

Air Toxics Hot Spots
Risk Assessment Guidelines

Technical Support Document

For the Derivation of

Noncancer Reference Exposure Levels

Air Toxicology and Epidemiology Branch
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Executive Summary

This document describes the methodology used in developing acute, 8-hour and chronic Reference Exposure Levels (RELs) for use in risk assessments conducted under California's Air Toxics Hot Spots and Toxic Air Contaminants programs. RELs are concentrations of a chemical at or below which adverse noncancer health effects are not anticipated to occur for a specified exposure duration. The basic methodology for REL development used previously by the Office of Environmental Health Hazard Assessment (OEHHA) and other agencies undertaking public health risk assessment remains unchanged. This consists of identification of a point of departure, such as an exposure level in an animal experiment or an epidemiological study at which no adverse effects (or at least minimal adverse effects) are observed, or a benchmark dose (a statistical estimate of a low response rate, typically 5%, in the dose response curve for the chemical of concern). Extrapolation from this point of departure to a health protective level for the target human population is by means of explicit models where possible, but more often by means of uncertainty factors.

This document addresses the SB 25 mandate to ensure that OEHHA's risk assessment methods adequately protect infants and children, and incorporates scientific advances since the methodologies for acute and chronic RELs were first developed. Methods are added for developing 8-hr RELs in addition to the traditional acute REL for infrequent 1-hr exposures, and the chronic REL for long-term, continuous exposures. We harmonize the methodologies for acute, eight-hour and chronic RELs to the extent possible. This document also defines special procedures for derivation of RELs based on certain toxicological endpoints such as trigeminal nerve transmitted irritation of the eyes, nose, and upper airway.

The following sections summarize the specific changes in methodology relative to the previous version of the Hot Spots guidelines for evaluation of noncancer health effects. These changes are described in detail in the main body of this report.

Use of Specific Models Rather than Uncertainty Factors when Possible

There are many information gaps in the data available for evaluating noncancer health impacts of chemicals and setting appropriate RELs. The standard approach has been to divide an animal no-observed-adverse-effect-level (NOAEL) by uncertainty factors (UFs) to help ensure that public health is protected. In recent years such techniques as the benchmark dose method (BMD) and physiologically based pharmacokinetic (PBPK) modeling have taken advantage of available data to quantitatively address uncertainties in the standard approach to noncancer REL derivation. OEHHA recommends the use of these techniques wherever possible in order to address quantitatively the adequacy of acute and chronic RELs to protect the health of both children and adults. However, in some cases the available dose-response data are not suitable for application of the benchmark dose approach. Furthermore, it must be noted that data are not available for many chemicals to use PBPK modeling. Thus, while PBPK is a useful tool, the

traditional paradigm (e.g., NOAEL or BMD divided by UFs) will still be most frequently used.

Value of Default Intraspecies Uncertainty Factor (UF_H)

The uncertainty factor used to account for intraspecies (inter-individual) variability in the human population (UF_H) has previously been assigned a default value of 10. Investigators have proposed subdividing the intraspecies uncertainty factor into $\sqrt{10}$ for toxicokinetic (UF_{H-k}) and $\sqrt{10}$ for toxicodynamic (UF_{H-d}) subfactors. The toxicokinetic uncertainty factor is meant to cover differences in humans in disposition of the toxicant (absorption, distribution, metabolism, and elimination), while the toxicodynamic uncertainty factor is meant to account for differences in response at the receptor level. However, it appears that a default toxicokinetic value of $\sqrt{10}$ may not be adequate for all chemicals, routes of elimination, or for the entire population, in particular the subpopulation of infants. A toxicokinetic subfactor of 10 is therefore recommended to protect infants, unless data are available to indicate that this subpopulation is not at higher risk due to differences in toxicokinetics. There may also be cases where a toxicokinetic subfactor larger than 10 is warranted based on chemical-specific factors. Currently, there are scant data available to indicate whether or not the toxicodynamic subfactor of $\sqrt{10}$ adequately protects infants and children. It is known that the developing organism can be many-fold more sensitive to toxicants such as lead (Pb), mercury (Hg), and diethylstilbestrol (DES) than a mature organism. Differentiating the contribution of toxicokinetic (TK) and toxicodynamic (TD) differences is difficult. Where data indicate, a toxicodynamic uncertainty factor (UF_{H-d}) larger than the traditional value of $\sqrt{10}$ may be used. For example, there are toxicological endpoints of particular concern for infants and children in terms of increased susceptibility such as neurotoxicity (OEHHA, 2001). Potential red flags or triggers that may indicate the need for the use of an increased UF to account for developmental toxicity include: neurotoxicity and neurobehavioral deficits, effects on the thyroid, mutagenicity, carcinogenicity, immunotoxicity, structure activity relationship models, endocrine agonist or antagonist activity, changes in cell proliferation, alteration of signal transduction and/or gene expression, or disruptions in maternal homeostasis. In addition, it is important to recognize impacts on the respiratory system by compounds that may induce or exacerbate asthma, as children are more impacted by asthma than adults, and allergic asthma may be viewed as resulting from impacts on the developing immune and respiratory systems. The assessor may increase the intraspecies uncertainty factor for toxicodynamics in these cases, particularly where no data exist for early life stage exposure.

Additional Three-fold Database Deficiency Factor

The United States Environmental Protection Agency (U.S. EPA) applies a general UF to Reference Concentrations (RfCs) and Doses (RfDs) for chemicals lacking adequate toxicological studies (U.S. EPA, 2002a) to account for the potential for deriving an under-protective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity. 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 a 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. This partially addresses the mandate under SB 25 to ensure that acute, chronic and eight-hour RELs are protective of infants' and children's health. The need for the additional database deficiency UF will be evaluated on a chemical-by-chemical basis and justified in the individual REL summaries.

Available data on mechanisms of toxicity, reactivity, potential for systemic distribution, and structure activity relationships, will be considered in the decision to apply the additional database deficiency UF. In addition, where evidence of effects at lower levels exists but available data are inadequate to use for a quantitative dose-response assessment, consideration will be given to applying a database deficiency UF.

Use of Modified Haber's Law for Duration Adjustments

Previously, OEHHA adjusted the lowest observed adverse effect level (LOAEL) or no observed adverse effect level (NOAEL) in a study by means of the modified Haber's Law procedure if the exposure duration of the study was different from the exposure duration of concern for an acute (1-hour) REL. OEHHA continues to recommend this adjustment, where appropriate, in developing acute RELs (and eight-hour RELs based on acute studies) for systemic toxicity and other endpoints where cumulation over time is anticipated. The current recommendation is to use a default value of 3 for the concentration exponent (n), rather than 2 as before, in the absence of compound-specific information.

The most sensitive health endpoint for a number of acute RELs and some chronic RELs is trigeminal nerve transmitted irritation of the eyes, nose or upper respiratory system. Trigeminal mediated irritation is a receptor-mediated mechanism, sometimes referred to as the common "chemical sense." It appears that Haber's Law does not apply to trigeminal irritation effects, so OEHHA will not use Haber's Law adjustments for instances in which a trigeminal mechanism for eye, nasal and respiratory irritation can be determined for the chemical and concentration of concern.

U.S. EPA Human Equivalent Concentrations (HEC) Procedure and Interspecies Extrapolation

OEHHA's previous guidelines endorsed the use of the U.S. EPA Human Equivalent Concentration (HEC) procedure for chronic RELs. This procedure adjusts the internal dose in an animal inhalation study to the human equivalent dose taking into account differences in breathing rates, surface area of the respiratory tract and deposition. The U.S. EPA HEC procedure has been used in the past instead of the toxicokinetic component of the interspecies uncertainty factor, resulting in a total UF_A of $\sqrt{10}$. However, the HEC procedure only adjusts the exposure and does not account for other aspects of kinetics such as absorption, distribution, metabolism and excretion. OEHHA will continue to use the U.S. EPA HEC procedure when appropriate, but will retain a toxicokinetic factor of 2 as part of the overall interspecies uncertainty factor (i.e., a total UF_A of 6) when it is used, to reflect the greater uncertainty involved in this procedure than in full compound- and species-specific pharmacokinetic models.

Physiologically Based Pharmacokinetic Modeling (PBPK)

PBPK modeling provides a scientific methodology for assessing interspecies differences and intraspecies variability. The PBPK approach requires chemical specific information or estimation techniques for parameters such as blood:air partition coefficients. The PBPK approach is potentially more accurate than other approaches such as the U.S. EPA's HEC procedure because it takes into account more parameters and uses chemical specific information. However, it requires much more data and therefore cannot be applied in all cases. The PBPK approach involves greater uncertainty when required parameters are estimated rather than measured. Validation of PBPK models with independent data is required for them to be used with confidence. While in many cases the variability in a parameter can be adequately incorporated into the model where data exist to characterize the distribution of this parameter, there is still residual uncertainty. Sensitivity analyses should be conducted to ascertain the importance of specific variables in the model output and gain understanding of model uncertainty. OEHHA will use this methodology when possible, instead of the default application of the pharmacokinetic portions of the intraspecies and interspecies uncertainty factors and in preference to the HEC procedure. This change will apply to all three types of Reference Exposure Levels.

Exposure Duration Adjustments for Developmental Toxicity Data

Developmental toxicity presents difficulties as a critical endpoint for REL development. Developmental toxicants can act during narrow temporal windows of fetal and postnatal development, often with multiple and/or poorly understood mechanisms. These chemicals can cause very specific anatomical lesions, more general impacts such as growth retardation, or functional deficits (e.g., behavioral changes). The tissue dose during the window of vulnerability may be the critical factor rather than the total dose, or vice versa. The developmental studies available to determine an acute, eight-hour or chronic REL may provide little clue as to the mechanism, window of temporal vulnerability, or relative importance of total dose versus peak tissue concentration as a determinant of toxicity.

In order to ensure that RELs based on developmental endpoints are protective, OEHHA will not use Haber's Law to adjust the NOAEL or LOAEL in an animal developmental study where the exposure duration of the study and averaging time of the REL (e.g., 1 hr) are different. Instead, since the actual timing and duration of the sensitive period are unknown, the NOAEL will serve as the basis of the REL without a time extrapolation adjustment. This should help ensure that the REL will be protective if the tissue or air concentration during a particular temporal window is more of a determinant of developmental toxicity than total dose.

Eight-hour Reference Exposure Levels

OEHHA has developed a methodology for a new class of Reference Exposure Levels for eight-hour exposure. This new type of REL is needed for the Hot Spots Program in order to refine the risk assessment approach for the large number of facilities that operate and emit chemicals for 8 hours per day, 5 to 7 days per week and to utilize the advanced

features in air dispersion modeling. The air dispersion modeling in the Hot Spots Program has traditionally modeled such emissions as if they were uniformly emitted over 24 hours a day, continuously. Advances in computer capabilities have made it feasible to model more accurately the ground level concentrations of these emission scenarios by using meteorology obtained during the time when the facilities are actually operating (generally daytime). The majority of the highly populated areas in California have significant diurnal-nocturnal meteorological differences that can affect the magnitude of the modeled risk and location of receptors.

The chronic noncancer health impacts on offsite workers (individuals working at other worksites in areas impacted by the facility emissions) have been traditionally assessed with the 24-hour chronic RELs. Because offsite workers generally work 8 hours not 24, the eight-hour RELs will ensure a more accurate assessment of the health impacts of their exposures. The eight-hour RELs will also be useful for assessing the health impacts of exposure of children in schools. The eight-hour RELs should be protective against repeated daily eight-hour exposures, so the pharmacokinetics will need to be carefully considered when setting the standards. The accumulation of the chemical or cumulative injury from repeated daily exposures will need to be considered if either the total dose or the area under the exposure x time curve is the determinant of toxicity (reflecting a possible role of cumulative injury). Therefore, some, but not all eight-hour RELs will have the same basis as the corresponding chronic REL.

Children's Health in Relation to Chronic and Eight-hour RELs

Children and infants show biochemical, physiological and behavioral differences from adults, which can result in higher tissue doses for some chemicals. The significance of the higher tissue doses can vary considerably, particularly for infants, depending on the mechanism of toxicity. This becomes especially important when developing RELs for eight-hour repeated or chronic continuous exposures. The chronic and eight-hour RELs are intended to be "safe levels" of lifetime or repeated eight-hour exposure to a particular chemical. The dose received by inhalation or by non-inhalation routes can be greater for infants and children than for adults in the same setting. Further, the internal dose and the toxicological consequences may be different for infants and children than it is for adults. For some chemicals it may be appropriate to use infant or child parameters for PBPK modeling, when PBPK modeling can be used for a chronic or eight-hour REL. For other chemicals, it may be more appropriate to take into consideration the greater exposure of children during exposure assessment as part of the total lifetime daily dose, and adult parameters for PBPK modeling may be the most appropriate.

Chronic Oral Reference Exposure Levels (RELs) and Children's Health

Some chemicals in the Air Toxics Hot Spots Program are evaluated for multi-pathway exposures; in particular, non-volatile chemicals that deposit on surfaces such as soil or food crops, and/or bioaccumulate in breast milk. Oral RELs are used in risk assessment to address these pathways. Oral RELs are expressed in terms of a "safe" dose in mg/kg body weight (BW)-day. Thus, the higher doses in mg/kg that children receive from oral or dermal pathway exposure, relative to adults, can be directly assessed, when

appropriate, by using the appropriate exposure variables for children (e.g., soil ingestion rates). Whenever possible, OEHHA will assess differences between children and adults using PBPK modeling when developing oral RELs. As in the case of the inhalation RELs, an intraspecies UF of 30 ($\sqrt{10} \times 10$) instead of 10 may be considered in some cases to protect children's health when insufficient data exist for PBPK modeling. Likewise, an additional UF may be considered for toxicodynamic susceptibility or where there are substantial data gaps.

1 Introduction

Hazardous substances are routinely released into the environment as a result of predictable continuous, intermittent or short-term emissions from facilities and predictable process upsets or leaks. As a result, the public living or working in communities surrounding industrial facilities is at risk of being exposed to airborne toxicants. Local air pollution control officers, industrial facility operators, and others have a need for clear guidance regarding the acute and chronic health effects of hazardous substances emitted into the air.

Under the Air Toxics Hot Spots Act (Senate Bill 1731, Statutes of 1992), the Office of Environmental Health Hazard Assessment (OEHHA) was required to develop risk assessment guidelines for stationary sources of airborne toxicants. In an initial response to this mandate, OEHHA followed the recommendations of a then current National Academy of Sciences/National Research Council review (NRC, 1994) of risk assessment practices by establishing uniform, science-based guidelines to be used in the derivation of acute and chronic Reference Exposure Levels (RELs) applicable to the general public exposed routinely to hazardous substances released into the environment. The products of this original guidelines development process were presented in the previous versions of the Technical Support Documents (TSDs) comprising the Air Toxics Hot Spots Risk Assessment Guidelines (OEHHA, 2000a). Application of these RELs in risk assessments is described in the Air Toxics Hot Spots Risk Assessment Guidance Manual (OEHHA, 2003).

This document builds on that earlier effort by updating the methodology for developing RELs for noncancer health endpoints and incorporating additional information that has since become available. In particular, it will address the mandate of the Children's Environmental Health Protection Act (Senate Bill 25, Escutia; Chapter 731, Statutes of 1999; "SB 25") to specifically consider children in evaluating the health effects of Toxic Air Contaminants (TACs). In recent years, there have been growing concerns regarding children's exposure to environmental chemicals; the California Legislature passed SB 25 to help address these concerns. OEHHA's initial response was to develop a prioritization rationale for identifying those TACs most likely to show differential health impacts on infants and children, and to identify the five highest priority TACs as mandated by the statute (OEHHA, 2001). The present document continues the process by presenting revised methodology for the development of RELs for use in the Air Toxics Hot Spots program that takes into account possible differential impacts of TACs or other Hot Spots chemicals on children's health. This document also presents updates to the methodology for REL development that reflect advances in the science of risk assessment since OEHHA's methodologies for acute and chronic RELs were previously presented. These advances include issues explored in various reports by the U.S. EPA (U.S. EPA, 2000; U.S. EPA, 2002a; U.S. EPA, 2004; U.S. EPA, 2006a; U.S. EPA, 2006b; U.S. EPA, 2006c; U.S. EPA, 2007b) and by committees of the National Academy of Sciences/National Research Council (NRC, 2001; NRC, 2007) issued since OEHHA completed development of the previous guidelines, as well as a variety of research papers and reviews published in the general scientific literature.

Quantitative risk assessment is used to derive noncancer health values including acute, chronic and the newly defined eight-hour RELs. OEHHA has aimed for consistency between the

recommended methods for developing acute, eight-hour and chronic RELs, and therefore has consolidated the previously separate guidance for acute and chronic RELs into a single TSD covering all three current types of RELs. The use of benchmark dose methodology, presented as an option in a previous document, is now recommended as the default method when data permit. Additional discussion of pharmacokinetic methods for interspecies extrapolation is presented, and, most importantly, these guidelines respond to new scientific understanding of the diversity in exposure and sensitivity of the human population, especially infants and children.

1.1 Objective

The objective of this document is to present our revised methods for deriving acute, eight-hour and chronic inhalation RELs for hazardous airborne substances. RELs are used in risk assessments to evaluate the potential for adverse noncancer public health impacts from facility emissions or similar localized sources in the Air Toxics Hot Spots Program, and from widespread exposures in the Toxic Air Contaminants program. The REL is an exposure at or below which adverse noncancer health effects are not expected to occur in a human population, including sensitive subgroups (e.g., infants and children), exposed to that concentration for a specified duration. These health-based RELs are applicable to risk characterization of air releases, defined in Health and Safety Code (H&SC) Section 44303, as:

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

These health guidance values are designed to be protective against the noncancer health effects of exposure to airborne chemicals. OEHHA has also developed or endorsed cancer potency factors that can be used to protect the general public against the cancer causing effects of carcinogenic TACs (OEHHA, 2005a). In some cases, a carcinogenic chemical can cause noncancer health impacts and thus may have both types of health values. The acute RELs are designed to protect against a 1-hour exposure duration occurring infrequently (e.g., no more than once every two weeks) (see Section 5.4.1). Chronic RELs are designed to protect against long-term exposure for 24 hours a day, and are used in the Air Toxics Hot Spots risk assessments to evaluate exposures anywhere from about 9 years up to a lifetime. Chronic exposure studies are defined by U.S. EPA and Cal/EPA based on traditional toxicological testing, as 12% of a standard lifetime (e.g., for humans, 8.4 years). This document updates our procedures for acute and chronic RELs in order to ensure that the potentially greater vulnerability of children and infants is taken into consideration. In addition, OEHHA is developing eight-hour RELs, designed to protect against routine exposures of that duration (which approximates an average workday) that could occur as often as daily.

Existing risk assessment methodologies use an uncertainty factor of 10 for intraspecies (inter-individual) variability in the human population (UF_H) which is assumed to protect children as well as other sensitive subpopulations. Such assumptions are crude but data have generally been lacking to use anything other than this assumption for most chemicals. This document evaluates available information in order to determine if more specific guidance for protecting children can

be incorporated into our standard procedures for determining noncancer guidance values protective of children.

One of the challenges in developing a standard public health protective approach for acute, eight-hour and chronic RELs is the variability in available data for different chemicals. Some well-studied chemicals have human data, extensive animal data, and data necessary for pharmacokinetic modeling of tissue dose, while other chemicals may have limited data based on animal studies. OEHHA needs an approach that allows development of a public health protective acute, eight-hour or chronic REL accounting for the potential greater vulnerability of children. Child protective default procedures need to be available in the absence of chemical specific information. However, more scientifically sophisticated methods can be employed when chemical specific data are available.

1.2 Legislative Mandates

OEHHA is responsible for conducting health effects assessments of airborne chemicals, including chemicals listed under Health and Safety Code (H&SC) Section 44321, that are used by the California Air Resources Board in its risk management activities. As defined under the Air Toxics “Hot Spots” Information and Assessment Act of 1987 (Assembly Bill 2588; Chapter 1252, Statutes of 1987; California H&SC Section 44300 *et seq.*, as amended), a risk assessment includes a comprehensive analysis of the dispersion of hazardous substances in the environment and the potential for human exposure, and a quantitative assessment of both individual and population-wide health risks associated with those levels of exposure. This document establishes a standardized procedure for generating the health-based values (acute, eight-hour and chronic RELs) used for assessing noncancer risks within the risk assessment process.

In preparing this document, OEHHA is responding to state legislation enacted in 1992 and 1999. SB 1731 (Chapter 1162, Statutes of 1992) required OEHHA to develop risk assessment guidelines for implementing the “Hot Spots” Act. The original guidelines were published as Technical Support Documents in 1999 – 2000 and as a condensed Guidance Manual in 2003 (OEHHA, 2003). This revision is in response to the Children’s Environmental Health Protection Act (SB 25), which requires the California Environmental Protection Agency (CalEPA) to consider children specifically in setting Ambient Air Quality Standards (AAQS) and in developing criteria for Toxic Air Contaminants (TACs). SB 25 requires OEHHA to consider the following in its health effects assessments and recommendations:

- (1) exposure patterns among infants and children that result in disproportionately high exposure,
- (2) special susceptibility of infants and children,
- (3) effects of simultaneous exposures to compounds with the same mechanisms of action, and
- (4) any interactions of air pollutants.

The law requires OEHHA to evaluate available information on the Ambient Air Quality Standards (AAQS) and to develop a list of Toxic Air Contaminants (TACs) that “may cause infants and children to be especially susceptible to illness”. OEHHA developed the document *Prioritization of Toxic Air Contaminants under the Children’s Environmental Health Protection Act* (OEHHA, 2001) to address the identification of the first five TACs with special impacts on

infants and children. That document underwent public comment and peer review by the State's Scientific Review Panel (SRP) on Toxic Air Contaminants. The statute requires OEHHA to evaluate 15 toxic air contaminants per year to ensure that our health effects assessments are adequate to protect infants and children, and use these assessments to update the list of TACs that may cause infants and children to be especially susceptible to illness. To help meet the requirements of SB 1731 and SB 25, OEHHA in this document describes and evaluates the methodology to estimate RELs that explicitly consider infants and children, and derives such levels for specific chemicals.

