Description of Uncertainty Factors: Excerpt from OEHHA (2008)

Uncertainty factors (UFs) are used in noncancer risk assessments when insufficient data are available to support the use of chemical-specific and species-specific extrapolation factors. The following information is excerpted from the recently updated OEHHA (2008) guidance document on derivation of noncancer reference exposure levels (RELs).

The table below (Table 4.4.1 from OEHHA, 2008) lists the types of UFs applied in noncancer risk assessment and provides the typical default values assigned to the factors. The excerpts from the OEHHA (2008) document that follow the table give more detailed information on each of the uncertainty factors, including the use of chemical-specific information where possible and the scientific basis for the default UFs. The focus of the excerpts is on information most relevant to noncancer assessments for a worker population. Thus, the section numbers below (taken from OEHHA, 2008) are not sequential, as certain sections were not included here. To see the full discussion and obtain the citations for the references in the excerpt below, consult OEHHA (2008).

Reference:

Office of Environmental Health Hazard Assessment (OEHHA, 2008). Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Air Toxic Hot Spots, Risk Assessment Guidelines.

Available to download at: http://www.oehha.ca.gov/air/hot_spots/rels_dec2008.html

TABLE 4.1.1 POSSIBLE DEFAULT UNCERTAINTY FACTORS USED IN DERIVING ACUTE, 8-HOUR AND RELS

Method or Factor	***Values Used***	***REL types***
LOAEL uncertainty factor (UF_L)		
Values used:	1 NOAEL or benchmark used 6 LOAEL, mild effect 10 LOAEL, severe effect 10 LOAEL, any effect	A, 8, C A A 8, C
Interspecies uncertainty factor (UF_A)		
Values used for a combined interspecies uncertainty factor (UF_A):	1 human observation √10 animal observation in nonhuman primates 10 where no data are available on toxicokinetic or toxicodynamic differences between humans and a non-primate test species	A, 8, C
Values used for the toxicokinetic component ($UF_{A\text{-}k}$) of the interspecies uncertainty factor:	1 where animal and human PBPK models are used to describe interspecies differences 2 for residual toxicokinetic differences in studies of non-primate species using the HEC approach or incomplete DAF model √10 non-primate studies with no chemical- or species-specific kinetic data	A, 8, C
Values used for the toxicodynamic component ($UF_{A\text{-}d}$) of the interspecies uncertainty factor:	1 where animal and human mechanistic data fully describe interspecies differences. (*This is unlikely to be the case.)* 2 for residual susceptibility differences where there are some toxicodynamic data √10 non-primate studies with no data on toxicodynamic interspecies differences	A, 8, C

TABLE 4.1.1 POSSIBLE DEFAULT UNCERTAINTY FACTORS USED IN DERIVING ACUTE, 8-HOUR AND RELS

Method or Factor	***Values Used***	***REL types***
Intraspecies uncertainty factor (UF_H)		
Values used for the toxicokinetic component of the intraspecies uncertainty factor, (UF_{H-k}) for systemic toxicants:	1 human study including sensitive subpopulations (e.g., infants and children) 1 where a PBPK model including measured inter-individual variability is used √10 for residual susceptibility differences where there are some toxicokinetic data (e.g., PBPK models for adults only) 10 to allow for diversity, including infants and children, with no human kinetic data	A, 8, C
Values used for the toxicodynamic component of the intraspecies uncertainty factor, (UF_{H-d}):	1 Human study including sensitive subpopulations (e.g., infants and children) √10 Studies including human studies with normal adult subjects only, but no reason to suspect additional susceptibility of children 10 Suspect additional susceptibility of children (e.g., exacerbation of asthma, neurotoxicity)	A, 8, C
Subchronic uncertainty factor (UF_S)		
Values used:	1 Study duration >12% of estimated lifetime √10 Study duration 8-12% of estimated lifetime 10 Study duration <8% of estimated lifetime	C
Database deficiency factor (UF_D)		
Values used:	1 No substantial data gaps √10 Substantial data gaps including, but not limited to, developmental toxicity	A, 8, C

Notes for Table 4.4.1: A = acute REL; 8 = eight-hour REL; C = chronic REL. "Toxicodynamic" refers to the processes involved in the toxic action at the system, tissue or cellular level. "Toxicokinetic" refers to processes involved in deposition, absorption, distribution, metabolism and excretion of the toxicant. Individual UFs are rounded after multiplication, so two factors of √10 cumulate to 10, but one is rounded down to 3. Cumulative UF values are normally limited to between 1 and 3,000: if the latter value is exceeded it is generally taken to indicate that the source data are insufficient to support derivation of a REL. The table presents suggested default values in particular situations; these may be modified in either direction by more specific data relating to the test and target populations considered.

