Air Toxics Hot Spots Program
Risk Assessment Guidelines

Part III
Technical Support Document
for the Determination of

Noncancer Chronic Reference Exposure Levels

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DETERMINATION OF NONCANCER CHRONIC REFERENCE EXPOSURE LEVELS

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Table of Contents

1. Introduction…… 5
1.1 Objective…… 5
1.2 Implementation of Risk Assessment Committee (RAAC) Recommendations…….. 6
1.3 Priority for Evaluation of Chemicals…….. 8
1.4 Criteria for Development of Chronic Reference Exposure Levels…… 8
1.5 Population of Concern……..…… 9
1.6 Exposure Concentration Averaging Period ……..…….. 10
1.7 Effects of Multiple Chemical Exposures …… 10
1.8 Preexisting Exposure Guidelines …… 11
1.8.1 U.S. EPA Reference Concentrations …… 11
1.8.2 U.S. EPA Reference Doses …… 11
1.8.3 Occupational Threshold Limit Values …… 11
1.8.4 California Ambient Air Quality Standards…….. 12
2. Hazard Identification…….. 12
2.1 Selection of Key Studies…….. 12
2.1.1 Human Data…… 12
2.1.2 Animal Data…… 14
2.2 Weight of Evidence…… 14
2.2.1 Strength of Associated Adverse Health Effect…… 14
2.2.2 Consistency of Associated Adverse Health Effect…….. 15
2.2.3 Specificity of Associated Adverse Health Effect…… 15
2.2.4 Temporal Association…… 15
2.2.5 Coherence of Adverse Health Effect…… 15
3. Dose Response Assessment…… 15
3.1 Estimation of Threshold or Low Response Concentrations…… 15
3.1.1 Use of No-Observed-Adverse-Effect-Levels (NOEL) …… 15
3.1.2 Use of Lowest-Observed-Adverse-Effect-Levels (LOAEL) …… 16
3.1.3 Estimation of a Benchmark Concentration (BMC) …… 17
3.2 Overview of Extrapolation from Study Data to Human Population…… 19
3.3 Effects of Exposure Continuity and Duration…….. 19
3.3.1 Differences between Continuous and Discontinuous Exposures…… 19
3.3.2 Differences between Lifetime and Less-than-Lifetime Exposures…… 20
3.4 Differences between Human and Animal Susceptibility to Toxic Effects of Chemicals… 21
3.4.1 Determination of an Human Equivalent Concentration…… 21
3.4.2 Accounting for Potentially Greater Human Susceptibility…… 25
3.5 Increased Susceptibility of Sensitive Individuals…… 26
3.6 Estimation of Inhalation Effects from Oral Exposure Data…… 27
3.7 Summary of Extrapolation and Uncertainty Factors Used to Derive Chronic RELs……. 28
3.8 Documentation of Chronic Reference Exposure Levels…… 28
3.9 Chronic Reference Exposure Level Summary…… 29
4.0 References…… 35

Appendix A Chronic Toxicity Summaries
Appendix B. Chemicals with OEHHA Chronic Reference Exposure Levels
Appendix C. ARB List of Chemicals to be Quantified
Appendix D. Table of Inhalation Chronic RELs and Hazard Index Target(s)

1. Introduction

Hazardous substances are routinely released into the environment due to predictable continuous or intermittent emissions from facilities. As a result, people living or working in communities surrounding such releases may be exposed to airborne toxicants. Local air pollution control officers and industrial facility operators have a need for clear guidance about assessing the chronic health effects of hazardous substances.

The National Academy of Sciences (NAS), through the National Research Council (NRC), recommended that the U.S. EPA more clearly define, and in some cases change, the methods and assumptions used to estimate the health risks of exposure to hazardous air pollutants (NRC, 1994). In particular, NAS has endorsed the development of biologically based quantitative methods for assessing the health effects of chemical exposure. This includes incorporating information on mechanisms of action and variability among populations and between individuals that might affect susceptibility to harm, such as age, lifestyle, genetic background, sex, and ethnicity. NAS acknowledged the continued need for default assumptions to address uncertainties in assessing risks among a population. NAS has recommended that U.S. EPA (1) identify each use of a default assumption in risk assessment; (2) clearly state the scientific and policy basis for each default assumption; and (3) articulate criteria for allowing departure from default assumptions. NAS 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, to identify data gaps, and to develop incentives to expedite the generation of data by other governmental agencies.

The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (Cal/EPA) has followed the NAS recommendations in this document by establishing uniform, science-based guidelines to be used in the estimation of chronic exposure levels to protect the general public from long-term exposure to hazardous substances released into the environment.

1.1 Objective

The objective of this document is to present a method for deriving inhalation exposure levels to protect the public from a lifetime of exposure to hazardous airborne substances. These health-based chronic exposure levels are primarily for risk characterization of routine industrial emissions. The guidelines for developing chronic inhalation exposure levels incorporate many recommendations of the U.S. EPA (1994) and NAS (NRC, 1994).

As defined under the Air Toxics “Hot Spots” Information and Assessment Act of 1987 (California Health and Safety Code Section 44300 *et seq.*), a risk assessment includes a comprehensive analysis of the dispersion of hazardous substances in the environment, 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 (chronic reference exposure levels) used for assessing chronic noncancer risks within the risk assessment process.

In preparing this document, OEHHA is responding to legislation enacted in California in 1992. Senate Bill (SB) 1731 (Statutes of 1992, Chapter 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 Contaminant 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 diversity within human populations and for uncertainty related to the applicability and completeness of the available data. To help meet these requirements, OEHHA developed methods to estimate chronic exposure levels and derived such levels for specific chemicals. The chronic exposure levels are designed for use in the Air Toxics "Hot Spots" Program and the Toxic Air Contaminant Program but may have a variety of applications to related programs.

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. This process includes workshops with the public and review by the Scientific Review Panel on Toxic Air Contaminants administered by the ARB.

The substances listed by the ARB to be quantified under the Air Toxics "Hot Spots" program were evaluated and considered for inclusion in this document. The substances on the Air Toxics "Hot Spots" Program List include those (1) determined to be carcinogenic by the International Agency for Research on Cancer (IARC), (2) listed by the U.S. EPA, including hazardous air pollutants, (3) determined to be hazardous by the U.S. National Toxicology Program (NTP), (4) determined by the ARB to be Toxic Air Contaminants, (5) determined to be hazardous by the State of California Hazard Evaluation System and Information Service, or (6) determined to be carcinogens or reproductive toxicants by the State of California under Proposition 65. The complete list of substances that must be quantified is contained in Appendix C of this document.

Other programs or agencies may also require review or development of chronic exposure levels for other mandated or regulatory purposes. The methods described in this Technical Support Document may be used in deriving these levels.

1.2 Implementation of Risk Assessment Advisory Committee (RAAC) Recommendations

The Cal/EPA RAAC is 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 has issued a report on its findings (RAAC, 1996). In the completion of this document, the RAAC recommendations were carefully considered.

In general, the committee recommendations were well addressed (Table 1). Complete implementation of all committee recommendations will require additional efforts 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.