OEHHA and the California Air Resources Board (CARB) have set up a procedure to facilitate the public comment and peer review process necessary for implementation of SB 1731 and SB 25 (Figure 1-1). This process includes internal OEHHA review, consultation with the California Air Pollution Control Officers Association (CAPCOA) and the California Air Resources Board (CARB), a public comment period, and public workshops. In addition, the Scientific Review Panel (SRP) on Toxic Air Contaminants, administered by the CARB, will review this document. OEHHA staff will respond to public comments on the changed methods and chemical-specific RELs, and update and revise the document as appropriate. The SRP will review the revised document, public comments and OEHHA's responses, and provide scientific input, which will be incorporated into the final draft.

FIGURE 1-1. PUBLIC AND PEER REVIEW PROCESS FOR ESTABLISHING REFERENCE EXPOSURE LEVELS



1.3 Summary of the Methodological Changes for Developing Acute, Eight-hour and Chronic RELs

- If sufficient data are available for REL development, then a benchmark dose approach will be preferred over the traditional NOAEL/UF approach, unless some specific feature or limitation of the data makes this impossible.
- If sufficient data are available, PBPK modeling (Appendix E) will be used to determine the tissue dose in a default human model if an animal toxicity study is used. The relationship determined by the PBPK model will replace the pharmacokinetic portion (UF_{A-k}) of the interspecies uncertainty factor (UF_A). A smaller residual UF_{A-k} of 2 may be used where the PBPK model is only a partial model (e.g., DAF for analogue chemical). In cases where a PBPK model is not available, UF_{A-k} is assigned a default value of $\sqrt{10}$, and the total UF_A would be 10.
- The HEC procedure (Appendix F) may be used in place of a part of the UF_{A-k} , leaving a residual value of 2 for this sub-factor (since the default value of the toxicodynamic component interspecies uncertainty factor, UF_{A-d} , is $\sqrt{10}$, this results in an overall value of $UF_A = 6$ when a HEC calculation is used, or 10 where no model of any kind is applied) (OEHHA, 2003). A modified HEC procedure using children's physiological values may be used as appropriate.
- The mechanism of toxicity and pharmacokinetics for chemicals will be evaluated when developing chronic and 8-hr RELs in order to help determine whether long-term total dose or shorter-term tissue concentration is the predominant factor for toxicity. Infants and children are potentially more vulnerable because of pharmacokinetic, pharmacodynamic, and exposure differences. Therefore if PBPK modeling is used to determine human equivalent concentration from an animal study, children's or infants' physiological and biochemical parameters may be used in the modeling as appropriate.
- Since children may also be more vulnerable because of metabolism (activation or deactivation), excretion differences, or special sensitivities of developing organs and tissues, PBPK modeling may be needed to model children's tissue doses when a worker study is used to determine a LOAEL or NOAEL.
- When an uncertainty factor approach is used due to the lack of data for compound-specific models of toxicokinetics and toxicodynamics, an overall intraspecies uncertainty factor (UF_H) of 30 rather than 10 (toxicokinetic component, $UF_{H-k} = 10$; toxicodynamic component, $UF_{H-d} = \sqrt{10}$) will be used as a default procedure to protect infants' and children's health, for example, in cases where differences in metabolism and excretion are key to the toxicological activity. For direct-acting chemicals whose site of action is the point of first contact, a UF_{H-k} of $\sqrt{10}$ may be sufficient. Where significant concern for toxicodynamic differences larger than three-fold is present, a larger UF_{H-d} may be applied, such that the total UF_H could be larger than 30..

- The LOAELs or NOAELs for RELs based on trigeminally-transmitted irritation will no longer be adjusted using modified Haber's Law when the exposure duration of the study is different from the exposure duration for which the REL is intended to be protective. In other cases, where the modified Haber's law procedure is applicable, the default value of the concentration exponent, used when chemical specific information is unavailable, for time extrapolation from longer to shorter REL averaging time will be 3, rather than 2 as previously.
- In order to ensure that RELs based on developmental endpoints are protective, OEHHA will not use Haber's Law to adjust the NOAEL or LOAEL in an animal developmental study where the exposure duration of the study and averaging time of the REL (e.g., 1 hr) are different. Instead, since the actual timing and duration of the sensitive period are unknown, the NOAEL will serve as the basis of the REL without a time extrapolation adjustment.
- If the available toxicology literature does not include developmental studies for a chemical, or has substantial toxicological data gaps, the toxicological endpoints associated with the chemical, the chemical's reactivity, mechanism of toxicity, structure activity relationships and other factors, will be evaluated to decide if an additional database deficiency factor, with a default value of 3, will be applied. A larger value may, in some extenuating circumstances, be applied.

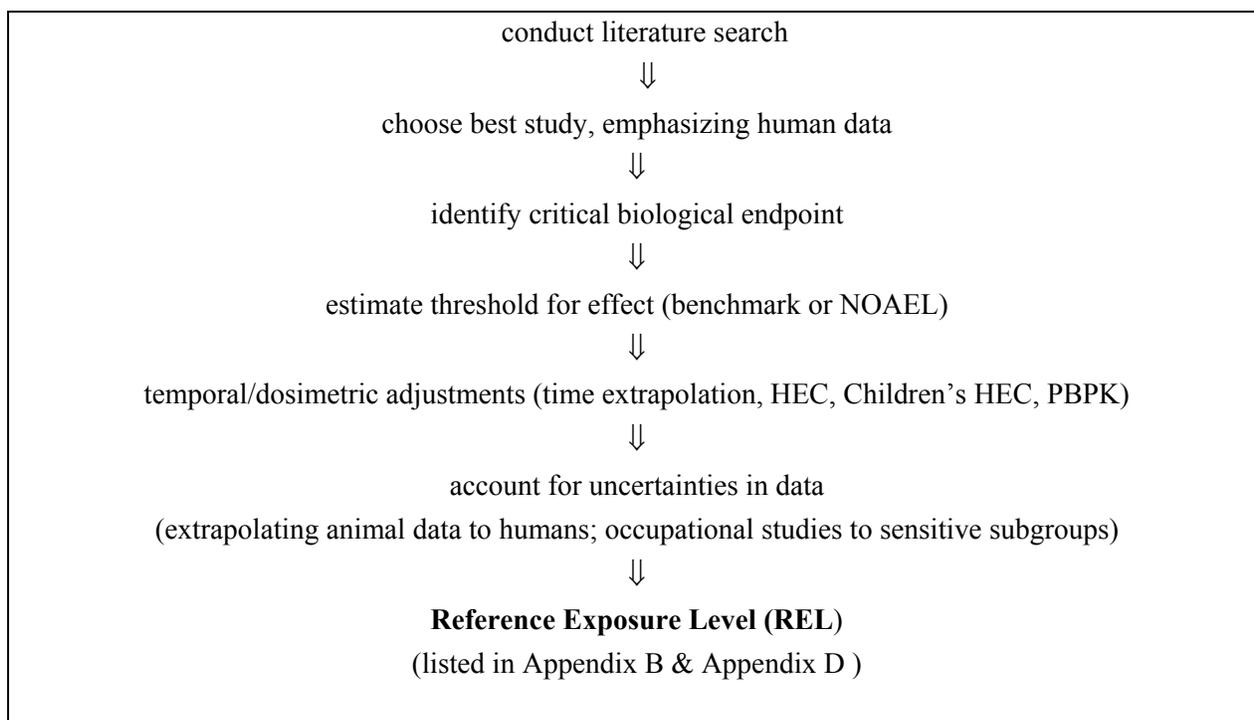
2 Reference Exposure Level (REL) Development Process

Reference Exposure Levels (RELs) are concentrations or doses at or below which adverse noncancer health effects are not likely to occur in the general human population, including sensitive subpopulations, for specified exposure durations. 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 are addressed using extrapolation and UFs.

RELs are based on the most sensitive relevant health effect reported in the medical and toxicological literature (see Section 4.0). One of the issues in selecting the appropriate health end point for REL development is the difficulty in distinguishing “adverse” health effects from “precursor” effects, which may be purely biochemical changes indicative of initial events in a chain of consequences which might (or might not) result in disease, and “adaptive” responses. The latter reflect impacts of a biological process which is not of itself harmful or is within the capacity of normal biochemistry and physiology to accommodate without impairment of overall function of the organism. NRC (2007) has considered this issue and points out the need for a health-protective and case-specific approach to selection of endpoints, noting that the concept of “adversity” is actually a continuum ranging from initial events such as contact and uptake of the toxicant, through distribution, metabolism and contact with the target tissue, to various grades of precursor event leading up to frank pathological changes. They point out also that the degree of response over this continuum at a specific dose level may vary widely between individuals, depending on their age, genetic constitution, nutrition, prior health status and many other factors, not all of which can necessarily be predicted. OEHHA concurs in recommending a cautious selection of endpoint, emphasizing the importance of considering precursor events and individual variability; this issue is discussed further in Section 4.3.2.

RELs are designed to protect the most sensitive individuals in the population including infants and children by the selection of appropriate toxicological endpoints and extrapolation models, and by the inclusion of margins of safety in the form of various UFs. Since uncertainty factors are incorporated to address data gaps and uncertainties, exposures that exceed the REL do not automatically indicate an adverse health impact.

Figure 2-1 depicts the steps involved in developing RELs. A complete literature search is conducted for each chemical, but the chemical summaries in Appendix D may only cite those studies contributing to the REL development and reflecting relevant routes of exposure. After identifying critical studies and toxicological endpoints, we identify a point of departure on the dose-response curve for extrapolating to the general human population. Various procedures for dose and time extrapolation and use of uncertainty factors are described in Section 4.

FIGURE 2-1. REL DEVELOPMENT PROCESS

NOAEL = No-Observed-Adverse-Effect Level; HEC = Human Equivalent Concentration; PBPK = physiologically-based pharmacokinetic models

2.1 List of Substances Considered

All substances listed by the California Air Resources Board (CARB), whose emissions must be quantified for the Air Toxics “Hot Spots” Program, are considered for evaluation and development of RELs. The substances included on the Air Toxics “Hot Spots” Program List are those substances found on lists developed by the International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency (U.S. EPA), the U.S. National Toxicology Program (NTP), the CARB (*i.e.*, the list used in the Toxic Air Contaminant Program), the Hazard Evaluation System and Information Service (State of California), or on the Proposition 65 list of carcinogens and reproductive toxicants (State of California). The complete list of substances whose emissions must be quantified is contained in Appendix C.

2.2 Hazard Index Approach

The Air Toxics “Hot Spots” Program uses RELs as indicators of potential adverse noncancer health effects. A “hazard index” (HI) approach is used to estimate potential health effects resulting from hazardous substances by comparing measured or modeled exposure levels with RELs. (For a detailed description of this method, please refer to the document entitled *The Air Toxics Hot Spots Program Guidance Manual for Preparation of Health Risk Assessments* (OEHHA, 2003)), which is available online at:

http://www.oehha.ca.gov/air/hot_spots/pdf/HRAguidefinal.pdf

Cumulative exposure (to multiple chemicals and from multiple sources) has become a concern in recent years. For many facilities a large number of chemicals may be emitted or may be present in the air at the location of the individual receptor or exposed population. To assess the cumulative impact of several chemicals present at the same time, it is important to consider the interaction of effects of the toxicants. These interactions may result in an overall effect that is equal to, less than, or greater than predicted from the effects observed with exposures to the individual chemicals (Ikeda, 1988; Jonker et al., 1990; DeVito et al., 2000). The potential for synergistic or antagonistic interactions has only been investigated for a small fraction of the millions of possible combinations of chemicals with potential human exposure. Effects of multiple chemical exposures on human health remain an area for future study.

One of the specific mandates of SB25 is the consideration of cumulative exposures to toxic chemicals, which has become a core concern for environmental justice in view of the tendency for disadvantaged communities to be located in areas with a high density of pollutant-emitting facilities, and near freeways and other heavily used traffic corridors with attendant local peak concentrations of mobile-source-related pollutants. They thus receive higher local pollutant exposures compared to the State-wide average. This adverse environmental milieu is often compounded by the presence of population factors tending towards more adverse health impacts, such as less access to health care, poor nutrition and poor housing. Cumulative exposures may consist of multiple sources of the same chemical impacting a single receptor, multiple chemical exposures from the same source, or combinations of these situations. The hazard index approach is useful in addressing the predicted effects of such cumulative exposures (Salmon, 2007).

In risk assessments using the HI approach for either acute, eight-hour or chronic exposures, the impacts of exposures to multiple chemicals which impact the same target organ are treated as additive by default. The concept of a threshold underlies the assumption of additivity in chemical interactions. Exposure to a single chemical in the air may not result in a toxic response if it is below the threshold necessary to elicit a response. However, simultaneous exposure to two similar chemicals at sub-threshold levels may result in a toxic response. This is taken into account by adding together the individual ratios of the modeled concentration to the REL for all chemicals that impact the same target organ or system.

This may underestimate the effect in cases in which interactions are synergistic, or overestimate it if the effects are either not additive or antagonistic. There are a few cases where synergism between different toxic chemical exposures has been identified, but most multiple exposure situations which have been examined quantitatively in fact do show simple additivity, at least at low to moderate doses. This is well illustrated by the work on PCBs (DeVito et al., 2000; Crofton et al., 2005), which also shows that synergism or antagonism, perhaps related to enzyme induction or inhibition may be observed at higher doses. Additivity was also seen for phthalates causing male reproductive tract malformations in rats following co-exposure to di(n-butyl) phthalate (DHP) and diethylhexyl phthalate (DEHP) during sexual differentiation (Howdeshell et al., 2007). These observations support the use of the additivity assumption by default for low-dose exposures, but also indicate the need to consider synergistic or antagonistic interactions between chemicals in those special cases where they have been identified.

Another limitation of the HI approach to assess the potential for health effects is the fact that different RELs have vastly different cumulative uncertainty factors depending on the quality of

the data. Thus the probability of adverse health impacts when the REL or HI is exceeded may be quite different with different chemicals.

For a particular target organ or system, the HI is calculated as follows (U.S. EPA, 2004):

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

where for i substances with the same toxicological endpoint,

HI = hazard index

C_i = concentration for the i^{th} substance

REL_i = REL for the i^{th} substance

Advances in computer capabilities and the development of software programs, such as the Air Resources Board's Hot Spots Analysis Reporting Program (HARP), have made assessment of chemical exposure from multiple stationary facilities more practical. However, it should be borne in mind that both the cumulative exposures and the health impacts in children may be different from those in adults, because of physiological, biochemical and behavioral factors (Hattis, 1996a; OEHHA, 2001; Miller et al., 2002).

3 Populations of Concern

RELs developed since the beginning of the Hot Spots Program are intended to protect the individuals who live or work in the vicinity of emissions of potentially toxic substances. The general population consists of individuals with a wide range of susceptibility. An individual's current level of susceptibility may be transitory or long lasting, and innate or induced by some prior exposure or event. The general population includes some people who are likely to be especially susceptible to developing adverse effects (e.g., infants, children, the elderly, pregnant women and those with acute or chronic illnesses). Individuals in the general population who may be at greater risk for developing adverse effects following chemical exposure include:

- those with increased exposure (e.g., infants, children, adults engaged in physical activity),
- those undergoing physiological change (e.g., infants, children and adolescents; pregnant women and their fetuses),
- individuals with impaired physiological conditions (e.g., elderly persons, persons with existing diseases, persons who are immunosuppressed),
- individuals with lower levels of protective biological mechanisms due to genetic or epigenetic variability within the population (U.S. EPA, 1994a) and
- members of communities impacted by multiple sources of exposure.

Less susceptible individuals are healthy adults without any genetic or biological predisposition that may increase sensitivity to the chemical of concern. RELs are intended to protect both individuals at low risk for chemical injury as well as identifiable sensitive subpopulations (groups of more highly susceptible individuals) from adverse health effects in the event of exposure. There have been concerns that infants and children in particular may be more sensitive to some toxic agents, and that this difference may not have been considered sufficiently in setting existing health protective standards. OEHHHA has therefore been mandated under SB 25 to ensure that RELs are also protective of infants and children, and other sensitive subpopulations. More useful scientific information has become available in the last few years to evaluate the special vulnerabilities of infants and children and to thus ensure that the RELs are protective.

The elderly constitute another important group where greater sensitivity to environmental toxicants may be anticipated. With aging, there is a general tendency for clearance mechanisms and other protective toxicokinetic processes to decline. There is also a tendency for reserve capacity, responsiveness of homeostatic mechanisms and ability to repair cellular damage to decline with age. Thus the elderly tend to show greater susceptibility to toxicants as a result of both toxicokinetic and toxicodynamic factors (ElDesoky, 2007). This has been shown as an important phenomenon for drugs, where adjustment of dose and even selection of therapeutic agents is modified for elderly patients (Ginsberg et al., 2005). The potentially enhanced sensitivity of older individuals has also been identified as a cause for concern, and a stimulus for additional research and regulatory activity, for environmental toxicants (Geller and Zenick,

2005). Although this document is primarily designed to address the mandate to consider the special susceptibilities of infants and children, the same principles developed here can also be used in identifying and responding to concerns for the enhanced sensitivity of the elderly.

Because the true range of variability is unknown, there may be a proportion of the population for whom the RELs will not be fully protective. It is OEHHA's intent that the levels will protect nearly all individuals, including those who are identifiable at the high end of susceptibility. However, they may not protect hypersensitive individuals (i.e., those who exhibit extremely rare or idiosyncratic responses that could not have been predicted from studying the health effects of the substance in animal studies, or population-based epidemiological studies of reasonable size).

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

Hattis has presented an analysis of human variability in threshold responses in pharmacodynamic and toxicological studies (Hattis, 1996a; Hattis, 1996b; Hattis et al., 1999). In many cases the variability in response in the general human population appears to be continuous and is well modeled by a log-normal distribution. The magnitude of the variability depends greatly on the endpoint and on the slope of the dose-response curve. In their analysis, some human threshold responses ranged over more than three orders of magnitude. Such continuous variability is hypothesized to reflect cumulative influences of a number of polymorphisms. These may be at various genetic loci, all of which individually have a small impact on the degree of dose dependence of the response, or there may be several polymorphisms at a single locus, associated with a variety of different levels of response. In other cases the response may be primarily influenced by a single gene, with two relatively common variants having markedly different properties. In this case the observed variability may appear to be heterogeneous, and is better described by a bimodal distribution or separate distributions.

3.1 Children as a Population of Concern

In response to the potentially greater vulnerability of infants and children to chemical exposure compared to adults (reviewed by OEHHA 2001), revised procedures for development and reassessment of noncancer health standards are outlined here. These are intended to ensure that age-related sensitivities are taken into consideration as far as possible in the development of noncancer health standards.

Many of the issues, which arise in ensuring adequate protection of children's health, are the same for acute, eight-hour, and chronic RELs. In this document, our approach in addressing these issues will be two-fold.

1. We have developed changes in the methodology for REL derivation in order to ensure that these health values are protective of children's health.
2. We have applied the changes in the methodology to individual RELs.

Over time, we will add new RELs, and address the adequacy of existing RELs that were developed with the initial methodologies. In recent years new methodologies have been developed to address uncertainties more quantitatively in determining health-protective levels and to ensure public health protection. OEHHA recommends expanding the use of techniques such as the benchmark dose method and physiologically based pharmacokinetic (PBPK) modeling wherever possible in order to improve the protection of public health with acute, eight-hour and chronic RELs for all members of the population, and for infants and children in particular. As noted in the introduction, data gaps will prevent PBPK modeling for many chemicals, and in some cases, will make benchmark dose analysis difficult. Thus, the traditional UF approach remains an important method.

3.2 Differences between Children and Adults

Children's potential vulnerability to toxic effects from chemicals can result from differences in exposure. For example:

- Children breathe more than adults on a per kg body weight basis and thus inhale more of the pollutant.
- For non-inhalation routes of exposure, children are also more exposed on a per kg body weight basis than adults because they eat more food, drink more water, have more dermal contact with soil, and have higher rates of inadvertent soil ingestion than adults.
- Children may consume more of one type of food than adults and have a less diverse diet.

Children may differ in terms of pharmacodynamics, particularly since more cell division and differentiation are occurring in children than in adults due to growth and organ development.

- Undifferentiated cells may be more prone to injury than are differentiated cells.
- Major organ development occurs in utero and during early postnatal development.
- Disruption of migration and differentiation of one type of cell may alter that of another.
- Some structures (e.g., the brain) continue to develop through adolescence.

Children and particularly neonates can be quite different pharmacokinetically from adults. Factors that affect absorption, distribution, metabolism, and elimination (ADME) of toxicants, often differ by age. Such factors include:

- Lung surface area available for absorption of gases, and airflow dynamics that alter deposition of inhaled particulates.
- Activating or detoxifying enzymes such as cytochrome P450 enzymes and Phase II conjugating enzymes are known to be present in infants in amounts and ratios different from adults. Fetal forms of cytochrome P450 are present and may differ in activity towards many substrates compared with the adult forms.

- Consequently, xenobiotic metabolism may occur through different pathways, be apportioned differently between competing pathways, and occur more slowly than in adults.
- Elimination may occur faster or more slowly than in adults.

These factors influencing vulnerability in children may change rapidly and may be present only for a period of weeks to months. In the case of prenatal development, periods of vulnerability could be as short as hours or days. In neonates, the variability in developmental stage appears to be wide for some processes including xenobiotic metabolism and renal clearance (Islam and Schlipkoter, 1989). Consequently inter-individual variability in susceptibility in a particular age range may be much greater than in adults, and thus harder to characterize. OEHHA addressed some of the behavioral, physiological and biochemical differences between children and adults in OEHHA (2001) and in Miller et al. (2002).