4.4.2 Extrapolation and Uncertainties in the Database

A BMC or observed NOAEL may be a concentration where adverse effects are observable rarely, or not at all, in a specific study, but this level may not be without effect among the general human population, which includes individuals who are more sensitive than average, or who may receive repeated or extended exposures. In development of a REL, systematic extrapolation methods must be used to relate the dose-response characteristics observed in the experimental (or epidemiological) data to those expected for the general human population in a community exposure situation. The REL must also address, and where possible quantify, uncertainties in the available data and variability in the target population. These issues are accounted for by means of explicit extrapolation models where these are available and appropriate input data can be obtained. Where these explicit models are unavailable, UFs have been used extensively with human or animal toxicity data to estimate "safe" or "acceptable" exposure levels for humans. Extrapolation methods are used by OEHHA in deriving RELs to account for exposure duration adjustments and discontinuity, interspecies differences in exposure and pharmacokinetics, and expected differences among members of the target human population (e.g., differences between adults and children). Extrapolation methods are based on identification of measurable attributes that are judged to be relevant to addressing an area of concern, and incorporation of these data into, ideally, a mechanistic model, or (failing an established mechanistic model) an empirical mathematical model of the exposure and toxicological response.

4.4.3 Types of Uncertainty and Variability

Model-based extrapolation procedures or, where these are unavailable, UFs are used by OEHHA in deriving RELs to account for:

(1) the magnitude of effect observed at a LOAEL compared with a NOAEL (Dourson and Stara, 1983; Mitchell et al., 1993);

(2) for chronic RELs, the potentially greater effects from a continuous lifetime exposure compared to a subchronic exposure (Lehman and Fitzhugh, 1954; Bigwood, 1973; Dourson and Stara, 1983).

(3) the potentially greater sensitivity of humans relative to experimental animals not accounted for by differences in relative inhalation exposure (Vettorazzi, 1977; Dourson and Stara, 1983);

(4) the potentially increased susceptibility of sensitive individuals, for example due to inter-individual variability in response (Vettorazzi, 1977; Hattis, 1996a; Ginsberg et al., 2002; Miller et al., 2002; Dorne and Renwick, 2005a) and

(5) other deficiencies in the study design (Lehman and Fitzhugh, 1954; Bigwood, 1973; Dourson and Stara, 1983; NRC, 1993; U.S. EPA, 1993).

The use of UFs for determining "safe" or "acceptable" levels has been discussed extensively in the toxicological literature (Vettorazzi, 1977; NRC, 1977-1987; Dourson and Stara, 1983; Alexeeff et al., 1989a; Alexeeff and Lewis, 1989b; U.S. EPA, 1994a; Dourson et al., 1996). As noted above, UFs are used when insufficient data are available to support the use of chemical-specific and species-specific extrapolation factors. In this document, five UFs will be described (see Table 4.4.1):

(1) LOAEL uncertainty factor – UF_L;

(2) subchronic uncertainty factor – UF_S;

(3) interspecies uncertainty factor – UF_A;

(4) intraspecies uncertainty factor – UF_H, and

(5) database deficiency factor - UF_D.

Historically, UFs have most often been order-of-magnitude factors, indicating the broad level of uncertainty in addressing the area of concern (Dourson and Stara, 1983). More recently, OEHHA and the U.S. EPA have used intermediate UFs, usually having a value of 3 (the rounded square root of 10) in areas estimated to have less residual uncertainty (U.S. EPA, 1994a). In special cases, other UF values may be considered appropriate. While the actual value of $\sqrt{10}$ is 3.16, in practice, a single intermediate UF is calculated as 3 rather than 3.16, while two such intermediate UFs cumulate to 10. Thus, cumulative UFs could equal 1, 3, 10, 30, 100, 300, 1000, or 3000.