Table 1. Implementation of RAAC Recommendations

RAAC Recommendation	*Implementation*
Formalized peer review program	This document is being reviewed by an advisory committee of non-governmental scientists (the state's Scientific Review Panel on Toxic Air Contaminants).
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 and by representatives of the Air Quality Management and Air Pollution Control Districts. A public comment period was held in October 1997. This version of the document will be distributed for comment to others, including external stakeholders.
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 and other authoritative bodies.
Coordinate effort with U.S. EPA	The project made use of all available risk assessment information from U.S. EPA. All U.S. EPA Reference Concentrations (RfCs) were adopted which were available in May 1996. Later RfCs are being evaluated on a case-by-case basis. U.S. EPA RfC and U.S. EPA Reference Dose (RfD) methods were followed in the development of new proposed RELs.
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 (3-fold) LOAEL uncertainty factors for the latter effects. Additional research will be needed to implement more sophisticated approaches to this problem.

1.3 Priority for Evaluation of Chemicals

The 95 chemicals for which chronic noncancer reference exposure levels (RELs) appeared in the California Air Pollution Control Officers Association (CAPCOA) Air Toxics "Hot Spots" Program (Revised 1992) Risk Assessment Guidelines (CAPCOA, 1993) were considered for evaluation. Additional chemicals were selected from the ARB list of Hot Spots substances for which emissions need to be quantified. These substances were selected primarily based on (1) the magnitude of current known emissions in California and (2) the availability of a strong scientific database on which to estimate a chronic REL. The combined list of the 118 substances that have been evaluated with the methods delineated in this Technical Support Document is provided in Appendix B. Chronic RELs for an additional three substances, acetaldehyde, diesel exhaust particulate, and perchloroethylene, have already been reviewed by the Scientific Review Panel and adopted by the ARB.

1.4 Criteria for Development of Chronic Reference Exposure Levels

Chronic reference exposure levels are concentrations or doses at or below which adverse health effects are not likely to occur. A central assumption is that a population threshold exists below which adverse effects will not occur in a population; however, such a threshold is not observable and can only be estimated. Areas of uncertainty in estimating effects among a diverse human population exposed continuously over a lifetime are addressed using extrapolation and uncertainty factors.

Protection against carcinogenicity and against adverse health effects of short-term exposures are not considered in these guidelines. For this reason, chemicals should be evaluated separately for their carcinogenic potential and additional acute health effects that may occur. Methods for these evaluations are provided in the OEHHA documents entitled Air Toxics Hot Spots Program Risk Assessment Guidelines. Part II. *Technical Support Document for Describing Available Cancer Potency Factors (1999)* and Part I. *Technical Support Document for the Determination of Acute Reference Exposure Levels for Airborne Toxicants (1999)*.

The concentration at or below which no adverse health effects are anticipated in the general human population 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.

RELs are used by the Air Toxics "Hot Spots" Program as indicators of potential adverse health effects. A "hazard index" approach is used to estimate potential health effects resulting from hazardous substances by comparing measured or modeled exposure levels with RELs. This approach assumes that the combination of multiple sub-threshold exposures could result in an adverse health effect. (Please refer to the document titled CAPCOA Air Toxics Hot Spots Program Revised 1992 Risk Assessment Guidelines (CAPCOA, 1993) for a detailed explanation

of this method. This document can be obtained from CAPCOA by calling (530) 676-4323 or through their website at http://www.capcoa.org.)

The health effects data for some chemicals are inadequate for the estimation of a REL. The amount of data and the quality of the information will ultimately determine whether a chronic REL is derived for a specific chemical. However, inclusions of margins of safety can be used to address the common data gaps encountered in risk assessment. In many cases, chronic RELs could not be developed. In these instances it was judged that the data were not relevant to inhalation exposure, that too much uncertainty existed in the calculation, or that development of a number based on the limited data could ultimately mislead or harm the public. As more data become available over time, some chronic RELs may be added or reevaluated.

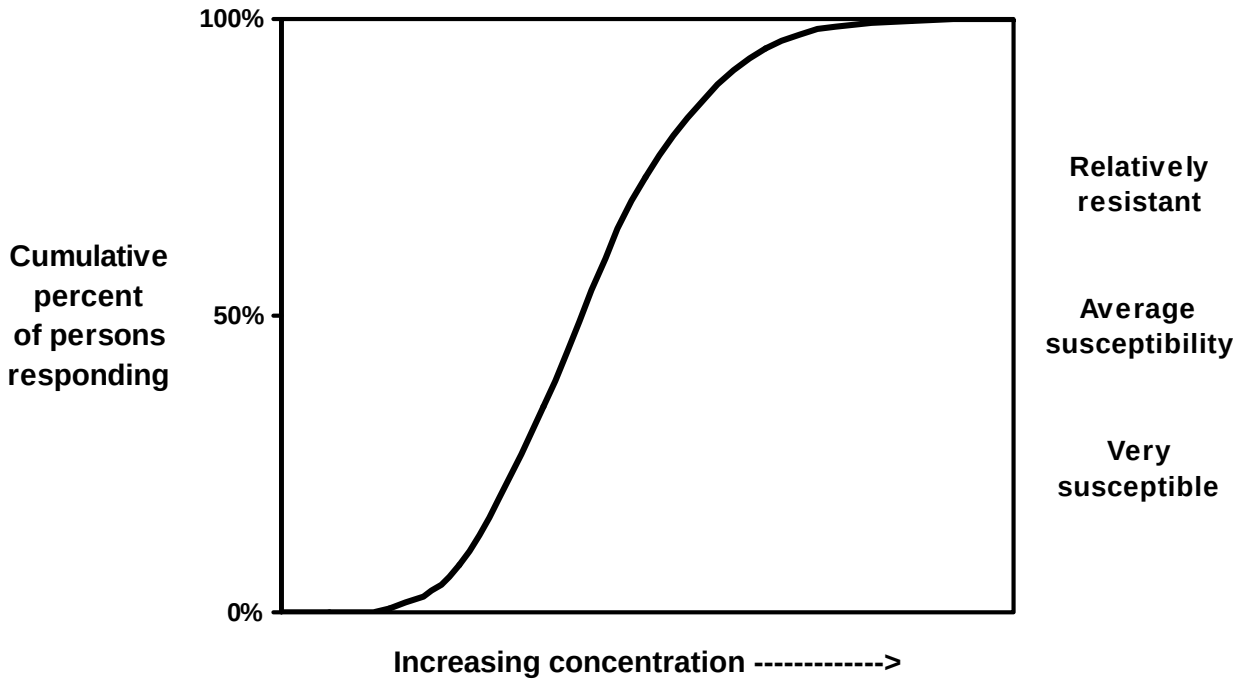
Exposure above a particular chronic REL may or may not lead to the development of adverse health effects. Conversely, there may be individuals exhibiting idiosyncratic responses (unpredictable health effects) at concentrations below the chronic RELs. Health effects associated with individual chemicals are presented in Appendix A.

1.5 Population of Concern

Chronic RELs are designed 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 (Figure 1). The susceptibility may be transitory or chronic. The general population includes some people who are likely to be especially susceptible to developing adverse effects (e.g., the very young, the elderly, pregnant women and those with acute or chronic illnesses). Chronic RELs are intended to protect individuals with low susceptibility for chemical injury as well as identifiable sensitive subpopulations (high-risk individuals) from adverse health effects. Less susceptible individuals are healthy adults without any genetic or biological predisposition that may increase the sensitivity to the chemical of concern. Highly susceptible or sensitive individuals may include those with increased exposure (e.g., children, adults engaged in physical activity), those undergoing greater 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, 1990). However, the chronic RELs may not necessarily protect hypersensitive individuals (those exhibiting idiosyncratic responses that cannot be predicted from studying the health effects of the substance).

Because the true range of variability is unknown, there may be a proportion of the population for whom the chronic RELs will not be fully protective. It is OEHHA's intent that the levels will protect nearly all individuals, including those identifiable at the high end of susceptibility.

