all possible health effects. Please refer to the text of this document and to the individual toxicology summaries for chemical-specific information.

[2] Refer to Table 7 for detailed categorization of lung function tests.

2.3 Identification of Adverse Effect

Several factors need to be considered when identifying an appropriate adverse health endpoint for each compound. These include weight of evidence, the strength, consistency, and specificity of the associated adverse health effect, the temporal association, and the coherence (scientific plausibility) of the health effect.

2.3.1 Weight of Evidence

Although a formal scheme has not been adopted, a descriptive analysis of the strengths and weaknesses of the studies used to derive acute RELs and other toxicity exposure levels is presented. Issues such as observation of a dose-response relationship, reproducibility of findings, mechanism of action, and consistency with other studies were given weight in the OEHHA evaluation of acute RELs.

2.3.2 Strength of Associated Adverse Health Effect

The strength of an association between chemical exposure and adverse effect is assessed. Strength of association can be measured in terms of high observed effect incidence or high relative risk, statistical significance of differences between control and exposed groups, and a positive dose-response relationship. For example, if an adverse effect noted in a low dose exposure group is not noted in a high dose exposure group, evidence for a causal association between the chemical exposure and the effect is greatly reduced.

2.3.3 Consistency of Associated Adverse Health Effect

Consistency of an association between chemical exposure and adverse effect is also evaluated. Relevant observations include similarity of effects noted in different studies and among different populations and/or species. For example, if an effect was noted in only one of many studies of a particular strain of laboratory rodent, evidence for a causal association between the chemical exposure and the effect is weakened.

2.3.4 Specificity of Associated Adverse Health Effect

If an adverse health effect is specific to exposure to a substance, the case for causality is strengthened. Arsine-induced hemolysis is an example of such a specific exposure-effect relationship. Such highly specific associations are unusual, however, as chemical exposures generally cause multiple effects and chemical-induced health effects are generally comparable to similar health effects observed in the absence of exposure. For example, eye, nose, and throat irritation, and headache may be observed following exposure to a wide variety of chemicals but may also be caused by other common stimuli (e.g., viral infection).

2.3.5 Temporal Association

To strengthen the causal relationship, the adverse health effect should occur at a time following exposure that is consistent with the nature of the effect. For example, respiratory irritation immediately following exposure to an irritant vapor such as chlorine gas is temporally consistent, whereas effects noted years later may not be. On the other hand, tumors noted immediately following exposure might be temporally inconsistent with a causal relationship, while tumors arising after a latency period of months or years would be temporally consistent.

2.3.6 Coherence of Adverse Health Effect

Coherence or scientific plausibility of the association is also examined. This is assessed in terms of evidence that the effects are consistent with the pharmacokinetics and mechanism of action of the chemical. For example, reports of asthma and dermatitis caused by nickel are consistent with abnormal immunotoxicity tests following exposure to nickel compounds.

2.4 Criteria for Studies Utilized to Identify Adverse Health Effects

Although a wide variety of information may be reviewed, only key studies are used to develop acute severity levels. The following criteria are used to determine the relevance and quality of data used for level development.

Published, peer-reviewed data are preferred; exceptions include well-conducted industry-sponsored studies that have been reviewed by other organizations but have not themselves been published in the literature, and doctoral dissertations. For example, an industry study (IRDC, 1985a) reviewed in a published article (Donald *et al.*, 1991) was chosen as the basis for the severe adverse effect level for toluene. A doctoral dissertation (Anglen, 1981) reviewed in a published article (Das and Blanc, 1992) was used as the basis for the chlorine REL (Appendix C). Abstracts and review papers are not used for level development (the latter are considered secondary sources). Studies involving a single chemical are given preference over those with multiple simultaneous exposures, especially if these are not quantified.

Only studies that consider non-carcinogenic endpoints are considered for this document. For a consideration of carcinogenic endpoints, please refer to the OEHHA document titled *Technical Support Document for Describing Available Cancer Potency Factors*. Studies using multiple exposure doses and clearly indicating dose-response information are preferred (e.g., the Kulle *et al.* (1987) study used as the basis for the formaldehyde REL). However, in some cases, an inadequate toxicology database may necessitate the use of older studies in which such information is unclear. Usually such studies are chosen if they are the only existing acute inhalation studies and are consistent with the general toxicology database (e.g., the Dudley and Miller (1937) study used for the hydrogen selenide REL).

2.4.1 Selection of Key Studies

An important step in the development of an acute REL is the identification of research studies that contribute most significantly to the weight of evidence as to the degree of hazard presented to humans by a particular substance (U.S.EPA, 1987; 1994a). These studies may involve a human population studied in an epidemiological, clinical, or experimental exposure setting, or they may involve experimental studies with animals. The key studies are given greatest weight in estimating a threshold for adverse effects and in identifying the nature of the critical adverse effect.

2.4.1.1 Human Data

Human data are logically most relevant to assessing human health effects associated with chemical exposures. Much of the available human exposure data is via inhalation. Principles for evaluating human exposure studies for use in determining health-based exposure levels have been discussed (NRC, 1986). Whenever possible, RELs were developed based on human data; of the 51 acute RELs in this document, 36 are based on human health effects.

Three types of human studies have been used in assessing health effects of chemicals: (1) epidemiological studies, (2) controlled exposure experiments, and (3) case reports. Each of these three study types can provide important information needed to protect public health. When using these studies for risk assessment, several factors are important in evaluating their quality and in determining the level of certainty associated with their use.

2.4.1.1.1 Epidemiological Data

Epidemiological studies generally produce data on effects of chemical exposure to a large number of persons. Areas of concern when interpreting epidemiological studies include exposure measurement, health effects measurement, and accounting for covariables and confounding variables (Lebowitz, 1983). The population studied may consist of the general public or employees exposed at the workplace to varying concentrations of airborne chemicals.

Exposure measures frequently represent the greatest weakness of available epidemiological studies. Continuous, long-term exposure monitoring of individual subjects is rarely available. Frequently it is necessary to use limited, short-term, exposure monitoring data, which in many cases are not specific to the individuals under study, in order to derive an estimate of what the individual exposures may have been. Occupational exposures may vary over time as industrial hygiene practices change and individuals change jobs. The degree to which air concentrations can be adequately estimated is critical in determining the usefulness of an epidemiological study.

Health effect measures in epidemiological studies also frequently differ from those reported in experimental animal studies and must be carefully examined. Human health effect measurement generally consists of recording observable effects and conducting non-invasive tests. Health effects data are compared with those compiled from a non-exposed group and may be presented as incidence, standardized mortality ratios, or relative risk ratios. Health effects with a long latency may be missed if the study duration is inadequate.

Covariables and confounding variables should be controlled or removed from the study. Co-exposure to other chemicals is an important concern as a potentially confounding effect. Occupational studies raise an additional concern in that generally healthy workers may be less sensitive to the adverse effects of chemical exposures than others in the general population, including children, the elderly, and persons with preexisting medical conditions. Bias may also be present where a workplace is disproportionate by gender (NRC, 1986). While occupational studies provide important information, they are rarely used as key studies for acute toxicity exposure level development, as the duration of exposure is generally over a much longer period of time than is relevant for the acute reference exposure levels.

Negative epidemiological studies present an additional difficulty in interpretation. Estimating the power of the study to detect adverse effects can be useful in providing an indication of the maximum incidence consistent with the failure to show that the exposed group was statistically different from the control group. Also, statistical confidence limits can be put around a negative finding, i.e. around the relative risk (RR) of 1.

2.4.1.1.2 Controlled Human Exposure Studies

Controlled exposure studies have the advantages of having quantified exposure concentrations and of being conducted with human subjects, thus combining two important features of human epidemiological and animal toxicity studies (Hackney and Linn, 1983). The limitations of such studies are that they may (1) involve small sample sizes, (2) be of very short exposure duration, and (3) assess effects through subjective measurements that might miss significant health effects. In spite of these potential shortcomings, controlled studies in human subjects, especially in sensitive subpopulations such as asthmatics, are given preference over animal studies in the acute REL development process. Human studies were used only if they were consistent with the standard ethical practices of investigation at the time they were conducted. The preferred study is a modern, ethical study approved by an Institutional Review Board for Human Studies.

2.4.1.1.3 Case Reports

Individual case reports of adverse effects associated with exposures to a chemical can be useful, especially as qualitative confirmation that effects observed and quantified in animals also occur in exposed humans. Multiple case histories with the same endpoint are especially relevant. However, these reports are generally not appropriate for quantitation because of the very small sample size and the unquantified exposures (Goldstein, 1983).

2.4.1.2 Animal Data

Many acute toxicity animal studies have been conducted, although studies that address the range of toxic effects (from mild to life-threatening) may not be available for many substances. Identification of the most appropriate animal species requires consideration of all available data relevant to prediction of human effects from animal observations. Studies of the most sensitive species have frequently been selected as key studies. Such an approach has the advantage of

offering maximal protection, especially since humans may be more sensitive than laboratory animals in response to chemical exposure (Lehman and Fitzhugh, 1954). However, the animal species most sensitive to a substance is not necessarily that most similar to humans in developing adverse effects from a particular exposure. In general, of the animals used in laboratory studies, non-human primates are considered to be the most similar in response to exposures to toxic substances.

Selection of the animal model and key study can be influenced by what is known about human health effects, and relevant areas of similarity and dissimilarity between humans and the animal species may be established (Calabrese, 1982). Comparison of human and animal pharmacokinetics and metabolism may be useful in selecting the relevant animal model for predicting human health effects. For example, hamsters and rabbits have much greater metabolic rates than monkeys (Plopper *et al.*, 1983). This may increase or decrease their susceptibility relative to humans. However, in most instances it is not possible to determine which species responds most like humans.

An experimental study should have a clear rationale and protocol, use Good Laboratory Practice Standards, and use appropriate analysis methods (CFR 1983 a, b). Experimental study designs and criteria recommended by the NTP have been reviewed (Chhabra *et al.*, 1990). Appropriate statistical analysis of the results is important (Muller *et al.*, 1984). However, the goal of protecting public health must be weighed with experimental design so that important endpoints are not missed and that responses of relevant species are not ignored. Furthermore, it is important that there not be disincentives to conducting good studies in order to avoid the establishment of reference exposure levels.

3. Dose Response Assessment

3.1 Severity of Adverse Effects

Following acute exposure, health effects of varying severity may be observed and are determined by the extent of exposure, or the dose. Although the relationship between exposure and health outcome is a continuous one, effects may be categorized into discrete severity levels. Specific toxic effects that may be observed at each level are identified for each chemical. The most easily specified health effect for which exposure indices can be developed is death. Less severe effects, though less well defined, may also result in significant adverse health consequences.

We have defined two additional graded categories of toxic effects. Except for death, these graded effect levels are not sharply demarcated but each merges into adjacent categories. Figure 3 depicts how the dose-response relationship is a continuous phenomenon. The dose is a factor of concentration and duration of exposure. In general, as dose increases, so does the severity of the response. Increased severity of physiologic response (from one acute severity level to the next) may involve the same receptor(s). For example, for hydrochloric acid, the REL (level protective against mild adverse effects) is protective of eye and nose irritation. At higher exposure concentrations, the severe adverse effect level is protective against severe eye, nose and throat irritation. And at higher concentrations still, the life-threatening level protects against lower

respiratory effects, including pulmonary edema, which may lead to death (Acute Toxicity Summary for Hydrochloric Acid, Appendix C).

Alternatively, for other compounds, increasing severity of response may involve different receptors or organ systems. For example, the REL for methanol is based on subtle neurological impairment, a mild adverse effect, while the level protective against severe adverse effect is protective against developmental or reproductive toxicity (Acute Toxicity Summary for Methanol, Appendix C).

It is important to note that exposure at or above the REL will not necessarily result in adverse health consequences. Conversely, there may be individuals exhibiting idiosyncratic responses who may experience unpredictable health effects at shorter exposure durations or at concentrations below these levels. For a list of several common reactions (symptoms) and observable findings (signs) that may be observed following exposure to hazardous substances and their categorization into the aforementioned levels, see Table 6. It is not practical to include a comprehensive listing of all reactions and endpoints reported or considered for the 51 chemicals evaluated so far; therefore, only commonly considered endpoints are listed. Please refer to individual chemical summaries (Appendix C) for a discussion of the reactions and toxicological endpoints reported for individual chemicals.

3.2 Levels of Adverse Effect

In developing acute exposure levels and RELs, we have applied the methods described in the NAS publication, *Guidelines for Developing Community Emergency Exposure Levels* (NRC, 1993). The three acute severity levels for one-hour exposure durations are defined below (also see Figure 3). However, the risk management concerns of emergency planning and response are not incorporated into these definitions. Instead, the levels are defined strictly based on toxicological and medical criteria. Appendix A lists 51 chemicals for which acute RELs have been developed by OEHHA. The toxicologic endpoints considered in deriving the RELs are also listed. The acute toxicity summaries are included with these guidelines as Appendix C.

3.2.1 Level Protective Against Mild Adverse Effects

The level protective against mild adverse effects refers to the concentration of an airborne substance (a gas, vapor, aerosol or aerosolized particle) below which exposure for one hour is predicted to result in no adverse health effects in nearly all of the population. Exposure to concentrations above this level may result in mild adverse health effects, such as enzyme induction or biochemical changes consistent with the mechanism of action, and reversible subcellular or cellular changes (U.S.EPA effect severity level 0-5, Table 5), mild irritation of the eyes, nose or throat or other minor physiologic changes of short duration, such as subtle neurologic changes detectable only by neuropsychological testing, not by clinical examination (e.g., REL for methanol).

This level is intended to be protective of adverse health effects which are long-lasting (i.e., those that persist beyond the duration of exposure) and those which affect judgment or impair the ability

to respond. For example, following exposure above the mild adverse effect level (but below the severe adverse effect level), an irritant gas might produce eye and nose irritation and an organic vapor may cause headaches; however, these effects are expected to resolve soon after exposure ceases.

3.2.1.1 Lower Airway Responsiveness

Lower airway effects are often the most sensitive physiologic response following inhalation exposure to certain chemicals. Because these endpoints are frequently used for REL development, we have defined specific criteria for tests of lower airway function to be considered in categorizing effect severity. In some individuals, the lower airways respond acutely to various stimuli by decreased airway diameter (Woolcock, 1994). Although various methods are used to measure pulmonary function, airway responsiveness is commonly and easily assessed and is a sensitive indicator of airway narrowing in response to external agents (Gold, 1994; Woolcock, 1994). While varying spirometric criteria have been used for the determination of airway hyperresponsiveness (Bernstein *et al.*, 1992; Cherniak *et al.*, 1995; Eschenbacher *et al.*, 1992; Jubber *et al.*, 1993; Wiebicke *et al.*, 1990), the standards used in this document are consistent with previously specified guidelines and research protocols (Aris *et al.*, 1995; Eiser *et al.*, 1983; Sterk *et al.*, 1993).