4.4.4 Application of Mechanistic Data in Interspecies and Intraspecies Extrapolation

It is necessary to determine what (if anything) is known of the mechanism of action of the toxic agent as a first step in evaluating which extrapolation methodologies or UFs should be applied to the point of departure (BMC, NOAEL or LOAEL) for the extrapolation to estimate a safe level for human exposure. This will determine whether there are data to support a mechanistic model, or if a more generic model would be applicable. If the information necessary to construct a model is lacking, then the UF approach is necessary. The size of the UFs used is based on information about variability in response to broad classes of toxic agents, tests systems and target populations, and is necessarily a policy choice. It may nevertheless be possible to narrow the bounds of the uncertainty if specific features such as the site of action (either the respiratory system or other point of first contact, as used in the HEC approach, or a systemic target), and the general type of toxic response can be identified.

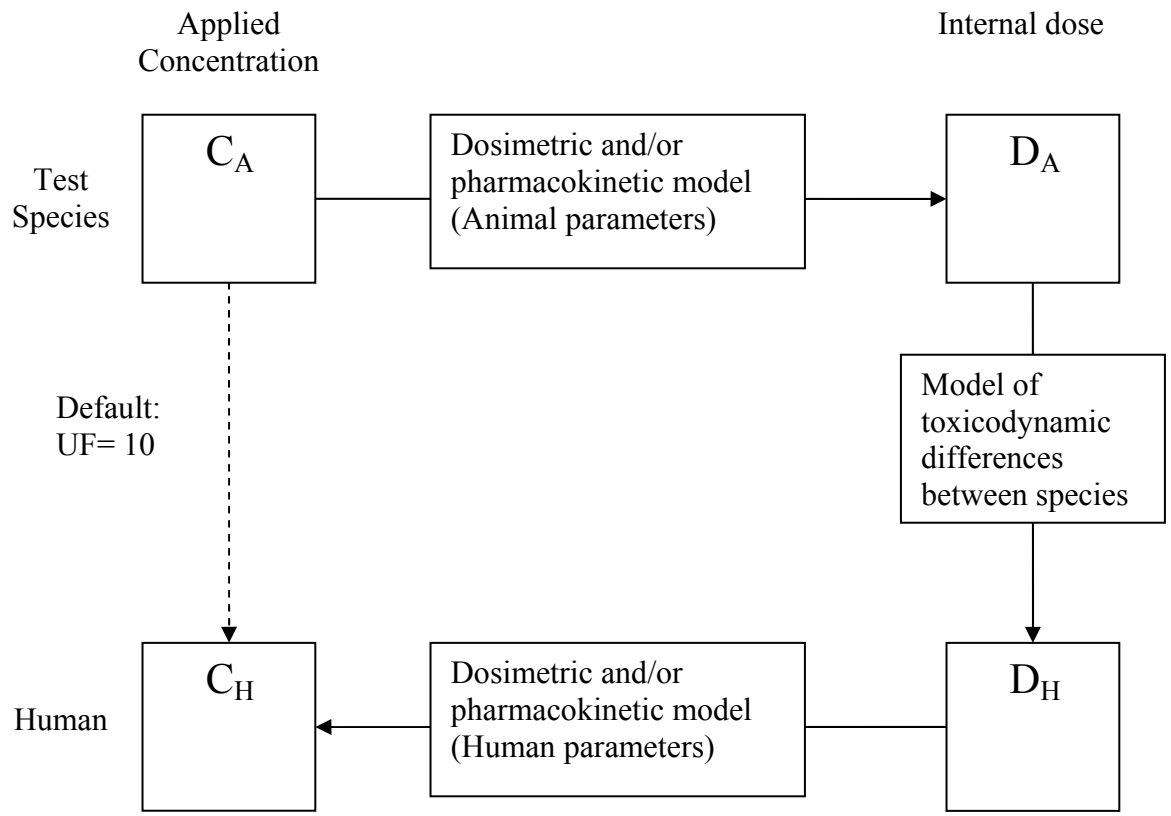
Extrapolation generally will be necessary to cover two basic areas of difference between the test system (e.g., animals in a toxicological experiment) and the target human population:

a) differences in absorption, distribution, metabolism and excretion (dosimetric and toxicokinetic adjustments), and
b) differences between species or individuals in their sensitivity to the toxic material (either the original substance or a metabolite) at the site of its action (toxicodynamic adjustments).