3.2.1 *Pharmacokinetic Differences*

3.2.1.1 Absorption

3.2.1.1.1 Inhalation

The lungs are the major route of entry of volatile airborne environmental pollutants and the majority of airborne semivolatile and nonvolatile pollutants. Exposure to environmental pollutants during lung development has the potential to significantly affect the overall growth and function of the respiratory system in children. The effects of exposure are likely to be different during each phase of development. Recent studies have found links between air pollution and preterm birth (Ritz and Yu, 1999; Sagiv et al., 2005; Wilhelm and Ritz, 2005), infant mortality (Loomis et al., 1999; Conceicao et al., 2001; Ha et al., 2001; Woodruff et al., 2006), deficits in lung function growth (Kunzli et al., 1997; Galizia and Kinney, 1999; Gauderman et al., 2004), and possibly, development of asthma (Gauderman et al., 2005; McConnell et al., 2006). The lungs are structurally immature in neonates and continue to mature throughout childhood (Fanucchi and Plopper, 1997; Plopper and Fanucchi, 2004; Fanucchi et al., 2006).

Lung development is a long-term, continuous process that continues for up to eight years after birth. Lung function growth continues through adolescence. The development of the human lung can be divided into six stages: embryonic, pseudo-glandular, canalicular, saccular, alveolar, and vascular maturation (Zeltner and Burri, 1987). The first four stages occur prior to birth during fetal development. By birth the alveolar stage has begun, and the newborn infant has about 10 million alveoli. By approximately age eight, when adult numbers of alveoli have developed, there are about 300 million alveoli. Concomitantly the alveolar surface area increases from about 3 m² at birth to about 75 m² in adults leading to an air-tissue gas exchange area some 25-fold larger in adults (Islam and Schlipkoter, 1989).

During the maturation time following birth, there are multifold increases in overall lung size, active cellular differentiation, cell division, branching morphogenesis, and alveolar formation (Tyralla et al., 1977; Harding et al., 2004). Episodic exposure to environmental pollutants,

specifically ozone, compromises postnatal morphogenesis of tracheobronchial airways in the monkey (Fanucchi et al., 2006).

Airways change in size and shape with maturation, altering deposition patterns. In animal models, exposure to environmental ozone during the early postnatal period alters the development of the distal pulmonary airways (Fanucchi et al., 2006). Lung function also continues to change, increasing until late adolescence in both males and females. Chronic airway disease and decreased lung function in children exposed to ambient air pollution may be due to repeating cycles of injury and repair altering normal lung maturation (Smiley-Jewell et al., 2000; Fanucchi et al., 2006).

Respiratory minute ventilation is increased in infants and children, resulting in a greater exposure per unit time on a weight basis and per unit surface area of lung, compared to adults. For inhalation exposures to equivalent chemical concentrations, both indoor and outdoor, infants and children are at the same or greater risk of exposure based on their much higher minute ventilation on a body weight and lung surface area basis (i.e., mL/kg/m²/min) (Snodgrass, 1992).

The deposition of inspired particles in the lungs is dependent on particle size and anatomical features of the respiratory tract. Deposition occurs primarily through impaction for coarser particles and through Brownian motion for finer particles. Greater fractions of inhaled particles less than five µm in diameter reach the distal airways compared to larger particles. Particle deposition tends to be greater in children because of the smaller diameters of the airways compared to adults, and models of particle deposition indicate larger deposition in the pulmonary region of 3 month old infants relative to adults (Ginsberg et al., 2004c; Snodgrass, 1992).

3.2.1.1.2 Other Routes

Ingestion is a major route by which infants and children are exposed to environmental chemicals (U.S. EPA, 2000). A number of factors may result in significant differences in the absorption of environmental pollutants by infants and children vs. adults. Most drugs administered by the oral route are absorbed into the systemic circulation by passive diffusion. The two factors most affecting this process are gastric pH and emptying time (Milsap and Jusko, 1994). Both processes vary with age from birth through infancy and childhood. At birth the gastric acidity is neutral (pH 6-8) due to the presence of amniotic fluid in the stomach (Avery et al., 1966). Following birth, gastric acid appears in the first one to two days of life and increases during the first weeks to months approaching adult levels by three months of age (Miller, 1941). Premature infants may continue to have lower gastric acidity due to immature acid secretion. The pH of the stomach influences the absorbed dose of ionizable chemicals, thus altering the potential dose to the infant (Agunod et al., 1969).

Gastric emptying time influences the fraction of an oral dose which is absorbed into the systemic circulation. The gastric emptying rate in neonatal infants is variable and prolonged and is affected by both gestational and postnatal age (Signer, 1975; Siegel et al., 1984). Absorption rates for several chemicals (e.g., phenobarbital, digoxin, arabinose and xylose) increase throughout the first year of life. While delayed absorption seen in neonates is partially due to slower gastric emptying and gastrointestinal motility, other factors such as lower pancreatic

enzyme function and bile acid secretion as well as a higher gastrointestinal pH also play a role (Alcorn and McNamara, 2003).

Not all absorption processes depend on passive diffusion: some toxic materials (especially metals) are carried by, or interfere with the operation of, physiological active transport processes, which show age-dependent changes. For instance, the decline in the absorption of lead by the gastrointestinal tract from 45% in children to 10% in adults probably reflects decreases in calcium receptors with age (Heath et al., 2003).

Skin permeability and hence dermal absorption change as the skin develops. Dermal absorption may be significantly higher in neonates due to an immature epidermis and increased skin hydration. The surface area/bodyweight ratio is also much higher in infants and children than adults (0.067 to 0.033 m²/kg vs. 0.025 m²/kg in adults) (Snodgrass, 1992). Severe toxicity has been observed in infants following topical application of hexachlorophene (Tyrala et al., 1977) and isopropanol (McFadden and Haddow, 1969) due to higher absorbed dose in infants relative to adults on a body weight basis. Alternatively, dermal administration may be the preferred therapeutic route in certain situations (e.g., theophylline in premature infants)

3.2.1.2 Distribution

Our knowledge of the distribution of chemicals in the body is perhaps best developed for pharmaceuticals, while much less is known about chemical distribution following environmental exposures. For this reason, the discussion that follows relies heavily on the pharmaceutical literature.

The distribution of absorbed chemicals in the infant and child is affected by a number of factors, primarily the concentration and types of plasma proteins and the relative size of fluid, fat and tissue compartments of the body (Milsap and Jusko, 1994). Total body water may be as high as 85 percent by weight in premature infants and 78 percent in full-term neonates versus 50-60 percent in adults (Friis-Hansen, 1961; Friis-Hansen, 1971). The percentage of body weight that is body water affects the volume of distribution of absorbed drugs and other chemicals. The apparent volume of distribution (V_d, measured in L/kg body weight) relates the amount of drug in the body to its plasma concentration. Chemicals that are water-soluble have higher volumes of distribution, while those that are lipophilic have lower volumes of distribution in infants. For example, gentamycin, theophylline and phenytoin show two to three-fold higher V_ds in neonates than in adults. Conversely, the V_d in neonates for diazepam, which is more lipophilic, is only one-third that of the adult value (Milsap and Jusko, 1994).

The binding of absorbed chemicals to plasma proteins depends upon the quantity of binding proteins available, the binding or affinity constant of the chemical for the protein(s), the number of available binding sites, and the presence of pathophysiological conditions, which may alter the binding interaction (Besunder et al., 1988). The affinity of plasma albumin for acidic drugs increases along with total plasma protein concentration from birth into early infancy (Morselli et al., 1980). The reduced plasma protein binding of drugs in newborns is probably due to lower total plasma protein concentration as well as such qualitative differences as persistence of fetal albumin with lower affinity for drugs and lower levels of γ -globulins and lipoproteins (Morselli et al., 1980). During early infancy plasma albumin, total protein concentrations, and α 1-acid

glycoprotein are lower and don't reach adult values until one year of age (Brodersen et al., 1983; Herngren et al., 1983). Three of the drugs noted above (theophylline, diazepam and phenytoin) all exhibit lower protein binding (1/3 to 1/10) in neonates versus adults (Morselli, 1976; Rane and Wilson, 1976; Morselli et al., 1980). In addition to the quantitative and qualitative differences in plasma proteins during early development, disturbances in acid-base balance and increased blood concentrations of endogenous substances such as free fatty acids and bilirubin can affect protein binding of drugs or the release (i.e., displacement) of bound drugs or other exogenous chemicals. Lower levels of albumin and elevated free fatty acids and bilirubin in the neonate may result in a larger Vd of and higher unbound concentrations of trichloroacetic acid (TCA), a metabolite of perchloroethylene (PCE) and trichloroethylene (TCE), in the blood (Muller et al., 1972; Ginsberg, 2000).

For some chemicals, the route of exposure affects the form of the chemical that appears in the blood. This in turn affects the binding and distribution of the absorbed chemical. For example, manganese appears to be absorbed from the gut primarily in the divalent form, with approximately 80% of it subsequently bound in plasma to β_1 -globulin and albumin (Foradori et al., 1967). These manganese-protein complexes are efficiently removed from the blood during the first pass through the liver and returned to the gut in bile for elimination, thus limiting their distribution. By contrast, the pulmonary route of exposure results in much higher blood levels of manganese which are more widely distributed in the body (Roels et al., 1997). In the blood, unbound manganese may be converted by ceruloplasmin to the trivalent cation which is then bound by transferrin. Transferrin-manganese complexes are much less efficiently removed by the liver and thus survive first pass elimination to circulate to other tissues throughout the body (Gibbons et al., 1976).

Other factors that affect tissue distribution of toxicants include higher organ to body weight ratios in infants and children than adults, and the lack of a mature blood:brain and other tissue:blood barriers. Morphine is three to ten times more toxic to newborn than to adult rats due primarily to the higher permeability of the newborn brain to morphine (Rozman and Klaassen, 1996), and the distribution of methylmercury to the brain is greater if exposure occurs in utero or neonatally (Ballatori and Clarkson, 1982). Brain size in infants and children is much greater than in adults relative to body weight. A newborn's brain is one-third the size of an adult brain while its body weight is only about four percent that of adults (i.e., 3.0 vs. 70 kg) (Snodgrass, 1992). Cerebral blood flow is greater per brain weight in children vs. adults. A five-year old child has a cerebral flow of about 71 ml/min-100 g vs. 51 ml/min-100 g in an adult (Chiron et al., 1992). Thus not only is there a relatively greater brain mass to body weight ratio in children, but the brain receives a higher blood flow.

Dosing of infants and children based on surface area instead of body weight is generally preferred although this applies mainly to drugs that are distributed in extracellular body water. Environmental chemicals, which are often lipophilic, may pose a greater risk to children due to the possibility of enhanced dermal uptake due to increased skin surface area and permeability. In addition, lipophilic agents would have decreased volumes of distribution in infants due to their lower body fat content compared to typical adults.

3.2.1.3 Metabolism

The development of xenobiotic metabolizing enzymes in utero and after birth affects the rates of activation of chemicals to toxic intermediates, and the detoxification and ultimately clearance of xenobiotic compounds. The most common metabolic enzymes include the so-called Phase I enzymes, cytochrome P450 (CYP) isoforms, which are involved primarily in oxidative reactions, and the Phase II enzymes involved in conjugating the xenobiotic or, more commonly, its metabolite with endogenous substrate rendering the molecule more amenable to excretion. Recent reviews have highlighted available information on the ontogeny of the Phase I enzymes primarily in liver tissue, the main organ of xenobiotic metabolism (Cresteil, 1998; Hines and McCarver, 2002). The metabolic capacity of the liver (as a function of body weight) generally increases rapidly to near adult levels early in life, but significant qualitative and quantitative differences exist in newborns and neonates. Most of the microsomal enzyme systems responsible for drug metabolism are present at birth and their activities increase with postnatal age (Morselli et al., 1980). Liver Phase I reactions (oxidation, reduction, hydroxylation) develop rapidly during infancy (Stromland et al., 1994). The total cytochrome P450 (CYP) content of human liver microsomes is unchanged from fetal life through the first year of postnatal life and is approximately one-third the total adult content (Streissguth et al., 1991). There are fetal isoforms of the CYP enzymes, and the exogenous chemical substrate kinetics of these forms are not well characterized. In general, the level of inducibility of fetal CYP forms is unknown (Pineiro-Carrero and Pineiro, 2004). The postulated development of individual cytochrome P450 (CYP) forms during infancy and childhood has been summarized in a previous document (OEHHA, 2001, see Table 5). Except for CYP3A4 and CYP3A7 these data are based on immunological analyses for the presence of CYP mRNA and protein rather than on the metabolism of specific chemical substrates. In general, three groups of CYP P450 could be described:

- (1) CYP3A7 and CYP4A1 present in fetal liver and active on endogenous substrates;
- (2) an early neonatal group including CYP2D6 and CYP2E1 which surge within hours of birth; and
- (3) a later developing neonatal group, CYP3A4, CYP2C's, and CYP1A2 (Cresteil, 1998).

Treluyer et al. (1997) observed that treatment of infants with barbiturates resulted in induction of CYP2C activity and increased metabolism of diazepam and tolbutamide. Total CYP3A protein, a major cytochrome P450 enzyme responsible for biotransformation of many exogenous compounds, is relatively constant in neonates and adults, but the isoforms change. CYP3A7 expression peaks in the neonatal liver and declines over time to undetectable levels in adult liver; CYP3A7 appears to be responsible for aryl hydrocarbon hydroxylase (AHH) activity in the fetus (Hakkola et al., 1998). CYP3A4 is the primary adult hepatic form of the 3A series, and is very low in neonatal liver increasing slowly after birth; at one month there is about one-third of the CYP3A4 activity as an adult liver (Rice and Barone Jr., 2000). CYP2E1 is an important enzyme catalyzing metabolism of a number of environmental contaminants including benzene, trichloroethylene and toluene. Following birth hepatic CYP2E1 increases gradually reaching about one-third of adult levels by one year of age and is essentially 100% of adult levels by 10 years of age (Rice, 1996). CYP2D6 levels are low in fetal hepatic tissue and rise after birth

reaching about two-thirds of the adult levels in infant's age one month to five-year old children (Treluyer et al., 1991). CYP2C9 and CYP2C19, the most abundant CYP 2 enzymes in adult human liver, appear in the week after birth, and are about 30% of adult levels up to one year of age (Treluyer et al., 1997). CYP1A2 appears between one and three months of age, and reaches about half of adult levels at one year (Hines and McCarver, 2002). Evidence from both substrate activation and immunological detection indicates CYP1A1 is expressed in fetal liver, where it can activate such xenobiotics as benzo[a]pyrene and aflatoxin B1 (Hines and McCarver, 2002). CYP1A1 appears to be less important in adult liver but present in inducible form in extrahepatic tissues (Hakkola et al., 1998), while CYP1B1 is present in both adult and fetal extrahepatic tissues. Studies of pharmaceutical clearance demonstrate the ontogeny of cytochrome P450 in infants and children, including gender-based differences (e.g., caffeine demethylation) (Kearns et al., 2003).

While there has been some study of the development of human CYP P450 enzymes and of the Phase II conjugation enzymes in the liver (reviewed in (Cresteil, 1998; Kearns et al., 2003; Hines and McCarver, 2002; McCarver and Hines, 2002)), there is less information about the timing of development of activity in other tissues. Watzka et al. (1999) observed sex- and age-related differences in CYP1A1 activity in the human brain, where enzyme activity increased dramatically from birth and reached adult levels by puberty. In the lung, animal studies have shown that exposure to environmental toxicants (sidestream tobacco smoke) can induce cytochrome P450 enzymes resulting in earlier activity (Gebremichael et al., 1995). The impacts on toxicity from activation of compounds by cytochrome P450 enzymes in early life depends on the rate of detoxification as well as capacity for repair. In neonatal rabbits, repair of injury to pulmonary Clara cells by toxicants activated by cytochrome P450 enzymes is decreased resulting in permanent structural changes in the adult animal (Miles, 1983).

The activity of phase II conjugation reactions, which are usually detoxifying, is generally lower at birth (Goldstein, 1983). Hence, there is concern that detoxification and elimination of chemicals are slower in infants. Conjugation with glucuronic acid is significantly lower at birth with activity 2.5-fold below adult levels (Lehman and Fitzhugh, 1954). Glucuronidation generally matures to adult levels in two months, although glucuronidation of some drugs does not reach adult levels until puberty (Calabrese, 1983). Reduced glucuronidation would result in slower removal of aniline, N-hydroxyarylamines, phenol, and benzene metabolites in neonates. Acetylation and sulfation reactions are generally high in newborn infants and rapidly reach adult levels. Thus, neonates may conjugate drugs or environmental chemicals with sulfate rather than glucuronic acid (e.g., acetaminophen). Acetylation by the N-acetyltransferases and sulfation by sulfotransferases are generally high in newborn infants and somewhat comparable to adult levels, although it may vary by tissue and by specific sulfotransferase (Renwick et al., 2000; McCarver and Hines, 2002). Infants are less susceptible to acetaminophen acute toxicity than adults due to their more active sulfation (Levy et al., 1975). There are several forms of glutathione (GSH) sulfotransferases (GSTs) with GST-P_i prevalent in the fetus and decreasing postnatally. GST-alpha and GST-mu are detected in fetal liver and increase over the first few years of life to adult levels (McCarver and Hines, 2002). GST-mu is involved in arene oxide detoxification. GST-alpha is two-fold more active in children 0.5 to 4 years of age than in adults. Plasma glutathione (GSH) is similar in children 0.5 to four years of age and in adults (U.S. FDA, 2006). Blood esterase activity, which is less than half that of adults at birth, is more depressed in premature infants than in full-term infants and doesn't reach the latter's activity for ten to twelve months.

Esterase activity in newborns is two to ten-fold lower than the adult level. Low esterase activity coupled with lower volume of distribution may account for prolonged effect of local anesthetics observed during delivery (Ecobichon and Stephens, 1973). Neonates and premature infants may be deficient in the detoxification of organophosphorus (OP) insecticides (Augustinsson and Barr, 1963; Cole et al., 2003; Costa et al., 2003; Costa et al., 2005). Epoxide hydrolase, important in detoxifying reactive epoxide metabolites, is present in fetal liver although at much reduced activity relative to adults (McCarver and Hines, 2002).

As a result of differing enzyme activity, some chemicals are metabolized by wholly different metabolic pathways depending on age. In infants, theophylline is N-methylated to caffeine, a minor pathway for adults in whom the majority of theophylline dose is N-demethylated or C-oxidized to monomethylxanthines or methyl-uric acid. Several studies have evaluated age-related pharmacokinetic differences in humans using information about drug disposition (Renwick and Lazarus, 1998; Renwick et al., 2000; Ginsberg et al., 2002; Hattis et al., 2003). Calculation of internal doses as the area under the blood concentration times time curve (AUC) for the same doses (mg/kg) indicated that the major difference from adults occurs in preterm and full-term neonates and young infants (Renwick et al., 2000). Higher AUC internal doses in neonates and young infants versus adults were noted for seven drugs which are substrates for glucuronidation, one with substrate specificity for CYP1A2, and four with substrate specificity for CYP3A4 metabolism, and inter-individual variation in elimination by these detoxification pathways did not differ by age group (Renwick et al., 2000). Ginsberg et al. (2002) evaluated pharmacokinetic information on 45 drugs in children and adults metabolized by different cytochrome P450 pathways, Phase II conjugations, or eliminated unchanged by the kidney. These authors noted half-lives in infants three to nine-fold longer than those of adults. In evaluating the inter-individual variability by age, Hattis et al. (2003) noted that the largest inter-individual variability occurred in the youngest children, apparently due to variability in development of critical metabolism and elimination pathways. Notably, these authors observed that for risk assessment modeling, unimodal distributions may be inadequate for young children and for overweight older children.

While the variations in pharmacokinetics with age are an important consideration in risk assessment, additional complexity is overlain by genetic polymorphisms rendering some individuals more susceptible than others. Perera et al. (1999) showed that:

1. There is significant transplacental transfer of polycyclic aromatic hydrocarbons (PAHs) and environmental tobacco smoke constituents from mother to fetus.
2. PAH-DNA adducts in maternal and newborn white blood cells are increased from environmental exposure.
3. The fetus is more sensitive to genetic damage than the mother.
4. Newborns with a specific restriction fragment length polymorphism (RFLP), CYP1A1 MspI, had elevated numbers of adducts compared to those without the RFLP.

The report of Canalle et al. (2004) indicated that genetic variants in xenobiotic metabolizing genes may play a significant role in the susceptibility to acute lymphoblastic leukemia (ALL), the most frequent malignancy in children. The case-control study involved 113 Brazilian children with ALL and 221 matched controls. Carriers of the rare GSTP1 Val allele were at

higher risk of ALL (odds ratio (OR) = 2.7; 95% CI = 1.1-6.8; $p = 0.04$). No difference was seen for GSTM1, GSTT1 or for the mutant CYP1A1*2 and CYP2E1*3 variants. However, when the mutant CYP variants were analyzed in combination with GSTM1 and the risk elevating GSTP1, the risk of ALL was increased (OR = 10.3; 95% CI = 1.0-111.8; $p = 0.05$) suggesting a combined effect.