Figure 1. Distribution of human susceptibility to adverse effects of chemical exposure



1.6 Exposure Concentration Averaging Period

The exposure period of concern in the development of chronic RELs is a full lifetime, which encompasses periods of potentially increased susceptibility to adverse health effects from chemical exposure, particularly during childhood and the later years of life. The chronic REL is intended to be protective for individuals exposed continuously over their lifetime. Scientific data available to assess these effects generally consist of discontinuous exposures over a shorter interval. In such cases default or chemical-specific assumptions are required to estimate concentrations causing comparable effects if exposures were to be continued over the entire lifetime. From a practical standpoint, chronic exposure for humans is considered to be greater than 12% of a lifetime of 70 years. Thus, human exposures of greater than 8 years are considered chronic exposures and are not adjusted either in their calculation or application.

1.7 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 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 have been tested for the potential that combined exposures

could have synergistic or antagonistic properties. The effects of multiple chemical exposures on human health remain an area for future study.

1.8 Pre-Existing Exposure Guidelines

Chronic exposure levels have been derived using several different approaches. Furthermore, inhalation exposure values estimated using a consistent basis to protect the general public, notably the U.S. EPA RfCs, are available for only a few dozen chemicals. Other values designed for the protection of the general public, in particular the U.S. EPA reference doses (RfDs), are available for many more chemicals but are intended primarily to deal with non-inhalation exposures to chemicals and are usually based on toxicity data obtained following ingestion or dermal exposure. It is very likely that the ingestion and dermal routes would underestimate the health effects of inhalation exposure, unless the health effect is an identifiable systemic effect. If the effect is systemic, then appropriate adjustments for absorption can be made. Occupational exposure guidelines, which are available for hundreds of substances, have been used in many states to derive inhalation exposure guidelines for the general public. These values, however, have an inconsistent basis and in many cases have not incorporated recently available data.

1.8.1 U.S. EPA Reference Concentrations

The U.S. EPA presented an inhalation reference concentration (RfC) method (Jarabek *et al.*, 1989; U.S. EPA, 1994). The RfC is comparable to earlier Acceptable Daily Intake (ADI) and RfD methods but addresses inhalation specific issues such as respiratory dynamics and inhalation delivered doses.

1.8.2 U.S. EPA Reference Doses

The U.S. EPA has employed an ADI approach for deriving levels to protect exposed populations from noncarcinogenic adverse effects of pesticides in foodstuffs and pollutants in ambient waters (Federal Register, 1980). U.S. EPA developed an oral reference dose (RfD) concept in 1987 (Barnes and Dourson, 1988). The RfD is comparable to previous ADI methods but presents a more developed protocol for study selection, identifying No Observed Adverse Effect Levels (NOAELs), applying uncertainty factors, and assessing the weight of evidence. As of May, 1996, U.S. EPA RfDs were available for over 200 substances (U.S. EPA, 1996). The major limitation of these values is that they are almost entirely based on noninhalation exposure data rather than inhalation exposure data.

1.8.3 Occupational Threshold Limit Values

Occupational exposure limits have been used to derive chemical exposure guidelines for the general public (National Air Toxics Information Clearinghouse, 1991; Robinson and Paxman, 1992). As of May, 1996, more than 600 American Conference of Governmental Industrial Hygienists (ACGIH) TLVs (ACGIH, 1996) and National Institute for Occupational Safety and Health (NIOSH) RELs (NIOSH, 1990) were available. These values have been attractive because of the large number of available values and the concept that they are intended to protect

a human population from inhalation exposures. However these values lack a consistent basis, are not designed for or recommended for protection of the general public, and in many cases may not prevent adverse health effects among most workers (Roach and Rappaport, 1990).

1.8.4 California Ambient Air Quality Standards

California Ambient Air Quality Standards (CAAQS) are available for criteria air pollutants (CAPCOA, 1993). Where defined according to a basis appropriate to lifetime exposures, the CAAQS was adopted as the chronic inhalation REL.

2. Hazard Identification

2.1 Selection of Key Studies

An important step in the development of a chronic 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, 1994). These studies may involve a human population studied in an epidemiological, clinical, case, 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.

2.1.1 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, 1985).

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.

2.1.1.1 Epidemiological Data

Epidemiological studies generally result in data on effects of chemical exposure to a large number of persons. Areas of concern include exposure measurement, health effects measurement, and accounting for covariables and confounding variables. The population studied often consists of 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 time period of the study is inappropriate.

Co-variables 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, 1985).

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.

2.1.1.2 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 usually (1) involve small sample sizes, (2) are of very short exposure duration, and (3) assess effects through noninvasive and sometimes subjective measurements that might miss significant health effects.

2.1.1.3 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. These reports are generally not appropriate for quantitation because of the very small sample size and the unquantified exposures (Goldstein, 1983). Exposures are frequently much higher than threshold doses, with serious injury occurring. Multiple case histories with the same endpoint are especially relevant.

2.1.2 Animal Data

Over 4,000 chronic animal exposure studies have been conducted. Many of these studies were primarily concerned with assessing chemical carcinogenic potential, though evaluations of noncancer health effects were generally included (Gold *et al.*, 1991).

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 endpoints have frequently been selected as key studies. The most sensitive endpoint will be influenced by the relative sensitivity of species tested and by the relative sensitivity of tests employed. 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. 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, 1983). Comparison of human and animal pharmacokinetics, metabolism, and mechanism of action may be useful in selecting the relevant animal model for predicting human health effects. However, in most instances it is not possible to determine which species is more like humans in response to a chemical exposure.

An experimental study should have a clear rationale and protocol, use Good Laboratory Practice Standards, and use appropriate analysis methods. 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 so that responses of relevant species are not ignored. Furthermore, it is important that there not be any disincentive to conducting good studies in order to avoid the establishment of reference exposure levels.

2.2 Weight of Evidence

U.S. EPA has used a categorical ranking of the weight-of-evidence for U.S. EPA RfCs (U.S. EPA, 1997). OEHHA has not adopted such a formal scheme, but a descriptive analysis of strengths and uncertainties of each REL has been presented. Issues such as observation of a dose-response relationship, reproducibility of findings, and mechanism of action were given weight in the OEHHA evaluation of chronic inhalation RELs.

2.2.1 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 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 exposure group was not noted in a high exposure group, evidence for a causal association between the chemical exposure and the effect is greatly reduced.

2.2.2 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, and consistency of effect for different routes of exposure. 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.

2.2.3 Specificity of Associated Adverse Health Effect

If an adverse health effect is specific to exposure to a substance, the case for causality is strengthened. Such highly specific relationships are unusual, however, as chemical exposures generally cause multiple effects and chemical-induced health effects are sometimes comparable to similar health effects of known or unknown etiology observed in the absence of exposure.

2.2.4 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 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, but tumors arising after a latency period of months or years would be temporally consistent.

2.2.5 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 what is known about the pharmacokinetics and mechanism of action of the chemical.

3. Dose Response Assessment

3.1 Estimation of Threshold or Low Response Concentrations

Noncancer health effects assessment has been rooted in 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 can not be demonstrated. The entire population of concern is not examined, rather a sub-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.

3.1.1 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 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 after consideration of certain factors, such as the demonstration in a prior study of toxicity at that concentration with a shorter exposure duration.