To be considered a mild effect, pulmonary function changes detected by spirometry must be the most sensitive adverse health effect observed for a particular chemical. Following inhalation exposure to the chemical, the following spirometric changes (compared to pre-exposure findings) are criteria for inclusion as a mild effect: (1) statistically significant but clinically insignificant changes in forced expiratory volume in 1 second (FEV_1) (i.e., <20% decrement in FEV_1 compared to pre-exposure baseline); or (2) statistically or clinically significant changes in specific airway resistance (SR_{aw}) or airway conductance (SG_{aw}) following inhalation challenge with the chemical of interest (clinical significance is a 100% increase in SR_{aw} or a 50% decrease in SG_{aw}) without a 20% drop in FEV_1 or symptoms consistent with bronchoconstriction, such as chest tightness, wheezing and shortness of breath (Table 7).

Table 7. System for categorization of pulmonary function into effect severity levels.

Endpoint[1]	Mild	Severe	Life-threatening
Spirometry Test Result (compared to baseline)	Statistically significant but < 20% decrement in FEV_1 [2]	$\geq$ 20% decrement in FEV_1	Not applicable
Methacholine Challenge Test Result	$\geq$ 100% increase in specific airway resistance (SR_{aw}) or $\geq$ 50% decrease in airway conductance (SG_{aw}) no symptoms of bronchoconstriction < 20% decrement in FEV_1	100% increase in specific airway resistance (SR_{aw}) or 50% decrease in airway conductance (SG_{aw}) accompanied by (1) symptoms of bronchoconstriction or (2) $\geq$ 20% decrement in FEV_1	Not applicable
Clinical Findings	None anticipated	Chest tightness, shortness of breath, wheezing Wheeze detected by examination Hypoxia or decreased oxygen saturation	Status asthmaticus Respiratory arrest

[1] *A finding under one endpoint category is sufficient to categorize a response into a particular severity level.*

[2] *Forced expiratory volume in one second.*

3.2.2 Level Protective Against Severe Adverse Effects

The hallmark of a severe adverse effect level outcome is a change in organ function and/or tissue damage that may be detectable by clinical examination (U.S.EPA effect severity levels 5-9, Table 5). For example, loss of balance, asthma exacerbation, hemolysis, cardiac ischemia and adverse outcomes of a pregnancy are all clinically significant findings. With some exceptions (such as adverse outcome of a pregnancy), effects may be reversible, although prolonged exposure may result in irreversible effects.

Exposure to an airborne substance above the level protective against severe adverse effects for one hour may lead individuals to seek assistance. Exposures above this level may be immediately disabling by adversely affecting one's judgment and the ability to take appropriate health-protective actions during or directly following the exposure. In addition to protection against immediate health effects, this level is meant to be protective of certain long-term effects potentially resulting from exposure to hazardous substances, such as reproductive endpoints. This document does not address carcinogenic effects. Exposure above this level may, but does not necessarily, result in prolonged or irreversible effects following cessation of exposure.

Although exposure at or above the level protective against severe adverse effects is undesirable and may require protective action, it does not *a priori* indicate that injury or illness would occur. This level is designed to protect the natural diversity of individuals within the population. With increasing exposure concentration or duration above the severe effect level, there is greater likelihood of serious or irreversible health effects occurring in a greater proportion of the population. Examples of adverse health effects above this level include severe eye irritation, marked upper or lower respiratory tract irritation (including dyspnea or bronchospasm), disorientation, blurred vision, vomiting, hemoglobinuria, arrhythmias and adverse outcomes of an existing or subsequent pregnancy.

Since the lower airway is often the most sensitive endpoint for severe adverse effects following inhalation exposure, criteria for pulmonary function testing considered under this level have been specified by OEHHA (Table 7). Pulmonary function test results considered under this level are a 20% or greater decrement in FEV_1 compared to baseline, with or without symptoms of bronchoconstriction such as wheezing, chest tightness and shortness of breath. Alternatively, a 100% increase in SR_{aw} or a 50% decrease in SG_{aw} compared to baseline, accompanied by symptoms of bronchoconstriction, is also consistent with a severe adverse effect. Another pulmonary function test result that is consistent with a severe adverse effect level endpoint is forced expiratory volume in 1 second to forced vital capacity ratio less than 70% ($FEV_1/FVC < 70\%$), which suggests obstructive airway disease. Other measures of the integrity of the lung, such as the diffusing capacity (D_L), a measure of the efficiency of gas exchange across the air-blood barrier, may be taken into consideration, but would not be the sole determinant of the acute severity exposure level.

Examples of aid that may be required above this level include: physical assistance needed because severe eye irritation hampers escape; medical intervention to prevent the progression of adverse health effects such as those due to hemolysis; and sheltering in place because activities outdoors may result in greater exposure and adverse health effects, such as vomiting, than a protected indoor setting.

As with all health effects, certain individuals may be more susceptible to adverse health consequences following exposure above the level protective against severe adverse effects. These sensitive individuals may suffer health effects that may require assistance at a lower level of exposure than the general population. For example, individuals with asthma, who are likely following exposure to sulfur dioxide to exhibit bronchoconstriction at a lower concentration than

the general population, may require greater protection from this substance than nonasthmatic persons. Acute severity exposure levels are designed to be protective for the range of susceptible persons in the general population.

3.2.3 Level Protective Against Life-threatening Effects

Any exposure above this level for more than one hour is potentially lethal, especially to sensitive individuals; and, as exposure duration increases, death becomes a high probability for all exposed persons (U.S.EPA severity effect level 10, Table 5). If death does not occur, the probability of severe, irreversible injury increases with increasing exposure duration or concentration. Examples of adverse health effects considered under this level include severe acute pulmonary edema and respiratory or cardiac arrest. Only exposures that are potentially life-threatening shortly after exposure (within minutes to days) are considered. Exposures with the potential to cause medical conditions that result in death months to years following exposure are not considered. For example, carcinogenic effects are not considered in this document. Health consequences that are immediately severe and may lead to death months later, such as pulmonary edema, are taken into account in developing the level protective against severe adverse health effects.

3.3 Estimation of Threshold or Low Response Concentrations

Noncancer health effects assessment has been based on the concept that a threshold concentration or dose exists below which no adverse effects would occur. While such thresholds are observed among individuals, the existence and magnitude of a population threshold below which no members of the population would experience adverse effects cannot be demonstrated. The entire population of concern is not examined, rather a sample of the population from which inferences are drawn is studied. Therefore, it is not possible to distinguish whether a concentration is truly below a population threshold level for an adverse effect or is rather a level associated with a relatively low incidence of adverse effects which cannot be distinguished from background rates in the population.

Two major strategies were used for dose-response assessment methods to determine thresholds of responses. These are the Benchmark Concentration (BC) approach and the No Observed Adverse Effect Level (NOAEL) approach. A description of an alternative approach that has been proposed but not yet adopted by U.S.EPA, Categorical Regression Analysis, is provided in Appendix D. As explained earlier, existing exposure guidelines were first reviewed, and if appropriate, adopted as RELs and other acute severity levels. When appropriate standards did not exist (the majority of cases), the methodologies described here were used.

Of the methods presented, the preferred one is the Benchmark Concentration approach. A comprehensive evaluation of the literature specific to a toxicant and of the quantal dose-response data is required to estimate levels using the BC method. Supporting toxicological data will not, however, always be sufficient to permit this level of quantification. Furthermore, the methods are not generally applicable for chemicals with large data gaps. We were able to use the BC approach to develop 2 RELs and several levels protective against severe or life-threatening effects. Limitations in available data preclude development of more RELs using the BC approach.

3.3.1 Benchmark Concentration

The importance of a dose-response relationship in the evaluation of effects of chemical exposure is well established. The NOAEL approach (explained below) does not explicitly incorporate this information. This led to explorations of the concept that a concentration estimated to be associated with a predefined low risk could provide an alternative to the NOAEL (Crump, 1984; Dourson *et al.*, 1985; Dourson, 1986; Gaylor, 1988; Gaylor, 1989; Hartung, 1987; Mantel and Bryan, 1961; Mantel *et al.*, 1975;). Crump (1984) proposed the term "benchmark dose" and extensively evaluated this concept. In this document, the term benchmark concentration (BC) is used since inhalation toxicology data are described in terms of air concentrations.

The BC method is a mathematical and statistical approach to calculate chemical exposure levels (Alexeeff *et al.*, 1992, 1993; Crump, 1984; Lewis and Alexeeff, 1989). In this document, the BC is defined as the 95% lower confidence limit of the concentration expected to produce responses in five of every 100 subjects exposed at this dose. A log-normal concentration versus response relationship is used to identify the concentration expected to produce a 5% increase in toxic response (TC_{05}) via a maximum likelihood estimate. This is graphically depicted in Figure 4.

3.3.1.1 Selection of Appropriate Benchmark Concentration Criteria

Suggested response levels for the BC have ranged from one in one million (Mantel and Bryan, 1961) to 10% (Dourson *et al.*, 1985). The 1 to 5% response range approximates the lower limit of adverse effect detection likely to occur in typical human epidemiological and laboratory animal studies (Gaylor, 1992). In 1995, using developmental toxicity data, the U.S.EPA Benchmark Dose Workshop concluded that a 1% response rate was likely to be too low, while either 5% or 10% response rates were adequate for the purposes of estimating a benchmark concentration (Barnes *et al.*, 1995). One reason for this conclusion was the large difference (29-fold) between observed NOAELs and the 1% benchmark using developmental toxicity data. Subsequently, the U.S.EPA (IRIS, 1997) has used a 10% response rate for benchmark concentrations when deriving chronic inhalation reference concentrations (RfCs). However, in the case of a steep dose-response relationship, the selection of benchmark incidence is less influential on the final value. For acute exposure studies, 1 and 5% incidence benchmark concentrations differed, on average, by less than 2-fold from the respective NOAEL (Fowles and Alexeeff, 1996). Therefore, OEHHA chose a 5% response rate for the BC.

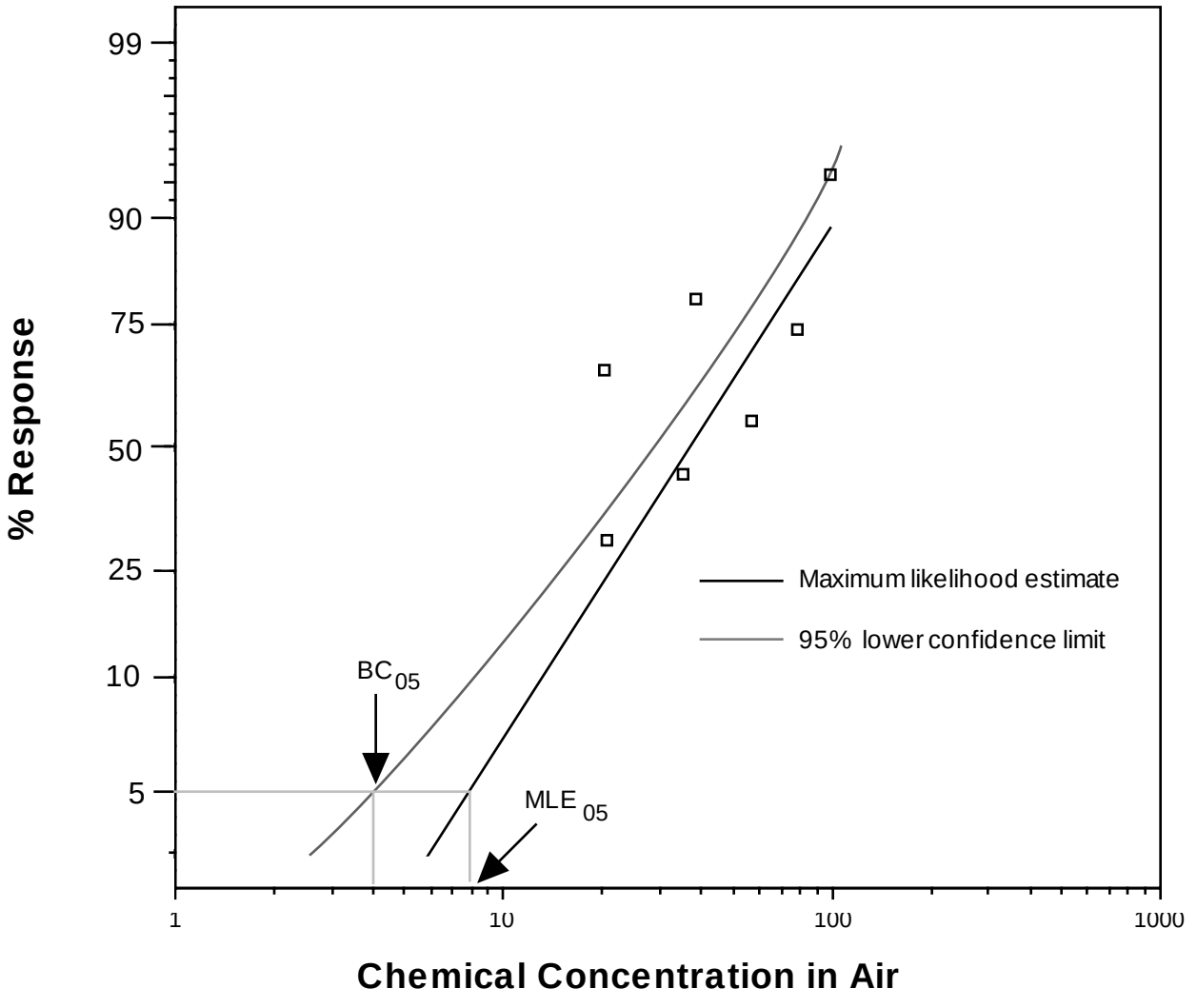

Figure 4. Log-probit modeling of dose-response data. A benchmark concentration (BC) was estimated for a 5% increase in response (MLE_{05}).

It is important to select an appropriate mathematical model for the type of data used for benchmark concentration calculations. The log-normal model is among the most widespread models used for toxicity testing and has traditionally been used extensively for determination of acute lethality and other dichotomous responses (Finney, 1971; Rees and Hattis, 1994). Furthermore, the log-normal distribution aspect of the model is biologically plausible and accounts for some degree of inter-individual variability (Rees and Hattis, 1994). Hattis (1996) showed that the log-normal relationship effectively modeled data from 126 human studies. The Weibull model is used by U.S.EPA when determining benchmark concentrations for the chronic inhalation RfCs (US EPA, 1997). However, a comparison of the Weibull and Probit models by OEHHA for acute inhalation toxicity data indicated that the Probit model provided a better statistical fit to relatively steep dose-response slopes. Furthermore, the uncertainty in the estimates using Probit, as measured by the distance between maximum likelihood estimates and the respective 95% confidence interval, was reduced (Fowles and Alexeeff, 1996). For these reasons, the Probit model was chosen over the Weibull model for use in deriving acute BCs for this document. The log-normal model is described as follows:

$$P(d) = a_0 + [(1 - a_0)\Phi(a_1 + (a_2 * \log_{10}d))]$$

where P(d) is the probability of a response occurring at dose d, Φ is the cumulative distribution function of the standard normal distribution, and a_0, a_1, and a_2 are background, intercept, and slope terms, respectively. The model makes no assumption of a background response in the test population in absence of control data. If controls were observed to exhibit a response, then that response was factored into the calculation.