3.2.1.4 Excretion

Many drugs are more slowly eliminated in neonates and infants than in adults (Kearns et al., 2003). A classic example is the toxicity associated with chloramphenicol in neonates resulting from a longer half-life (10 hr) compared to adults (2-5 hr) (Miles, 1983). This difference would also apply to some environmental contaminants in the drinking water. Differences in volume of distribution, metabolism, and the maturity of renal and hepatic elimination processes all play a role. Premature infants may have very low glomerular filtration rates (GFRs) (0.6 to 0.8 mL/min) (Plunkett et al., 1992; Milsap and Jusko, 1994). Studies with a large number of drugs have shown that the large majority of these agents are more slowly eliminated in neonates and infants than in adults. While this may be partly due to an increased volume of distribution for water-soluble drugs and their metabolites, additional factors may also be involved. At birth, glomerular function is more developed than tubular function and this persists for six months (Guignard et al., 1975; Hook and Hewitt, 1977; Arant Jr., 1978). At birth, the GFR is lower (2-4 mL/min), increases in the first few days (8-20 mL/min) and slowly increases to adult values by 8-12 month old infants (Robillard et al., 1999; Kearns et al., 2003). Over the first two to three weeks of life, Guignard et al. (1975) reported a two-fold increase in insulin clearance. The GFR values in neonates ranged from 6.0 to 32.2 mL/min/m² with a mean value of 10.8 ± 1.0 mL/min/m², $n = 22$. Premature infants may have GFRs as low as 0.6 to 0.8 mL/min (Plunkett et al., 1992; Milsap and Jusko, 1994). Early increases in GFR are related to: increases in cardiac output, decreases in peripheral vascular resistance, increases in mean arterial pressure, increased surface area of the kidney for filtration, and increased membrane pore size (Morselli et al., 1980; Plunkett et al., 1992). For the first two to three months of life, GFR is lower than that of adults. Clearance values at 10 to 30 times lower than seen in adults have been reported for some compounds (e.g., aminoglycoside antibiotics) (Morselli et al., 1980; Morselli, 1989). These age-related changes in renal function lead to decreased body clearance and prolonged blood half-lives in neonates for any chemical that relies upon renal excretion for elimination.

Studies in animals have shown that newborn and young animals have a reduced capacity to excrete chemicals into the bile compared to adult animals. Klaassen (1972) observed that the blood concentration of ouabain, a drug whose primary route of excretion is the bile, was seven-fold higher in seven-day old rats than in 39-day old rats. Ouabain is 40-fold more toxic in newborn than adult rats. Similarly both indocyanine green and sulfobromophthalein and their respective glucuronides were excreted more slowly in the bile of neonates than in adult rats (Klaassen, 1973). Ballatori and Clarkson (1982) found that the long half-life of methylmercury in neonatal rats was due to their inability to excrete the chemical in the bile, which is the main elimination route in adults. It is anticipated that these findings are indicative of likely deficiencies in the biliary excretion of certain environmental chemicals in human neonates and young children (Hattis, 1996a).

The use of various toxicokinetic factors in assessing children's risk is the subject of a recent comprehensive review (Ginsberg et al., 2004c). These authors conclude that children are more toxicokinetically variable than adults because of their variable growth and maturation rates, in addition to the factors that create toxicokinetic variability in adults that relate to genetics, nutrition, disease, body composition, and prescription (and other) drug use. Children also present the problem of variable growth rates, which can make even small age bins (subdivisions) relatively heterogeneous, especially if one is concerned about protecting the tails of the distribution (e.g., 90th percentile). With greater variability, it is also more likely that a substantial fraction of a certain age group will lie outside the half-log toxicokinetic variability range we normally allocate to the adult defaults.

3.2.2 *Pharmacodynamic Differences*

Much more information exists for pharmacokinetics as a function of age than for pharmacodynamics. Many changes in pharmacodynamics occur with age and the mechanisms underlying toxic effects are of great interest to toxicologists, however, quantitative data are sparse.

The maturation of various systems, including the immune system, the nervous system, the reproductive system, the digestive system, and the blood-brain barrier, reflects qualitative and quantitative changes in receptors with age. Age-related differences in the LD₅₀, which reflect changes in the dose-response curve with age, may be related to receptor changes. Examples of pharmacodynamic differences in the pharmaceutical literature include development of Reye's syndrome following aspirin administration in children but not adults (Belay et al., 1999), and greater risk for developing hypersensitivity reactions, including Stevens-Johnson syndrome, when treated with lamotrigine (Guberman et al., 1999). Windows of susceptibility to various toxicants are seen during development. In humans, autism has been associated with thalidomide exposure during days 20 to 24 after conception (Stromland et al., 1994). Diphenylhydantoin, an anticonvulsant used to treat epilepsy, may cause human malformations including craniofacial anomalies and growth abnormalities (Eluma et al., 1984; Orup Jr. et al., 2003). In mice it causes different types and frequencies of malformations depending on when during gestation it is administered (Eluma et al., 1984; Buehler et al., 1994). Other agents known to cause human developmental toxicity include aminopterin, diethylstilbestrol (DES), ethyl alcohol in alcoholic beverages, etretinate, isotretinoin (retinoic acid), lead, and methylmercury.

In the case of ethyl alcohol, exposure in utero is associated with Fetal Alcohol Syndrome (FAS), a distinctive constellation of abnormalities at birth. In its more severe form, the syndrome is characterized by dysmorphogenesis of the head, heart, limbs and brain, deficits in IQ and memory, and behavioral problems such as hyperactivity and adolescent antisocial behavior (Streissguth et al., 1991). Similarly, lowered IQ and behavioral problems manifesting during childhood and later have also been associated with early life exposures to lead (Needleman et al., 1990) and cigarette smoke (Williams et al., 1998; Maughan et al., 2001; Yolton et al., 2005). As a result, the insidious nature of exposure to toxic agents during development may become more evident later in life, years after cessation of the toxic exposure. Delayed neurotoxicity has been seen both in humans following developmental exposure to methylmercury in contaminated seafood, and in monkeys experimentally exposed to methylmercury in utero through puberty. Among humans with developmental exposure to methylmercury, the manifestations of Minamata

disease were delayed for several years in some individuals following cessation of exposure, and got progressively worse in others (Harada, 1995). Compared to an unexposed cohort, individuals exposed to methylmercury 20-30 years previously experienced significant deficits in motor function and impairments in visual, auditory and somatosensory systems (reviewed in Rice and Barone (2000). Similarly in monkeys, significant impairments of somatosensory and motor functions were observed up to 11 years following cessation of methylmercury exposure compared to controls (Rice, 1996). Developmental neurotoxicity is also a feature of human exposure to PCBs, as was initially noticed in children who suffered exposure to PCBs as a result of rice oil contamination, such as the Yusho and YuCheng incidents (Jacobson et al., 1990; Chen et al., 1994). Subsequent studies have shown neurotoxic impacts of a wide range of PCBs and related compounds, by mechanisms involving both direct impacts on the central nervous system and interference with neurodevelopment via disruption of the regulation and effects of thyroid hormones (Darras, 2008).

While the specifics of the mechanisms underlying the toxicodynamic responses to these compounds have not been elucidated in most cases, the data generally indicate a significantly greater vulnerability of developing versus mature systems. In addition, it is important to recognize that the deleterious effects of exposure may not be immediately apparent, and in fact, may not be evident until much later in life.

3.3 Risk Assessment Considerations

The U.S. EPA recently developed a document entitled: *A Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2006c). This document presents considerations and questions for the risk assessor when evaluating the effects of life-stage at exposure on the toxic response or health outcome. A number of useful questions that the risk assessor should consider when evaluating the database on any chemical are discussed in the framework document. It should be noted that for the majority of chemicals in the Air Toxics Hot Spots Program, there will be limited data and this matrix of questions will likely remain unanswered for the risk assessor. Some of the considerations for dose-response assessment are noted below:

- Are there life-stage specific outcomes in the database for the chemical, particularly those with adequate information to conduct a quantitative dose-response assessment?
- What is the most susceptible life-stage evident in the available data or by inference from other information?
- Are there known windows of susceptibility or developmental processes likely to be susceptible to the agent?
- Are there differences in the mechanism of toxicity in immature and mature animals or humans?
- Are there known toxicodynamic differences by life-stage (for example, receptors, repair mechanisms, enzymes or processes involved in signal transduction or other key developmental processes)?

- Are there likely differences in toxicokinetics that can be modeled or estimated? Do those differences change over life-stages and how? Are there data to describe toxicokinetic differences coinciding with the most susceptible life-stage?

4 REL Development Methodologies

OEHHA has developed uniform approaches for acute and chronic Reference Exposure Level (REL) development. The first descriptions of these approaches appeared in the *Air Toxics Hot Spots Program Risk Assessment Guidelines, Part III Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels, April 2000* (OEHHA, 2000a) and the *Air Toxics Hot Spots Program Risk Assessment Guidelines, Part I: The Determination of Acute Reference Exposure Levels for Airborne Toxicants* (OEHHA, 1999).

As noted in the Executive Summary and Introduction, OEHHA is updating these REL development methodologies. A complete literature search is conducted for each chemical, but the chemical summaries in Appendix D may only cite those studies contributing to the REL development and reflecting relevant routes of exposure. After identifying critical studies and toxicological endpoints, we identify a point of departure on the dose-response curve for extrapolating to the general human population. Various procedures for dose and time extrapolation and use of uncertainty factors are described in Section 4.4.

4.1 Criteria for Studies Utilized to Identify Adverse Health Effects

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

Peer reviewed papers published in the open scientific literature are the usual and preferred source of the data used in REL development, but other sources that may be used include government reports such as National Toxicology Program (NTP) studies, full laboratory reports of Good Laboratory Practices (GLP) compliant or otherwise well-conducted studies, and documents that have been reviewed by other impartial organizations but have not themselves been published in the literature, such as doctoral dissertations. These alternative sources are normally only used if they, or at least an appropriate summary of them are publicly available online or by request. Occasionally it may be necessary to request additional data from the author of a published study: these data may be used in REL development, and will be detailed in the REL summary. Review papers are not used for REL development as they are considered secondary sources. Studies involving a single chemical are given preference over those with multiple simultaneous exposures, especially if these are not quantified. Studies using multiple exposure doses and clearly indicating dose-response information are preferred, but in some cases an inadequate toxicology database may necessitate the use of older studies in which such information is unclear. Such studies are used only if there is no other relevant study available, and they are consistent with the general toxicology database.

4.1.1 Selection of Key Studies

An important step in the development of any REL is the identification of peer-reviewed research studies that contribute most significantly to the weight of evidence as to the degree of hazard presented to humans by a particular substance. The studies may involve a human population studied in an epidemiological, clinical, or experimental exposure setting, or they may involve

experimental studies with animals. These key studies are given greatest weight in estimating the dose-response relationship for adverse effects, and in identifying the nature of the critical adverse effect.

4.1.1.1 Human Data

Human data are logically most relevant to assessing human health effects associated with chemical exposures. Principles for evaluating human exposure studies for use in determining health-based exposure levels have been discussed (OEHHA, 1999; OEHHA, 2000a; OEHHA, 2003; OEHHA, 2005a). Whenever possible, RELs have been based on human data with relevant routes of exposure (principally inhalation). Of the 51 acute RELs originally developed, 36 were based on human health effects (OEHHA, 1999), while of the first 80 chronic RELs, 22 were based on human data (OEHHA, 2005a).

Human studies used in assessing health effects of chemicals have included epidemiological studies, controlled exposure experiments, and 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. It should be noted that controlled studies of exposure in infants and children are rare outside of clinical trials.

4.1.1.1.1 Epidemiological Data

Epidemiological studies generally produce data on effects of chemical exposure to a large number of persons. Areas of concern when interpreting epidemiological studies include exposure measurement, health effects measurement, and accounting for co-variables and confounding variables (Rothman and Greenland, 2005). The population studied may consist of the general public or employees exposed in 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. Also, analytical methods have changed and in many cases improved over the years, and earlier measurements may be much less accurate, or not comparable to more recent data (due to different techniques and equipment for trapping and quantifying, especially for particles and fibers, and recent development of biological monitoring methods). Thus, estimating exposure levels that existed in workplaces many years ago is difficult, and exposure measurements in population-based environmental studies may be even more problematic. Nevertheless, 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. Measurements of human health effects generally consist of recording observable effects, including clinical reports of disease or

disability. If tests are conducted specifically for a study, those tests are usually non-invasive, but standard clinical hematology, X-rays and other standard medical results may also be available. Health effects data are compared with those compiled from a non-exposed group and may be presented as incidence, standardized mortality ratios (SMR), odds ratio (OR) or relative risk (RR) ratios. Health effects with a long latency may be missed if the exposure duration or length of follow-up in the study is inadequate.

For epidemiological studies to be useful, co-variables and confounding variables need to be controlled or removed from the study. Co-exposure to other chemicals is also an important concern as a potentially confounding or modifying effect. Occupational studies raise an additional concern in that generally healthy workers may be less sensitive to the adverse effects of chemical exposures than some others in the general population, including children, the elderly, carriers of genetic polymorphisms, which affect sensitivity, and persons with preexisting medical conditions. Gender-specific effects may be obscured by bias that may be present where a workplace is disproportionate by gender (NRC, 1986a).

“Negative” epidemiological studies (i.e., those not presenting an outcome different from the null hypothesis, properly described as “non-positive”) present additional difficulties in interpretation. Estimating the power of the study to detect adverse effects is important to indicate the maximum incidence consistent with the observed null result. In addition, statistical confidence limits can be put around an observed null result. Although non-positive epidemiological studies may be useful as supporting evidence in favor of a REL derived from another data set, it is unlikely that such studies would themselves provide useful data for deriving a REL.

4.1.1.1.2 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 include:

- (1) involve small sample sizes,
- (2) have a very short exposure duration,
- (3) use narrowly focused response measurements that might miss significant health effects and
- (4) usually only involve relatively healthy adults.

In spite of these potential shortcomings, controlled studies in human subjects, especially in sensitive subpopulations such as asthmatics, are given preference over animal studies in the REL development process, particularly for acute RELs. Human studies were used only if they were consistent with the standard ethical practices of investigation at the time they were conducted. The preferred study is a modern, ethical study approved by an Institutional Review Board for Human Studies. Although data from exposure of infants and children would help OEHHA address its mandate to protect children’s health, controlled studies of exposures to infants and children are rare outside the context of clinical trials of potentially beneficial pharmaceuticals. Controlled exposures of children or infants to environmental chemicals are difficult to justify

ethically, even at presumably safe levels, because their lack of maturity may result in increased and unpredicted susceptibility; also, there are issues surrounding their free and informed consent with children.

4.1.1.1.3 Case Reports

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

4.1.1.2 Animal Data

Animal toxicity studies are the most widely available source of data for REL development. However, studies that address all the toxic endpoints of interest, which include, specifically, pre- and postnatal developmental toxicity as well as effects on adults, are not always available, and studies with the specific exposure periods of one hour, eight hours, or with chronic exposure may not have been done.

Identification of the most appropriate animal species requires consideration of all available data relevant to prediction of human effects from animal observations. Studies of the most sensitive species have frequently been selected as key studies. Such an approach has the advantage of offering maximal protection, especially since humans may be more sensitive than laboratory animals in response to chemical exposure (Lehman and Fitzhugh, 1954). However, the animal species most sensitive to a substance is not necessarily that most similar to humans in developing adverse effects from a particular exposure. In general, of the animals used in laboratory studies, non-human primates are considered to be the most similar in response to exposures to toxic substances, but to date only the acute REL for hydrogen cyanide was developed using data from a controlled exposure of a non-human primate (the cynomolgus monkey, *Macaca fascicularis*). Such studies are relatively rare; those that are conducted typically involve less than lifetime exposure and a small number of individuals and thus have limited statistical power.

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 test animal species (Calabrese, 1983). Comparison of human and animal pharmacokinetics and metabolism may be useful in selecting the relevant animal model for predicting human health effects. For example, hamsters and rabbits have much greater metabolic rates than monkeys (Plopper et al., 1983). This may increase or decrease their susceptibility to toxic substances relative to humans. However, in most instances it is not possible to determine which species responds most like humans.

An experimental study should have a clear rationale and protocol, use Good Laboratory Practice (GLP) standards (or equivalent), and use appropriate analysis methods, including statistical analysis (U.S. FDA, 2006). Experimental study designs and criteria recommended by the NTP have been reviewed (Chhabra et al., 1990). However, the goal of protecting public health must

be weighed with experimental design so that important endpoints are not missed and responses of relevant species are not ignored.

Previously some chronic RELs (e.g., naphthalene and 1,3-butadiene) were calculated using data from the standard 2-year NTP chronic toxicity/carcinogenicity study (OEHHA, 2000a). In many cases shorter screening studies, used for determining appropriate dose levels for the two-year study, are also reported and may contain additional useful information on noncancer toxic endpoints. In an NTP study using the inhalation route, groups of 50 rats and mice (6-8 weeks old) of both sexes are exposed for two years to two or three concentrations of a chemical, and the animals are examined for changes in approximately 30 organs. Although the NTP study has been considered a gold standard for assessing chronic adverse effects, the protocol specifies young adult (8-10 week old rats or mice) animals as the starting point, so it does not include exposures of fetal, neonatal, pre-pubertal or adolescent animals. Thus, the study design may miss or underestimate effects in young animals. Two current animal tests most relevant to children's health are (1) the developmental toxicity study, in which pregnant females are exposed during specific periods of gestation, and (2) the two-generation reproductive study, in which parents and offspring are exposed to the chemical. The absence of one or both of these studies from a chemical's database creates a serious data gap relating to children's environmental health and may result in the application of a data deficiency uncertainty factor (UF_D , typically $\sqrt{10}$, but possibly higher) to address a lack of developmental data (Section 4.4.9.1).

4.2 Weight of Evidence Evaluations and Criteria for Causality

A "weight-of-evidence" approach is generally used to describe the body of evidence on whether or not exposure to a chemical causes a particular effect. Under this approach, the number and quality of toxicology and epidemiological studies, as well as other sources of data on biological plausibility, are considered in making a scientific judgment (OEHHA, 2005b). OEHHA has not adopted a categorical ranking of the weight-of-evidence, but provides a descriptive analysis of strengths and uncertainties of the evidence considered as part of the toxicity review supporting each REL. The U.S. EPA on the other hand has used a formal scheme of this type for their RfCs (U.S. EPA, 1994a).

Many of the proposed criteria for determination of causality are based on analyses of epidemiological studies (OEHHA, 2005b). These same criteria are however of general applicability to animal toxicology studies, although the degree of emphasis and extent of likely problems differ between these two data types. In analyzing animal studies, the nature and extent of the exposure and the characteristics of the exposed animals are generally well controlled. Under these circumstances, issues such as observation of a dose-response relationship, reproducibility of findings, and mechanism of action (including consideration of its relevance to humans) are key elements of the weight-of-evidence. On the other hand, for epidemiological studies the nature and extent of the exposure is often uncertain quantitatively and even qualitatively, and the exposed population is substantially more diverse than in a controlled animal experiment. Selected methodological issues that are considered in the review of the epidemiologic literature include:

- 1) the sample size of the study, which affects the power to detect an effect;
- 2) the extent to which the analysis or design takes into account potential confounders, or other risk factors;
- 3) over-adjustments for potential confounders, which would lead to underestimating effects of the toxin;
- 4) selection bias, or whether the study groups were comparable; including consideration of the “healthy worker effect” and survivor bias,
- 5) the potential for bias in ascertaining exposure and, in particular, nondifferential exposure misclassification, which biases effect size estimates towards the null.

Criteria for evaluating associations between exposure and health effects have been recommended by the International Agency for Research on Cancer (IARC, 2006) (<http://monographs.iarc.fr/ENG/Preamble/index.php>), and standard epidemiology texts (Lilienfeld and Lilienfeld, 1980; Rothman and Greenland, 1998). Much discussion has ensued over the last two centuries on causal inference. Most epidemiologists utilize similar sets of causal guidelines, proposed by Bradford Hill (1971), which OEHHA has employed (OEHHA, 2005b).

It should be noted that the causal criteria are guidelines for judging whether a causal association exists between a factor and a disease, rather than hard-and-fast rules. Lilienfeld and Lilienfeld (1980) note that:

“In medicine and public health, it would appear reasonable to adopt a pragmatic concept of causality. A causal relationship would be recognized to exist whenever evidence indicates that the factors form part of the complex of circumstances that increases the probability of the occurrence of disease and that a diminution of one or more of these factors decreases the frequency of that disease. After all, the reason for determining the etiological factors of a disease is to apply this knowledge to prevent the disease.”

Commonly used causal criteria, based on those of Bradford Hill (1971), are described briefly below. These considerations are described in more detail in Rothman and Greenland (1998), the Surgeon General’s Reports on Smoking (U.S. DHHS, 2004), and OEHHA’s environmental tobacco smoke (ETS) document (OEHHA, 2005b).

4.2.1 Strength of Association

A statistically significant strong association, which is easier to detect if there is a high relative risk, between a factor and a disease is often viewed as an important criterion for inferring causality because, all other things being equal, a strong and statistically significant association makes alternative explanations for the disease less likely. However, as discussed in Rothman and Greenland (1998), the fact that a relative risk is small in magnitude does not exclude a causal association between the risk factor and the outcome in question. Since it is more difficult to

detect (i.e., reach statistical significance) a small magnitude risk, they are just as likely to be causal as larger magnitude risks.

When assessing all evidence, it is important to consider the strength of the study design (particularly controlling for confounding variables, obtaining an unbiased sample, measurement error) and the level of statistical significance (i.e., the ability to exclude a Type I [false positive] error). The power of the study to detect biologically meaningful effects (i.e., the risk of a Type II [false negative] error) is important in considering studies that do not reach traditional (i.e., $P < .05$) statistical significance, particularly if the biological endpoint is serious. If the outcome is serious and the study small (i.e., low power), a larger P value (e.g., $P < .10$) may be adequate evidence for identifying an effect.

There are a number of examples of statistically significant, small magnitude associations that are widely accepted as causal, such as causal links between air pollution and cardiovascular/pulmonary mortality and between second-hand smoke exposure and various cancers and heart disease. From a public health perspective, even a small magnitude increase in risk for a common disease can mean large numbers of people affected by the health outcome when exposure is frequent and widespread, as measured by the population attributable risk or attributable fraction. Small magnitude of association must not be confused with statistical significance, which is much more important.