In general, OEHHA has considered a NOAEL without an associated LOAEL identified in the same study (termed a free-standing NOAEL) to be acceptable for use in deriving a chronic REL, as long as the overall health hazard information for that substance is consistent with the NOAEL study. For example, in many cases shorter duration studies involving slightly higher concentrations have reported adverse health effects.

3.1.2 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 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 not considered adverse may be termed the lowest observed effect level (LOEL); this is identical to the NOAEL (U.S. EPA 1994). If a NOAEL is not identifiable from the literature, it is estimated for the purposes of risk assessment from the lowest exposure concentration reported to produce the adverse effect or LOAEL. An uncertainty factor is applied to the LOAEL to estimate the NOAEL:

$$\text{LOAEL}/\text{UF} = \text{NOAEL}$$

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. This factor has been considered appropriate for both inhalation (U.S. EPA, 1994) and oral routes of exposure.

The effectiveness of a ten-fold LOAEL-to-NOAEL uncertainty factor was examined for several inhalation (Mitchell *et al.*, 1993, Alexeeff *et al.*, 1997, Kadry *et al.*, 1995) and oral (Dourson and Stara, 1983) exposure data sets. Mitchell *et al.* (1993) evaluated the LOAEL-to-NOAEL ratio for 107 subchronic and chronic inhalation studies. They reported that 15 of the 107 studies had LOAEL-to-NOAEL ratios of 10 or greater. Alexeeff *et al.* evaluated 210 acute

inhalation studies for 66 chemicals and reported that the LOAEL to NOAEL ratio for mild effects had 90th and 95th percentiles of 5.0 and 6.2, respectively. In contrast, the ratio of the LOAEL for serious effects to the NOAEL for all effects had 90th and 95th percentiles of 12 and 40, respectively. 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 followed U.S. EPA guidance and precedent in the use of this uncertainty factor. U.S. EPA use of an uncertainty factor less than ten appears to be somewhat subjective and lacking in specific criteria as to when it is appropriate. OEHHA thus developed specific criteria for use of an intermediate uncertainty factor: (1) the effect was of low severity (U.S. EPA grade 5 or below as described in Table 2) and (2) the effect was observed in less than 50% of subjects. The concurrence of these two characteristics suggests that the exposure is likely to be relatively nearer to the NOAEL. It is suggested that an evaluation of the LOAEL to NOAEL relationship be undertaken to better evaluate the use of this adjustment factor. Results of such an analysis could be used to improve the exposure level setting procedure in the future.

Information above the dose-response slope could also be used in deriving an intermediate LOAEL UF, on the grounds that a lesser UF would be adequate where the dose-response slope was steep compared with a case where a shallow dose-response relationship is observed. Where adequate data are available, it is likely that a benchmark concentration would be used.

3.1.3 Estimation of a Benchmark Concentration (BMC)

The importance of dose-response relationships in the evaluation of effects of chemical exposure is well established. The NOAEL approach 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 (Mantel and Bryan, 1961; Mantel *et al.*, 1975; Crump, 1984; Dourson *et al.*, 1985; Dourson, 1986; Hartung, 1987; Gaylor, 1988; Lewis *et al.*, 1988; Gaylor, 1989). Crump (1984) proposed the term “benchmark dose” and extensively evaluated this concept.

Suggested risk levels have ranged from one in one million (Mantel and Bryan, 1961) to 10% (Dourson *et al.*, 1985). U.S. EPA has recently adopted the use of a 10% benchmark derived using a Weibull model in the derivation of chronic RfCs (U.S. EPA, 1997). The OEHHA has suggested the use of a benchmark of 1% incidence, and has used a 5% benchmark in the derivation of acute inhalation RELs (OEHHA, 1999). The range approximates the lower limit of adverse effect detection likely to occur in typical human epidemiological and laboratory animal studies (Gaylor, 1992). In the case of a steep dose-response relationship, the selection of benchmark incidence is not critical. For many acute exposure studies, 1 and 5% incidence benchmark concentrations differed only slightly from the study NOAEL (Fowles and Alexeeff, 1997).

Table 2. U.S. EPA effect severity levels (U.S. EPA, 1994).

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

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.

Several RfCs based on benchmark concentration analyses by U.S. EPA are presented in this document. Several differences exist between the use of BMCs by U.S. EPA in its RfC development and that previously employed by OEHHA. Given the current lack of consensus in a methodology to incorporate benchmark concentrations in the development of inhalation reference exposure levels, OEHHA did not develop additional chronic inhalation RELs using the benchmark concentration approach. For some chemicals an alternative benchmark analysis is provided, however. It is suggested that this be considered an area of future analysis in order to

evaluate the BMC procedure further and to develop values using the approach in the development of RELs.

3.2 Overview of Extrapolation from Study Data to Human Population

A NOAEL observed in a study may be a concentration that would cause adverse effects among the general human population exposed continuously over their lifetime. The chronic REL must also address uncertainties in the available data. These areas of uncertainty are accounted for with the use of extrapolation factors or uncertainty factors.

Extrapolation methods are used by OEHHA in deriving chronic RELs to account for (1) exposure discontinuity and (2) interspecies differences in exposure. Extrapolation factors are based on identification of measurable attributes that are judged to be relevant to addressing an area of concern.

Uncertainty factors are used by OEHHA in deriving chronic RELs to account for: (1) the magnitude of effect observed at a LOAEL compared with a NOAEL (Mitchell *et al.*, 1993; Dourson and Stara, 1983); (2) the potentially greater effects from a continuous lifetime exposure compared to a subchronic exposure (Bigwood, 1973; Dourson and Stara, 1983; Lehman and Fitzhugh, 1954); (3) the potentially greater sensitivity of humans relative to experimental animals not accounted for by differences in relative inhalation exposure (Dourson and Stara, 1983; Vettorazzi, 1976); and (4) the potentially increased susceptibility of sensitive individuals (Vettorazzi, 1976). In this document these four uncertainty factors will be termed (1) LOAEL uncertainty factor (discussed in Section 3.1.2); (2) subchronic uncertainty factor (discussed in Section 3.3); (3) interspecies factor (discussed in Section 3.4); and (4) intraspecies factor (discussed in Section 3.5), respectively.

The use of uncertainty factors for determining “safe” or “acceptable” levels has been discussed extensively in the toxicological literature (Alexeeff and Lewis, 1989; Bigwood, 1973; Dourson and Stara, 1983; NAS, 1977; U.S. EPA, 1994; Vettorazzi, 1976). Uncertainty factors are used when insufficient data are available to support the use of chemical-specific and species-specific extrapolation factors. Historically, uncertainty factors have most often been order-of-magnitude factors, indicating the broad level of uncertainty in addressing the area of concern. More recently OEHHA and U.S. EPA have used 3-fold (the rounded geometric mean of 1 and 10) uncertainty factors in areas estimated to have less residual uncertainty (U.S. EPA, 1997). While the geometric mean is 3.16, an examination of U.S. EPA RfCs demonstrated that, in practice, a single intermediate UF is calculated by U.S. EPA as 3.00 rather than 3.16, while two intermediate UFs usually accumulate to 10. Thus, cumulative uncertainty factors could equal 1, 3, 10, 30, 100, 300, 1000, or 3000.

3.3 Effects of Exposure Continuity and Duration

3.3.1 Differences between Continuous and Discontinuous Exposures

Studies of adverse health effects associated with long-term exposures of humans or experimental animals generally involve discontinuous exposures. Commonly encountered exposure scenarios involve exposures of 6 to 8 hours per day for 5 days per week. OEHHA RELs, however, are intended to protect the general public who could be exposed continuously. In practice, discontinuous facility emissions are generally adjusted to a continuous daily or annual average.