The 95 percent lower confidence limit on concentration (LCL) takes into account the variability of the test population and is dependent on the number of subjects in the study. The 95% LCL was recommended by the Benchmark Dose Workshop for use in benchmark calculations (Barnes *et al.*, 1995). The advantages of the BC are that it reflects the shape of the dose-response curve and takes into account the number of subjects involved in the study. In addition, it is not necessary to obtain a no-observed adverse-effect level in order to determine an exposure level and the BC does not require an additional uncertainty factor if the NOAEL is estimated from a lowest-observed adverse effect level (see section 3.3.2 below).

In spite of its advantages, the experimentally derived BC value contains areas of uncertainty. For example, the studies used to estimate the BC may have been performed with animals rather than humans. Also, the experimental duration of exposure may differ from that which is of interest for the establishment of exposure levels. Additionally, the dose of toxicant delivered to the target tissue may differ between species and among humans and may depend on the type of activity in which the individual is engaged. In general, higher levels of activity result in increased respiratory rates and in increased doses of inhaled chemicals delivered to the lungs, and possibly systemically. Another area of uncertainty is that there can be a large degree of variability in the number of people who respond at any exposure dose. For example, there may be over a 10-fold variability in the irritation threshold (the concentration of a substance at which irritation of the eyes, nose and/or throat is first detectable) for chlorine (Anglen, 1980). The BC will likely need to be modified by UFs to account for these concerns.

The use of UFs to estimate chemical exposure levels from BCs is based on similar recommendations for calculating U.S.EPA's "reference dose" or RfD (Barnes *et al*., 1995). Uncertainty factors are applied to the BC for the following areas of uncertainty (Table 8):

(1) animal to human extrapolation: 3-fold.

(2) human intraspecies variability: 10-fold when estimating an exposure level based on an animal study, or 3-fold when based on a human study performed in healthy adults. This UF is reduced to 1 if using data that includes an assessment of sensitive human sub-populations. This UF can also be 10 if data indicate a wide variability in response in the human population.

Table 8. Uncertainty Factors Used with Benchmark Concentrations

Type of Study	Intraspecies Variability	Interspecies Uncertainty	Total Uncertainty
Animal	10	3	30
Human (average)	3 (10)	1	3 (10)
Human (sensitive)	1	1	1

The BC is considered by some investigators to account for interspecies as well as experimental variability (Barnes *et al.*, 1995). To acknowledge the greater degree of certainty in a BC for acute inhalation toxicity compared to the NOAEL approach, an UF of 3, instead of the conventional 10, is applied when estimating the acute chemical exposure level from animal data (Table 8).

$$\text{Acute Toxicity Exposure Level} = BC/(UFs)$$

where $1 \leq UF \leq 10$

The rationale for the above UFs is illustrated in Figures 5 and 6. When using animal data, a BC has greater precision than a NOAEL at estimating a true threshold of response in the animal population. This is because the estimate of the number of animals affected at a given concentration can be estimated with accuracy. The result of using more precise methodology is a reduction in the total uncertainty involved in extrapolating to a threshold of response for sensitive individuals. The precise magnitude of this reduction is, by definition, unknown. It is clear that the increased precision in estimating an animal threshold does not reduce human variability in response. Therefore, OEHHA proposes that the typical 10-fold UF for interspecies

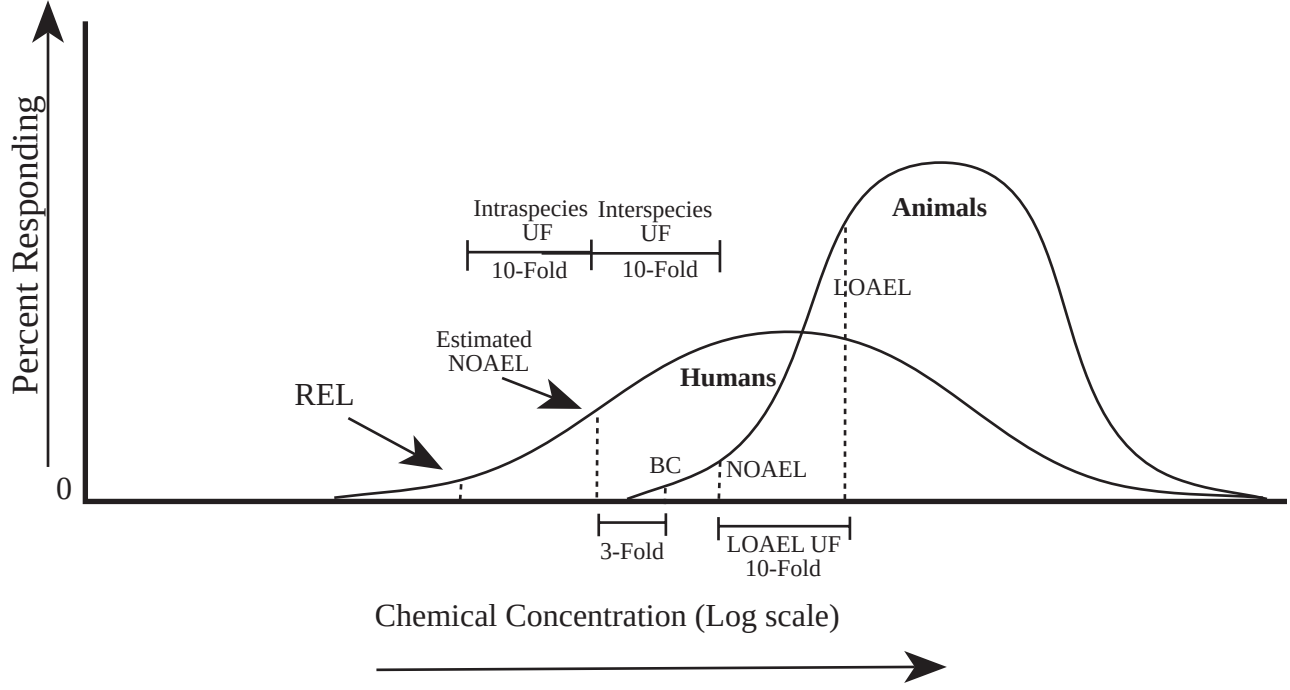

Figure 5. Estimation of a human threshold from animal data. Hypothetical distributions of human and laboratory animal responses to increasing concentrations of a chemical are shown.

LOAEL (Lowest observed adverse effect level): An example of an experimental LOAEL is shown, in this case the experimental LOAEL represents approximately 25% incidence in the experimental animal population. If no NOAEL is determined in the experiment, a NOAEL is estimated using an uncertainty factor of up to 10.

NOAEL (No observed adverse effect level): An example of an animal experimental NOAEL is shown. The NOAEL can be estimated from the LOAEL using an uncertainty factor of up to 10.

Estimated NOAEL (humans): A NOAEL for average humans is estimated from the animal data using an uncertainty factor of up to 10.

BC (Benchmark concentration): An example of an experimental benchmark concentration is shown. In this case, the BC represents less than 10% incidence in the animal population, and, when combined with an uncertainty factor of 3, provides an estimate for a NOAEL in average humans. A further uncertainty factor of up to 10 is needed to protect sensitive individuals.

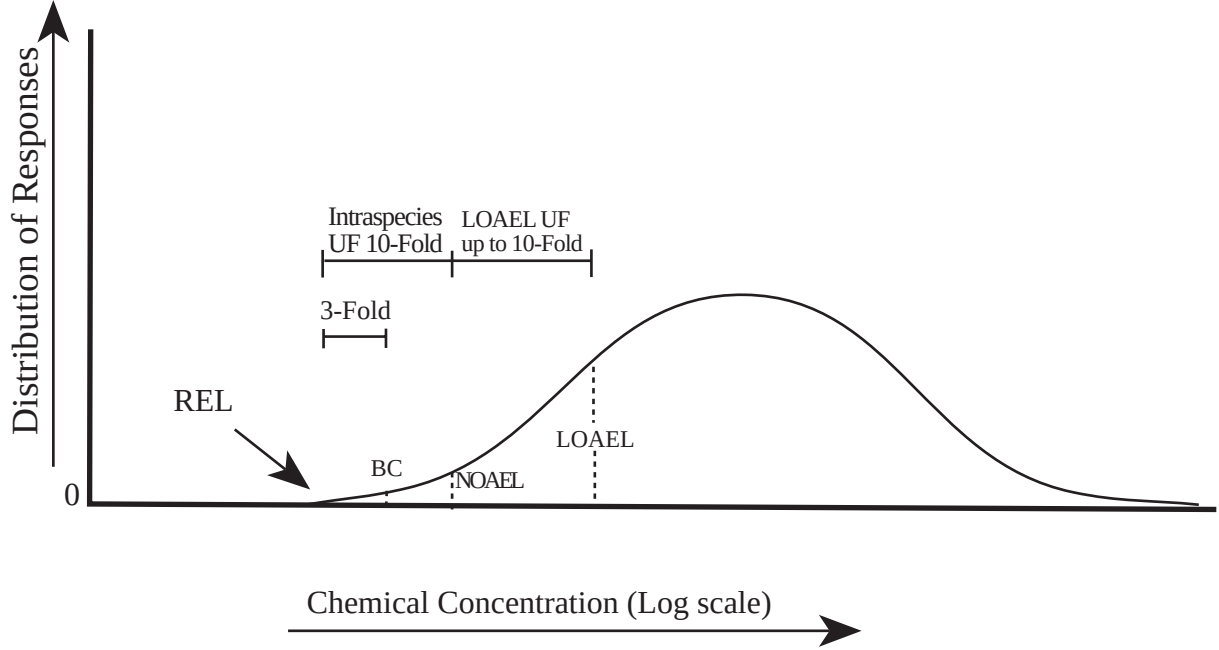

Figure 6. Estimation of an REL that is at or below the threshold for sensitive individuals from healthy human experimental data. A hypothetical distribution of human responses to an increasing concentration of a chemical is shown.

LOAEL (Lowest observed adverse effect level): An example of an experimental LOAEL is shown. In this case the experimental LOAEL represents a 25% incidence in the general population. If no NOAEL is determined in the experiment, a NOAEL is estimated using an uncertainty factor of up to 10.

NOAEL (No observed adverse effect level): An example of an experimental NOAEL is shown. The NOAEL can be estimated from the LOAEL using an uncertainty factor of up to 10. In the case shown, the NOAEL represents less than 10% incidence in the general population and, when combined with an uncertainty factor of up to 10, results in a reference exposure level that is protective of the vast majority of individuals.

BC (Benchmark concentration): An example of an experimental benchmark concentration is shown. In the case shown, the BC represents less than 10% incidence in the general population, and, when combined with an uncertainty factor of up to 3, results in a reference exposure level that is protective of the vast majority of individuals.

differences be reduced to 3-fold (the rounded geometric mean of possible UFs between 1 and 10). While the geometric mean is 3.16, U.S.EPA uses a single intermediate UF of 3.00 rather than 3.16, while two intermediate UFs accumulate to 10 (U.S.EPA, 1994a). Thus, to maintain consistency with U.S.EPA practice, UFs of 3 would generally be used for intraindividual variability to reflect decreased residual uncertainty when using a BC. However, there may be some circumstances where it is appropriate to use an uncertainty factor of 10 in this approach, for example, where evidence indicates a wide variability in response to a toxicant in the human population. When a REL is derived by applying the BC to an animal study, the UF for human variability remains 10-fold. However, in the case of a BC calculation from a study involving healthy human subjects, an UF of 3 is proposed since the total uncertainty in estimating a threshold for sensitive humans is reduced by using human, rather than animal, studies. Finally, if a BC can be determined in a study of a sensitive population, no UFs need be applied (U.S.EPA, 1994a; NRC, 1993).

As with the NOAEL method, if the duration of the experiment differs from that for which one is developing the REL, time extrapolation is performed to determine an appropriate exposure concentration. The principles used in time extrapolation in the example below will be described in detail in section 3.4.1.

Example:

Formaldehyde is used as an example to illustrate the use of the benchmark concentration to calculate an acute reference exposure level. The most sensitive noncancer endpoint for formaldehyde toxicity is eye irritation. Kulle and colleagues (1987) observed mild to moderate eye irritation in human subjects exposed to formaldehyde for 3 hours. Using a log-probit analysis (Crump, 1983), OEHHA calculated a 3-hour BC_{05} of 0.44 ppm formaldehyde (see Figure 7). The 3-hour BC_{05} was adjusted to a 1-hour exposure level using the formula $C^n * T = K$, where n=2. (See Section 3.4.1 on Time Extrapolation for the rationale for the use of this equation.) These calculations are summarized below:

180-minute acute exposure level = 0.44 ppm
C = 60-minute acute exposure level
$C^2 * (60 \text{ min}) = (0.44 \text{ ppm})^2 * (180 \text{ min})$
C = 0.76 ppm

Figure 7 contains a graphic representation of the derivation of a BC for formaldehyde.

3.3.2 Use of No-Observed-Adverse-Effect-Levels (NOAEL)

A No-Observed-Adverse-Effect-Level (NOAEL) may be defined as an exposure level with no biologically or statistically significant increase in the frequency or severity of adverse effects among an exposed population relative to a control group. The NOAEL must be tempered by