4.2.2 Consistency of Association

If several investigations find an association between a factor and a disease across a range of populations, geographic locations, times, and under different circumstances, then the factor is more likely to be causal. Consistency argues against hypotheses that the association is caused by some other factor(s) that varies across studies. Unmeasured confounding is an unlikely explanation when the effect is observed consistently across a number of studies in different populations, or when controlling for known confounders.

Relevant observations include similarity of effects noted in different studies. For example, if an effect was noted in only one of many studies of a particular strain of laboratory rodent, or in only one of many epidemiological studies, evidence for a causal association between the chemical exposure and the effect is weakened. Associations that are replicated in several studies of the same design and among different populations (or species for animal studies) or geographical regions, using different epidemiological approaches, or considering different routes or sources of exposure are more likely to represent a causal relationship than isolated observations from single studies (IARC, 2006). If there are inconsistent results among investigations, possible reasons are sought (such as adequacy of sample size or control group, methods used to assess exposure, range in levels of exposure, over-correction for known confounders), and results of studies judged to be rigorous are emphasized over those of studies judged to be methodologically less rigorous. For example, studies with the best exposure assessment are more informative for assessing the association than studies with limited exposure assessment, all else being equal.

4.2.3 *Temporality*

Temporality means that the factor associated with causing the disease occurs in time prior to development of the disease. 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 (in rodents) or years (in rodents or humans) would be temporally consistent. An issue of temporal association that is sometimes difficult to clarify is the distinction between an effect due to chronic exposure and an acute effect due to repeated acute exposures. It may be inappropriate to develop a chronic REL based on an endpoint that is essentially an acute health effect seen repeatedly with daily workplace exposure.

4.2.4 *Coherence and Biological Plausibility*

A causal interpretation cannot conflict with what is known about the biology of the disease. The availability of experimental data or mechanistic theories consistent with epidemiological observations strengthens conclusions of causation. For example, the presence of known carcinogens in tobacco smoke supports the concept that exposure to tobacco smoke could cause increased cancer risk. Similarly, if the mechanism of action for a toxicant is consistent with development of a specific disease, then coherence and biological plausibility can be invoked. It should be noted that our understanding of the biology of disease, and therefore biological plausibility, changes in light of new information which is constantly emerging from molecular biology (including epigenetics), and from new clinical and epidemiological investigations revealing effect influenced by genetic polymorphisms, pre-existing disease, and so forth.

4.2.5 *Dose-response*

A basic tenet of toxicology is that increasing exposure or dose generally increases the response to the toxicant. A progressively increasing response with increased exposure makes it difficult to argue that the factor is not associated with the disease. To argue otherwise necessitates that an unknown factor varies consistently with the dose of the substance and the response under question. While increased risk with increasing levels of exposure is considered to be a strong indication of causality, absence of a graded response does not exclude a causal relationship (IARC, 2006). The dose-response curves for specific toxic effects may be non-monotonic. For instance, where the dose response shows saturation in an observable or experimentally achievable exposure range, the effect of exposures in this range could be nearly maximal, with any additional exposure having little or no effect. In some instances, a response is seen strongly in susceptible subpopulations, and the dose-response is masked by mixing susceptible and non-susceptible individuals in a sample. Further, there are examples of U-shaped or inverted U-shaped dose-response curves, (e.g., for endocrine disruptors) (Almstrup et al., 2002; Lehmann et al., 2004). Finally, timing of exposure during development may mask an overall increase in risk with increasing dose.

4.2.6 Specificity

Specificity is generally interpreted to mean that a single cause is associated with a single effect. It may be useful for determining which microorganism is responsible for a particular disease, or associating a single carcinogenic chemical with a rare and characteristic tumor (e.g., liver angiosarcoma and vinyl chloride, or mesothelioma and asbestos). However, the concept of specificity is not a particularly helpful criterion when studying diseases that are multi-factorial or toxic substances that contain a number of individual constituents, each of which may have several effects and/or target sites.

4.2.7 Experimental Evidence

While experiments are often conducted over a short period of time or under artificial conditions (compared to real-life exposures), experiments offer the opportunity to collect data under highly controlled conditions that allow strong causal conclusions to be drawn. Experimental data that are consistent with epidemiological results, and *vice versa*, strongly support conclusions of causality. There are also “natural experiments” that can be studied with epidemiological methods, such as when exposure of a human population to a substance declines or ceases; if the effect attributed to that exposure decreases, then there is evidence of causality. One example of this is the drop in heart disease death and lung cancer risk after smoking cessation.

4.3 Hazard Identification

4.3.1 Definition of Adverse Effect

The general aim in developing health-protective levels such as RELs is to define a level at which no impairment of the health of an exposed human is anticipated. Risk assessment guidance has therefore historically focused on the identification of an adverse effect as critical in determining health-protective levels. Thus, U.S. EPA has used a general definition of ‘adverse effect’ as “any effect resulting in functional impairment and/or pathological lesions that may affect the performance of the whole organism, or that reduce an organism’s ability to respond to an additional challenge” (U.S. EPA, 1994a).

However, the definition of an “adverse effect” has proved to be a source of significant difficulty and controversy. Not all effects reported for a substance are necessarily considered adverse; some adaptive biochemical responses such as enzyme induction are not considered necessarily adverse, unless they are identified as precursor events consistent with the mode of action for more obviously adverse pathophysiological events (Sherwin, 1983; American Thoracic Society (ATS), 2000a).

Within the health-disease spectrum, health effects could range from mild symptoms of ill health to exacerbations of terminal illnesses of diverse kinds; an inordinate depletion of cell, tissue, and organ reserves; subclinical disease; and mortality. Reserve loss involves both reversible and irreversible alterations of the cell population and includes metabolic abnormalities and alterations of the intercellular milieu. Therefore, the earliest adverse effect is an altered ecology at the cellular level. Irreversible abnormalities that appear relatively minor may have a serious

impact on health by increasing susceptibility to disease in general, or by exacerbating other disease processes (Sherwin, 1983).

NRC (2007) has pointed out that this continuum of responses presents a basic difficulty in defining any particular effect as adverse or otherwise:

“Dividing effects into dichotomous categories of ‘adverse’ and ‘non-adverse’ is problematic. Adverse effects usually develop along a continuum, starting with the uptake of a toxicant, distribution and metabolism, contact with a target organ, biologic change, physiologic response and repair, and clinical disease. Thus with some doses and hosts, biologic changes occur, but the body has sufficient defense mechanisms for detoxification or adaptation, and there is little or no adverse cumulative effect, particularly at low doses. In other situations, biologic changes are measurable and are precursors of an adverse clinical change, so an adverse effect, or the precursor of an adverse effect, could be defined in terms of a chemical metabolite or biologic change that is an indicator of both exposure and effect. The same biologic change could have little impact at a small dose (and so be termed ‘non-adverse’) but produce a much larger impact at a greater dose or in a more vulnerable person (and thus be termed ‘adverse’).”

The U.S. EPA considers both the biological and statistical significance of effects when determining if the observed effect can be defined as adverse. Their determination also takes into account what is known about the underlying mode of action (U.S. EPA, 2002a). Biological significance is the determination that the observed effect (e.g., a biochemical change, a functional impairment, or a pathological lesion) is likely to impair the performance or reduce the ability of an individual to function or to respond to additional challenges from the agent. For some quantal endpoints (e.g., birth defects, tumors, or some discrete pathological changes), criteria are already established to decide the type and incidence of effects, which may be considered adverse, and statistical tools to support the decision. However, changes in continuous measures such as body weight, enzyme changes, and physiological measures, are more difficult to use as endpoints because the amount of change considered to be biologically significant has not been well defined (U.S. EPA, 2002a).

In particular, relatively subtle alterations in such continuous measures such as cellular proliferation, maturation, gene activation or suppression, and altered signal transduction, can lead to serious outcomes in developing humans. Thus it can be difficult, but important to the protection of developing infants and children, to determine the biological significance of seemingly minor alterations in an enzyme. Some changes in enzyme activity or levels can produce severe effects in a developing organism if they produce a change in signal transduction. For example, fetal exposure to chlorpyrifos alters receptor numbers and activity in serotonergic neurons in adults (Aldridge et al., 2004). Also, brief inhibition of cyclooxygenase-2 during the perinatal period alters neurodevelopment and severely inhibits reproductive behavior in the adult male rat (Amateau and McCarthy, 2004).

OEHHA therefore follows NRC (2007) in recommending a cautious and health-protective approach to the consideration of whether a given biological endpoint is appropriate to consider frankly “adverse,” or is a biologically significant precursor lesion, in which case it would be a suitable endpoint for consideration in a risk assessment, or is rather a non-adverse adaptive or incidental change. An example of the necessary decision process is shown in the determination

of a Public Health Goal for perchlorate in drinking water (Ting et al., 2006). Here the decision was made to use the precursor biochemical alteration of impaired iodine uptake, a known effect of the perchlorate ion resulting from inhibition of the active transport protein responsible for iodide translocation, the NIS symporter. This is clearly shown at higher doses to impact thyroid hormone synthesis and this in turn is known to have severe impacts on central nervous system development in the human fetus and infant and on IQ deficits in the human newborn. It was concluded that even modest impacts on the iodine uptake process had the potential to impact sensitive targets, such as the fetus of a woman with suboptimal iodine intake.

4.3.2 Nature of Adverse Effects

The toxic effects of chemicals are of varying types and degrees of severity. Following an acute (one-hour) exposure to a substance released into the atmosphere, effects on the upper and lower respiratory tract may be observed as so-called “portal of entry” effects. Toxic effects from airborne substances may also be due to exposure via the skin and eyes. Systemic effects, such as hemolysis or central nervous system injury, may result from absorption of material through the lungs, and, to a lesser extent, through the skin.

Toxic effects do not have to be observed immediately to be considered due to an acute exposure, but may instead appear hours to days after that exposure. For example, a brief exposure to phosgene may result in pulmonary edema several hours later. In the case of benzene, death may result from leucopenia days following high-level acute exposure.

Certain chemicals, after a single exposure, have the potential to produce delayed adverse effects. Often acute toxicity tests do not have a sufficient follow-up period to allow thorough assessment of the potential for delayed health effects from single exposures. With respect to two kinds of delayed effects, cancer and reproductive or developmental harm, there is more information available. Carcinogenicity is treated separately in risk assessment and cancer potency factors for carcinogens are described in the *Air Toxics Hot Spots Program Risk Assessment Guidelines Part II: Technical Support Document for Describing Available Cancer Potency Factors* (OEHHA, 2005a). Reproductive and developmental toxicants are considered here because substantial research effort has been devoted toward specifically identifying such delayed effects.

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

4.3.3 Severity of Effects

Adverse effects may occur with a range of severity from mild (sensory or subjective effects, or statistically significant incidence of precursor changes, which are reversible) to severe (clinically significant pathological changes, disabling or strongly objectionable sensory effects, persistent or irreversible histological or functional damage), or even to life-threatening. These effect levels

have been used in a variety of ways including in models of progressive dose-response such as that used in U.S. EPA's categorical regression methodology.

The endpoint of choice for determination of a REL, which is intended to protect the health of the community at large, will generally be a mild effect. However, more severe effects may be used if these are in fact the most sensitive endpoint (for example irreversible developmental effects), or if no data on mild effects are available. Under such circumstances, additional models or UFs may be used as described in the following section in order to provide adequate health protection for the majority of the exposed population.

4.3.4 Target Organs

The nature of the target organs or systems involved in a given toxicological response is important since this is considered for hazard index (HI) calculations (Section 2.2). Consideration of the cumulative impact of exposure to multiple chemicals is one of the requirements of SB25, and a key objective for environmental justice considerations. The target organs or systems are described by general categories that may include varied effects: categories and effects currently used in existing acute and chronic RELs are shown in Appendix H. For example, the target system, "respiratory system," includes upper airway irritation as well as lower airway effects, such as bronchoconstriction. Obviously this list of specific endpoints is not exclusive, and may be augmented or amended as new RELs are developed. In order for the acute and chronic REL HI target organs to be consistent, developmental and reproductive effects, which were previously combined, have been separated into two categories. New target organ categories may need to be added, based on the toxicological data used to develop additional RELs.

For simplicity, this approach to HI calculations assumes additivity when multiple toxicants impact the same organ system or biochemical target. Other possible modes include independent (non-additive), synergistic or antagonistic. The description of synergism or antagonism is difficult, and probably requires determination of joint dose-response functions on a compound-specific basis. There are relatively few compounds for which synergism or antagonism have been documented. It is unclear whether this is because such interactions are genuinely infrequent, or because the standard toxicological screens are not designed to identify these effects, and also because the database on the toxicology of chemical mixtures is relatively small.

In using the additive HI approach it is necessary to define what constitutes the "same" toxicological endpoint, which when impacted by multiple toxicants results in effectively cumulative damage (Salmon, 2007). This might be the same molecular target, the same physiological process, or perhaps the same anatomical unit. The traditional basis has usually been the anatomical unit by default, since actual mechanisms and physiological interactions between organs are frequently unknown. More recently, the availability of information on toxicological mechanisms has prompted discussion of both broader and narrower frames of reference. The concept of a single molecular target is attractively simple, but may be too narrow when multiple control or functional systems give input to a single critical system or process downstream from the molecular targets of various toxicants. Because the precise relative contributions of exposure to multiple substances that principally affect different areas of the same physiologic system are unknown, the assumption of additivity across a single major organ system may either under- or over-estimate the effects of chemical interactions in certain cases.

However, in most cases this approach provides an appropriate health protective assumption. We have indicated in Appendix B, Table B-1 which toxicological endpoints are relevant to the specific REL for each chemical. While the REL is based on the most sensitive endpoint, other toxicological endpoints are manifested at exposures close to that which induces the toxicological endpoint that serves as the basis for the REL. Therefore, some chemicals should be evaluated for impacts on multiple target organs or systems. In addition, predisposing conditions are known to increase susceptibility to some chemicals. The target organs for those predisposing conditions should also be included in the HI approach.

4.4 Dose-Response Assessment

4.4.1 Estimation of Threshold or Low Response Concentrations

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

There may also be cases where no threshold exists in the general population for a particular effect. This situation may occur for responses for which there is no theoretical threshold due to the mechanism of toxicity. The most accepted example of this is chemical carcinogenesis, particularly for genotoxic carcinogens. However, there may, at least in principle, be other types of toxicity which do not show a threshold at any dose level.

Even where a true threshold exists in the dose response of a particular individual to a chemical exposure, there may in fact be no identifiable threshold in the response of the general population. This may occur in the case where some individuals in a diverse population show a threshold whereas others do not, which is at least theoretically possible if genetic polymorphisms exist which inactivate a protective mechanism. However, the most likely case is where a true threshold in the response occurs in all individuals at low doses, but the background rate or extent of that toxic response in the population is already above zero due to population-wide exposure to that pollutant or another causative factor which produces the same end-point or disease. In this case, any increment in exposure to the pollutant of concern will cause an increase in the prevalence or severity of the disease, in spite of the existence of a threshold in the individual dose-response relationship. A probable example of this is seen in the neurodevelopmental effects of lead exposure in children, which recent risk assessments have described using linear or other continuous dose-response functions (Carlisle and Dowling, 2006). The data available for criteria pollutants such as ozone or particulate matter are consistent with linear no-threshold dose-response curves for cardiovascular mortality (Daniels et al., 2000; Schwartz et al., 2001; Schwela, 2000; Vedal et al., 2003).

Where these special cases are demonstrated to exist on the basis of population health data, or appear likely based on mechanistic studies, it will be appropriate to use these data to develop risk-based or continuous-response models to describe the population impacts of exposure to these pollutants, rather than relying on the threshold dose-response description to identify a “safe” exposure level. It should be noted that lack of a true threshold does not necessarily imply linearity of response at all doses (although at sufficiently low dose levels any continuous non-threshold dose-response curve will necessarily approach linearity). Conversely, the observation of a non-linear dose-response curve does not necessarily imply the existence of a threshold. However, in the majority of cases for noncancer effects the existence of a threshold in the dose response is both plausible, and often, within the acknowledged limitations, demonstrable (U.S. EPA, 1993). Therefore, the threshold assumption is regarded as the default for noncancer risk assessment, and is most often used.

Two major strategies are used for dose-response assessment methods to estimate “thresholds” of responses from study data. These are the benchmark dose (BMD) or benchmark concentration (BMC) approach and the no-observed-adverse-effect-level (NOAEL) approach. In both approaches, uncertainty factors (UF) are applied to account for various uncertainties in extrapolating from the study results to the general population. These are described in Sections 4.4.2 through 4.4.9.

Of the methods presented, the BMC approach is preferred. Quantal or continuous dose-response data for a toxicant (measured for at least two dose levels and a control) are required to estimate levels using the BMC method. Supporting toxicological data will not, however, always be sufficient to permit this level of quantification. In most cases, the method will allow determination of a benchmark concentration even with relatively sparse data; however, obviously the confidence in the result will be lower in this case. The alternative NOAEL method may give the appearance of providing a result more easily with poor data, but in fact the uncertainty in such a result can be extremely large, and the situation is not improved by the inability to quantify this uncertainty. OEHHA has used the BMC approach to develop two acute RELs (OEHHA, 1999; Collins et al., 2005). More recently a number of chronic RELs have been developed using this approach (Collins et al., 2003; Collins et al., 2004). Based on recent experience with the benchmark method, new REL values will be developed using the BMC approach whenever data of sufficient quality to support this methodology are available.

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

A No-Observed-Adverse-Effect-Level (NOAEL) in a human or animal study may be defined as an exposure level with no biologically or statistically significant increase in the frequency or severity of adverse effects among the exposed group 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 experimental group or population. 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 (U.S.

EPA, 1994a). Alternatively, a NOAEL could be many-fold lower than a true population threshold due to study design and dose spacing (Gaylor, 1992; Leisenring and Ryan, 1992).

The U.S. EPA (1994a) determined that a NOAEL not associated with any biological effect (a “no-observed-effect-level” or NOEL) identified from a study with only one dose level is unsuitable for derivation of an RfC for chronic exposure. Because there is a limited availability of multi-dose studies for the variety of chemicals considered, OEHHA may use a NOAEL without an associated LOAEL (lowest-observed-adverse-effect-level) identified in the same study (termed a free-standing NOAEL) in deriving a REL, but only if there are no other suitable studies, and so long as the overall health hazard data (including any case reports or studies with shorter durations) for that substance are consistent with the NOAEL study.

4.4.1.1.1 Derivation of Reference Exposure Levels (RELs) Using NOAELs

Reference Exposure Levels are derived by the application of UFs to the NOAEL for a critical endpoint. The application and values of UFs, which are similar for the NOAEL and BMC approaches, are described below.

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

Prior to the determination of a NOAEL, the literature is examined to identify the relevant endpoints. Toxicological endpoints are evaluated to determine the most sensitive effect (occurring at the lowest exposure level), and a dose-response relationship is determined. The most sensitive adverse effect of relevance to human health (termed the “critical effect”) is used as the basis of the REL, and as noted above this is usually a mild adverse effect.

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

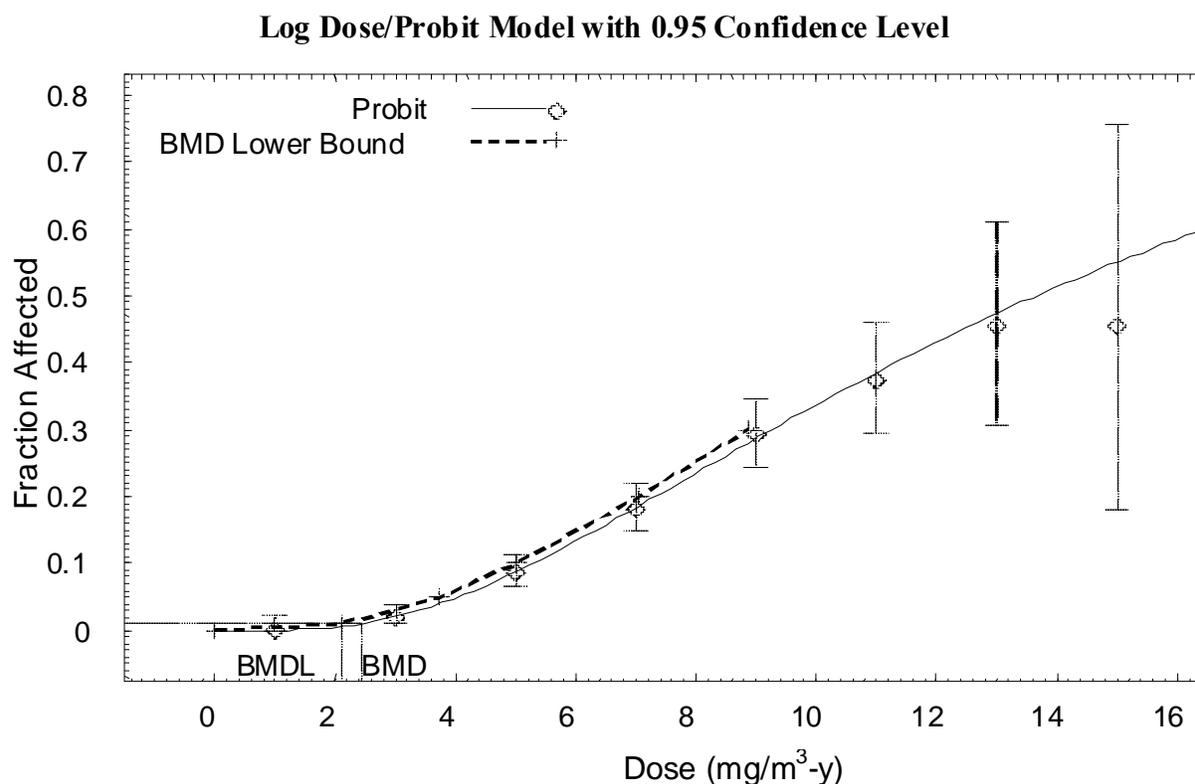
A Lowest-Observed-Adverse-Effect-Level (LOAEL) may be defined as the lowest exposure level in a study or series of studies with a biologically and/or statistically significant increase in the frequency or severity of adverse effects among an exposed population relative to a control group. The highest exposure concentration which results in biological effects that are not considered adverse may be termed the lowest-observed-effect-level (LOEL); this is identical to the NOAEL (U.S. EPA, 1994a). If a NOAEL is not identifiable from the literature, it must be estimated from the lowest exposure concentration reported to produce the adverse effect; this is the lowest observed adverse effect level (LOAEL). An UF is applied to the LOAEL to estimate the NOAEL. Use of a LOAEL should be a last resort; use of the BMC methodology is preferable whenever possible. Where experimental data showing intermediate response rates are very limited, this may place constraints on the benchmark response rate and curve-fitting model used. However, even in these cases the overall uncertainty is likely to be both smaller and better quantified by the BMC methodology than by a LOAEL-based derivation.