The default approach adopted for the chronic RELs presented in this document to account for differences in effects associated with discontinuous and continuous inhalation exposures to substances is an equivalent time-weighted average approach. This is the same approach used in the derivation of U.S. EPA RfCs (U.S. EPA, 1994).

The default approach to estimating an equivalent time-weighted average concentration (C_{AVG}) from the observed concentration (C_{OBS}) in non-occupational studies may be summarized as:

$$C_{AVG} = C_{OBS} \text{ x (H hours per 24 hours) x (D days per 7 days)}$$

The default approach to estimating an equivalent inhalation-weighted average concentration (C_{AVG}) from the observed concentration (C_{OBS}) for occupationally exposed humans is:

$$C_{AVG} = C_{OBS} \text{ x (10 m}^3\text{/day occupational exposure / 20 m}^3\text{/day total exposure)}$$
$$\text{x (D days per 7 days)}$$

3.3.2 Differences between Lifetime and Less-than-Lifetime Exposures

Studies of adverse health effects associated with exposures of humans or experimental animals generally involve less-than-lifetime exposures. Commonly encountered exposure scenarios involve occupational exposures of 5 to 20 years, or exposures to experimental animals over approximately 10% of their lifetime. The OEHHA chronic RELs, however, are intended to protect the general public who could be exposed over their entire lifetime.

The default approach used in this document is to adopt the method of U.S. EPA to use a 1 to 10-fold uncertainty factor for subchronic exposures. Subchronic exposures have frequently been defined as those less than 10% of average life-span, except in the case of mice and rats where 13 weeks has been considered subchronic.

U.S. EPA has incorporated intermediate UFs, though their rationale for selecting a subchronic uncertainty factor has not been clearly presented, and in practice appears to be based on subjective judgment. To implement an intermediate subchronic UF in response to U.S. EPA and RAAC recommendations, but using a consistent method, OEHHA used the following approach: (1) exposures less than 8% of expected lifetime were given a 10-fold UF, (2) exposures from 8 to 12% of expected lifetime were given a 3-fold UF, and (3) exposures greater

than 12% of expected lifetime were given a 1-fold UF. Average life-spans assumed for humans and experimental animals are presented in Table 3.

Table 3. Average Life-spans for Humans and Experimental Animals

Species	***Approximate average Life-span (years)***[1]	***Subchronic exposure duration (weeks)***[2]
Baboon	55	≤ 286
Cat	15	≤ 78
Dog	15	≤ 78
Guinea pig	6	≤ 31
Hamster	2.5	≤ 13[3]
Human	70	≤ 364
Mouse	2	≤ 13[3]
Rabbit	6	≤ 31
Rat	2	≤ 13
Rhesus monkey	35	≤ 182

[1] U.S. EPA (1988).
[2] Subchronic exposures are usually defined as those over less than 10% of average lifetime (U.S. EPA, 1994).
[3] Special rule adopted by U.S. EPA that exposures of 13 weeks or less are subchronic regardless of species involved (U.S. EPA, 1994).

Unlike the extensive exposure concentration-duration-effect analyses that have been conducted for acute lethality data in experimental animals, only limited work has been done to compare the differences between acute, sub-chronic, chronic and lifetime exposure scenarios.

Kadry and associates (1995) showed that among a small data set (6 chemicals) subchronic NOAEL to chronic NOAEL ratios were less than 10. However, in a study of published animal NOAELs for a larger group of pesticides, Nair and associates (1995) found that 19 of 148 (13%) subchronic to chronic NOAEL ratios differed by more than 10-fold. Recently, the U.S. EPA reported that, based on an analysis of responses to 100 substances, the subchronic to chronic ratios formed a distribution with a median value of 2 and an upper 95th percentile of 15 (Swartout, 1997); the value of 10 represents the 90th percentile.

3.4 Differences between Human and Animal Susceptibility to Toxic Effects of Chemicals

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, risk assessment of chemicals must often rely on observations of experimental animals. Of the many thousands of chemicals in existence, most have not been studied in human populations, and, where human studies exist, frequently

there is very poor knowledge of exposures, and confounding factors render cause and effect conclusions difficult.

These differences can be addressed by considering two specific issues: (1) the determination of an equivalent human concentration and (2) accounting for the potential for greater human susceptibility to an equivalent dose.

3.4.1 Determination of a Human Equivalent Concentration

The human equivalent concentration (HEC) approach used by U.S. EPA for RfCs (U.S. EPA, 1994) was adopted by OEHHA for derivation of chronic inhalation RELs. U.S. EPA has proposed a number of different HEC schemes depending on the physicochemical characteristics of the substance (reactive gases, water soluble gases, water-insoluble gases, and particles) and on the site of toxic action (respiratory effects and systemic effects). Some of the proposed HEC approaches are very data-intensive and have not been used in practice.

U.S. EPA has to date implemented only three categories: (1) gases with respiratory effects, (2) gases with systemic effects, and (3) particles with respiratory effects. Of 41 RfCs based on animal data presented by U.S. EPA, 18 were classified as gases with respiratory effects, 20 were classed as gases with systemic effects, and 3 were considered as particulates with respiratory effects. Thus OEHHA also limited its use of HEC extrapolation to these scenarios. The methods employed have been presented in detail in U.S. EPA (1994) and will be briefly reviewed here.

3.4.1.1 Gases with Respiratory Effects

The regional gas dose ratio (RGDR) is calculated as the relative minute volume (MV) to relative surface area (SA) for the lung region of concern:

$$RGDR = (MVa/MVh) / (SAa/SAh)$$

Default lung surface area estimates presented by U.S. EPA (1994) were used (Table 4).

Table 4. Default Lung Surface Area Estimates (U.S. EPA, 1994)

Species	**Extrathoracic surface area (cm^2)**	**Tracheobronchial surface area (cm^2)**	**Pulmonary surface area (cm^2)**
Guinea pig	30	200	9,000
Hamster	14	20	3,000
Human	200	3,200	540,000
Mouse	3	3.5	500
Rabbit	30	300	59,000
Rat	15	22.5	3,400

Minute volume (volume inhaled per minute) is the product of inhaled volume and respiratory rate. Minute volumes (MV) in L/min for five animal species were estimated from body weights (BW) in kg with allometric relationships presented by U.S. EPA (1994):

$$\log_e(MV) = b_0 + b_1 \log_e(BW)$$

where b_0 and b_1 are empirically derived factors from a database of MV and BW values for various species and strains.

Body weights were estimated from the published experimental study under review or, when necessary, from strain and gender specific default values presented by U.S. EPA (1994). Intercept (b_0) and slope (b_1) values are presented in Table 5.