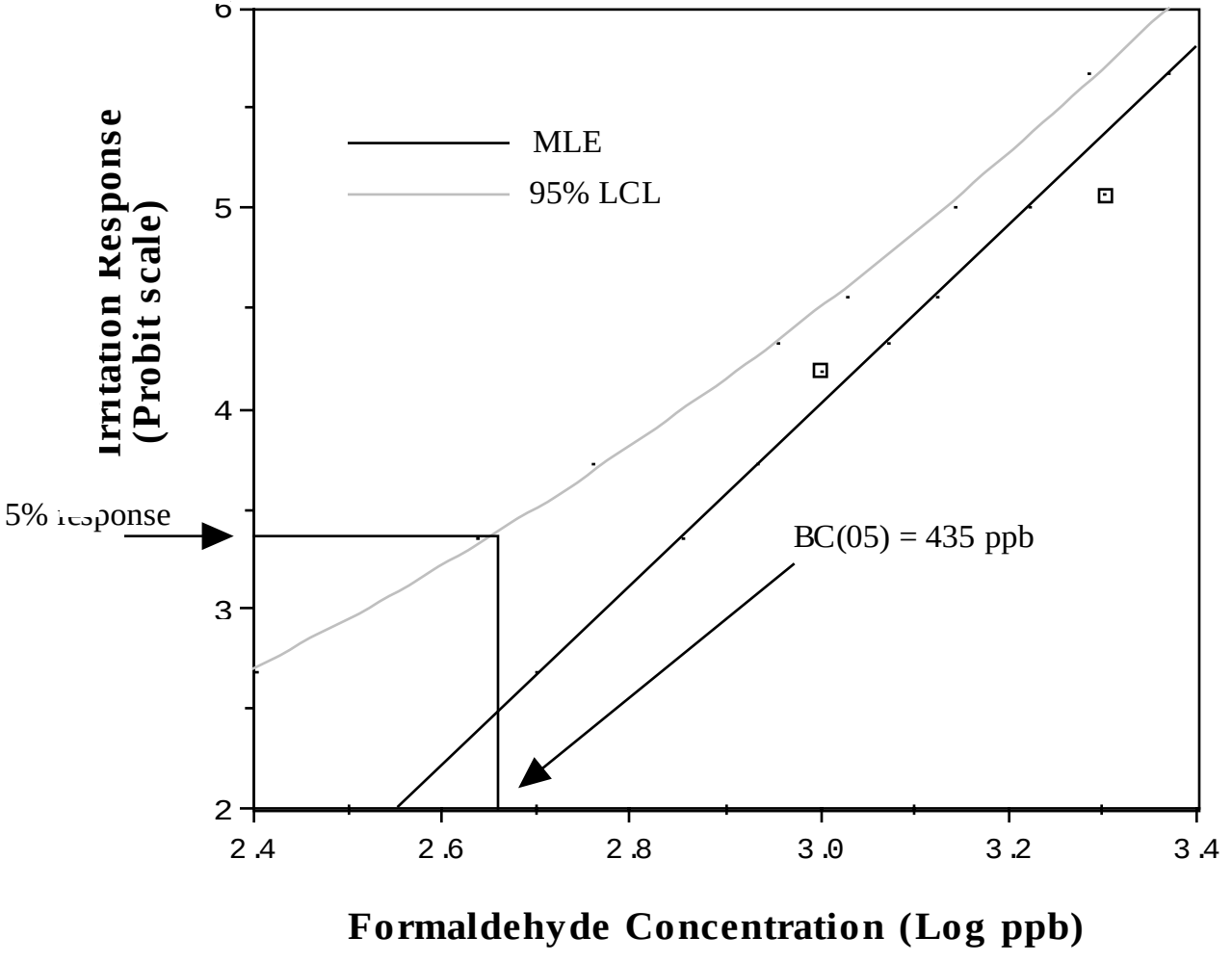

Figure 7. This figure depicts the derivation of the benchmark concentration [BC(05)] for formaldehyde. These data, taken from Kulle and colleagues (1987), are the result of 3-hour exposures to formaldehyde resulting in mild to moderate irritation. The BC(05) is the 95% lower confidence limit (LCL) of the dose producing a 5% response rate.

appropriate statistical interpretation. A NOAEL is sometimes incorrectly viewed as an estimate of a threshold level for adverse effects. However, a NOAEL could be associated with a substantial (1-20%) but undetected incidence of adverse effects among the exposed population, or alternatively it could be many-fold lower than a true population threshold (Gaylor, 1992; Leisenring and Ryan, 1992). This is so because only a subset of individuals from the population has been observed, and because the experiment may not have been designed to observe all adverse effects associated with the substance. Therefore one may not safely conclude that the study concentration or dose is not associated with any adverse effects. Experimental exposure levels are usually selected following a range-finding experiment. U.S.EPA (1994a) determined that a NOAEL not associated with any biological effect (a "no observed effect level" or NOEL) identified from a study with only one dose level is unsuitable for derivation of an RfC for chronic exposure; likewise, a NOEL is inadequate for determining acute severity levels. Because there is a limited availability of multi-dose studies for the variety of chemicals considered, OEHHA considers a NOAEL without an associated LOAEL identified in the same study (termed a free-standing NOAEL) to be acceptable for use in deriving an acute REL if there are no other suitable studies and as long as the overall health hazard information for that substance is consistent with the NOAEL study.

3.3.2.1 Derivation of Acute Reference Exposure Levels Using NOAELs

The NOAEL approach is based on the application of uncertainty factors (UFs) to the maximum dose level causing no observable adverse effects for that endpoint (California Department of Health Services, 1991):

NOAEL / UF = acute reference exposure level.

The NOAEL is an estimate of a threshold level for the absence of toxic effects in a study population and is determined directly from the observations reported in a specific scientific study. Prior to the determination of a NOAEL, the literature is examined to identify the relevant toxicity endpoints, such as lethality or respiratory tract irritation. Toxic endpoints are evaluated and a dose-response relationship is determined. Acute severity effect levels are then established: (1) the most sensitive adverse effect is used to define the NOAEL for the REL (usually a mild adverse effect); (2) severe adverse effects, such as chemical injury which would be irreversible without medical intervention and reproductive endpoints, are used to identify NOAELs for the level protective against severe adverse effects; and (3) lethality or potentially fatal effects are used to identify NOAELs for the level protective against life-threatening effects.

3.3.3 Use of Lowest-Observed-Adverse-Effect-Levels (LOAEL)

A Lowest-Observed-Adverse-Effect-Level (LOAEL) may be defined as the lowest exposure level with a biologically and/or statistically significant increase in the frequency or severity of adverse effects among an exposed population relative to a control group. The highest exposure concentration which results in biologic effects that are <u>not</u> considered adverse may be termed the lowest observed effect level (LOEL); this is identical to the NOAEL (U.S.EPA, 1994a). If a NOAEL is not identifiable from the literature, it is estimated from the lowest exposure

concentration reported to produce the adverse effect; this is the lowest observed adverse effect level (LOAEL). An uncertainty factor is applied to the LOAEL to estimate the NOAEL:

$$LOAEL/UF = NOAEL$$

A one-to-ten-fold uncertainty factor has been proposed to account for the higher health risk potentially associated with a LOAEL compared with a NOAEL (U.S.EPA, 1994a). In general, a factor of 10 has been used in most previous assessments by U.S.EPA and OEHHA. An uncertainty factor is applied to calculate a threshold level (NOAEL) from the LOAEL.

The relationship between LOAELs and NOAELs has been examined for chronic exposures. The effectiveness of a ten-fold LOAEL-to-NOAEL uncertainty factor was confirmed for several inhalation exposure data sets (Gift *et al.*, 1993). Kadry and associates (1995) showed that among a small data set (4 chemicals) LOAEL to NOAEL ratios were less than 5. However, where only a LOAEL has been observed, the magnitude of the difference between the observed concentration and the maximum concentration where adverse effects would not be detected is uncertain. OEHHA staff consider a10-fold UF for extrapolation from a LOAEL to a NOAEL to be protective when applied to all types of studies.

The RAAC recommended that OEHHA delineate situations where uncertainty factors less than 10 could be used in the REL development process. Although the use of an uncertainty factor less than 10 (an intermediate uncertainty factor) may be appropriate under certain circumstances, application of UFs less than 10 to acute exposures by other organizations (e.g., AIHA's ERPGs, see Section 1.8.1) appears to be subjective and guidance in specific criteria as to when it is appropriate is lacking. As discussed elsewhere, use of the benchmark concentration approach can address this issue directly. However, in most circumstances there is insufficient data for a benchmark concentration approach. Consequently, OEHHA developed specific criteria for the use of an intermediate uncertainty factor. Based on an analysis of LOAELs and NOAELs reported in various toxicological studies, we found that in certain circumstances (extrapolating from a LOAEL to a NOAEL for both mild (sensory) irritation and lethal effects), UFs less than 10 are justified (Alexeeff *et al.*, 1997). OEHHA uses UFs less than 10 in the following cases: (1) for extrapolating from a LOAEL to a NOAEL for mild adverse effects; and (2) for potentially lethal effects (life-threatening level). In the case of the mild adverse effect, an analysis by Alexeeff *et al.*, (1997) (Appendix F) of LOAEL to NOAEL ratios for over 100 datasets indicated that the 95^{th} percentile of that ratio is 6.2. The distribution is skewed to the right. For some chemicals, a UF of 10 may not be adequate. OEHHA has chosen a UF of 6 to extrapolate from the LOAEL to the NOAEL based on the analysis. OEHHA has followed precedence set by U.S.EPA (1994a) in the use of an intermediate uncertainty factor of 3 when using lethality data to determine a level protective against life-threatening effects. It is suggested that further analysis of the LOAEL to NOAEL relationship be undertaken to better evaluate the use and magnitude of this adjustment factor. Results of such a detailed analysis could be used to improve the exposure level setting procedure in the future.

Example: Thirty six healthy human volunteers reported eye irritation after being exposed to 0.06 ppm acrolein for 5 minutes (Darley *et al.*, 1960). Subjects wore carbon-filter respirators during exposure, so that only the eyes were exposed to the test mixture. An uncertainty factor of 6 was applied for estimation of a NOAEL from the 5-minute LOAEL of 0.06 ppm. An additional uncertainty factor of 10 was applied to account for sensitive individuals, resulting in a total uncertainty factor of 60. For a complete derivation of this REL for Acrolein see Appendix C.

If there exist multiple, non-identical NOAELs and LOAELs for the same compounds, the study of the best quality reporting the highest value for a NOAEL (preferred) or the lowest value for the LOAEL is used for the development of acute severity levels. Preferably, a study should report a NOAEL as well as a LOAEL. However, this is not always done. As stated above, a free-standing NOAEL (i.e., a NOAEL reported at the highest exposure concentration studied, with no reported LOAEL) is used as the basis for an acute toxicity exposure level only when there are no other appropriate studies on which to base the level and the dose-response data are consistent with other dose response information reported in the scientific literature.

3.3.4 Accounting for Uncertainties in the Database

Acute RELs and other toxicity exposure levels must address uncertainties in the available data. These areas of uncertainty are accounted for with the use of extrapolation factors or uncertainty factors. Uncertainty factors are used extensively with human or animal toxicity data to estimate "safe" or "acceptable" exposure levels for humans (Dourson and Stara, 1983). Uncertainty factors are used by OEHHA in deriving acute RELs to account for the following, discussed below :

1) potentially greater susceptibility to the toxic effects of exposure to substances in humans compared with laboratory animals (Dourson and Stara, 1983; Vettorazzi, 1976);

2) the uncertainty involved in extrapolating from LOAELs to NOAELs (Gift *et al.*, 1993; Dourson and Stara, 1983);

3) the large range of individual variability in the human population, e.g., low risk vs. high risk individuals (Vettorazzi, 1976; Hattis, 1996).

4) other deficiencies in the study design (Bigwood, 1973; Dourson and Stara, 1983; Lehman and Fitzhugh, 1954; NRC, 1993);

The use of uncertainty factors for determining "safe" or "acceptable" levels has been discussed extensively in the toxicologic literature (Alexeeff *et al.*, 1994; Bigwood, 1973; CDHS, 1991; Dourson and Stara, 1983; NAS, 1977; U.S.EPA, 1989; Vettorazzi, 1976). While most of the applications have focused on long-term exposure, many of the factors are applicable to acute inhalation exposure and are based on acute experiments. Uncertainty factors used for each chemical are presented in Table 9.

Table 9. Uncertainty factors used in derivation of acute RELs

Chemical	Interspecies	Sensitive Individuals	LOAEL to NOAEL[2]	Methodology Used[3]	Total UF
Acrolein	N/A	10	6	NOAEL	60
Acrylic acid	10	10	N/A	NOAEL	100
Ammonia	N/A	3	N/A	BC	3
Arsenic	10	10	10	NOAEL	1000
Arsine	10	10	N/A	NOAEL	100
Benzene	10	10	N/A	NOAEL	100
Benzyl chloride	10	10	6	NOAEL	600
Carbon disulfide	10	10	N/A	NOAEL	100
Carbon monoxide[1]	N/A	1	1	NOAEL	1
Carbon tetrachloride	10	10	10	NOAEL	1000
Chlorine	N/A	10	N/A	NOAEL	10
Chloroform	10	10	N/A	NOAEL	100
Chloropicrin	10	10	N/A	NOAEL	100
Copper	N/A	10	N/A	NOAEL	10
Dioxane	N/A	10	6	NOAEL	60
Epichlorohydrin	N/A	10	6	NOAEL	60
Ethylene glycol monobutyl ether	N/A	10	N/A	NOAEL	10
Ethylene glycol monoethyl ether	10	10	N/A	NOAEL	100
Ethylene glycol monoethyl ether acetate	10	10	10	NOAEL	1000
Ethylene glycol monomethyl ether	10	10	10	NOAEL	1000
Formaldehyde	N/A	10	N/A	BC	10
Hydrochloric acid	N/A	1	N/A	NOAEL	1
Hydrogen cyanide	10	10	N/A	NOAEL	100
Hydrogen fluoride	N/A	10	N/A	NOAEL	10
Hydrogen selenide	10	10	6	NOAEL	600
Hydrogen sulfide	N/A	1	1	NOAEL	1
Isopropyl alcohol	N/A	10	N/A	NOAEL	10
Mercury	10	10	10	NOAEL	1000
Methanol	N/A	10	N/A	NOAEL	10
Methyl bromide	10	10	N/A	NOAEL	100

Chemical	Interspecies	Sensitive Individuals	LOAEL to NOAEL[2]	Methodology Used[3]	Total UF
Methyl chloroform	N/A	10	N/A	NOAEL	10
Methyl ethyl ketone	N/A	10	6	NOAEL	60
Methylene chloride	N/A	10	N/A	NOAEL	10
Nickel	N/A	1	6	NOAEL	6
Nitric acid	N/A	1	N/A	NOAEL	1
Nitrogen dioxide[1]	N/A	1	N/A	NOAEL	1
Ozone[1]	N/A	1	1.3	LOAEL	1.3
Perchloroethylene	N/A	10	6	NOAEL	60
Phenol	N/A	10	N/A	NOAEL	10
Phosgene	10	10	N/A	NOAEL	100
Propylene oxide	10	10	6	NOAEL	600
Sodium hydroxide	N/A	10	6	NOAEL	60
Styrene	N/A	10	N/A	NOAEL	10
Sulfates[1]	N/A	1	N/A	NOAEL	1
Sulfur dioxide[1]	N/A	1	1	NOAEL	1
Sulfuric acid/oleum	N/A	1	N/A	NOAEL	1
Toluene	N/A	10	N/A	NOAEL	10
Triethylamine	N/A	10	N/A	NOAEL	10
Vanadium	N/A	10	N/A	NOAEL	10
Vinyl chloride	N/A	10	N/A	NOAEL	10
Xylenes	N/A	10	N/A	NOAEL	10

[1] *The California Ambient Air Quality Standard was used as the basis for the acute REL; uncertainty factors may differ from those described in this document since different methodology was used for the derivation.*

[2] *N/A = Not applicable; when used in "Interspecies" column, indicates that human study was used as basis for REL; when used in "LOAEL to NOAEL" column, indicates that NOAEL was reported in study.*

[3] *NOAEL = No observed adverse effect level methodology; BC = Benchmark concentration methodology.*

3.3.4.1 Differences Between Human and Animal Susceptibility

Although it is preferable to use human studies, risk assessment of chemicals must often rely on observation of experimental animals. Of the many thousands of chemicals in existence, most have not been studied in human populations, and where human studies exist, there is often poor knowledge of exposure. Furthermore, confounding factors may render cause and effect conclusions difficult. A great wealth of scientific information shows that species differ markedly in anatomic, physiologic, and metabolic characteristics, and can vary greatly in terms of susceptibility to adverse effects from exposure to chemicals. However, the differences between animal and human responses to toxic substances have not been delineated for all compounds of interest.