As will be described in greater detail below, both these types of difference need to be considered either by means of a model, or by an UF, both for extrapolation from the test species (usually a rodent) to the human, and to allow for the likely range of inter-individual variation among members of a human population which is diverse in age, sex, genetic background, health status, diet, and lifestyle.

A general scheme for extrapolation between test and target species is shown Figure 4.2 below.

FIGURE 4.2. INTERSPECIES EXTRAPOLATION



C_A = Applied concentration (e.g., BMC, LOAEL or NOAEL) in an animal experiment.
D_A = Dose of compound or active metabolite at site of action in animal.
D_H = Similarly effective dose of compound or active metabolite at site of action in a human.
C_H = Human equivalent applied concentration.

In this diagram and that which follows, the term "model" is used in the formal sense rather than implying that a detailed quantitative model of the transition is actually available. In practice such a quantitative model is usually not available, or may be incomplete, in which case the uncertainty caused by this deficiency needs to be recognized by inclusion of an UF. As will be described in Sections 4.4.7.2.1 and 4.4.8.2.1 below, detailed models are sometimes available to describe interspecies and intraspecies differences in pharmacokinetics. Unfortunately at this time there are few cases where quantitative pharmacodynamic models are available, so these extrapolations almost always utilize UFs to account for pharmacodynamic differences within humans and between species. Model parameters may be defined as single values appropriate to the test species and the default human, or as distributions representing uncertainty in the values of these parameters. In principle, variability in the values of key parameters in the animal

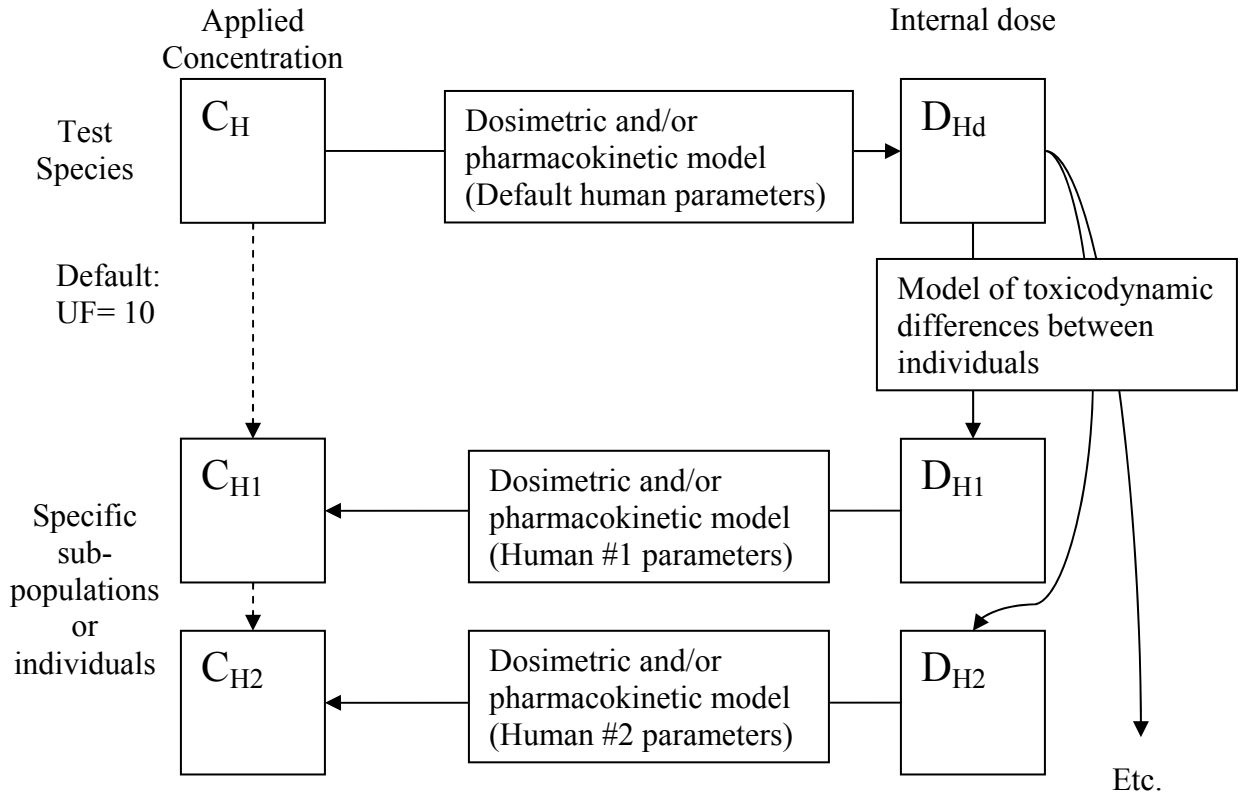
models could also be represented by distributions, although in practice such variation is usually small due to the standardized genotype and environment of laboratory animals.