If there exist multiple, non-identical NOAELs and LOAELs for the same compound and critical effect, the study of the best quality reporting the highest value for a NOAEL (preferred) or the lowest value for the LOAEL is used for the development of RELs.

4.4.1.2 Benchmark Concentration

The importance of a dose-response relationship in the evaluation of effects of chemical exposure is well-established. The NOAEL approach, does not explicitly incorporate information on the shape of the dose-response curve and is highly dependent on the test doses chosen by the original investigators. 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, 1986; Hartung, 1987; Gaylor, 1988; Gaylor et al., 1998). Crump (1984) proposed the term “benchmark dose” and extensively evaluated this concept. In this document, the term benchmark concentration (BMC) is used since inhalation toxicology data are usually described in terms of air concentrations.

The BMC method allows a mathematical and statistical approach to the calculation of RELs (Crump, 1984; Lewis and Alexeeff, 1989; Alexeeff et al., 1992; Alexeeff et al., 1993; Barnes et al., 1995; Collins et al., 2005; Starr et al., 2005). In this document, the BMC is defined as the 95% lower confidence limit of the concentration expected to produce toxic responses in a chosen percentage of subjects (the benchmark response rate) exposed at this dose. A suitable mathematical function is fitted to the concentration versus response relationship using likelihood methodology. The function used is selected according to defined quality of fit criteria. The concentration expected to produce the benchmark response rate, and the lower confidence bound on that concentration are identified from the fitted curve. In the case of quantal data in an animal toxicity experiment, the benchmark response rate is usually selected at 5% (see Section 4.4.1.2.1 below). Other types of data, including continuous measures of toxic response, and data from epidemiological studies, require an appropriate benchmark response rate to be identified on a case-by-case basis. An example of the benchmark dose methodology is graphically depicted in Figure 4-1.

FIGURE 4-1 LOG-PROBIT MODELING OF DOSE-RESPONSE DATA FOR SILICA¹

¹Data from (Hnizdo et al., 1993; Collins et al., 2005).

In spite of its advantages, there are sources of uncertainty in the experimentally derived BMC value. For example, the studies used to estimate the BMC have usually been performed with animals rather than humans e.g., (Kuwabara et al., 2006). Also, the experimental duration of exposure may differ from that which is of interest for the establishment of RELs. Additionally, the dose of toxicant delivered to the target tissue may differ between species and among humans and may depend on the type of activity in which the individual is engaged. Another area of uncertainty is that there can be a large degree of variability in the number of people who respond at any exposure. For example, there may be over a 10-fold variability in the irritation threshold (the concentration of a substance at which irritation of the eyes, nose and/or throat is first detectable) for chlorine (Anglen, 1981). In order to estimate a health protective level such as a REL for the population of concern, the BMC is therefore modified by UFs, except where explicit extrapolation models are available to allow for these differences.

$$\text{BMC} / \text{UF} = \text{REL}$$

Most frequently, the characteristics of the BMC are chosen so that its properties are similar to that of the NOAEL described below. Thus, similar UFs (Table 4.4.1) are applied with both approaches. Specific data sets may however result in the use of UFs different from what would be used with a standard NOAEL, determined on a case-by-case basis; the rationale would be described in each toxicity summary for the individual chemicals.

4.4.1.2.1 Selection of Appropriate Benchmark Concentration Response Rate

A response range of 1% to 5% approximates the lower limit of adverse effect detection likely to occur in typical human epidemiological studies, and in large laboratory animal studies the detectable response rate is typically in the 5 to 10% range (Gaylor, 1992). In 1995, using animal developmental toxicity data, the U.S. EPA concluded that a 1% response rate was likely to be too low to be detected and therefore too uncertain to use as a point of departure, while either 5% (BMC₀₅) or 10% (BMC₁₀) response rates were adequate for the purposes of estimating a benchmark concentration (Barnes et al., 1995). One reason for this conclusion was the large difference (29-fold) between observed NOAELs and the 1% benchmark using developmental toxicity data. Subsequently, the U.S. EPA (2007a) used a 10% response rate for benchmark concentrations when deriving chronic inhalation reference concentrations (RfCs). More recently, RfC determinations for various endpoints by the U.S. EPA have used either 5% or 10% as the benchmark response rate, depending on the statistical uncertainty in the data (U.S. EPA, 2002a; U.S. EPA, 2004). OEHHA has used the 5% response rate in several chronic RELs, and showed that the lower 95% confidence bound on the BMC₀₅ typically appears equivalent for risk assessment purposes to a NOAEL in well designed and conducted animal studies where a quantal measure of toxic response is reported (Lewis and Alexeeff, 1989; Alexeeff et al., 1992; Alexeeff et al., 1993; Barnes et al., 1995; Collins et al., 2004; Collins et al., 2005; Starr et al., 2005; Alexeeff et al., 2006; Brown et al., 2006). Therefore, OEHHA typically uses a 5% response rate as the default for determination of the BMC from quantal data (*i.e.* the effect is either present or it is not) in animals (Fowles et al., 1999).

Other response rates may be selected if the data indicate that this is appropriate. For instance, large epidemiological studies examining a relatively severe endpoint such as clinical disease may support the use of a 1% response criterion, as in the case of the chronic REL recently developed for respirable crystalline silica (Collins et al., 2005). In that case, the size of the epidemiological database was large and thus there was high confidence in the response at low exposures. In the case of a steep dose-response relationship, the selection of response rate is less influential on the final value. For acute lethality studies, 1 and 5% response rate benchmark concentrations differed, on average, by less than 2-fold from the respective NOAEL (Fowles et al., 1999).

Various criteria have been proposed for selecting an appropriate benchmark response rate for continuous data such as body weight, blood cell numbers, and levels of enzyme activity (U.S. EPA, 1995; Gaylor et al., 1998; Crump, 2002; Sand et al., 2003). One criterion is statistical confidence, e.g., criteria based on some multiple (1.0 - 3.0) of the standard deviation of the reported measurements, either above or below the mean, particularly in controls or low-dose groups. A standard deviation of 2.33 from the mean identifies values at the first and 99th percentiles, extreme values even if not adverse. If values greater than the 98th to 99th percentile are abnormal, then a concentration that changes the mean by one standard deviation yields roughly 10% excess risk in subjects in the abnormal range (Crump, 1995). A second criterion is scientific judgment as to what constitutes a biologically relevant perturbation in a measured parameter, such as one that exceeds the likely range of physiological compensation. Some clinical guidelines are generally accepted as cutoff points although they are not necessarily thresholds. These might include:

- (1) reduction in lung function (>20% of expected forced expiratory volume (FEV)) as clinically significant
- (2) a carboxyhemoglobin level of 1.1 to 1.3%, and
- (3) a pesticide worker's blood cholinesterase level less than 80% of the individual's baseline level.

The choice of an appropriate benchmark criterion for continuous data is currently based on the particular nature of those data, including supporting information on severity of the effect and possible mechanisms of repair or compensation, rather than on any overall policy-based guidance. In the development of the chronic REL for carbon disulfide, OEHHA used as the benchmark response rate a five percent reduction in peroneal motor conduction velocity (BMC₀₅), a mild effect and definitely within the range of normal variation. In some cases, population shifts in a continuous variable such as FEV₁, blood pressure, birth weight, thyroid hormone levels (Ting et al., 2006) or IQ (*e.g.* effects of lead as reported by Lanphear et al. (2005)) may result in pushing more individuals into a high-risk category, and thus small shifts can be considered adverse.

4.4.1.2.2 Selection of Confidence Limits

The benchmark dose or concentration is selected by fitting an assumed dose-response curve to the observed response data. Mathematical curve fitting of this type necessarily involves recognition of uncertainty and variability in the input data. Fitted curves or interpolated values are generally described in terms of both maximum likelihood estimates (MLE) and confidence bounds on these estimates. Variation around the predicted values is generally assumed to follow a χ^2 (chi-squared) distribution, and the χ^2 statistic is used as a criterion of fit quality and in deriving "p" values and confidence limits on estimates. The 95% lower confidence limit (LCL) of the concentration at the chosen benchmark response rate or level is generally used as the BMC, rather than the MLE. This is preferred since it takes into account sources of uncertainty intrinsic to the source data, including the variability of the test population and the number of subjects in the study. This provides an incentive for the generation and use of higher quality data, unlike the NOAEL/LOAEL methodology, which makes no explicit quantitative allowance for uncertainty in the underlying data. Use of the 95% LCL in a benchmark calculation also takes into account the quality of fit for the dose-response curve. The Benchmark Dose Workshop (Barnes et al., 1995) recommended using the 95% LCL in benchmark dose calculations. With robust data sets the 90, 95, and 99% LCLs are close to each other and to the MLE (Sand et al., 2002).

4.4.1.2.3 Selection of Models to fit the Dose-Response Curve

It is important to select an appropriate mathematical model for the type of data used for benchmark concentration calculations (Filipsson et al., 2003). The U.S. EPA's Benchmark Dose Software (BMDS) contains a variety of models (U.S. EPA, 2006a).

For dichotomous data, the models include the following:

- (1) gamma distribution,
- (2) logistic,
- (3) multistage,
- (4) probit,
- (5) quantal linear,
- (6) quantal quadratic, and
- (7) Weibull models.

The quantal linear and the quantal quadratic are special cases of the Weibull model in which the exponents are one and two, respectively. The probit and logistic models can be run using either the dose or the logarithm of the dose. These models are useful for data where the subjects at each level of exposure did or did not experience a specific adverse effect such as eye irritation, liver enlargement, or an impaired nervous system (based on passing or failing a specific test). For nested dichotomous data, such as found in animal developmental data in which individual offspring are nested in litters, the models available are:

- 1) NLogistic (logistic nested),
- 2) NCTR (National Center for Toxicological Research), and
- 3) Rai & Van Ryzin (after the authors who described the model).

For continuous data such as body weight, enzyme activity level, blood cell counts, IQ, and nerve conduction velocity, the models available are the:

- (1) linear,
- (2) polynomial,
- (3) power, and
- (4) Hill.

To date the models most used by OEHHA are those for dichotomous data. Usually each model is fit to a dose-response data set of the most sensitive endpoint available, and both the MLE and the lower 95% confidence bound benchmark confidence level ($BMCL_{05}$) of the effective dose (ED_{05}) are derived from each model. When the number of subjects is very large as in the case for some occupational epidemiological exposures such as respirable, crystalline silica, the MLE_{01} and $BMCL_{01}$ (a one percent benchmark) can be determined (Collins et al., 2005). The models that give an acceptable fit ($p \geq 0.10$ by χ^2) are further examined. Some models may fit the entire range of the data equally well by the χ^2 test, but one may be better than another in describing the shape of the dose-response curve at the lower end of the dose range, which is critical in defining a benchmark such as $BMCL_{05}$. If more than one model gives an acceptable fit to the data, then some judgment is used in balancing a model's goodness of fit (as possibly indicated by a much higher p value or as determined visually from the plotted curve) versus the level of health protection provided by the $BMCL_{05}$ derived using that model. From the perspective of protecting public health, the lowest value of the $BMCL_{05}$ from a model having an acceptable fit might be taken. However, with certain data sets, some models (including the often used log-probit model) may indicate an MLE which is very far from the BMCL value (Murrell et al., 1998). For well-fitting models, the BMCL is seldom less than one third of the corresponding MLE, unless the overall precision of the data is poor. The analyst should also beware of attempts to fit complex models to data sets with insufficient precision to specify all the model parameters accurately (U.S. EPA, 2006a). Thus there must be allowance for professional

judgment by toxicologists and statisticians. These considerations are discussed in the summary for each REL derived by the benchmark method.

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.

TABLE 4.4.1. POSSIBLE DEFAULT UNCERTAINTY FACTORS USED IN DERIVING ACUTE, 8-HOUR AND CHRONIC RELS

<i>Method or Factor</i>	<i>Values Used</i>	<i>REL types</i>
<i>LOAEL uncertainty factor (UF_L)</i>		
<i>Values used:</i>	1 NOAEL or benchmark used	A, 8, C
	6 LOAEL, mild effect	A
	10 LOAEL, severe effect	A
	10 LOAEL, any effect	8, C
<i>Interspecies uncertainty factor (UF_A)</i>		
<i>Values used for a combined interspecies uncertainty factor (UF_A):</i>	1 human observation	A, 8, C
	$\sqrt{10}$ animal observation in nonhuman primates	
	10 where no data are available on toxicokinetic or toxicodynamic differences between humans and a non-primate test species	

TABLE 4.4.1. POSSIBLE DEFAULT UNCERTAINTY FACTORS USED IN DERIVING ACUTE, 8-HOUR AND CHRONIC RELS

<i>Method or Factor</i>	<i>Values Used</i>	<i>REL types</i>
<i>Values used for the toxicokinetic component (UF_{A-k}) of the interspecies uncertainty factor:</i>	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 $\sqrt{10}$ non-primate studies with no chemical- or species-specific kinetic data	A, 8, C
<i>Values used for the toxicodynamic component (UF_{A-d}) of the interspecies uncertainty factor:</i>	1 where animal and human mechanistic data fully describe interspecies differences. <i>(This is unlikely to be the case.)</i> 2 for residual susceptibility differences where there are some toxicodynamic data $\sqrt{10}$ non-primate studies with no data on toxicodynamic interspecies differences	A, 8, C
<i>Intraspecies uncertainty factor (UF_H)</i>		
<i>Values used for the toxicokinetic component of the intraspecies uncertainty factor, (UF_{H-k}) for systemic toxicants:</i>	1 human study including sensitive subpopulations (e.g., infants and children) 1 where a PBPK model including measured inter-individual variability is used $\sqrt{10}$ 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
<i>Values used for the toxicodynamic component of the intraspecies uncertainty factor, (UF_{H-d}):</i>	1 Human study including sensitive subpopulations (e.g., infants and children) $\sqrt{10}$ 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
<i>Subchronic uncertainty factor (UF_S)</i>		

TABLE 4.4.1. POSSIBLE DEFAULT UNCERTAINTY FACTORS USED IN DERIVING ACUTE, 8-HOUR AND CHRONIC RELS

<i>Method or Factor</i>	<i>Values Used</i>	<i>REL types</i>
<i>Values used:</i>	1 Study duration >12% of estimated lifetime √10 Study duration 8-12% of estimated lifetime 10 Study duration <8% of estimated lifetime	C
<i>Database deficiency factor (UF_D)</i>		
<i>Values used:</i>	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.

4.4.4 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:

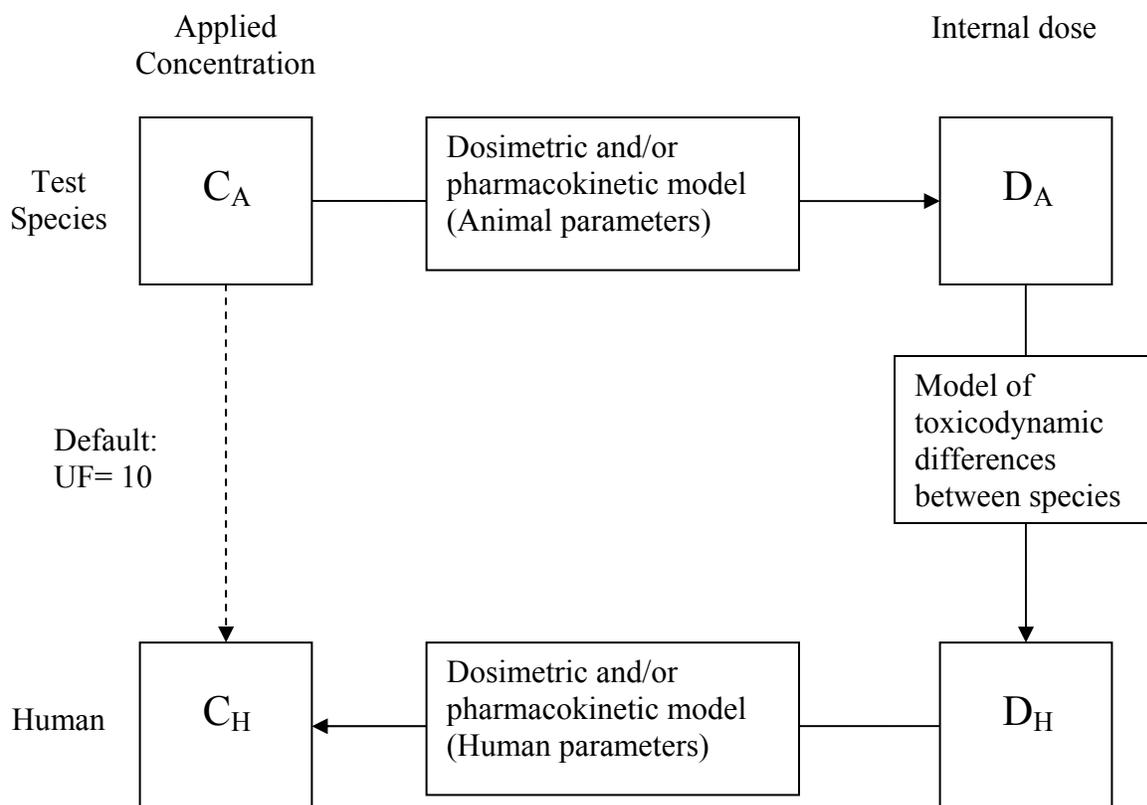
- a) differences in absorption, distribution, metabolism and excretion (dosimetric and toxicokinetic adjustments), and

- 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.

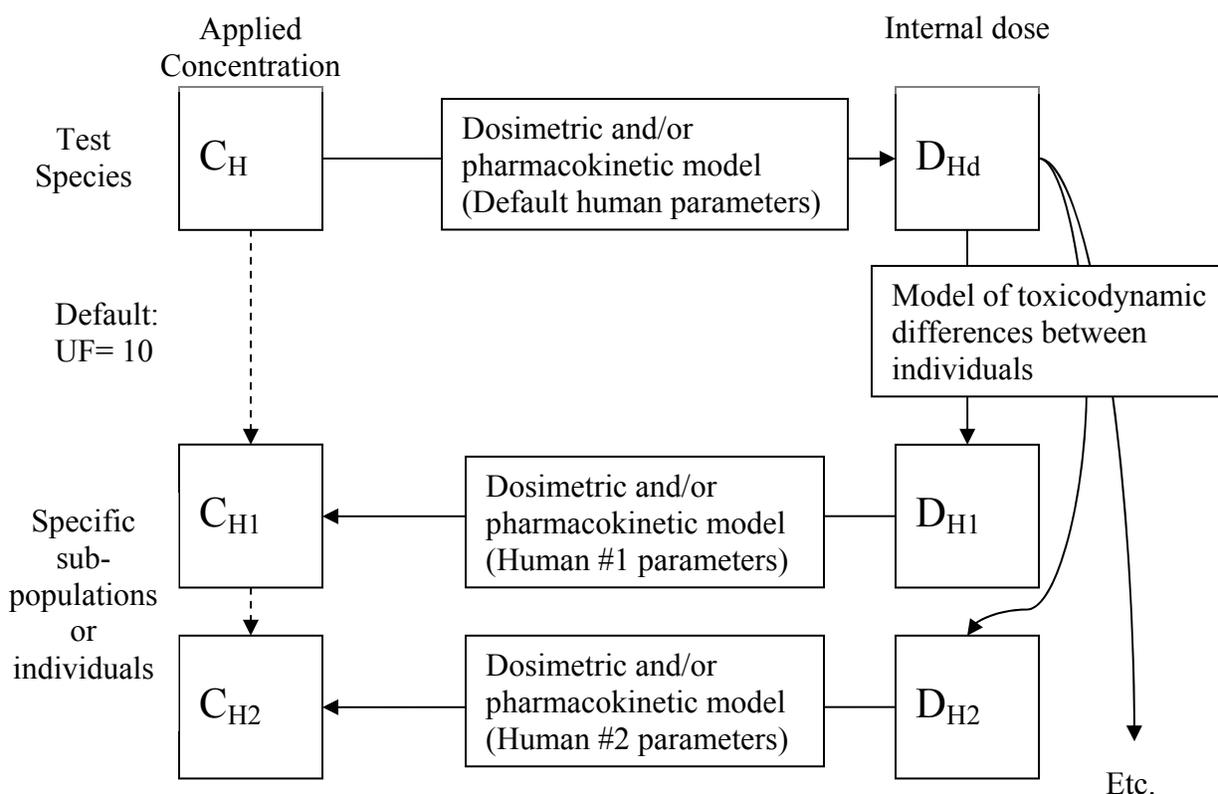
C_H = Human equivalent applied concentration.

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.