Table 5. Intercept and Slope Parameters for Estimating Minute Volume from Body Weight

Species	**b_0**	**b_1**
Guinea pig	-1.191	0.516
Hamster	-1.054	0.902
Mouse	0.326	1.05
Rabbit	-0.783	0.831
Rat	-0.578	0.821

3.4.1.2 Gases with Systemic Effects

Gases leading to systemic health effects were calculated using the default assumptions used by U.S. EPA for all systemic RfCs developed to date. The default methodology adjusts the average exposure concentration by the regional gas dose ratio (RGDR), which for systemically-acting gases is assumed to be the ratio of the animal blood:air partition coefficient $(H_{b/g})_A$ to the human blood:air partition coefficient $(H_{b/g})_H$. The following formulae describe the calculation of the RGDR and HEC:

$$RGDR = (H_{b/g})_A / (H_{b/g})_H$$
$$HEC = \text{Average exposure concentration} \times (H_{b/g})_A / (H_{b/g})_H$$

Where the relevant blood:air coefficients are unknown, U.S. EPA recommends assuming that $(H_{b/g})_A$ is equal to $(H_{b/g})_H$ and thus the RGDR for systemic effects is assumed to equal one. This assumption was used for all 20 RfCs that have been developed for systemically-acting gases. Chemical-specific data, where available, were used to estimate the HEC for additional REL values determined by OEHHA. Where species-specific, but not chemical-specific, data were available, the default assumption of RGDR = 1 was used. Where both species-specific and chemical-specific data were lacking, no HEC calculation was used, and a 10-fold interspecies UF was applied.

3.4.1.3 Particulates with Respiratory Effects

The methodology used by U.S. EPA to derive a regional deposited dose ratio (RDDR) and corresponding human equivalent concentration for particulates with respiratory effects is more data-intensive than that applied to gases (U.S. EPA, 1994). U.S. EPA has developed a computer program, the *U.S. EPA RDDR Program* (U.S. EPA, 1994). To ensure consistency with U.S. EPA RfCs, this program was used to calculate RDDR and HEC for OEHHA RELs for particulates with respiratory effects. Experimentally-determined values for the particle distribution, characterized by the mass median aerodynamic diameter (MMAD) and geometric standard deviation (sigma g), were input into the program, along with the identity of the experimental species and experimentally-determined or estimated body weights. Minute volumes were estimated from body weights and default estimates of lung surface areas were used. The program outputs deposition and RDDR estimates for different lung regions.

A detailed presentation of the RDDR methodology has been presented previously (U.S. EPA, 1994). Briefly, the method estimates fractional deposition in different lung regions for both animal species and humans, and calculates the RDDR as the ratio of animal fractional deposition to human fractional deposition. Fractional deposition is assumed to be dependent on minute volume, MMAD, sigma g, and prior deposition in regions through which the particles have already passed. Deposition efficiency (DE), which is unaffected by prior deposition, is calculated from minute volume, MMAD, and sigma g using a fitted logistic function. The function uses impaction diameter (x) estimated from MMAD and minute volume and is fitted for a given species with two parameters (α and β, Table 6):

$$\text{Flow rate (Q)} \approx MV / 30$$
$$x = MMAD^2 \times Q$$
$$DE = 1 / (1 + e^{\alpha + \beta \log_{10} x})$$

Then, fractional deposition is determined by sequentially determining deposition in extrathoracic (ET), tracheobronchial (TB), and pulmonary (PU) regions.

Table 6. Parameters for Deposition Efficiency Equation

Species	α (ET)	β (ET)	α (TB)	β (TB)	α (PU)	β (PU)
Human	7.13	-1.96	3.30	-4.59	0.52	-1.39
Rat	6.60	-5.52	1.87	-2.09	2.24	-9.46
Mouse	0.66	-2.17	1.63	-2.93	1.12	-3.20
Hamster	1.97	-3.50	1.87	-2.86	1.15	-7.22
Guinea pig	2.25	-1.28	2.52	-0.87	0.75	-0.56
Rabbit	4.31	-1.63	2.82	-2.28	2.58	-1.99

3.4.2 Accounting for Potentially Greater Human Susceptibility

The default approach adopted is to apply a 10-fold uncertainty factor 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. A factor of 10 is generally incorporated for extrapolation from animals to humans. This is truly an "uncertainty" factor since we are unsure how humans would respond in contrast to the animals tested. However, the uncertainty factor is based on the potential for greater sensitivity of humans and the larger surface area of humans (Krasovoskii, 1976; Lewis and Alexeeff, 1989; Rall, 1969; Weil, 1972). This uncertainty factor methodology is in contrast to practice used in cancer risk assessment where an allometric surface area correction and a 95% confidence interval of the slope of the dose response is used. This approach is identical to that used by U.S. EPA (1994) and recommended by NAS for drinking water standards. Limited support for the concept of a ten-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. Further evaluation of the interspecies uncertainty factor could be done by following the work of Hertzberg (1989) using the categorical regression analysis. 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 ratio of 10 represented approximately the 85th percentile.

U.S. EPA (1994) has used human equivalent concentration (HEC) extrapolation and a 3-fold intermediate interspecies uncertainty factor. Thus, U.S. EPA has generally used a 3-fold uncertainty factor for RfC derivation, because its HEC derivation may account for part of the

species differences in susceptibility. The differences accounted for would be the dosimetric difference between the species. The remaining 3-fold uncertainty factor is to account for pharmacodynamic or response differences between the species. This modified approach was also used by OEHHA in this document where there were sufficient data to justify this approach. Chemical-specific data were used where available. When chemical-specific data were lacking but species-specific data were available, health protective default assumptions were used. Where both chemical- and species-specific data were unavailable, a 10-fold interspecies uncertainty factor was used.

The 10-fold default uncertainty factor would only be applied after consideration of other factors that potentially might affect the validity of the default assumption. Such factors include differences between humans and the test species, such as in absorption, distribution, and metabolism, that would serve as a basis for predicting interspecies differences in susceptibility. It would only be applied in those cases where an HEC could not be estimated.

3.5 Increased Susceptibility of Sensitive Individuals

Chronic RELs are intended to protect identifiable sensitive individuals from harm due to chemical exposure. However, RELs may not necessarily protect hypersensitive individuals who may develop an idiosyncratic response (including allergic hypersensitivity).

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 *et al.*, 1987; U.S. EPA, 1994; Eichelbaum *et al.*, 1992; Grandjean, 1992).

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, persons with existing diseases such as lung, heart or liver disease, and persons engaging in physical activity (U.S. EPA, 1994). 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 of long-term chemical exposures, 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. Animals in poor health were more likely to experience adverse effects from chronic oral exposure to chemicals than were healthy animals (Chizhikov, 1973).

A 10-fold uncertainty factor is used to account for the known variability within the human population. This factor accounts for the potential for greater susceptibility in subpopulations, including infants and children. A high degree of intraindividual variability (2-to-30-fold) in

response to chemical exposure has been reported (Krasovskii, 1976; Weil, 1972). Intraspecies variability has been recently modeled suggesting a 10-fold factor will protect the 85th percentile (Gillis *et al.*, 1997). In accordance with U.S. EPA guidelines (U.S. EPA, 1994), when a chronic 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. Thus, for chronic RELs derived from NOAELs or LOAELs, OEHHA has generally applied a 10-fold uncertainty factor to address the greater susceptibility of sensitive individuals. This is identical to assumptions previously employed by U.S. EPA (1994).

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 ten-fold factor was health-protective in most cases. However, it should be noted that dose-response curves for acute lethality exposures are likely to be steeper than those for non-lethal chronic exposures since many more population-based variables are likely to be involved.

Because the true variability is unknown, there may be a portion of the population for whom the chronic RELs will not be protective. It is OEHHA's intent that 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.

3.6 Estimation of Inhalation Effects from Oral Exposure Data

Strong weight is given to inhalation exposure-based health effects data. If adequate inhalation data are unavailable, oral exposure data are also considered. Route-to-route extrapolation under certain circumstances has been supported by U.S. EPA (1994) and the NRC (1986). Under some circumstances, the use of route-to-route extrapolation has been questioned. For example, where chemicals act at the portal of entry, route-to-route extrapolation may not be possible.