A similar scheme (Figure 4.3) may be applied in considering extrapolation from the default adult specified in the interspecies extrapolation to other specific individuals, or (when a quantitative model is available, by replacing defined single parameter values with distributions) to a range of such individuals encompassing the expected extent of variation in the target population (intraspecies extrapolation).

If C_H is the human equivalent concentration of an effect threshold such as the NOAEL or $BMCL_{05}$ (adjusted for duration and for any other uncertainties), and a sufficient number of human cases (*i*), or an appropriate range of a distribution, is considered so that all but rare hypersensitive individuals are represented, then the REL is set at the level of the lowest individual equivalent concentration, or at an appropriate lower bound on the distribution of C_{Hi} values. In order to provide a REL, which is protective of children's health, it is necessary that at least some of the cases considered, or distribution values included in the models, represent children.

A selection of useful model types and extrapolation procedures is given below. It should be noted that this selection is exemplary rather than prescriptive, and that the models used in any particular case will be determined by the availability of data and mechanistic information for that toxic agent and type of effect.

FIGURE 4.3 INTRASPECIES EXTRAPOLATION



C_H = Human equivalent applied concentration (default human adult).
D_{Hd} = Dose of compound or active metabolite at site of action in a default human.
D_{H1} = Similarly effective dose at site of action in human #1.
D_{H2} = Similarly effective dose at site of action in human #2.
C_{H1} = Equivalent applied concentration in human #1
C_{H2} = Equivalent applied concentration in human #2

4.4.5 Extrapolating from LOAELs to NOAELs

The use of the BMC methodology allows derivation of a point of departure suitable for REL determination even when an actual NOAEL has not been observed in the experiment. Since this approach uses an empirical model fit to the actual experimental data over the range of doses examined, it is the preferred way to address the uncertainty inherent in deriving a REL from such an experiment. When this model-based extrapolation is not possible due to limitations of data quality or reporting, an observed LOAEL may be used as the basis of the REL. The UF approach is then used to estimate a health-protective level. This is a last resort, when data are entirely unsuitable for a benchmark dose analysis (e.g., all dose groups except control show 100% response rate). It should be recognized that use of the LOAEL methodology fails to reveal or quantify the actual uncertainty and variability contained in the source data, and can be influenced by the study design. A one-to-ten-fold uncertainty factor (UF_L) has been proposed to

account for the higher health risk potentially associated with a LOAEL compared with use of a NOAEL (U.S. EPA, 1994a). Historically, a factor of 10 has been used in U.S. EPA and OEHHA assessments. This UF_L is applied to estimate a threshold level (NOAEL) from the LOAEL:

$$LOAEL/UF_L = NOAEL$$

The relationship between LOAELs and NOAELs for acute, and some chronic, exposures has been examined by various authors. The effectiveness of a 10-fold LOAEL to NOAEL UF was confirmed for several data sets with inhalation exposure (Gift et al., 1993; Kadry et al., 1995; Alexeeff et al., 1997; Alexeeff et al., 2002) and oral exposure (Dourson and Stara, 1983). 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. (2002) evaluated 215 acute inhalation studies for 36 chemicals and reported that the range of LOAEL to NOAEL ratios for mild effects had 90th and 95th percentiles of 5.0 and 6.3, 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 (Alexeeff et al., 1997). Kadry et al. (1995) showed that among a small data set (four 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 LOAEL and the hypothetical NOAEL is uncertain.