To account for this area of uncertainty, a default factor of 10 is generally incorporated for extrapolation from animals to humans based on an assumption that an average human is likely to be at most 10-fold more susceptible to the effects of the substance than experimental animals. This is truly an "uncertainty" factor since we are unsure how humans would respond in contrast to the animals tested (Figure 5). However, the uncertainty factor is based on the potential for greater sensitivity of humans and the larger surface area of humans, suggesting a 2- to 100-fold uncertainty factor (Krasovskii, 1976; Lewis and Alexeeff, 1989; Rall, 1969; Watanabe *et al.*, 1992; Weil, 1972; Willhite *et al.*, 1986).

The use of uncertainty factor methodology is in contrast to practice in cancer risk assessment, where an allometric surface area correction and a 95% upper confidence limit of the slope of the dose response is used. The UF approach is identical to that used by U.S.EPA (1994a) and recommended by NAS for drinking water standards. Limited support for the concept of a 10-fold uncertainty factor was provided by Dourson and Stara (1983). Khodair and associates (1995) showed that among a small data set (6 chemicals) animal NOAEL to human NOAEL ratios were less than 4. Clearly, additional work in this area is warranted. Recently, Schmidt *et al.* (1997) evaluated interspecies variation between human and five other animal species. Sixty compounds had human data that could be matched to one or more animal species. The animal to human Maximum Tolerated Dose (MTD) ratio of 10 represented approximately the 85th percentile. In other words, an UF of 10 to account for interspecies variability would be protective for 85% of chemicals. Thus, use of this factor alone would not likely be protective of most individuals. However, this adjustment is not made without consideration of an intraspecies variability factor as well. An analysis by Stickney *et al*. (1997) indicated that the use of the 10-fold interspecies and 10-fold intraspecies uncertainty factors together would be protective of the 99th percentile of the population. The use of interspecies uncertainty factors and the degree of protection afforded by those uncertainty factors for different endpoints (e.g., lethality, irritation) warrants further research.

In Figure 1, we indicate that a dosimetric adjustment, such as the Human Equivalent Concentration (HEC) adjustment used by U.S.EPA might be appropriate in some circumstances. We did not conduct any HEC adjustments in developing the RELs for chemicals presented in Appendix C. However, we may in the future use dosimetric adjustment to partially account for differences in animals and humans with respect to dose at a specified concentration.

3.3.4.2 Increased Susceptibility of Sensitive Individuals

Acute RELs are intended to protect identifiable sensitive individuals from harm due to chemical exposure. However, RELs may not necessarily protect individuals who may develop an idiosyncratic response which cannot be predicted from scientific investigation of the chemical. Susceptibility to harm from chemical exposure may vary among individuals due to genetic variability within the population, resulting in lower levels of protective biological mechanisms or increased metabolic activation (Hattis, 1996; U.S.EPA, 1994a; Eichelbaum *et al.*, 1992; Grandjean, 1992). Additionally, susceptibility to chemical-related health effects may vary over time for the same individual due to changing factors such as age, health status, and activity level.

Thus, sensitive individuals may include children, pregnant women and their fetuses, elderly persons, those with existing diseases such as lung, heart or liver disease, and persons engaging in physical activity (U.S.EPA, 1994a). Other factors, such as acute illness, may cause short-term variations in individual susceptibility. Seasonal changes in absorption and toxicity have also been noted in laboratory animals (Barton and Huster, 1987).

Healthy workers, the subject of most epidemiological studies, are often found to have lower rates of morbidity and mortality than the general population (Monson, 1986; Wen *et al.*, 1983). In studies of experimental animals, highly homogeneous, healthy strains are generally used. Such strains may have much less variability in response than a more heterogeneous human population. Chizhikov (1973) found that animals in poor health were more likely to experience adverse effects from chronic oral exposure to chemicals than were healthy animals.

A 10-fold uncertainty factor is used to account for variability within the human population. But, in this case, the factor is not actually accounting for something unknown; instead it is accounting for the variability in the general population which we know exists but do not have enough data to quantify (Figure 6). This factor accounts for the greater susceptibility to chemical toxicity of various sensitive subpopulations, including infants and children.

A high degree of interindividual variability (2-to-30-fold) in response to chemical exposure has been reported (Krasovskii, 1976; Weil, 1972). Hattis (1996) has shown that human variability in response to some medications may range over more than 3 orders of magnitude (>1,000-fold). Similar interindividual variability has been shown in airway responsiveness and lung volume among normal and asthmatic subjects (Bylin *et al.*, 1995; O'Connor *et al.*, 1987). In a study of asthmatic subjects, Horstman *et al.* (1986) found that there was a 7-fold distribution in the range of sulfur dioxide concentrations required to produce bronchoconstriction. Thus, it is reasonable to conclude that asthmatics may be at least seven times as sensitive to the effects of sulfur dioxide as normal individuals. The interindividual variability has been recently modeled, indicating a distribution that ranges from 1 to >20 with a value of 10 for the 85^{th} percentile (Gillis *et al.*, 1997). Thus, based on this analysis, the use of a 10-fold uncertainty factor would not be protective of approximately 15% of the population. Further research into the considerations, circumstances, subpopulations, and endpoints of greater susceptibility is needed.

For acute RELs derived from NOAELs or LOAELs in healthy adults, OEHHA has applied a 10-fold uncertainty factor to address the greater susceptibility of sensitive individuals. In accordance with U.S.EPA guidelines (U.S.EPA, 1994a), when an exposure level is estimated from a study that includes the assessment of a sensitive human sub-population, an intraspecies factor of 1 is used. Since the true degree of variability of response in the human population is unknown, the effectiveness of this method in providing protection to nearly all individuals is uncertain. A summary of uncertainty factors used for acute REL development is given in Tables 9 and 10.

Table 10. Uncertainty factors used in the derivation of acute RELs

Methodology, study type	Nature of uncertainty	Uncertainty Factor
Benchmark concentration, animal study	Interspecies	3
	Intraspecies	10
Benchmark concentration, human study	Interspecies	1
	Intraspecies--study includes sensitive subjects	1
	Intraspecies--study does not include sensitive subjects	3 or 10
NOAEL, animal study	Interspecies	3 or 10
	Intraspecies	10
NOAEL, human study	Interspecies	1
	Intraspecies--study includes sensitive subjects	1
	Intraspecies--study does not include sensitive subjects	10
NOAEL, any study	LOAEL--mild effects	6
	LOAEL--other than mild effects	10

As noted by Dourson and Stara (1983), the steepness of the dose-response relationship affects the adequacy of the uncertainty factor for sensitive individuals. They summarized the range of dose

response slopes reported by Weil (1972), indicating that, based on studies of acute lethality, a 10-fold factor was health-protective in most cases. However, in our experience, dose response curves for acute lethality exposures are generally steeper than those for non-lethal exposures (Table 11).

Table 11. Comparison of slopes of mild and lethal effects[a].

Chemical	Mild Effects[b]	Lethality[c]
Acrolein (irritation)	3.3	14.4
Ammonia (irritation)	6.9	14.3
Vinyl chloride (CNS effects)	7.5	31.9

[a] *Log-normal dose-response slope values are the mean of up to 5 studies.*

[b] *Human data for mild effects include: Hine et al., 1961; MacEwen et al., 1970; IBT, 1973; Verberk et al., 1977; Lester et al., 1963.*

[c] *Animal LC_{50} studies include: U.S.EPA 1992a; U.S.EPA 1992b; Philippin et al., 1970; Champeix and Catilina 1967; Silver and McGrath 1948; Appelman et al., 1982; Kapeghian et al., 1982; Prodan et al., 1975.*

Because the true variability is unknown, there may be a portion of the population for whom the acute RELs will not be protective. It is OEHHA's intent that, to the maximal extent possible, the levels will protect the general population including those in the high end of susceptibility. As information defining susceptible individuals becomes available, it is our intent to adjust the methodology as necessary to protect such individuals.

3.4 Effects of Exposure Duration

Studies of adverse health effects associated with exposures in humans or experimental animals are generally conducted for time periods different from that which is of interest in the acute exposure scenario. Typical exposure scenarios involve several hours for human exposures and several daily exposures for two weeks in animals. OEHHA acute RELs, on the other hand, are designed to be protective for one-hour exposures (with the exception of some reproductive/developmental toxicants where the REL is for several hour exposures).

Acute inhalation toxicology studies (exposure duration of 8 hours or less) are preferred over other exposure routes. In their absence, studies using exposures of longer durations may be employed if appropriate (e.g., symptoms noted after short period of time; reproductive/developmental endpoints). If inhalation toxicity data are unavailable, studies on other exposure routes may be used. Studies that include an adequate follow-up period (hours to days, depending on the chemical and endpoint) to account for delayed health effects are preferred to those that terminate observation immediately following exposure. In order to adjust experimental exposure durations to one-hour, OEHHA uses a method termed "time extrapolation."

3.4.1 Time Extrapolation

"Haber's Law" states that the product of the concentration (C) and time of exposure (T) required to produce a specific physiologic effect is equal to a constant level or severity of response (K), or $C * T = K$ (Rinehart and Hatch, 1964). When the duration of experimental exposure differs from the desired exposure duration for which an acute exposure level is being calculated (in this case 1 hour), a modification of Haber's Law is used to adjust the experimental exposure duration to the desired duration of the acute exposure level:

$$C^n * T = K,$$

where n is a chemical-specific parameter greater than zero (ten Berge, 1986). When n is equal to 1 ($n=1$), the toxicity of a chemical is equally dependent on changes in concentration and duration of exposure; when n is less than 1 ($n<1$), the duration of exposure is a greater determinant of toxicity than the concentration; finally, when n is greater than 1 ($n>1$), the toxicity of a chemical is determined to a greater extent by exposure concentration than by duration. Ideally, the magnitude of n should be determined for all chemicals by evaluating the concentration versus response relationships for several different exposure durations. However, this information is available for only a limited number of substances. Empirically derived values of the exponent n range from 0.8-3.5 (ten Berge, 1986). The time-concentration-response relationship depends on the time-frame considered and the endpoint measured. There are usually multiple "n" values for a single chemical that are applicable to different response endpoints. For example, the "n" for irritation of ammonia is 4.6, while the "n" for lethality of ammonia is 2.

A risk assessment document published by the NAS (NRC, 1987) includes a general statement that Haber's Law does not apply for "some irritants". However, no specific references are cited by NAS in support of this statement. It is likely that the basis of this statement is the observation that for some substances, irritation appears to be solely concentration dependent. However, the modified Haber's Law presented here is able to accommodate any such empirical observations. For example, in those cases for which data exist to allow the determination of a concentration-time relationship for irritants (e.g. chlorine, ammonia), an analysis by OEHHA revealed that both concentration and time of exposure contributed to the overall severity of effect, as described by $C^n * T = K$. As concentration becomes the more important factor, the value of "n" will increase. Values of "n" greater than 3 suggest a strong predominance of concentration over time.

A modified Haber's Law was applied to all of the chemical data sets analyzed in this document. This is consistent with a role for both concentration and time in the determination of the magnitude of irritation and other acute effects.

Examples of time extrapolation using different empirically derived values of "n" are given as follows.

Example:

(a)For illustrative purposes, an example of time extrapolation for carbon tetrachloride is used. The empirically derived value for "n" in this case is 2.8 (ten Berge, 1986). A NOAEL for lethality in rats of 7,300 ppm for 1.5 hours was reported by Adams *et al.* (1952). A 1-hour level protective against life-threatening effects is estimated as follows:

$$C^{2.8} (1 \text{ hr}) = 7{,}300^{2.8} (1.5 \text{ hr}),$$

where C represents the desired 1-hour concentration in ppm. Solving this equation for C yields a value of 8,440 ppm.

(b)The example of ammonia is given to further illustrate time extrapolation. The empirically derived value for the exponent "n" for ammonia is 4.6 (refer to Acute Toxicology Summary for Ammonia, Appendix C for further information on its derivation). A hypothetical 6-hour exposure study in a sensitive human population reported that the no adverse effect level for severe mucous membrane irritation was 48 mg/m^3 ammonia. The equivalent 1-hour concentration for this effect is calculated as follows:

$$C^{4.6} (1 \text{ hr}) = 48^{4.6} (6 \text{ hr}),$$

where C represents the 1-hour concentration for the effect described above. Solving for C yields a 1-hour concentration of 71 mg/m^3.

The value for the exponent "n" used by OEHHA in the acute toxicity summaries was chosen as follows. First, when an empirically derived value for the exponent was available from the open literature, this was adopted for time extrapolation, using the modification of Haber's Law as described above. The values from the American Institute of Chemical Engineers (AICE, 1989) are included in Table 12, but were not used in the Technical Support Document since AICE (1989) does not give references for the sources of data. When a derived value was not available and there were insufficient data from which to determine a value *de novo*, a default value for "n" was used. As seen in Table 12, the published or OEHHA derived values for "n" range from 0.8 to 4.6. The mean value in this range rounds to 2, while the interquartile range (25%-75%), where most of the "n" values are found, is from 1 to 2.2.

As noted in Section 1.6.1, the time extrapolation to one hour in the case of repeated dose studies for reproductive/developmental endpoints was not considered appropriate by the Scientific Review Panel. OEHHA chose a single day's exposure for each chemical (ranged from 1 to 8

hours) as the exposure duration for which the REL is to be applied. Thus, no time extrapolation is used for reproductive-developmental toxicants.