4.4.6 Extrapolating from Study Duration to REL Reference Period

The target reference period for development of a REL is one hour (single or infrequent exposure) for acute RELs, eight hours with potential for repeat exposures for the eight-hour RELs, and lifetime/annual average for the chronic RELs. Acute RELs are typically based on data from short-term exposures of a few minutes to a few hours, and eight-hour or chronic RELs typically involve data from extended repeat-dosing studies. However, the experimental duration, or exposure period in an animal or human study, is not generally the same as the REL reference period. Scaling procedures may therefore be required to extrapolate from the specific duration (and extent of repetition) of the studies to the REL reference period. Since these are specific to the type of REL being developed they are described in the subsequent sections dealing with procedures specific to the individual REL types.

4.4.6.1 Eight-hour and Chronic RELs

The dose-response for most toxicological processes is assumed to follow some form of dose-time integral over moderate periods of exposure. For medium-term adjustments in repeat-exposure animal studies such as six to eight hours to twenty-four, or five days a week to seven, a simple concentration multiplied by time ($C \times T$) dependence, often referred to as Haber's Law, is assumed, so these results are adjusted by simple proportion, as described in Section 7.2.1.

The default approach to extrapolating from subchronic to chronic exposures used by OEHHA (Section 7.2.2) for development of chronic RELs is to use a 1 to 10-fold subchronic uncertainty factor (UF_S) for subchronic exposures (Table 4.4.1). Chronic studies in standard toxicological testing paradigms are those where the exposure duration is 12% or more of the expected lifetime of the test species, while subchronic studies are repeat-dosing studies shorter than this but longer than standard sub-acute protocols. The same adjustment is used for human studies where the average exposure duration is less than 12% of lifetime (70 years). For exposures less than 8% of expected lifetime a 10-fold UF_S is applied, while for exposures from 8 to 12% of expected

lifetime a 3-fold UF_S is applied. Where exposures are longer than 12% of expected lifetime there is no adjustment, i.e., $UF_S = 1$.

4.4.6.2 Acute RELs

For shorter study periods such as those of a few minutes to hours that are considered in development of acute RELs and some eight-hour RELs, the basic $C \times T$ dependence is modified by means of exponents. Most commonly, an expression of the form $C^n \times T$ is used to reflect acute toxic responses where concentration is a more important determinant of response than duration over the time period of the observation. Application of this modified Haber's Law procedure in development of acute RELs is described in Section 5.4.1.

4.4.6.3 Exposure Duration REL Adjustments for Developmental Toxicants

Historically, duration adjustment of inhalation exposures for developmental toxicity studies has not been done (U.S. EPA, 2002a). Unlike subchronic and chronic toxicity studies, in which months or even years of exposure may be needed before tissue damage becomes evident, developmental toxicity is frequently the result of exposure during a small window of time during gestation in which exposure may only be on the order of hours during a critical stage of development. Because the timing and duration of the sensitive period of gestation is usually unknown, the standard experimental protocol is to expose pregnant animals for several hours per day over several days during gestation in order to increase the power of the study to detect an effect. As a result, time extrapolation to the REL must take into account two principal toxicokinetic issues to prevent, in particular, underestimation of developmental toxicity - peak tissue concentration and total tissue dose (e.g., area under the concentration-time curve (AUC)). Instances of developmental toxicants that operate predominantly by one or the other toxicokinetic factors have been observed. For example, prenatal exposure of mice to short, high exposures of ethylene oxide on day 7 of gestation was found to cause more adverse developmental effects than mice exposed to the same $C \times T$ multiple but at longer, lower exposures (Weller et al., 1999). Alternatively, pregnant rats administered all-trans-retinoic acid indicated that AUC, and not maximum plasma concentrations, was the most appropriate pharmacokinetic marker of developmental toxicity (Tzimas et al., 1997). The following procedures are designed to be health-protective even in the case where a developmental effect is the result of a possibly very brief sensitive period during a single day of exposure to the toxicant (U.S. EPA, 2004).

4.4.6.3.1 Developmental REL Duration Adjustment from Shorter to Longer Exposures

When the principal toxicokinetic process involved in the developmental toxicity of a non-accumulating chemical is unknown, the U.S. EPA Technical Panel recommends that duration adjustment procedures from discontinuous to continuous exposures be based on equivalent multiples of concentration (C) and duration (T) for inhalation developmental toxicity studies as it is used for other health effects from inhalation exposure (U.S. EPA, 2002a). This $C \times T$ approach favors a health protective overestimation of risk when adjusting the exposure duration from a shorter period to a longer period of exposure, as has been shown experimentally in dose-rate studies of developmental toxicants (Weller et al., 1999). The pharmacokinetic basis for this duration adjustment assumes that the total tissue dose during a single-day exposure period is the

critical quantity in determining the level of response and ensures that the AUC, as well as the peak tissue level, will not be increased in the duration adjustment. Correspondingly, OEHHA will use this time adjustment procedure when estimating a chronic REL based on a developmental study. The default approach for duration adjustment of a developmental endpoint from discontinuous exposure to chronic continuous exposure is the same as that used for a chronic toxicity duration adjustment, and can be summarized as:

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

where C_{AVG} is the time-weighted average concentration, and C_{OBS} is the observed concentration.

Time extrapolation to an eight-hour REL must also take into account pharmacokinetic processes affecting a developmental endpoint, from either a single eight-hour exposure or multiple daily eight-hour exposures during gestation. Thus, estimation of the eight-hour REL will also use the daily average C x T time adjustment when extrapolating from a shorter exposure time to an eight-hour REL. The same daily average C x T adjustment should also be used when an acute REL is based on a developmental study involving exposure of animals for less than an hour for one or more days during gestation.

As more information becomes available on PBPK modeling of developmental toxicants for interspecies extrapolation from the exposed animal species to humans, modeling of blood and tissue levels may confirm the C x T adjustments on the REL exposure durations to ensure they do not exceed the peak tissue concentration or total tissue dose at the NOAEL.

4.4.6.3.2 Developmental REL Duration Adjustment from Longer to Shorter Exposures

For acute REL development, time duration adjustment will often require extrapolation from multi-hour exposure to the 1-hour exposure duration of the acute REL. Dose-rate exposure studies have shown that a C x T approach from a long exposure duration to a shorter exposure duration could underestimate the response of developmental toxicants (Weller et al., 1999). To avoid underestimation of risk when the pharmacokinetic nature of the developmental toxicant is unknown, OEHHA recommends no duration adjustment on the exposure concentration when extrapolating from a longer exposure duration per day down to a one-hour exposure. This procedure primarily protects against higher peak tissue concentrations that would occur if a C x T time adjustment was applied. Preferably, the acute studies used as the basis of an acute REL would be those with exposure duration nearest one hour, in order to reduce the uncertainty of this approach. This approach would also apply to eight-hour RELs in which the primary study used daily exposures greater than eight hours (i.e., no time extrapolation would be applied).

4.4.6.3.3 Duration Adjustment for Bioaccumulating Developmental Toxicants

An additional pharmacokinetic issue to consider involves chemicals in which discontinuous daily exposures may take one to two weeks of gestational exposure before tissue saturation occurs. Many developmental studies begin exposures following conception. Conceivably, the critical point of gestation for developmental effects may have passed before maximal fetal/maternal blood levels were attained during the exposure period. For example, the aromatic hydrocarbon 1,2,4-trimethylbenzene shows a gradual increase in prior-to-shift blood levels (and the AUC) in humans over a 5-day period with daily eight-hour exposures (Jarnberg and Johanson, 1999).

Ideally, in animal studies of a bioaccumulating toxicant, maternal exposures would occur prior to the beginning of gestation so tissue saturation at a given exposure concentration is already present when development begins. Multi-generation studies often expose animals for at least several weeks prior to mating and could resolve this concern. In lieu of multi-generation studies and studies that started exposure prior to gestation, a modifying UF may be considered for those chemicals that slowly accumulate to maximal tissue levels during gestational exposure, to account for the potential underestimation of dose during the window of developmental susceptibility. Alternatively, a fractional adjustment of the exposure level can be made if sufficient pharmacokinetic data are available to identify the time to tissue saturation and tissue saturation levels. This pharmacokinetic adjustment would prevent exceedance of peak tissue levels or total tissue dose at critical time points in fetal development.

For major bioaccumulators such as dioxins and some metals, developmental exposure studies in which exposure occurred only during gestation is not sufficient for establishing eight-hour or chronic RELs based on developmental toxicity. These types of toxicants can accumulate in body tissues over extended periods of time prior to gestation, leading to very high maternal body burdens that may be detrimental to the fetus during gestation. Lack of sufficient chronic exposure and multi-generation studies and lack of adequate pharmacokinetic modeling information that can predict body tissue burdens may require application of a modifying UF for pharmacokinetic deficiencies in calculating the REL.

4.4.6.3.4 Effects of Exposure Continuity

Acute, eight-hour and chronic RELs are intended to protect members of the general population from the types of exposures resulting from facility emissions or ambient levels of air pollutants. Such emissions may show variations diurnally, seasonally or over the long term. Modeling and interpretation of such exposure patterns are covered in the Exposure Assessment section of the Hot Spots Technical Support Documents (OEHHA, 2000b). It may also be necessary to apply models or adjustments to the exposures received by the subjects (animal or human) of studies used as the basis for derivation of acute, eight-hour or chronic RELs, where animal experiments or human studies involve discontinuous or repeated exposure patterns. Specific adjustment procedures are prescribed for derivation of RELs, which are different for the three types of REL. They are therefore described separately in Sections 5, 6 and 7, covering issues specific to each type of REL.

4.4.7 Accounting for Potentially Greater Human Susceptibility

4.4.7.1 Introduction

Greater sensitivity of humans compared to animal test species for a variety of toxicological endpoints have been shown Dourson and Stara (1983). A well-known example is teratogenesis by various agents including thalidomide Brown and Fabro (1983). In general, interspecies UFs are applied to the animal study results to account for potentially greater human susceptibility (see Section 4.4.7.3). However, a preferred approach to interspecies extrapolation is to employ chemical-specific kinetic models to assess species differences in relevant tissue dosimetry. If chemical specific models are not available, generic approaches such as the human equivalent concentration (HEC; the air concentration of an agent that induces the same magnitude of toxic

effect in humans as that seen in experimental animals) and/or an animal to human uncertainty factor (UF_A) may be applied. As described above (Section 4.4.4), this factor may be regarded as consisting of toxicokinetic and toxicodynamic factors, which may be considered separately where explicit models are available to describe some aspects of the extrapolation, especially toxicokinetics. Differences in acute behavioral toxicity of toluene in rats and humans are partly described by a toxicokinetic model: there are residual differences in sensitivity between species based on the tissue dose levels which might relate to actual sensitivity differences at the cellular level, or to differences in the sensitivity and comparability of the tests used in the two species (Benignus et al., 1998; Bushnell et al., 2007).

4.4.7.2 Kinetic Modeling in Interspecies Extrapolation

As part of the scientific basis for this update of the risk assessment guidelines, OEHHA conducted a pilot investigation of the application of physiologically based pharmacokinetic (PBPK) modeling to dosimetric adjustments in noncancer risk assessment. The aim was to derive alternate dosimetric adjustment factors (DAFs) or human equivalent concentration (HEC) factors based on metrics of internal dosimetry such as peak concentrations (C_{max}) and areas under the blood or tissue concentration x time curves (AUCs). The chemicals selected for this pilot study were: ethylbenzene, vinyl chloride, toluene, styrene/styrene oxide, naphthalene/naphthalene oxides, and formaldehyde. All of these chemicals occur in outdoor and indoor air and have some prior PBPK model availability for rat or human. Initial comparisons were limited to rat/human conversions for adults and immature animals/children. In addition, since the overall objective is to improve the scientific basis for predictive toxicological criteria for air pollutants the investigation also included a series of straight chain aliphatic aldehydes: $CH_3(CH_2)_nCHO$ ($n = 0$ to 8). Several aliphatic aldehydes have been observed in outdoor (Uebori and Imamura, 2004) and indoor (Arcus et al., 1995) air sampling or are known to originate in building materials or furnishings.

4.4.7.2.1 PBPK Models

The type of PBPK model used by OEHHA is dependent on the physicochemical characteristics and toxicokinetic properties of the agent in question (See Appendix E for more detail; see U.S. EPA (2006b) for a general description of PBPK modeling). Broadly speaking, gaseous agents fall into one of three categories.

- Category 1 gases are reactive gases that interact mainly at the site of contact; either the nasal or respiratory tracts (RT) as portals of entry.
 - For agents in Category 1, OEHHA used either a 4- compartment RT model of the type described by Sarangapani et al. (2004) that is similar to a 3-compartment default model of the RT recommended by Hanna et al. (2001), with uptake defined by regional mass transfer coefficients. Depending on the agent being studied, for some Category 1 gases, OEHHA used nasal models as described by Frederick et al. (1998).

- Category 2 gases tend to be less reactive and water soluble, and have effects both locally, on the RT, and systemically.
 - For Category 2 gases, OEHHA used RT-PBPK models of the type described by Sarangapani et al. (2004). These models included both RT compartments and body compartments for remote distribution and metabolism as recommended by Hanna (2001).
- Category 3 gases are less water soluble, less reactive, and therefore scrubbed less efficiently in the respiratory tract, and mainly have remote systemic effects.
 - For Category 3 gases, with mainly remote effects, OEHHA used either a one-compartment or, alternatively, a two-compartment lung model as described by Evelo et al. (1993), consisting of a high-perfusion alveolar exchange compartment and a low-perfusion bronchial compartment. In some instances flow-limited model components may be augmented or replaced with diffusion-limited components based on physicochemical/kinetic properties and improved model performance (e.g., dioxin).

Particle exposures are defined mainly by air concentration ($\mu\text{g}/\text{m}^3$), size distribution including mean mass aerodynamic diameter (MMAD, μm) and geometric standard deviation (σg), breathing rate, nose versus mouth contributions, and particle solubility. The prototypical human model is the Human Respiratory Tract Model for Radiological Protection from the International Commission on Radiological Protection (ICRP, 1994). This model provides tables of deposition fractions by RT region, age, sex, breathing rate and particle size. Computer models are available to predict RT clearance for a given exposure, and particle deposition and ICRP clearance parameters, e.g., Humorap 2 (Sanchez, 2002). A more complete deposition and clearance model for humans and rats is the multiple path particle deposition (MPPD) model of The Chemical Industry Institute of Toxicology (CIIT) and the Netherlands National Institute for Public Health and the Environment (RIVM) (Anjilvel and Asgharian, 1995; Brown et al., 2005; Jarabek et al., 2005). This model provides several particle number and mass-based dose metrics, although mass/surface area metrics need to be derived from graphic outputs of deposition and user supplied regional RT surface areas (Sarangapani et al., 2003). Another advantage of this model is a number of built in human child parameters for different ages. However, this model is very complex and longer-term simulations may not run successfully. Additional particle deposition and clearance models may be much simpler and adequate in many instances (Snipes, 1989a; Snipes et al., 1989b). The main dose metric of the Snipes model is mg/lung or lung burden. Also Yu and Xu (1987) provide a deposition model description for humans, rats, hamsters and guinea pigs that may be useful in many cases.

4.4.7.2.2 HEC Adjustment

The development of reference exposure concentrations (RfCs) by the U.S. EPA (1994a) requires the conversion by dosimetric adjustment of the NOAELs and LOAELs observed in laboratory animal experiments to human equivalent concentrations (HECs) for ambient exposure conditions (U.S. EPA, 1994a). The HEC procedure estimates the concentration for human exposure, which would be equivalent to the animal exposure, by adjusting for differences in minute volume and

surface area of various regions of the respiratory tract between the experimental species and humans. The conversion of animal exposures to HECs is described in detail in Appendix F and involves the use of regional deposited dose ratios (RDDR) for particles or regional gas dose ratios (RGDR) for gases. Category 1 gases are highly reactive and/or soluble, and they do not accumulate in the blood. For these compounds, the conversion factor usually reduces to a ratio of alveolar ventilation (AV_A) to regional surface area (RSA_A) for the animal test species, divided by the same ratio for the human (AV_H / RSA_H). Adjustments for extrathoracic (ET), tracheobronchial (TB) and pulmonary (PU) regions or the total lung can be calculated (U.S. EPA, 1994a). For pulmonary exposures to a category 1 gas from rat data, adult and child specific dosimetric adjustment factors (DAFs) may be derived as follows:

$$DAF = (AV_A / RSA_A) / (AV_H / RSA_H)$$

$$DAF (\text{Adult}) = (120 \text{ cm}^3/\text{min}/3400 \text{ cm}^2) / (7000 \text{ cm}^3/\text{min}/633,000 \text{ cm}^2) = 3.19$$

$$DAF (\text{Child}) = (120 \text{ cm}^3/\text{min}/3400 \text{ cm}^2) / (914 \text{ cm}^3/\text{min}/21,500 \text{ cm}^2) = 0.83$$

At the other extreme of reactivity and solubility are Category 3 gases that have predominantly systemic effects. In the default methodology, the average exposure concentration is adjusted with a RGDR that represents the ratio of the blood:air partition coefficient in experimental animals to that in humans [$RGDR = (H_{b/g})_A / (H_{b/g})_H$] (see Appendix F.1.2). Category 2 gases fall somewhere between categories 1 and 3 on the continuums of reactivity and solubility. They are moderately soluble and/or reactive and may have both local (respiratory tract) and systemic effects. In practice, in the absence of data sufficient to perform more sophisticated modeling, these compounds are treated as either Category 1 or Category 3 gases depending on their physicochemical properties and the data available for the specified toxicological endpoint.

Thus, a given rat NOAEL or LOAEL concentration would be multiplied by these factors to give human equivalent concentrations (HECs) for adults and children, respectively. The U.S. EPA derives RfCs by dividing the HECs by appropriate UFs. While this is a standard methodology, it is obvious that no chemical-specific information, other than a broad characterization of gas category, is involved. The method essentially adjusts for a potential difference in absorption based on physiological and anatomical differences between species. This methodology is described in greater detail and reviewed in Appendix F which also considers extensions necessary to allow for human intraspecies variability, including age differences.

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 (Table 4.4.1). 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 Increased Susceptibility of Sensitive Individuals

4.4.8.1 Introduction

RELs are intended to protect identifiable sensitive individuals from harm due to chemical exposure. Susceptibility to harm from chemical exposure may vary among individuals due to genetic and epigenetic variability within the population, resulting in lower levels of protective biological mechanisms. Predisposition to increased metabolic activation or to decreased detoxification are just two examples of how genetic variability influences response to toxicants (Hattis et al., 1987; Eichelbaum et al., 1992; Grandjean, 1992; U.S. EPA, 1994a; Autrup, 2000). Additionally, susceptibility to chemical-related health effects may vary over time for the same individual due to changing factors such as age, health status, and activity level. It should be recognized that RELs may not necessarily protect individuals who may develop an idiosyncratic

response, such as allergic hypersensitivity, that cannot be predicted from scientific investigation of the chemical.

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

Healthy workers, the subject of most epidemiological studies, are often found to have lower rates of morbidity and mortality than the general population (Wen et al., 1983; Monson, 1986) (Rothman and Greenland, 1998, p 119). In studies of experimental animals, highly homogeneous (inbred), healthy strains are generally used. Such strains are likely to have much less variability in response than the heterogeneous human population. Chizhikov (1973) found that animals in poor health were more likely to experience adverse effects from chronic oral exposure to chemicals than were healthy animals.

Finally, OEHHA is required to protect infants and children in developing Reference Exposure Levels. There are a number of differences in response to toxicant by age, which in some cases, increase the susceptibility of infants and children. These are described more fully elsewhere in Section 3.1.1 and Miller et al. (2002) and OEHHA (2001).

4.4.8.2 Pharmacokinetic Factors in Inter-individual Variability

4.4.8.2.1 Physiologically Based Pharmacokinetic (PBPK) Models of Inter-individual Variability

PBPK models can give useful predictions of how the body handles a particular chemical and its metabolites. The models address issues of internal body or tissue dosimetry, route-to-route extrapolation and, in some cases, interspecies extrapolation. To date, relatively few published models for various environmental pollutants address infant and child exposure and pharmacokinetics in a systematic fashion. This is parallel to the bulk of toxicity testing in animals, which is usually initiated in young adult animals.

However, this issue has received more attention in recent years than previously. Several authors have undertaken systematic modeling studies using child-specific physiological, biochemical and exposure parameters for various toxicants of interest (Pelekis et al., 2001; Pelekis et al., 2003; Price et al., 2003; Clewell et al., 2004; Ginsberg et al., 2004b). These studies are summarized and evaluated in Appendix E. OEHHA has used these published results and also undertaken a series of original investigations (also described in detail in Appendix E) to explore both the feasibility of using child-specific PBPK models when the necessary supporting data are available, and the appropriate values for UFs or other limited analyses where the data required for a full chemical-specific model are not available.

PBPK models are meant to increase the accuracy of risk assessment and inform as to the adequacy of the traditional NOAEL/UF approach to deriving RELs. These models are used only where there are adequate data available. While in many cases the variability in a parameter can be adequately incorporated into the model where data exist to characterize the distribution of this

parameter, there is still residual uncertainty. Further, many parameters may have limited data available. Sensitivity analyses should be conducted in a chemical specific PBPK modeling exercise to ascertain the importance of specific variables to the model output, and to gain understanding of model uncertainty.

OEHHA's approach to applying PBPK modeling to assess children's environmental health risks has been similar to that of Pelekis et al. (2001). We have used a case study approach using published PBPK models of selected environmental toxicants and adjusting anatomical and physiological parameters to simulate infant and child ages from newborn to 18 years. Results are then compared to those using adult models. In these models, we have scaled metabolic parameters as a function of body weight. Where possible we have focused on dose metrics involving toxicologically relevant metabolites. Initial findings by this approach were presented at the 2001 Children's Environmental Health Symposium (Brown, 2001). Of the seven chemicals studied with oral and inhalation exposures (vinyl chloride, DCM, TCE, chloroform, arsenic, butadiene, and naphthalene), three chemicals showed greater internal doses in children compared to adults: DCM, TCE, and butadiene, all via the inhalation route.