On the basis of these data and following earlier precedents, OEHHA considers a 10-fold UF_L for extrapolation from a LOAEL to a NOAEL to be protective when applied to all types of studies. However, OEHHA has also attempted to delineate situations where UFs less than 10 could be used in the REL development process. The use of an UF less than 10 may be appropriate under certain circumstances, but application of UFs less than 10 has sometimes been somewhat subjective, and guidance as to when it is appropriate is lacking. Consequently, OEHHA has developed criteria for use of an intermediate UF for acute RELs (see Section 5). These criteria are based primarily on data from acute exposures. When the effect is of low severity, the exposure is likely to be relatively nearer to the NOAEL. Conversely, more severe effects indicate the likelihood of a higher LOAEL to NOAEL ratio. However, extending this concept to evaluating chronic exposures or repeated 8-hour exposures is more complicated in this case because multiple effects are more likely to be seen, and serious and persistent effects such as developmental neurotoxicity may occur at low doses. Further, the 8 hour RELS are for repeated exposures, and chronic RELs are for continuous exposure – the exposure does not cease, so effects that are of no consequence for a short period of time may indeed be adverse chronically. Recommended default values of UF_L for acute, eight-hour and chronic REL derivations are therefore as follows:

(1) Where the observed effect level used as the basis of the REL is a NOAEL or equivalent benchmark, the value of UF_L is 1.

(2) When the acute REL is based on a LOAEL, where the observed effect is mild for acute exposures (U.S. EPA grade 5 or below, Table 5.5.1), the value of UF_L is 6.

(3) When the acute REL is based on a LOAEL, where the observed effect is moderate to severe, the value of UF_L is 10.

(4) When the chronic REL is based on a LOAEL, the value of UF_L is 10; except in chemical-specific circumstances where there is an indication that the LOAEL is closer to the NOAEL. One such indicator used in the previous guidance is when the percent of the population responding at the LOAEL is ≤ 30.

(5) When the 8-hour REL for repeat exposures is based on a LOAEL, and the effect is essentially an acute response, then the guidelines for the acute REL derivation are followed. When the 8-hour REL for repeat exposures is based on a study where the effect is essentially a chronic response, the guidelines for chronic REL derivation are followed.

These default values may be replaced by more specific values where appropriate data are available (e.g., for specific toxicological endpoints or chemical classes). However, the use of a LOAEL as the basis of a REL is to be avoided wherever possible, by using data sets in which a NOAEL is also observed or, preferably, by applying the BMC methodology to a study where a range of response levels with increasing dose is measured.

4.4.7.3 Uncertainty Factor for Animal to Human Extrapolation (UF_A)

Where data are insufficient to allow development of an extrapolation model, the default approach has been to apply a 10-fold uncertainty factor (UF_A) to animal data 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, to the specific chemical. However, the UF is based on the potential for greater sensitivity of humans and the larger surface area of humans compared with experimental animals (Rall, 1969; Weil, 1972; Krasovskii, 1976; Lewis and Alexeeff, 1989). This UF methodology is in contrast to the practice used in cancer risk assessment where an allometric surface area correction and a 95% confidence interval of the slope of the dose response are used. The UF approach was used by the U.S. EPA (1994a) and recommended by NRC (1977-1987) for drinking water standards. Dourson and Stara (1983) provided limited support for the concept of a ten-fold UF. Khodair et al. (1995) showed that among a small data set (six chemicals) animal NOAEL to human NOAEL ratios were less than four. 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.
The U.S. EPA has used human equivalent concentration (HEC) extrapolation and a 3-fold UF_A for RfC derivation (U.S. EPA, 1994a). In the U.S. EPA method, this intermediate value is chosen since the HEC derivation is assumed to have accounted for the toxicokinetic part of the difference between the species. However, this HEC extrapolation addresses only some of the differences; in particular, only respiratory regional exposure and deposition of the parent compound is considered; any differences in metabolism and elimination are ignored. The remaining 3-fold UF is to account for pharmacodynamic or response differences between the species. This modified approach was also previously used by OEHHA for derivation of chronic RELs where sufficient data were available. OEHHA continues to recommend the HEC methodology where data are insufficient to support a full PBPK model. However, it is recommended that the toxicokinetic part of the UF_A be reduced to 2, rather than 1 to reflect the presence of remaining uncertainties in toxicokinetics due to metabolism and excretion. In some

instances, it may be appropriate to retain a larger UF_A, for example if differences in deposition between the test species and humans are known to be large. OEHHA has also examined the effect of child-specific parameters on the HEC calculation.