Table 12. Value of the exponent *n* for various gases and vapors

Chemical	*n*	Species/Effect	References, Comments
Acrolein	1.2	rat/lethality (local irritant)*	US EPA (1992a,b), derived by OEHHA
Acrylonitrile	1.1	rat/lethality (systemic)	Dudley & Neal (1942); Appel *et al.* (1981), derived by ten Berge *et al.* (1986)
Allyl chloride	0.5	rat/lethality (local irritant)	Adams *et al.* (1940), derived by OEHHA
Ammonia	4.6	human/irritation	Rosenbaum *et al.* (1993)
	2.02	rat/lethality (local irritant)	Appelman *et al.* (1982)
Arsine	2.2	rat/lethality (systemic)	IRDC (1985b), derived by OEHHA for 0.5 to 1 hr (n dependent on exposure duration)
	1.0	rat/lethality (systemic)	IRDC (1985), derived by OEHHA for 4 hr to 1 hr (n dependent on exposure duration)
	2	mice/lethality (systemic)	Levvy (1947)
Benzene	2	not given	AICE (1989)
Bromine	2.2	mice/lethality (local irritant)	Bitron & Aharonson (1978), derived by ten Berge *et al.* (1986)
Carbon monoxide	1	not given	AICE (1989)
Carbon tetrachloride	2.8	rat/lethality (systemic)	Adams *et al.* (1952), derived by ten Berge *et al.* (1986)
Chlorine	2.8	rat/lethality (local irritant)	Zwart & Woutersen (1988), derived by OEHHA for 0.5 hr to 1 hr (n dependent on exposure duration)
	1.0	rat/lethality (local irritant)	Zwart & Woutersen (1988), derived by OEHHA for 4 hr to 1 hr (n dependent on exposure duration)
	1.3	mouse/lethality (local irritant)	Zwart & Woutersen (1988), derived by OEHHA
	3.5	mouse/lethality (local irritant)	Bitron & Aharonson (1978), derived by ten Berge *et al.* (1986)
Chlorine pentafluoride	2	rat, mouse, dog, monkey/lethality (local irritant)	Darmer *et al.* (1972), derived by ten Berge *et al.* (1986)
Crotonaldehyde	1.2	rat/lethality (local irritant)	Rinehart (1967), derived by ten Berge *et al.* (1986)
Dibutylhexamethylene-diamine	1	rat/lethality (local irritant)	Kennedy & Chen (1984), derived by ten Berge *et al.* (1986)
1,2-dichloroethylene	2	(not applicable)/lethality (systemic)	US EPA (1996), based on the mid-point range of n values from lethality data of ten Berge *et al.* (1986)
Dimethyldichloro-silane	2	(not applicable)/lethality (local irritant)	US EPA (1996), based on the mid-point range of n values from lethality data of ten Berge *et al.* (1986)
Ethylene dibromide	1.2	rat/lethality (systemic)	Rowe *et al.* (1952), derived by ten Berge *et al.* (1986)

Table 12. Value of the exponent *n* for various gases and vapors (*cont.*)

Chemical	*n*	Species/Effect	References, Comments
Ethylene imine	1.1	rat, guinea pig/lethality (local irritant)	Carpenter *et al.* (1948), derived by ten Berge *et al.* (1986)
Fluorine	1.9	rat/lethality (local irritant)	US EPA (1996), derived from LC_{50} data of Keplinger & Suissa (1968)
	1.8	mouse/lethality (local irritant)	US EPA (1996), derived from LC_{50} data of Keplinger & Suissa (1968)
	1.6	guinea pig/lethality (local irritant)	US EPA (1996), derived from LC_{50} data of Keplinger & Suissa (1968)
Formaldehyde	2	not given	AICE (1989)
Hydrazine	2	(not applicable)/lethality (systemic)	US EPA (1996), based on the mid-point range of n values from lethality data of ten Berge *et al.* (1986)
Hydrogen chloride	1	rat, mouse/lethality (local irritant)	Darmer *et al.* (1972), derived by ten Berge *et al.* (1986)
	1.5	rat/lethality (local irritant)	Hartzell *et al.* (1985), derived by OEHHA
Hydrogen cyanide	2.7	numerous species/lethality (systemic)	Barcroft (1931), derived by ten Berge *et al.* (1986)
Hydrogen fluoride	2	rabbits, guinea pigs/lethality (local irritant)	Machle (1934), derived by ten Berge *et al.* (1986)
Hydrogen fluoride (low humidity)	1	rat/lethality (local irritant)	Haskell Lab. (1988), derived by OEHHA
Hydrogen sulfide	2.2	cat, rabbit/lethality (systemic/local irritant)	Lehmann (1892), derived by ten Berge *et al.* (1986)
	8.2	lethality (systemic/local irritant)	Arts *et al.* (1989)
Methyl bromide	4.0	severe morbidity (systemic/local irritant)	Pharmaco LSR, Inc. (1994) derived by OEHHA, DPR 1996
	1	not given	AICE (1989)
Methylenechloro-bromide	1.6	rat/lethality (systemic)	Torkelson *et al.* (1960), derived by ten Berge *et al.* (1986)
Methylhydrazine	1.0	squirrel monkey/lethality (systemic and local irritant)	Haun *et al.* (1970), derived by OEHHA
	1.0	dog/lethality (systemic and local irritant)	Haun *et al.* (1970), derived by OEHHA
Methyl isocyanate	1.1	human/eye irritation	Mellon Inst. (1963), derived by OEHHA
	0.5	rat/lethality (local irritant)	Kimmerle & Eben (1964), derived by OEHHA
	0.7	rat/lethality (local irritant)	Dow Chem. (1990), derived by OEHHA
Methyl mercaptan	2	(Not applicable)/lethality (systemic and local irritant)	US EPA (1996), based on the mid-point range of n values from lethality data of ten Berge *et al.* (1986)
Methyl t-butyl ether	2.0	lethality (systemic)	Snam Progretti (1980), derived by ten Berge *et al.* (1986)

Table 12. Value of the exponent *n* for various gases and vapors (*cont*.)

Chemical	*n*	Species/Effect	References, Comments
Nitrogen dioxide	3.5	guinea pig, mouse, dog, rat, rabbit/lethality (local irritant)	Hine *et al.* (1970), derived by ten Berge *et al.* (1986)
Nitric acid	3.5	not applicable (local irritant)	US EPA (1996), based on NO_2 from Hine *et al.* (1970)
Perfluoroisobutylene	1.2	rat/lethality (local irritant)	Smith *et al.* (1982), derived by ten Berge *et al.* (1986)
Phosgene	1	lethality (local irritant)	Rinehart & Hatch (1964)
Propylene oxide	2.2	rat/lethality (local irritant)	Rowe *et al.* (1956), derived by OEHHA
	1.5	guinea pig/lethality (local irritant)	Rowe *et al.* (1956), derived by OEHHA
Sulfur dioxide	1	not given	AICE (1989)
Tetrachloroethylene	2.0	rat/lethality (systemic)	Rowe *et al.* (1952), derived by ten Berge *et al.* (1986)
Toluene	2.5	not given	AICE (1989)
Trichloroethylene	0.8	rat/lethality (systemic)	Adams *et al.* (1951), derived by ten Berge *et al.* (1986)

* Parentheses denotes whether the chemical acts locally or systemically to produce the effect.

When extrapolating from an exposure duration that is greater than 1-hour to a 1-hour level, the value of n=2 was used by OEHHA. The value of n=2 was chosen because it represents a whole number near the midpoint of the range of values, as described above. When extrapolating from an experimental exposure duration of less than 1 hour to a 1-hour level, the value of n=1 was used. Using a value of n=1 is more health-protective than a value of n=2. A value of n=1 results in a relatively rapid decrease in the derived REL when extrapolations are made from shorter to longer exposures. For example, when extrapolating from a 10 minute exposure to a 60 minute exposure for chloropicrin, using n=1 results in an extrapolated NOAEL of 132 ppb; when using n=2, the extrapolated NOAEL is 320 ppb. The default values for "n" bracket the interquartile range of possible values, and they are applied using health protective assumptions (Table 13).

Table 13. Exponents used by OEHHA for extrapolation to 1-hour acute RELs[1].

	Exponent (n)
From less than 1 hour	1
From greater than 1 hour	2

[1] *Exponent, n, used in the formula* $C^n T = K$

4.0 Supporting Data

The summaries describing the development of the REL for each chemical are found in Appendix C. In addition, a list of abbreviations is provided in Appendix E. All acute toxicity exposure level estimates (including those for RELs) will include a discussion of the information upon which the calculations are based. This discussion includes the following key elements.

1. Physical and chemical properties: Descriptions include information on volatility, reactivity, stability, toxic secondary compounds, flammability, density, water solubility, color, taste, odor, and some additional properties.

2. Occurrence and use: The typical uses of the chemical are described as well as where it is likely to be found.

3. Routes of exposure: The routes of exposure that may lead to toxic effects are mentioned for each substance. Since the intent of this document is to provide information on airborne toxicants, the data presented focuses on inhalation exposure studies and may be supplemented by relevant non-inhalation toxicology studies. If inhalation data are unavailable or are of poor quality for a particular chemical, other routes of exposure may be considered for the development of acute severity levels. For extrapolation from oral to inhalation exposures, methodology presented by U.S.EPA (1994a) should be used (see the Acute Toxicity Summary for carbon tetrachloride, Appendix C, as an example).

4. Summary of toxic effects: Toxic effects are described for relevant endpoints. Where possible, all of the following attributes are mentioned: endpoint, test species, concentration or dose, duration and frequency of exposure, type of effect level (such as NOAEL), reversibility of findings, uncertainty factors applied, and acute severity levels calculated. Endpoints of toxicity testing include, but are not restricted to, lethality, upper and lower respiratory effects, including mucous membrane irritation, and systemic effects. Results from studies on a chemical's mutagenicity, reproductive and developmental toxicity and immunotoxicity are also mentioned, where appropriate.

5. Pharmacokinetics and metabolism: A brief discussion of pharmacokinetics is included if information is available. This may include significant routes of absorption, distribution, metabolism, and excretion. The inhalation route of exposure is examined preferentially. Metabolites of the parent compound are identified.

6. Other planning levels: Inhalation exposure levels from other sources, such as TLVs, EEGLs, SPEGLs, and IDLHs are examined. It is important to compare acute severity levels developed by OEHHA with existing values as a quality assurance measure and also to determine whether the use of other existing guidelines might lead air pollution control officers and planners into predicting that exposures are safe at potentially toxic concentrations. The most scientifically valid and health-protective level is generally recommended by OEHHA; however, a discussion of the strengths and weaknesses of each existing level is not included in the toxicity summaries.

7. Quality assurance measures: Weak or conflicting data are reviewed. Studies are evaluated for any recognized violations of sound laboratory or statistical practices. Any study with significant flaws is not used to justify RELs or acute exposure levels.

8. Sources of data: In the absence of well-documented experimental dose-response studies in humans, reliance on toxicological data from animal studies and human data from workplace and other accidental exposures is appropriate. In addition, *in vitro* toxicity studies are consulted.

9. References: If a complete literature database search is available for a chemical but only a few were used for the acute toxicology summaries, only the latter are cited in the document; however, the complete reference list will be made available on request. OEHHA has completed literature searches for all of the chemicals for which acute RELs were developed in this document.

5.0 Areas for Further Research

- There are a number of chemicals lacking adequate data on acute toxicity. While we were able to develop RELs for the 51 compounds in this document, we could not develop levels protective against severe adverse effects or life-threatening effects in a number of instances due to the limitations of the database. The following chemicals fall into that category: acrolein; acrylic acid; inorganic arsenic compounds; benzyl chloride; chloroform; chloropicrin; copper compounds; dioxane; epichlorohydrin; ethylene glycol monobutyl ether; ethylene glycol monoethyl ether acetate; hydrogen sulfide; isopropyl alcohol; inorganic mercury compounds; methanol; methyl chloroform; methylene chloride; inorganic nickel compounds; nitric acid, ozone; perchloroethylene; phenol phosgene; propylene oxide; selenium compounds; sodium hydroxide; sulfates, sulfur dioxide; sulfuric acid; toluene; triethylamine; vanadium pentoxide; xylenes. Research is needed to adequately characterize the full-spectrum of effects following acute exposure of these substances.

- There are about 450 chemicals on the Air Toxics Hot Spots list of substances to be quantified (Appendix B). This is the list of substances which facilities must report in their emissions inventories. We have to date only evaluated information on 52 of these compounds and developed acute RELs for 51 of these compounds. While not all of the 450 chemicals have reported emissions in California, more work needs to be done in analyzing available literature for the remaining compounds.

- The application of uncertainty factors to account for extrapolation from a LOAEL to a NOAEL warrants further analysis. When evaluating dose-response relationships, the slope of the dose-response curve determines the distance between the LOAEL and the NOAEL from a particular study. Some endpoints tend to have steep dose-response slopes and may not warrant a 10-fold uncertainty factor to extrapolate from a LOAEL to a NOAEL; other endpoints have a shallow dose-response slope and may warrant a 10-fold (or higher) uncertainty factor for extrapolating from the LOAEL to the NOAEL. In this document, we

have used an intermediate uncertainty factor of 6 to extrapolate from the LOAEL to a NOAEL for mild irritation and a factor of 3 for that extrapolation for lethality. This is based on an analysis of the distribution of the LOAEL to NOAEL ratios for 112 datasets. If further analysis suggests revisions of the UF, it will be revised in future acute REL updates. With further analysis, we may also be able to adjust the uncertainty factor for this extrapolation for other toxicological endpoints.

- A related issue is the application of subchronic or repeated exposure studies to evaluating acute toxicity. We have not used subchronic exposures routinely to evaluate acute toxicity RELs. In addition, there are issues such as cumulative tissue injury that may be seen with repeated exposures that impact the quantitative analysis of acute toxicity. Further research into these areas is warranted.

- An interspecies factor of 10 is commonly used to extrapolate from animal studies to the human response. In some cases, there may be reason that a smaller uncertainty factor could be used. For example, in lethality studies, the exposure to irritant chemicals producing lung edema may have very similar dose-response slopes because the basic loss of cellular integrity at high doses is not a phenomenon that would be very different from one species to another. The available analyses supporting use of the 10-fold interspecies uncertainty factor were conducted on studies of toxicity by the oral route of administration. Further analysis of available data on chemicals for which there is both human and animal data for the same endpoints, and by the inhalation route of exposure is warranted. In addition, the existing analyses are limited in terms of toxicological endpoints examined. Interspecies variability may differ significantly for different toxicological endpoints. This is another area where research is needed.

- The uncertainty factor typically used to account for intraspecies (interindividual) variability in the human population is 10. Interindividual variability has been recently modeled indicating a distribution that ranges from 1 to 720 for a specified set of chemicals (Gillis *et al*., 1997). The value of 10 represented the 85^{th} percentile in this analysis. Further research into the factors contributing to interindividual variability, better characterization of sensitive subpopulations, and endpoints characterized by large interindividual variability is warranted. Furthermore, the degree of protection of infants and children, a sensitive subpopulation by virtue of both increased exposure and potential increased susceptibility, afforded by a 10-fold interindividual uncertainty factor needs more research.

- We have used time extrapolation with a modified Haber's Law to extrapolate from the experimental duration in the acute study to an equivalent concentration for a one-hour exposure. There are empirical data for the value of n in Haber's equation for some chemicals. More data would be valuable for additional chemicals. Further analysis of the validity of the Haber's Law application for different toxicological endpoints such as irritation would also be useful.

- We currently use an additive approach to assessing the impacts of multiple chemicals on a target organ. Some interactions may be synergistic and others antagonistic. There is a need

for key studies on the additivity or synergism of chemicals that act on the same target organ. Further literature evaluation would also be helpful to elucidate whether the additive approach is the most valid approach.