Available data support the use of an additional uncertainty factor for non-inhalation studies (Owen, 1990). Inhalation absorption coefficients for 32 of 34 (94%) substances were at most 10-fold higher than oral absorption coefficients for the same substance. The median inhalation/oral absorption coefficient ratio was 1.0. Fifteen (44%) substances were predicted to have greater inhalation than oral absorption, and 7 (21%) were predicted to have at least 2-fold greater inhalation absorption. Two of 34 (6%) substances with greatly (> 10-fold) increased inhalation absorption relative to oral absorption were metals with very low oral absorption (<1%). Inhalation absorption of beryllium and elemental mercury was estimated as 500-fold and 7,500-fold higher than corresponding oral absorption, respectively.

Additional evidence that differences between toxic effects following oral and inhalation exposures generally differ within a 10-fold dose range was provided by Pepelko (1987; 1991). Inhalation and oral doses associated with a 25% additional risk of cancer RRD(25) were

estimated for various chemicals. Carcinogens were more potent via oral exposure compared with inhalation exposure in 15 of 23 rodent data sets, and 20 oral exposure data sets (87%) predicted inhalation results within a 10-fold factor. Greater than 10-fold differences in potency were found in rats exposed to asbestos, vinyl chloride, or hydrazine. Proposed explanations for these results were: (1) greater potency via inhalation due to longer residence time of asbestos fibers in the deep lung than in the gut; (2) underestimates of low-dose inhalation potency of vinyl chloride due to exposures at saturation concentrations; and (3) variability in the study quality and design for hydrazine.

While route-specific differences in absorption and potency may occur, no additional uncertainty factor was applied for non-inhalation data. Instead, attempts were made to adjust for absorption when possible, and if data indicated that the oral and inhalation absorption varied greatly but could not be accounted for, then the oral study was not used.

3.7 Summary of Extrapolation and Uncertainty Factors Used to Derive Chronic RELs

The REL is derived from application of extrapolation and uncertainty factors to the NOAEL, LOAEL, or BMC. All values are computed without rounding except for the final REL, which is rounded to a single significant digit.

OEHHA used a maximum overall factor of 3,000 in this document. This is consistent with U.S. EPA practice in deriving RfCs and with their most recent guidance on the subject (U.S. EPA, 1994). The range of factors used by U.S. EPA and OEHHA in deriving RfCs and chronic RELs is summarized in Table 7.

3.8 Documentation of Chronic Reference Exposure Levels

The documentation of the development of RfCs and chronic reference exposure levels is presented in Appendix A. These summaries present the information upon which the calculations are based. This discussion includes the following key elements.

- Chronic REL summary
- Physical and chemical properties: Descriptions include information on volatility, density, water solubility, color.
- Occurrence and use: The typical uses of the chemical are described as well as where it is likely to be found.
- Effects of human exposure: A brief discussion of pharmacokinetics and metabolism is included if available and relevant. Studies are described in some detail providing information on study design; study population; exposure concentration, duration, and continuity; duration of study; methods used to test for adverse effects; and adverse effects noted.
- Effects of animal exposure: Effects of animal exposures are reviewed in a manner comparable to that presented for human exposure.
- Derivation of the chronic REL: The derivation of the chronic REL is presented tabularly. Strengths and weakness of the REL are presented, and areas of uncertainty are discussed.

3.9 Chronic Reference Exposure Level Summary

The 95 chemicals for which chronic noncancer reference exposure levels (see definition below) appeared in the Air Toxics "Hot Spots" Program Revised 1992 Risk Assessment Guidelines (California Air Pollution Control Officers Association, 1993) were initially evaluated. Of these, 22 had U.S. EPA RfCs which were adopted as chronic inhalation RELs. Data on an additional 56 substances from the 1992 list were extensively evaluated and chronic inhalation RELs were derived using U.S. EPA RfC methodology. For 17 of the original 95, no chronic REL was developed, either because (1) no emissions were reported in California by the ARB, (2) existing health effects data were considered inadequate, (3) evaluation of the substance was pending review in the Toxic Air Contaminant process, (4) chronic inhalation RELs had already been approved by the Scientific Review Panel and adopted by the ARB, (5) California Ambient Air Quality Standards already existed, or (6) no non-pesticidal uses were found for the substance.

In addition, OEHHA developed chronic inhalation RELs for 42 other chemicals on the list of substances for which emissions need to be quantified. These substances were selected primarily based on (1) the magnitude of current known emissions in California and (2) the availability of a strong scientific database on which to estimate a chronic REL. Chronic RELs for an additional three substances, acetaldehyde, diesel exhaust particulates, and perchloroethylene, have already been adopted by the Air Resources Board. Thus OEHHA plans to propose chronic REL values for 121 substances. The first 40 chronic RELs are listed in Table 8.

A comparison of U.S. EPA RfCs and additional RELs estimated by OEHHA as presented in this document suggests that the OEHHA RELs are similar to values that might have been developed by U.S. EPA (Table 9). Cumulative uncertainty factors for OEHHA RELs were smaller than those for U.S. EPA RfCs (Figure 1). The primary difference appears to be the frequent use by USEPA of a 3 to 10-fold database deficiency factor, which has not been used in deriving OEHHA RELs. Individual uncertainty factors tended to be slightly greater for OEHHA RELs, which may be due in part to U.S. EPA limiting RfC development to chemicals with generally good health hazard databases.

The OEHHA REL development process emphasized the use of human exposure data whenever possible. Human data were used for the key study for a higher percentage of chemicals than was the case for U.S. EPA RfCs (Table 10). This result was achieved even though the additional chemicals evaluated by OEHHA might be anticipated to have less comprehensive health data than those previously selected by U.S. EPA for RfC development.

Table 7. Extrapolation Methods and Uncertainty Factors Used for Proposed OEHHA Chronic RELs

Method or Factor	***Values Used***
Discontinuous exposure extrapolation	Calculated according to U.S. EPA time-weighted average approach (animal exposure data) Calculated according to U.S. EPA occupational inhalation-weighted average approach (human occupational exposure data)
Human equivalent concentration (HEC) extrapolation	Calculated according to U.S. EPA RfC approach (inhalation data) Calculated according to U.S. EPA RfD approach (non-inhalation data)
Subchronic uncertainty factor	1 (>12% of estimated lifetime) 3 (8-12% of estimated lifetime) 10 (<8% of estimated lifetime)
LOAEL uncertainty factor	1 (no observed effect) 3 (mild and low incidence (<50%) effect) 10 (moderate to severe, high incidence effect)
Interspecies uncertainty factor	1 (human observation) 3 (animal observation) (for residual susceptibility differences not accounted for by U.S. EPA HEC approach) 10 (animal observations where chemical- and species-specific data were unavailable)
Intraspecies uncertainty factor	1 (sensitive subpopulation) 10 (normal subpopulation)
Route-to-route extrapolation (non-inhalation data)	3,500 $\mu g/m^3$ per mg/kg-day
Modifying factor	1 (OEHHA proposed chronic RELs) 1 to 10 (U.S. EPA RfCs)
Cumulative uncertainty factor	1 to 3,000 (OEHHA proposed chronic RELs) 30 to 3,000 (U.S. EPA RfCs)