Where both chemical- and species-specific data are unavailable, and therefore a HEC cannot be estimated, a 10-fold UF_A is normally used. The 10-fold default UF_A would only be applied after consideration of other factors that potentially affect the validity of the default assumption. Such factors include differences between humans and the test species in absorption, distribution, and metabolism, which would serve as a basis for predicting interspecies differences in susceptibility. In some cases, data may indicate that a larger UF_A is appropriate. An exception is made for data from studies of non-human primates, where a default UF_A of $\sqrt{10}$ is used because of their similarities to humans (See Table 4.4.1).

4.4.8.2.2 Uncertainty Factor for Variability within the Human Population (UF_H)

Where data are insufficient to permit development of a reliable model, an intraspecies uncertainty factor (UF_H) has traditionally been used to account for variability within the human population. This factor is intended to account for the greater susceptibility to chemical toxicity of various sensitive subpopulations, including infants and children. Previously, OEHHA has, like the U.S. EPA generally applied a 10-fold UF_H to address variability in response among individual members of the general population (U.S. EPA, 1994a).

4.4.8.2.2.1 Contribution of Kinetic Factors to UF_H

The variability in human response to toxicants may result from differences in toxicokinetics and toxicodynamics. The UF_H typically used in OEHHA's risk assessment methodology is thus considered to be composed of two sub-factors to allow for both toxicokinetic (UF_{H-k}) and toxicodynamic (UF_{H-d}) differences (Table 4.4.1).

Some studies suggested that the overall 10-fold factor was reasonable to account for intraspecies variability in humans. Gillis et al. (1997) suggested, based on modeled intraspecies variability, that for chronic exposures, a 10-fold factor will protect the 85th percentile. Within this overall 10-fold UF_H, the values of the two sub-factors UF_{H-k} and UF_{H-d} were both assumed to be $\sqrt{10}$, which equals 3.16. However, more recent studies have indicated that a value higher than $\sqrt{10}$ should be considered for the pharmacokinetic component of the intraspecies uncertainty factor (UF_{H-k}), especially for substances that are bioactivated, since the enzymes involved in both Phase I (primarily CYP) and Phase II (numerous conjugating reactions) of xenobiotic metabolism have shown pronounced polymorphism in many cases (Renwick and Lazarus, 1998; Hattis et al., 1999).

4.4.8.3 <u>Contribution of Toxicodynamic Factors to UF_H</u>

A subfactor UF_{H-d} to account for toxicodynamic differences between individuals has generally been assigned a default value of $\sqrt{10}$. This assumption is consistent with the previous assumptions about likely human interindividual variability. However, although there are some specific data on individual susceptibility for pharmaceutical agents (for example, bumetanide: (Skowronski et al., 2001)), there is little basis other than this precedent for setting a default value

of UF_{H-d} that would be suitable for the kind of toxic chemicals of concern to the Air Toxics Hot Spots program. However, there are grounds for suspecting that the differences between infants or children and adults may be greater for certain endpoints, as discussed in Section 3.3.2. In these cases (such as chemicals causing neurotoxicity, or suspected of causing or exacerbating asthma) it may be appropriate to select a different, and larger, value for UF_{H-k} on a chemical-specific basis. Such choices will be explained and justified in the description of the individual RELs where they are applied.

4.4.9 Uncertainty Associated with Deficiencies in the Overall Database

In some cases, the database on an environmental chemical may be insufficient to be confident that the REL will be protective. Since this type of deficiency necessarily implies a lack of adequate data, it is accommodated by application of a database deficiency uncertainty factor (UF_D), usually a value of $\sqrt{10}$ (Table 4.4.1). This is similar to the U.S. EPA modifying factor of 1 to 10 to account for data uncertainties in their procedures for calculating RfDs (U.S. EPA, 1993). As noted in U.S.EPA (2002a), "the database UF is intended to account for the potential for deriving an underprotective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity. In addition to identifying toxicity information that is lacking, review of existing data may also suggest that a lower reference value might result if additional data were available. Consequently, in deciding to apply this factor to account for deficiencies in the available data set and in identifying its magnitude, the assessor should consider both the data lacking and the data available for particular organ systems as well as life stages." Although this was not used in the previous version of the Hot Spots guidance, OEHHA now recommends an additional three-fold UF to apply in developing an REL for chemicals with substantial toxicological data gaps, including, but not limited to, developmental toxicity. In some cases, it may be appropriate to apply a database deficiency factor larger than three-fold. The need for the additional database deficiency UF will be evaluated on a chemical-by-chemical basis, and justified in the individual REL summaries. Examples of situations where this might be considered appropriate include where a structurally related chemical indicates potentially more toxicity for the compound of concern than has been evaluated experimentally. Thus, structure-activity analysis may be brought to bear on use of the database deficiency factor. Another example is where there is a metabolite for which data indicate a concern for a type or severity of toxic response which has not been evaluated experimentally for the parent compound. Similarly, this factor might be applied where a preliminary study was reported but the sample sizes used were too small or the number of doses used was inadequate to characterize an effect accurately.