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Appendix A

Acute Reference Exposure Levels Summary Table

and Table of Hazard Index Target Organs

Table A-1. Acute Reference Exposure Levels (RELs), Averaging Times, and Toxicologic Endpoints

Chemical Name (CAS #)	REL ($\mu g/m^3$)	Avg time (h)	Sp.[1]	Toxicologic Endpoints	Severity[2]
Acrolein (107-02-8)	1.9×10^{-1}	1	H	Eye Irritation	Mild
Acrylic Acid (79-10-7)	6×10^{3}	1	R	Respiratory Irritation	Mild
Ammonia (7664-41-7)	3.2×10^{3}	1	H	Eye and Respiratory Irritation	Mild
Arsenic and Inorganic Arsenic Compounds	1.9×10^{-1}	4	M	Reproductive/Developmental	Severe
Arsine (7784-42-1)	1.6×10^{2}	1	M	Hematologic System	Severe
Benzene (71-43-2)	1.3×10^{3}	6	R	Reproductive/developmental	Severe
Benzyl Chloride (100-44-7)	2.4×10^{2}	1	M& R	Eye and Respiratory Irritation	Mild
Carbon Disulfide (75-15-0)	6.2×10^{3}	6	R	Reproductive/Developmental	Severe
Carbon Monoxide[3] (630-08-0)	2.3×10^{4}	1	H	Cardiovascular System	Mild
Carbon Tetrachloride (56-23-5)	1.9×10^{3}	7	R	Reproductive/Developmental	Severe
Chlorine (7782-50-5)	2.1×10^{2}	1	H	Respiratory Irritation	Mild
Chloroform (67-66-3)	1.5×10^{2}	7	R	Reproductive/Developmental	Severe
Chloropicrin (76-06-2)	2.9×10^{1}	1	M	Eye and Respiratory Irritation	Mild
Copper and Compounds	1×10^{2}	1	H	Respiratory Irritation	Mild
1,4-Dioxane (123-91-1)	3×10^{3}	1	H	Eye and Respiratory Irritation	Mild
Epichlorohydrin (106-89-8)	1.3×10^{3}	1	H	Eye and Respiratory Irritation	Mild
Ethylene Glycol Monobutyl Ether (111-76-2)	1.4×10^{4}	1	H	Eye and Respiratory Irritation	Mild
Ethylene Glycol Monoethyl Ether (110-80-5)	3.7×10^{2}	6	R	Reproductive/Developmental	Severe
Ethylene Glycol Monoethyl Ether Acetate (111-15-9)	1.4×10^{2}	6	Rb	Reproductive/Developmental	Severe
Ethylene Glycol Monomethyl Ether (109-86-4)	9.3×10^{1}	6	R	Reproductive/Developmental	Severe
Formaldehyde (50-00-0)	9.4×10^{1}	1	H	Eye Irritation	Mild
Hydrogen chloride (7647-01-0)	2.1×10^{3}	1	H	Eye and Respiratory Irritation	Mild
Hydrogen Cyanide (74-90-8)	3.4×10^{2}	1	Mk	CNS[4] - serious	Severe
Hydrogen Fluoride (7664-39-3)	2.4×10^{2}	1	H	Eye and Respiratory Irritation	Mild
Hydrogen Selenide	5×10^{0}	1	GP	Eye and Respiratory Irritation	Mild
Hydrogen Sulfide (7783-06-4)[3]	4.2×10^{1}	1	H	Respiratory Irritation	Mild
Isopropyl Alcohol (67-63-0)	3.2×10^{3}	1	H	Eye and Respiratory Irritation	Mild
Mercury (Inorganic) (7439-97-6)	1.8×10^{0}	1	R	Reproductive/Developmental	Severe
Methanol (67-56-1)	2.8×10^{4}	1	H	CNS[4] - mild	Mild
Methyl Bromide (74-83-9)	3.9×10^{3}	1	H	CNS- mild (anorexia, nausea, headache;	Mild
Methyl Chloroform (71-55-6)	6.8×10^{4}	1	H	CNS - mild	Mild
Methyl Ethyl Ketone (78-93-3)	1.3×10^{4}	1	H	Eye and Respiratory Irritation	Mild
Methylene Chloride (75-9-2)	1.4×10^{4}	1	H	CNS - mild	Mild

Chemical Name (CAS #)	REL ($\mu g/m^3$)	Avg time (h)	Sp.[1]	Toxicologic Endpoints	Severity[2]
Nickel and Nickel Compounds	6×10^0	1	H	Respiratory Irritation; Immune Response	Mild
Nitric Acid (7697-37-2)	8.6×10^1	1	H	Respiratory Irritation	Mild
Nitrogen Dioxide[3] (10102-44-0)	4.7×10^2	1	H	Respiratory Irritation	Mild
Ozone[3] (10028-15-6)	1.8×10^2	1	H	Eye and Respiratory Irritation	Mild
Perchloroethylene (127-18-4)	2×10^4	1	H	CNS - mild; Eye and Respiratory Irritation	Mild
Phenol (108-95-2)	5.8×10^3	1	H	Eye and Respiratory Irritation	Mild
Phosgene (75-44-5)	4×10^0	1	R	Respiratory Irritation	Mild
Propylene Oxide (75-56-9)	3.1×10^3	1	M	Eye and Respiratory Irritation	Mild
Sodium Hydroxide (1310-93-2)	8×10^0	1	H	Skin, Eye, and Respiratory Irritation	Mild
Styrene (100-42-5)	2.1×10^4	1	H	Eye and Respiratory Irritation	Mild
Sulfates[3]	1.2×10^2	1	H	Respiratory Irritation	Mild
Sulfur Dioxide[3] (7446-09-5)	6.6×10^2	1	H	Respiratory Irritation	Mild
Sulfuric Acid and Oleum	1.2×10^2	1	H	Respiratory Irritation	Mild
Toluene (108-88-3)	3.7×10^4	1	H	CNS - mild; Eye and Respiratory Irritation	Mild
Triethylamine (121-44-8)	2.8×10^3	1	H	CNS - mild; Eye Irritation	Mild
Vanadium Pentoxide (1314-62-1)	3×10^1	1	H	Respiratory Irritation	Mild
Vinyl Chloride (75-01-4)	1.8×10^5	1	H	CNS - mild; Eye and Respiratory Irritation	Mild
Xylenes (m,o,p-isomers)	2.2×10^4	1	H	Eye and Respiratory Irritation	Mild

[1] Species used in key study for REL development: D = dog; GP = guinea pig: H = human; M = mouse; Mk = monkey; R = rat; Rb = rabbit

[2] Refers to effect severity levels-- see Hazard Identification section of main text or Table 6

[3] California Ambient Air Quality Standard

[4] CNS = Central Nervous System.

Table A-2. Hazard Index Target Organs

Chemical Name (CAS #)	Target Organs
Acrolein (107-02-8)	Respiratory System; Eye
Acrylic Acid (79-10-7)	Respiratory System; Eye
Ammonia (7664-41-7)	Respiratory System; Eye
Arsenic and Inorganic Arsenic Compounds	Reproductive/Developmental
Arsine (7784-42-1)	Hematologic System
Benzene (71-43-2)	Reproductive/developmental; Immune System; Hematologic System;
Benzyl Chloride (100-44-7)	Respiratory System; Eye
Carbon Disulfide (75-15-0)	Reproductive/Developmental; Nervous System
Carbon Monoxide (630-08-0)	Cardiovascular System
Carbon Tetrachloride (56-23-5)	Reproductive/Developmental; Nervous System; Alimentary Tract
Chlorine (7782-50-5)	Respiratory System; Eye
Chloroform (67-66-3)	Nervous System; Reproductive/Developmental
Chloropicrin (76-06-2)	Respiratory System; Eye
Copper and Compounds	Respiratory System
1,4-Dioxane (123-91-1)	Respiratory System; Eye
Epichlorohydrin (106-89-8)	Respiratory System; Eye
Ethylene Glycol Monobutyl Ether (111-76-2)	Respiratory System; Eye
Ethylene Glycol Monoethyl Ether (110-80-5)	Reproductive/Developmental
Ethylene Glycol Monoethyl Ether Acetate (111-15-9)	Reproductive/Developmental; Nervous System
Ethylene Glycol Monomethyl Ether (109-86-4)	Reproductive/Developmental
Formaldehyde (50-00-0)	Eye; Respiratory System; Immune System
Hydrogen Chloride (7647-01-0)	Respiratory System; Eye
Hydrogen Cyanide (74-90-8)	Nervous System
Hydrogen Fluoride (7664-39-3)	Respiratory System; Eye
Hydrogen Sulfide (7783-06-4)	Headache and Nausea in Response to Odor
Isopropyl Alcohol (67-63-0)	Respiratory System; Eye
Mercury (Inorganic) (7439-97-6)	Reproductive/Developmental
Methanol (67-56-1)	Nervous System

Chemical Name (CAS #)	Target Organs
Methyl Bromide (74-83-9)	Nervous System; Respiratory Irritation; Reproductive/developmental
Methyl Chloroform (71-55-6)	Nervous System
Methyl Ethyl Ketone (78-93-3)	Respiratory System; Eye
Methylene Chloride (75-9-2)	Nervous System
Nickel and Nickel Compounds	Respiratory System; Immune System
Nitric Acid (7697-37-2)	Respiratory System
Nitrogen Dioxide (10102-44-0)	Respiratory System
Ozone (10028-15-6)	Eye; Respiratory System
Perchloroethylene (127-18-4)	Nervous system; Eye; Respiratory System
Phenol (108-95-2)	Respiratory System; Eye
Phosgene (75-44-5)	Respiratory System
Propylene Oxide (75-56-9)	Respiratory System; Eye; Reproductive/developmental
Selenium: He_2S	Respiratory System; Eye
Sodium Hydroxide (1310-93-2)	Eye; Skin; Respiratory System
Styrene (100-42-5)	Respiratory System; Eye;
Sulfates	Respiratory System
Sulfur Dioxide (7446-09-5)	Respiratory System
Sulfuric Acid and Oleum	Respiratory System
Toluene (108-88-3)	Nervous System; Eye; Respiratory System; Reproductive/developmental??
Triethylamine (121-44-8)	Nervous System; Eye
Vanadium Pentoxide (1314-62-1)	Respiratory System; Eye
Vinyl Chloride (75-01-4)	Nervous System; Eye; Respiratory System
Xylenes (m,o,p-isomers)	Eye; Respiratory System

Appendix B

Substances Listed Under the Air Toxics Hot Spots Act for Which Emissions Must be Quantified

Appendix B

Substances for which Emissions Must Be Quantified

75070	Acetaldehyde
60355	Acetamide
67641	Acetone
75058	Acetonitrile
98862	Acetophenone
53963	2-Acetylaminofluorene [PAH-Derivative, POM]
107028	Acrolein
79061	Acrylamide
79107	Acrylic acid
107131	Acrylonitrile
107051	Allyl chloride
7429905	Aluminum
1344281	Aluminum oxide (fibrous forms)
117793	2-Aminoanthraquinone [PAH-Derivative, POM]
92671	4-Aminobiphenyl [POM]
61825	Amitrole
7664417	Ammonia
6484522	Ammonium nitrate
7783202	Ammonium sulfate
62533	Aniline
90040	o-Anisidine
-	Anthracene [PAH, POM], (see PAH)
7440360	Antimony
*	Antimony compounds
	including but not limited to:
1309644	Antimony trioxide
7440382	Arsenic
1016	Arsenic compounds (inorganic)
	including but not limited to:
7784421	Arsine
1017	Arsenic compounds (other than inorganic)
7440393	Barium
*	Barium compounds
-	Benz[a]anthracene [PAH, POM], (see PAH)
71432	Benzene
92875	Benzidine (and its salts) [POM]
1020	Benzidine-based dyes [POM]
	including but not limited to:
1937377	Direct Black 38 [PAH-Derivative, POM]
2602462	Direct Blue 6 [PAH-Derivative, POM]
16071866	Direct Brown 95 (technical grade) [POM]
-	**Benzo[a]pyrene [PAH, POM], (see PAH)**
-	Benzo[b]fluoranthene [PAH, POM], (see PAH)
271896	Benzofuran
98077	Benzoic trichloride {Benzotrichloride}
-	Benzo[j]fluoranthene [PAH, POM], (see PAH)
-	Benzo[k]fluoranthene [PAH, POM], (see PAH)
98884	Benzoyl chloride
94360	Benzoyl peroxide
100447	Benzyl chloride
7440417	Beryllium
*	Beryllium compounds
92524	Biphenyl [POM]
111444	Bis(2-chloroethyl) ether {DCEE}
542881	Bis(chloromethyl) ether
103231	Bis(2-ethylhexyl) adipate
7726956	Bromine
*	Bromine compounds (inorganic)
	including but not limited to:
7758012	Potassium bromate
75252	Bromoform
106990	1,3-Butadiene
141322	Butyl acrylate
71363	n-Butyl alcohol
78922	sec-Butyl alcohol
75650	tert-Butyl alcohol
85687	Butyl benzyl phthalate
7440439	Cadmium
*	Cadmium compounds
156627	Calcium cyanamide
105602	Caprolactam

2425061	Captafol
133062	Captan
63252	Carbaryl [PAH-Derivative, POM]
1050	Carbon black extracts
75150	Carbon disulfide
56235	Carbon tetrachloride
463581	Carbonyl sulfide
1055	Carrageenan (degraded)
120809	Catechol
133904	Chloramben
56757	Chloramphenicol
57749	Chlordane
108171262	Chlorinated paraffins (average chain length, C12; approximately 60% chlorine by weight)
7782505	Chlorine
10049044	Chlorine dioxide
79118	Chloroacetic acid
532274	2-Chloroacetophenone
1058	Chlorobenzenes
	including but not limited to:
108907	Chlorobenzene
25321226	Dichlorobenzenes (mixed isomers)
	including:
95501	1,2-Dichlorobenzene
541731	1,3-Dichlorobenzene
106467	p-Dichlorobenzene {1,4-Dichlorobenzene}
120821	1,2,4-Trichlorobenzene
510156	Chlorobenzilate [POM] {Ethyl-4,4'-dichlorobenzilate}
13909096	1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea {Methyl CCNU}
67663	Chloroform
107302	Chloromethyl methyl ether (technical grade)
1060	Chlorophenols
	including but not limited to:
120832	2,4-Dichlorophenol
87865	Pentachlorophenol
95954	2,4,5-Trichlorophenol
88062	2,4,6-Trichlorophenol
95830	4-Chloro-o-phenylenediamine
76062	Chloropicrin
126998	Chloroprene
95692	p-Chloro-o-toluidine
7440473	**Chromium**
*	Chromium compounds (other than hexavalent)
18540299	Chromium, hexavalent (and compounds)
	including but not limited to:
10294403	Barium chromate
13765190	Calcium chromate
1333820	Chromium trioxide
7758976	Lead chromate
10588019	Sodium dichromate
7789062	Strontium chromate
-	Chrysene [PAH, POM], (see PAH)
7440484	Cobalt
*	Cobalt compounds
1066	Coke oven emissions
7440508	Copper
*	Copper compounds
1070	Creosotes
120718	p-Cresidine
1319773	Cresols (mixtures of) {Cresylic acid}
	including:
108394	m-Cresol
95487	o-Cresol
106445	p-Cresol
98828	Cumene
80159	Cumene hydroperoxide
135206	Cupferron
1073	Cyanide compounds
	including but not limited to:
74908	Hydrocyanic acid
110827	Cyclohexane
66819	Cycloheximide
1163195	Decabromodiphenyl oxide [POM]
1075	**Dialkylnitrosamines**
	including but not limited to:
924163	N-Nitrosodi-n-butylamine
1116547	N-Nitrosodiethanolamine
55185	N-Nitrosodiethylamine
62759	N-Nitrosodimethylamine