Table 8. Proposed OEHHA Chronic Inhalation REL Summary

Substance (CAS #)	*Listed in CAPCOA (1993)*	*U.S. EPA RfC*	*Chronic Inhalation REL ($\mu g/m^3$)*	*Hazard Index Target(s)*	*Human Data*
Ammonia (7664-41-7)	☑	☑	100	Respiratory system	☑
Benzene (71-43-2)	☑		60	Cardiovascular system; development; nervous system; immune system	☑
Chlorinated dioxins (1746-01-6)& dibenzofurans (5120-73-19)	☑		0.00004	Alimentary system; immune system; reproductive system; development; endocrine system; respiratory system; cardiovascular system	
Chlorine (7782-50-5)	☑		0.06	Respiratory system	
Chloroform (67-66-3)	☑		300	Alimentary system; kidney; development	
Di(2-ethylhexyl)-phthalate (117-81-7)	☑		10	Alimentary system; respiratory system	
Dioxane (1,4-) (123-91-1)	☑		3,000	Alimentary system; kidney; cardiovascular system	
Ethylbenzene (100-41-4)		☑	1,000	Development; alimentary system; kidney	
Ethyl chloride (75-00-3)	☑	☑	10,000	Development; alimentary system	
Ethylene glycol (107-21-1)			400	Respiratory system; kidney; development	☑
Ethylene glycol ethyl ether (110-80-5)	☑	☑	200	Reproductive system; cardiovascular system	
Ethylene glycol ethyl ether acetate (111-15-9)	☑		300	Development	
Ethylene glycol methyl ether (109-86-4)	☑	☑	20	Reproductive system	
Ethylene glycol methyl ether acetate (110-49-6)	☑		90	Reproductive system	
Formaldehyde (50-00-0)	☑		3	Respiratory system; eyes	☑
Hexane (n-) (110-54-3)		☑	200	Nervous system	☑
Hydrogen chloride (7647-01-0)	☑	☑	7	Respiratory system	
Hydrogen cyanide (74-90-8)	☑	☑	3	Nervous system; endocrine system; cardiovascular system	☑
Hydrogen sulfide (7783-06-4)	☑		9	Respiratory system	

Table 8. Proposed OEHHA Chronic Inhalation REL Summary (continued)

Substance (CAS #)	*Listed in CAPCOA (1993)*	*U.S. EPA RfC*	*Chronic Inhalation REL ($\mu g/m^3$)*	*Hazard Index Target(s)*	*Human Data*
Isopropanol (67-63-0)			7,000	Kidney	
Manganese & manganese compounds	☑	☑	0.05	Nervous system	☑
Mercury & mercury compounds (inorganic)	☑	☑	0.3	Nervous system	☑
Methanol (67-56-1)	☑		10,000	Development	
Methyl bromide (74-83-9)	☑	☑	5	Respiratory system; nervous system; development	
Methyl t-butyl ether (1634-04-4)		☑	3,000	Kidney; eyes; alimentary system	
Methyl chloroform (71-55-6)	☑		1,000	Nervous system	
Methylene chloride (75-09-2)	☑		400	Cardiovascular system; nervous system	☑
Methyl ethyl ketone (78-93-3)			10,000	Alimentary system; kidney	
Naphthalene (91-20-3)	☑		9	Respiratory system	
Nickel & compounds (except nickel oxide)	☑		0.05	Respiratory system; immune system	
Nickel oxide (1313-99-1)			0.1	Respiratory system; immune system	
Phenol (108-95-2)	☑		600	Alimentary system; cardiovascular system; kidney; nervous system	
Phosphoric acid (7664-38-2)		☑	10	Respiratory system	
Propylene (115-07-1)			3,000	Respiratory system	
Propylene glycol monomethyl ether (107-98-2)		☑	2,000	Nervous system	
Propylene oxide (75-56-9)	☑	☑	30	Respiratory system	
Styrene (100-42-5)	☑	☑	1,000	Nervous system	☑
Toluene (108-88-3)	☑	☑	400	Nervous system; alimentary system; development	☑
Trichloroethylene (79-01-6)	☑		600	Nervous system; eyes	☑
Xylenes (m-, o-, p-)	☑		700	Nervous system; respiratory system	☑

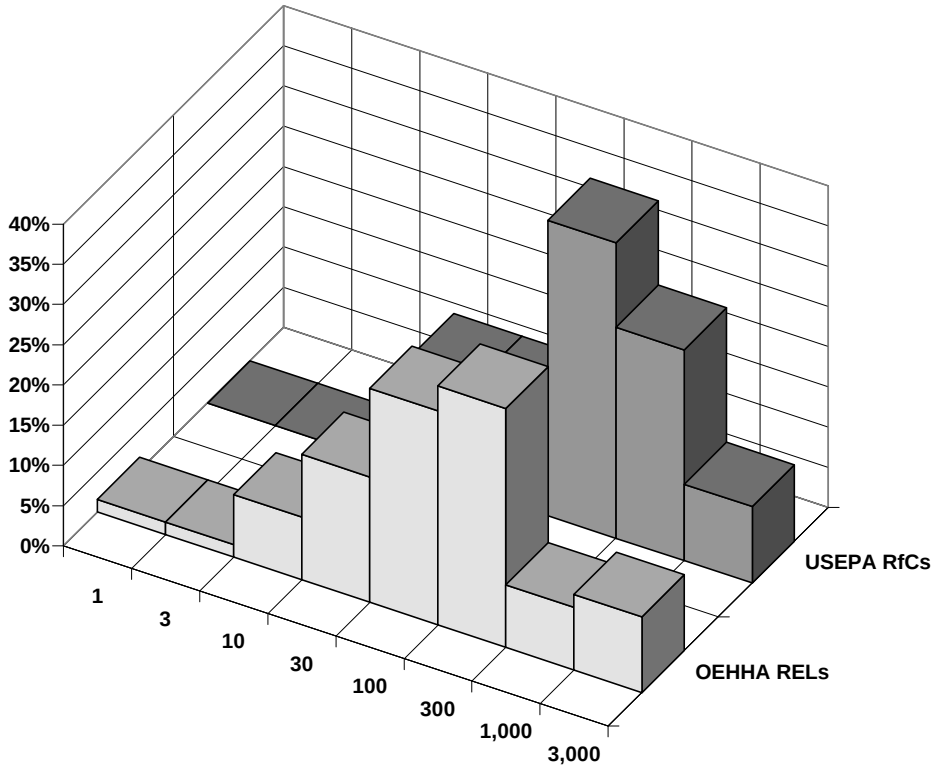
Table 9. Geometric Mean of the Uncertainty Factors Incorporated for Proposed OEHHA Chronic Inhalation RELs and U.S. EPA RfCs

Uncertainty Factor	***OEHHA RELs Derived from Inhalation Data***	***U.S. EPA RfCs***
LOAEL	2.6	1.9
Subchronic	2.2	2.1
Interspecies	2.4	2.7
Intraspecies	9.3	8.9
Modifying factor	1.0	2.4
Cumulative	134	238

Table 10. Comparison of Relative Use of Human and Animal Data in Deriving U.S. EPA RELs and Proposed OEHHA Chronic Inhalation RELs

Reference Level	***Human data***	***Animal data***
U.S. EPA RfCs	9/43 (21%)	33/43 (79%)
Proposed OEHHA chronic inhalation RELs (derived from inhalation data)	19/63 (30%)	43/63 (70%)
Proposed OEHHA chronic inhalation RELs (including those derived from non-inhalation data)	20/75 (27%)	56/75 (73%)
Overall	29/118 (25%)	89/118 (75%)

Figure 2. Distribution of Cumulative Uncertainty Factors for Inhalation Data Based OEHHA Chronic Inhalation RELs and U.S. EPA RfCs



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