4.4.9.1 <u>Database Deficiency Factor for Lack of Developmental Toxicity Data</u>

Under SB 25, OEHHA is mandated to ensure that our health standards take into account the potential greater vulnerability of infants and children to chemical exposure and toxicity. Some chemicals can affect the developing fetus or development in infants and children. If studies in immature animals are lacking, it may be impossible to predict effects on developing organs and tissues. OEHHA will use a database deficiency factor (UF_D), with a default value of between $\sqrt{10}$ and 10, when animal developmental studies are not available for a chemical in order to help ensure that RELs protect infants and children. The rationale for application of this uncertainty factor will be presented in the individual toxicity summary.

7.2.2 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. The OEHHA chronic RELs, however, are intended to protect the general public who could be exposed over their entire lifetime. In traditional toxicity testing paradigms, studies that expose experimental animals for at least 12% of the expected lifetime for the test species are considered chronic exposure studies. RELs based on such chronic animal studies are not adjusted for less-than-lifetime exposures. Similarly using this convention, 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. Although a potential source of uncertainty, this approximation appears reasonable for the majority of chemicals.
There are certain situations, such as in cancer risk assessment, where dependence on cumulative dose over long periods up to and including a lifetime (subject to weighting during critical periods early in life) may reasonably be assumed. Models of dose-time cumulation over relatively short timescales have been explored for various acute toxicity endpoints, and are described elsewhere in this document. However, for most situations involving chronic noncancer toxicity an explicit description of the time/dose relationship over longer intervals (including several weeks or months to a full lifetime) is not available. Toxicity studies tend to be conducted for specific periods representing subchronic, chronic and lifetime exposures, but these are seldom directly related to one another, and frequently report different endpoints. Subchronic exposures are those with duration less than 12% of expected lifetime for the test species, except in the case of mice and rats where the U.S. EPA has considered 13 weeks subchronic. Therefore, the default approach to extrapolating from subchronic to chronic exposures used by OEHHA and the U.S. EPA is to use a 1 to 10-fold uncertainty factor, UF_S for subchronic exposures.

The UF_S to extrapolate from subchronic to chronic exposures is determined as follows:

(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 ≥12% of expected lifetime were given a 1-fold UF.

Average life spans assumed for humans and experimental animals are presented in

TABLE 7.2.1. AVERAGE LIFE-SPAN FOR HUMANS VS. EXPERIMENTAL ANIMALS

Species	Approximate average Life-span (years)[1]	Subchronic exposure duration (weeks)[2]
Human	**70**	**≤ 364**
Baboon	55	≤ 286
Cat	15	≤ 78
Dog	15	≤ 78
Guinea pig	6	≤ 31
Hamster	2.5	≤ 13[3]
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 12% of average lifetime (U.S. EPA, 1994a).
3 Special rule adopted by U.S. EPA that exposures of 13 weeks or less are subchronic regardless of the species involved (U.S. EPA, 1994a).

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 chlorinated chemicals) subchronic NOAEL to chronic NOAEL ratios were less than 10. Nessel et al. (1995) reported that for 9 inhalation studies the mean and median subchronic NOAEL to chronic NOAEL ratios were 4.5 and 4.0 respectively (range = 1 to 8). However, in a study of published animal NOAELs for a larger group of pesticides, Nair and associates (1995) found that 19 of 148 (13%) of the subchronic to chronic NOAEL ratios differed by more than 10-fold. 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; the value of 10 represents the 90th percentile (Swartout, 1997). This supports the selection of a default maximum value of 10 for the UF_S.