621647	N-Nitrosodi-n-propylamine
10595956	N-Nitrosomethylethylamine
615054	2,4-Diaminoanisole
1078	Diaminotoluenes (mixed isomers) including but not limited to:
95807	2,4-Diaminotoluene {2,4-Toluenediamine}
334883	Diazomethane
226368	Dibenz[a,h]acridine [POM]
224420	Dibenz[a,j]acridine [POM]
-	Dibenz[a,h]anthracene [PAH, POM], (see PAH)
194592	7H-Dibenzo[c,g]carbazole
-	Dibenzo[a,e]pyrene [PAH, POM], (see PAH)
-	Dibenzo[a,h]pyrene [PAH, POM], (see PAH)
-	Dibenzo[a,i]pyrene [PAH, POM], (see PAH)
-	Dibenzo[a,l]pyrene [PAH, POM], (see PAH)
132649	**Dibenzofuran [POM]**
-	Dibenzofurans (chlorinated) (see Polychlorinated dibenzofurans) [POM]
96128	1,2-Dibromo-3-chloropropane {DBCP}
84742	Dibutyl phthalate
-	p-Dichlorobenzene {1,4-Dichlorobenzene} (see Chlorobenzenes)
91941	3,3'-Dichlorobenzidine [POM]
72559	Dichlorodiphenyldichloroethylene {DDE} [POM]
75343	1,1-Dichloroethane {Ethylidene dichloride}
94757	Dichlorophenoxyacetic acid, salts and esters {2,4-D}
78875	1,2-Dichloropropane {Propylene dichloride}
542756	1,3-Dichloropropene
62737	Dichlorovos {DDVP}
115322	Dicofol [POM]
- -	Diesel engine exhaust
9901	Diesel engine exhaust, particulate matter
9902	Diesel engine exhaust, total organic gas
#	Diesel fuel (marine)
111422	Diethanolamine
117817	Di(2-ethylhexyl) phthalate {DEHP}
64675	Diethyl sulfate
119904	3,3'-Dimethoxybenzidine [POM]
60117	4-Dimethylaminoazobenzene [POM]
121697	N,N-Dimethylaniline
57976	7,12-Dimethylbenz[a]anthracene [PAH-Derivative, POM]
119937	3,3'-Dimethylbenzidine {o-Tolidine} [POM]
79447	Dimethyl carbamoyl chloride
68122	Dimethyl formamide
57147	1,1-Dimethylhydrazine
131113	Dimethyl phthalate
77781	Dimethyl sulfate
534521	4,6-Dinitro-o-cresol (and salts)
51285	2,4-Dinitrophenol
42397648	1,6-Dinitropyrene [PAH-Derivative, POM]
42397659	1,8-Dinitropyrene [PAH-Derivative, POM]
25321146	Dinitrotoluenes (mixed isomers) including but not limited to:
121142	--2,4-Dinitrotoluene
606202	--2,6-Dinitrotoluene
123911	1,4-Dioxane
-	Dioxins (Chlorinated dibenzodioxins) (see Polychlorinated dibenzo-p-dioxins) [POM]
630933	Diphenylhydantoin [POM]
122667	1,2-Diphenylhydrazine {Hydrazobenzene} [POM]
1090	Environmental Tobacco Smoke
106898	Epichlorohydrin
106887	1,2-Epoxybutane
1091	Epoxy resins
140885	Ethyl acrylate
100414	Ethyl benzene
75003	Ethyl chloride {Chloroethane}
-	Ethyl-4,4'-dichlorobenzilate (see Chlorobenzilate)
74851	Ethylene
106934	Ethylene dibromide {1,2-Dibromoethane}
107062	Ethylene dichloride {1,2-Dichloroethane}
107211	Ethylene glycol
151564	Ethyleneimine {Aziridine}
75218	Ethylene oxide
96457	Ethylene thiourea
1101	Fluorides and compounds including but not limited to:
7664393	Hydrogen fluoride
1103	Fluorocarbons (brominated)

1104	Fluorocarbons (chlorinated)
	including but not limited to:
76131	Chlorinated fluorocarbon {CFC-113}
50000	Formaldehyde
- -	Gasoline engine exhaust
	including but not limited to:
- -	Gasoline engine exhaust (condensates & extracts)
9910	Gasoline engine exhaust, particulate matter
9911	Gasoline engine exhaust, total organic gas
1110	Gasoline vapors
111308	Glutaraldehyde
1115	Glycol ethers and their acetates
	including but not limited to:
111466	Diethylene glycol
111966	Diethylene glycol dimethyl ether
112345	Diethylene glycol monobutyl ether
111900	Diethylene glycol monoethyl ether
111773	Diethylene glycol monomethyl ether
25265718	Dipropylene glycol
34590948	Dipropylene glycol monomethyl ether
629141	Ethylene glycol diethyl ether
110714	Ethylene glycol dimethyl ether
111762	Ethylene glycol monobutyl ether
110805	Ethylene glycol monoethyl ether
111159	Ethylene glycol monoethyl ether acetate
109864	Ethylene glycol monomethyl ether
110496	Ethylene glycol monomethyl ether acetate
2807309	Ethylene glycol monopropyl ether
107982	Propylene glycol monomethyl ether
108656	Propylene glycol monomethyl ether acetate
112492	Triethylene glycol dimethyl ether
126078	Griseofulvin
76448	Heptachlor
118741	Hexachlorobenzene
87683	Hexachlorobutadiene
1120	Hexachlorocyclohexanes
	including but not limited to:
58899	Lindane
77474	Hexachlorocyclopentadiene
67721	Hexachloroethane
680319	Hexamethylphosphoramide
110543	Hexane
302012	Hydrazine
7647010	Hydrochloric acid
-	Hydrocyanic acid (see Cyanide compounds)
7783064	Hydrogen sulfide
123319	Hydroquinone
-	Indeno[1,2,3-cd]pyrene [PAH, POM], (see PAH)
1125	Isocyanates
	including but not limited to:
822060	Hexamethylene-1,6-diisocyanate
101688	Methylene diphenyl diisocyanate {MDI} [POM]
624839	Methyl isocyanate
-	Toluene-2,4-diisocyanate (see Toluene diisocyanates)
-	Toluene-2,6-diisocyanate (see Toluene diisocyanates)
78591	Isophorone
67630	Isopropyl alcohol
80057	4,4'-Isopropylidenediphenol [POM]
7439921	Lead
1128	Lead compounds (inorganic)
	including but not limited to:
301042	Lead acetate
-	Lead chromate (see Chromium, hexavalent)
7446277	Lead phosphate
1335326	Lead subacetate
1129	Lead compounds (other than inorganic)
108316	Maleic anhydride
7439965	Manganese
*	Manganese compounds
7439976	Mercury
*	Mercury compounds
	including but not limited to:
7487947	Mercuric chloride
593748	Methyl mercury {Dimethylmercury}
67561	Methanol
72435	Methoxychlor [POM]
75558	2-Methylaziridine {1,2-Propyleneimine}
74839	Methyl bromide {Bromomethane}
74873	Methyl chloride {Chloromethane}
71556	Methyl chloroform {1,1,1-Trichloroethane}
56495	3-Methylcholanthrene [PAH-Derivative, POM]

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 3697243  5-Methylchrysene [PAH-Derivative, POM]
  101144  4,4'-Methylene bis(2-chloroaniline) {MOCA} [POM]
   75092  Methylene chloride {Dichloromethane}
  101779  4,4'-Methylenedianiline (and its dichloride) [POM]
   78933  Methyl ethyl ketone {2-Butanone}
   60344  Methyl hydrazine
   74884  Methyl iodide {Iodomethane}
  108101  Methyl isobutyl ketone {Hexone}
   80626  Methyl methacrylate
 1634044  Methyl tert-butyl ether
  443481  Metronidazole
   90948  Michler's ketone [POM]
    1136  Mineral fibers (fine, manmade)
            (fine mineral fibers which are manmade and are
            airborne particles of a respirable size greater
            than 5 microns in length, less than or equal to
            3.5 microns in diameter, with a length to
            diameter ratio of 3:1)
          including but not limited to:
    1056    Ceramic fibers
    1111    Glasswool fibers
    1168    Rockwool fibers
    1181    Slagwool fibers
    1135  Mineral fibers (other than manmade)
          including but not limited to:
 1332214    Asbestos
12510428    Erionite
    1190     Talc containing asbestiform fibers
 1313275  Molybdenum trioxide
       -  Naphthalene [PAH, POM], (see PAH)
 7440020  Nickel
       *  Nickel compounds
          including but not limited to:
  373024    Nickel acetate
 3333393    Nickel carbonate
13463393    Nickel carbonyl
12054487    Nickel hydroxide
 1271289    Nickelocene
 1313991    Nickel oxide
12035722    Nickel subsulfide
    1146  Nickel refinery dust from the pyrometallurgical
          process
   61574  Niridazole
 7697372  Nitric acid
  139139  Nitrilotriacetic acid
   98953  Nitrobenzene
   92933  4-Nitrobiphenyl [POM]
 7496028  6-Nitrochrysene [PAH-Derivative, POM]
  607578  2-Nitrofluorene [PAH-Derivative, POM]
  302705  Nitrogen mustard N-oxide
  100027  4-Nitrophenol
   79469  2-Nitropropane
 5522430  1-Nitropyrene [PAH-Derivative, POM]
  156105  p-Nitrosodiphenylamine [POM]
  684935  N-Nitroso-N-methylurea
   59892  N-Nitrosomorpholine
  100754  N-Nitrosopiperidine
  930552  N-Nitrosopyrrolidine
      - -  PAHs (Polycyclic aromatic hydrocarbons) [POM]
          including but not limited to:
    1151   PAHs, total, w/o individ. components reported
    1150   PAHs, total, with individ. components also
            reported
  120127    Anthracene
   56553    Benz[a]anthracene
   50328    Benzo[a]pyrene
  205992    Benzo[b]fluoranthene
  205823    Benzo[j]fluoranthene
  207089    Benzo[k]fluoranthene
  218019    Chrysene
   53703    Dibenz[a,h]anthracene
  192654    Dibenzo[a,e]pyrene
  189640    Dibenzo[a,h]pyrene
  189559    Dibenzo[a,i]pyrene
  191300    Dibenzo[a,l]pyrene
  193395    Indeno[1,2,3-cd]pyrene
   91203   Naphthalene
       #  PAH-Derivatives (Polycyclic aromatic hydrocarbon
          derivatives) [POM]
            (including but not limited to those substances
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            listed in Appendix A with the bracketed
            designation [PAH-Derivative, POM])
    56382  Parathion
  1336363  PCBs (Polychlorinated biphenyls) [POM]
    82688  Pentachloronitrobenzene {Quintobenzene}
    79210  Peracetic acid
   127184  Perchloroethylene {Tetrachloroethane}
    50066  Phenobarbital
   108952  Phenol
   106503  p-Phenylenediamine
    90437  2-Phenylphenol [POM]
    75445  Phosgene
  7723140  Phosphorus
      - -  Phosphorus compounds:
  7803512    Phosphine
  7664382    Phosphoric acid
 10025873    Phosphorus oxychloride
 10026138    Phosphorus pentachloride
  1314563    Phosphorus pentoxide
  7719122    Phosphorus trichloride
   126738    Tributyl phosphate
    78400    Triethyl phosphine
   512561    Trimethyl phosphate
    78308    Triorthocresyl phosphate [POM]
   115866    Triphenyl phosphate [POM]
   101020    Triphenyl phosphite [POM]
    85449  Phthalic anhydride
      - -  Polychlorinated dibenzo-p-dioxins {PCDDs or
           Dioxins} [POM]
           including but not limited to:
     1086   Dioxins, total, wo individ. isomers reported
             {PCDDs}
     1085   Dioxins, total, with individ. isomers also
             reported {PCDDs}
  1746016    2,3,7,8-Tetrachlorodibenzo-p-dioxin {TCDD} [POM]
 40321764    1,2,3,7,8-Pentachlorodibenzo-p-dioxin [POM]
 39227286    1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin [POM]
 57653857    1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin [POM]
 19408743    1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin [POM]
 35822469    1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin [POM]
      - -  Polychlorinated dibenzofurans {PCDFs or
           Dibenzofurans} [POM]
           including but not limited to:
     1080   Dibenzofurans (Polychlorinated dibenzofurans)
             {PCDFs} [POM]
 51207319    2,3,7,8-Tetrachlorodibenzofuran [POM]
 57117416    1,2,3,7,8-Pentachlorodibenzofuran [POM]
 57117314    2,3,4,7,8-Pentachlorodibenzofuran [POM]
 70648269    1,2,3,4,7,8-Hexachlorodibenzofuran [POM]
 57117449    1,2,3,6,7,8-Hexachlorodibenzofuran [POM]
 72918219    1,2,3,7,8,9-Hexachlorodibenzofuran [POM]
 60851345    2,3,4,6,7,8-Hexachlorodibenzofuran [POM]
 67562394    1,2,3,4,6,7,8-Heptachlorodibenzofuran [POM]
 55673897    1,2,3,4,7,8,9-Heptachlorodibenzofuran [POM]
        #  POM (Polycyclic organic matter)
            (including but not limited to those substances
            listed in Appendix A with the bracketed
            designation of [POM], [PAH, POM], or
            [PAH-Derivative, POM])
    57830  Progesterone
  1120714  1,3-Propane sultone
    57578  beta-Propiolactone
   123386  Propionaldehyde
   114261  Propoxur {Baygon}
   115071  Propylene
    75569  Propylene oxide
        -  1,2-Propyleneimine (see 2-Methylaziridine)
   110861  Pyridine
    91225  Quinoline
   106514  Quinone
     1165  Radionuclides
           including but not limited to:
 24267569    Iodine-131
     1166    Radon and its decay products
    50555  Reserpine [POM]
        #  Residual (heavy) fuel oils
  7782492  Selenium
        *  Selenium compounds
           including but not limited to:
  7446346    Selenium sulfide
     1175  Silica, crystalline
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7440224  Silver
      *  Silver compounds
1310732  Sodium hydroxide
 100425  Styrene
  96093  Styrene oxide
7664939  Sulfuric acid
 100210  Terephthalic acid
  79345  1,1,2,2-Tetrachloroethane
7440280  Thallium
      *  Thallium compounds
  62555  Thioacetamide
  62566  Thiourea
7550450  Titanium tetrachloride
 108883  Toluene
      -  2,4-Toluenediamine (see 2,4-Diaminotoluene)
   1204  Toluene diisocyanates
         including but not limited to:
 584849    Toluene-2,4-diisocyanate
  91087    Toluene-2,6-diisocyanate
  95534  o-Toluidine
8001352  Toxaphene {Polychlorinated camphenes}
  79005  1,1,2-Trichloroethane {Vinyl trichloride}
      -  1,1,1-Trichloroethane (see Methyl chloroform)
  79016  Trichloroethylene
      -  2,4,6-Trichlorophenol (see Chlorophenols)
 121448  Triethylamine
1582098  Trifluralin
  95636  1,2,4-Trimethylbenzene
 540841  2,2,4-Trimethylpentane
  51796  Urethane {Ethyl carbamate}
7440622  Vanadium (fume or dust)
 108054  Vinyl acetate
 593602  Vinyl bromide
  75014  Vinyl chloride
  75354  Vinylidene chloride
   1206  Wood preservatives (containing arsenic and
   1210  Xylenes (mixed xylenes)
         including:
 108383    m-Xylene
  95476    o-Xylene
 106423    p-Xylene
7440666  Zinc
      *  Zinc compounds
         including but not limited to:
1314132    Zinc oxide
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