In follow up work we have attempted to standardize the modeling approach for different chemicals as much as possible and focus on inhalation exposures only. For example, we have employed several of the age specific regressions for model parameters suggested by Price et al. (2003). Also in a few cases we have used more elaborate lung modeling, for example as proposed by Sarangapani et al. (2002) for styrene and styrene oxide, as opposed to the simpler lung modeling of Evelo et al. (1993) for butadiene. Two or three similar child models were used with differing fractional tissue flows more heavily weighted towards rapidly perfused tissues than in adults. Details are provided in Appendix E.

The published studies and the OEHHA case studies of PBPK modeling show clearly that infants in the first year of life are likely to show increased internal dosages via the inhalation route for a variety of agents and their metabolites and longer clearance times (see Appendix E). It is also apparent that the current default intraspecies UF (UF_{A-k}) for kinetic effects of $\sqrt{10}$ is inadequate to protect neonates and young infants from some chemicals, as further discussed below.

It is worth noting that the large majority of studies and PBPK modeling exercises involve relatively short-term exposures that represent environmental, occupational, or therapeutic scenarios. Extreme situations of short-term high exposures or very long-term low exposures were not simulated. Despite this limitation, the results are considered indicative of the unique toxicokinetics of infants and children for some environmental pollutants. As such, a revised PK UF should be broadly applicable to acute (one-hour), eight-hour, and chronic RELs.

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).

4.4.8.2.2.2 Infants and Children

The difference in toxicokinetics is even more pressing when considering infants and children as part of the affected population. As discussed in Section 3.1, it has been suggested that children may be both more sensitive, and more diverse, than adults, as a result of both pharmacodynamic and pharmacokinetic factors affecting toxicity. Several revisions in this version of OEHHA's risk assessment methodology are designed to address this concern. An additional 10-fold UF (presumably to account for both toxicokinetic and toxicodynamic factors) has been mandated by Congress to specifically protect children in assessments conducted for pesticides in accordance with the Federal Food Quality Protection Act (FQPA), assuming infants and children are more sensitive than adults, unless data to the contrary exist. U.S. EPA (2002b) has developed guidelines for evaluating data to determine an appropriate value (generally between 1 and 10) for the FQPA-specified uncertainty factor. In the following discussion, the approach will be to determine an appropriate value to substitute for the default value for the two separate components of UF_H , rather than to specify additional overall UFs.

In Appendix E we have summarized the more relevant data and studies bearing on the size of the default UF to protect infants and children adequately from the adverse effects of toxic air contaminants. Obviously, these studies and data are not ideal since they rely heavily on the pharmacology literature where most drugs are administered orally and not by inhalation. In addition, drug literature frequently focuses on the parent compound rather than downstream metabolites, which are often of interest to environmental toxicologists due to their frequent involvement in toxic modes of action. Modeling of environmental toxicants also presents difficulties, the foremost being a lack of relevant metabolic parameters at various stages of human development. Infant and child metabolism of environmental agents is usually estimated by scaling from adult human or animal values, a limitation when there are qualitative as well as quantitative differences in infant vs. adult metabolism (e.g., theophylline). Table 4.4.2 summarizes the PK UF values indicated by the PBPK modeling of various test chemicals by OEHHA and others. Of the 25 chemicals and metabolites in this table, 13 have UF_{H-k} greater

than $\sqrt{10}$. This results primarily from the differences in toxicokinetics between infants and adults, resulting in higher internal dosages of the compounds and longer clearance half-lives. The details of these modeling exercises are given in Appendix E (text and tables; model parameters; and model equations).

4.4.8.2.2.3 Value of UF_{H-k} to Account for Toxicokinetic Differences by Age

Based on the limited information presently available, OEHHA thinks it is appropriate to increase the default UF_{H-k} from its previous value of $\sqrt{10} = 3.16$ in order to protect neonates and young infants from potential adverse effects of airborne toxicants. OEHHA will apply a UF_{H-k} value of 10 as a default for gases acting systemically, and for particles that involve systemic exposure via dissolution and absorption in the lung or via the gastro-intestinal tract. Thus, in these cases, the overall default intraspecies UF would be 30. Gases that act solely at the portal of entry (i.e., lung or upper respiratory tract for inhaled toxicants) without involvement of metabolic activation or other complex kinetic processes would use a UF_{H-k} of $\sqrt{10}$. These are default values applicable to acute, eight-hour and chronic RELs derived from animal studies or epidemiological studies of healthy adult populations (e.g., workers). An exception to this procedure is when an exposure level is estimated from a study that includes the assessment of a sensitive human subpopulation, where a default UF_{H-k} of 1 may be appropriate.

Because the true extent of variability is frequently unknown, there may be a portion of the population for whom the chronic RELs will not be protective. When information defining susceptible individuals is available, such data will be incorporated by means of pharmacokinetic models or adjustment of UFs as necessary to protect those individuals. Ideally, more chemical-specific data in sensitive subgroups would obviate the need for the use of a default UF_H . Unfortunately, such data are rarely available for children (or even immature animals) with environmentally relevant toxicants.

TABLE 4.4.2. CHEMICALS STUDIED BY OEHHA IN PBPK ANALYSES, GROUPED BY MODELED UF_{H-k} FOR INFANTS AND CHILDREN (SEE APPENDIX E)

$UF_{H-k} \leq \sqrt{10}$	$UF_{H-k} > \sqrt{10}$ to 9.9	$UF_{H-k} \geq 10$
Furan	MTBE	Butadiene/Butadiene
Perchloroethylene	Styrene/Styrene oxide	monoxide/Diepoxybutane
Naphthalene/Naphthalene oxides	Ethylene/Ethylene oxide	Dichloromethane
Carbon tetrachloride	Vinyl chloride	TCE and metabolites
Chloroform	Toluene	Benzo[a]pyrene
Arsenic and metabolites†	m-Xylene	
Ethylbenzene*	Toluene/Xylene mixtures	
1,1-Dichloroethylene‡	Isopropanol	
Benzene*		
Bromochloromethane*		
Methyl chloroform*		
Diethyl ether*		

*Note that simulation results for these chemicals are not shown in the text but are based on parameters in Haddad et al. (2001) and Gargas et al. (1986) using the same approach as for toluene and xylene. †Based on PBPK model of Yu (1999). ‡ Based on PBPK model of El-Masri et al. (1996a,b).

4.4.8.3 Contribution of Toxicodynamic Factors to UF_H

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 3.2.2. 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 Database Deficiency Factor for Lack of Developmental Toxicity Data

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.

4.4.9.2 Estimation of Inhalation Effects from Oral Exposure Data

Strong weight is given to inhalation exposure-based health effects data. If adequate inhalation data are not available, oral exposure data are also considered. Both the U.S. EPA (1994a) and the NRC (1986b) support route-to-route extrapolation under certain circumstances. Route-to-route extrapolation may sometimes be inappropriate (e.g., where chemicals act at the portal of entry).

Use of oral exposure studies to develop RELs requires consideration of kinetic differences between routes, including differences in absorption across the lung versus the gastrointestinal tract. Wherever possible, such extrapolations should be undertaken using PBPK models which allow for the route-specific features of uptake and distribution of the specific chemical.

Where data are unavailable to support this approach it may be possible to use default assumptions or limited data to allow for route-to-route differences, at least in simple and straightforward cases. While route-specific differences in absorption and potency may occur, no additional UF is generally applied for non-inhalation data. Instead, attempts should be made to adjust for absorption and other kinetic differences (e.g., first pass metabolism following oral

exposure) when possible. Owen (1990) found that the median inhalation/oral absorption coefficient ratio was 1.0 for 34 substances. For 32 of the substances (94%), inhalation absorption coefficients were at most 10-fold higher than oral absorption coefficients for the same substance. The two exceptions (6%) with much greater absorption by inhalation were metals with very low oral absorption (<1%): inhalation absorption of beryllium and elemental mercury was estimated to be 500-fold and 7,500-fold higher, respectively, than corresponding oral absorption. Fifteen substances (44%) were predicted to have greater inhalation than oral absorption, and 7 substances (21%) were predicted to have at least 2-fold greater inhalation than oral absorption. Pepelko (1987; 1991) provided additional evidence that differences between toxic effects following oral and inhalation exposures are generally within a 10-fold dose range. 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, hexavalent chromium (Cr^{VI}), hydrazine, or vinyl chloride.

4.4.10 Summary of Uncertainty Factors

A summary of UFs used for acute, eight-hour and chronic REL development is given in Table 4.4.1.

4.5 Supporting Data

Summaries describing the development of the acute, eight-hour and chronic RELs for each chemical are found in Appendix D. In addition, a list of acronyms is provided in Appendix A. All toxicity summaries for the newest RELs include a discussion of the information upon which the calculations are based. This discussion includes the following key elements:

1. Physical and chemical properties: Descriptions include information on volatility, reactivity, stability, toxic secondary compounds, flammability, density, water solubility, color, odor, and some additional properties.
2. Occurrence and use: The typical major uses of the chemical are described as well as where it is likely to be found. If available, measured ambient air levels are provided.
3. Routes of exposure: The routes of exposure that may lead to toxic effects are mentioned for each substance. Since the intent of this document is to provide information on airborne toxicants, the data presented focuses on inhalation exposure studies and may be supplemented by relevant non-inhalation toxicology studies. If inhalation data are unavailable or are of poor quality for a particular chemical, other routes of exposure may be considered for the development of RELs. For extrapolation from oral to inhalation exposures, ideally a PBPK model dealing with both routes is used. Failing that, methodology presented by U.S. EPA (1994a) should be used.
4. Summary of toxic effects: Toxic effects are described for relevant endpoints. Where possible, all of the following attributes are mentioned: endpoints, test species, concentration

or dose, duration and frequency of exposure, type of effect level (such as benchmark dose or NOAEL), reversibility of findings, UFs applied, and RELs derived. Note: while an overview of the toxicity of the chemical is provided in the summary, only the papers deemed key to the REL are described in detail.

5. Pharmacokinetics and metabolism: A discussion of pharmacokinetics is included if information is available. This may include information on absorption, distribution, metabolism, and excretion. The inhalation route of exposure is examined preferentially. Metabolites of the parent compound are also identified when known. Where data are available to support it, a pharmacokinetic model may be derived; if used in the derivation it is described in the summary.
6. Children's sensitivity to the chemical relative to adults: A discussion of the potential for infants' and children's differential sensitivity to the chemical is provided, and any adjustments to the REL to protect children's health are described. Effects on other potentially sensitive subpopulations are also considered.
7. Quality assurance measures: Weak or conflicting data are reviewed. Studies are evaluated for any recognized violations of sound laboratory or statistical practices.
8. Sources of data: In the absence of well-documented experimental dose-response studies in humans, reliance on toxicological data from animal studies and human data from workplace and other exposures is appropriate. In addition, in vitro toxicity studies are sometimes reviewed, particularly for information on mechanism of action.
9. Oral RELs: Substances emitted to the air may deposit on soil, water or plants with subsequent human exposure via non-inhalation routes. Since oral exposure is the predominant non-inhalation pathway, non-inhalation RELs are referred to as oral RELs. Where appropriate, oral RELs are included to capture the contribution of this pathway, for example, for the nonvolatile compounds anticipated to be present in the air adsorbed to particulate matter. In the absence of adequate inhalation data, oral REL data may be used in the development of inhalation RELs.

5 Acute Reference Exposure Levels

This section presents methods for deriving acute (one-hour) inhalation Reference Exposure Levels (RELs) for toxic air contaminants (TACs). The acute REL is an exposure that is not likely to cause adverse effects in a human population, including sensitive subgroups (such as infants and children), exposed to that concentration for one hour on an intermittent basis.

As with all health effects, certain individuals may be more susceptible to adverse health consequences following exposure above the acute REL. These sensitive individuals may suffer health effects at a lower level of exposure than the general population. For example, individuals with asthma, who following exposure to sulfur dioxide are likely to exhibit bronchoconstriction at a lower concentration than the general population, may require greater protection from this substance than non-asthmatic persons. Acute RELs are designed to be protective for the range of susceptible persons in the general population including infants and children.

5.1 Time Frame of Interest

In the Air Toxics Hot Spots Program, routine industrial emissions are evaluated for potential public health impacts. Facility emissions may fluctuate considerably, with daily and hourly maximum and minimum concentrations. The commonly used air dispersion models can be used to model concentrations hour by hour throughout a year, giving an indication of the one-hour maximum exposure concentrations. The hourly fluctuations are a reflection of the changing meteorological conditions that are included in the model. Section 5.4.1 provides more description of the underlying assumptions and applicability of the acute REL.

In general, the one-hour modeled maximum concentrations in the Air Toxics Hot Spots Program are used in a HI approach in order to evaluate “acute” exposures and potential public health impacts from such exposures. The HI is the ratio of the one-hour maximum modeled ground level concentration (GLC) to the acute reference exposure level (REL). If the ratio exceeds one, then the risk manager needs to consider whether risk reduction is appropriate. An exceedance of one does not mean adverse effects will occur. Rather, it is an indication of the erosion of the margin of safety for exposure to that chemical

5.2 Exposure Duration and Patterns

As indicated in Section 5.1, the focus of acute RELs is on short-term exposures. A one-hour exposure is used as the timescale for which toxicity is assessed, which is consistent with the hour-by-hour monitoring or modeling that is generally conducted for facilities under the Hot Spots Program. Sometimes it is necessary to extrapolate from other durations of experimental exposure or from reports of human exposure situations, to a 1-hour exposure duration. This is described in Section 5.4, and is also discussed on a chemical-by-chemical basis in the toxicity reviews for many compounds.

5.2.1 Exposure Concentration Averaging Period

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

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

A related exposure issue is the fact that peak exposures are superimposed on lower long-term exposures to the same compound. This is also not reflected in the standard acute toxicology design. For some compounds this will result in an increased body burden relative to the typical toxicology experimental design and in a potential lowering of the acute exposure needed to produce an adverse effect. For sensitizers, peak exposures in occupational settings can increase the response to much lower levels. It is not clear whether sensitization occurs at environmental exposures, but it is an uncertainty. Chronic exposures to particulate matter pollution can result in elevated risk factors for heart disease such as atherosclerosis; peak exposures may trigger a cardiovascular event such as a myocardial infarction. The U.S. EPA’s approach is to assume that the peak exposures are at least 10 times the monthly average so that the acute exposure can be considered to be relatively independent of the longer-term chronic exposure to the same substance (U.S. EPA, 1994b). This may be generally true for specific industrial emissions (but not for regional air pollution).

Despite these limitations, it is imperative to examine whether short-term exposures to peak concentrations might result in adverse public health impacts. OEHHA’s RELs should be compared to the modeled one-hour maximum (or multi-hour as noted for specific reproductive/developmental toxicants) concentrations used in the HI approach to risk assessment. OEHHA recommends that these acute RELs be used to evaluate exposures that occur no more frequently than every two weeks in a given year. The two-week interval was chosen because in most acute toxicology experiments two weeks is the duration of time an animal is observed for signs of adverse outcomes following exposure.

An assumption in making this recommendation is that the REL is protective of adverse health effects that are not cumulative. Thus, the effects of each peak exposure are independent of previous or subsequent peak exposures that occur as often as every two weeks. This recommendation is only valid for substances that do not bioaccumulate. Also, the assumption of independence of peak exposures is geared to typical ambient environmental exposures, and not occupational exposures or exposures to environmental tobacco smoke indoors, for example. When bioaccumulation is known to occur and body burden is associated with an adverse effect, or where cumulative tissue damage occurs with repeated exposures, longer inter-exposure periods should be specified.

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

In evaluating chemicals with developmental toxicity, we found that the standard experimental paradigm of repeated exposure over several days did not lend itself easily to extrapolation to a one-hour acute REL. Since developmental endpoints are frequently manifested in a small window of time during gestation, the standard protocol is to expose pregnant animals for several hours per day over several days during gestation in order to increase the power of the study to detect an effect. Issues that affect the extrapolation to one hour include not only when the sensitive gestational period is, but also toxicokinetic issues. Whether or not a single one-hour exposure could produce a reproductive or developmental adverse outcome depends on the toxicokinetics governing the concentration of the chemical in maternal and fetal tissues, timing of exposure, mechanism of action, and other factors. These issues are not easily taken into account in extrapolating to a one-hour acute REL. Thus, for those acute RELs addressing a developmental endpoint determined under our previous methodology, the REL was for the exposure duration chosen for a single day in the experimental protocol. In this revised methodology, OEHHA proposes to use the exposure concentration in a developmental toxicity study as the basis of the one-hour REL, regardless of the daily exposure duration in the study. Given the seriousness of developmental endpoints and our mandate to ensure our risk assessment methods adequately protect infants and children, this is justified. It is rarely clear in a developmental toxicity study if the toxicity depends on tissue concentration during a discrete time interval or on total dose over the course of exposure. This may be particularly important for developmental endpoints where short time periods of extreme vulnerability to toxicants may be accompanied by uncertainties in toxicological mechanisms. The duration of the period of vulnerability may itself be highly uncertain.

5.3 Human Equivalent Concentration (HEC) Procedure for Acute RELs

When animal studies are used for acute REL development, the U.S. EPA HEC procedure (described in Appendix F) may be used as a partial adjustment for interspecies toxicokinetic differences, in which case the 10-fold interspecies UF is reduced to 6 ($UF_{H-k} = 2$, $UF_{H-d} = \sqrt{10}$). The modifications of the HEC procedure to account for children may also be used. These procedures will be used where applicable as the acute RELs are updated to reflect additional available research and to fulfill the mandates of SB 25 to account for potentially greater vulnerability of children when setting health standards.

5.4 Effects of Exposure Duration – Special Considerations for Acute Effects

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

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

5.4.1 Concentration and Time Extrapolation using Haber's Law

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

$$C^n * T = K$$

where n is a chemical-specific parameter greater than zero (ten Berge et al., 1986). When n is equal to one ($n = 1$), the toxicity of a chemical is equally dependent on changes in concentration and duration of exposure; when n is less than one ($n < 1$), the duration of exposure is a greater determinant of toxicity than the concentration; finally, when n is greater than one ($n > 1$), the toxicity of a chemical is determined to a greater extent by exposure concentration than by duration.

5.4.1.1 Value of the concentration exponent, n

Ideally, the magnitude of n should be determined for all chemicals by evaluating the concentration versus response relationships for several different exposure durations. However, this information is available for only a limited number of substances. Empirically-derived values of the exponent n range from 0.8-3.5 (ten Berge et al., 1986). The time-concentration-response relationship depends on the time-frame considered and the endpoint measured. There are usually multiple “ n ” values for a single chemical that are applicable to different response endpoints. For example, the “ n ” for irritation of ammonia is 4.6, while the “ n ” for lethality of ammonia is 2 (See Appendix G.). As concentration becomes the more important factor, the value of n will increase. Values of n greater than three suggest that concentration has a strong predominance over time.

The value for the exponent n used by OEHHA in acute toxicity summaries is chosen as follows. First, when an empirically derived value for the exponent is available from the open literature, this is adopted for time extrapolation, using the modification of Haber’s Law as described above. Appendix G shows published or OEHHA derived values for n which were used in acute RELs previously developed by OEHHA (1999).

When a derived value is not available and there are insufficient data from which to determine a value *de novo*, a default value for n must be used. The published or OEHHA derived values for n shown in Appendix G range from 0.8 to 4.6. The mean value in this range rounds to 2; the interquartile range (25%-75%) is from 1 to 2.2. Previously, the mean value of $n = 2$ was used by OEHHA (1999) when extrapolating from an exposure duration that is greater than one hour to a 1-hour level. However, when this issue was considered by NRC (2001) they concluded that it would be more appropriate to use the value $n = 3$, which approximates the 95th percentile of the range of values reported by ten Berge (1986). OEHHA now therefore recommends the use of $n = 3$ when extrapolating from experimental exposures greater than one hour to the 1-hour period of concern for the acute RELs. Use of this exponent makes concentration much more important than time, and is thus health-protective when extrapolating from greater than one hour exposures to one-hour exposures.

When extrapolating from an experimental exposure duration of less than one hour to a 1-hour level, the value of $n = 1$ was used. Using a value of $n = 1$ is more health-protective than a value of $n = 3$. A value of $n = 1$ results in a relatively rapid decrease in the derived REL when extrapolations are made from shorter to longer exposures. For example, when extrapolating from a 30 minute exposure at the published NOAEL of 60 ppm (Purser et al., 1984) to a 60 minute exposure for hydrogen cyanide, using $n = 1$ results in an extrapolated 1-hour NOAEL of 30 ppm; when using $n = 3$, the extrapolated NOAEL is 48 ppm.

In summary, the default exponents used by OEHHA in the formula $C^n T = K$ for extrapolation to 1-hour acute RELs are as follows:

- From less than 1 hour $n = 1$
- From greater than 1 hour $n = 3$

5.4.1.2 Haber's Law and Irritants

The applicability or otherwise of Haber's Law to irritants has been the subject of various studies. The NAS has suggested that Haber's Law does not apply for "some irritants" (NRC, 1986a; NRC, 1986b; NRC, 1993). This statement is apparently based on the observation that for some substances, irritation appears to be solely concentration dependent. In fact, the time course of response to the small number of sensory irritants for which data are available suggests that although the response follows a modified dose/time integral relationship (like most other toxicities) over very short time scales of a few seconds or minutes, this relationship has reached a plateau where the level of response is dependent only on concentration well within the one-hour time scale of concern for acute REL derivation (Shusterman et al., 2006).

Response to mild sensory irritants is detected through binding to the trigeminal nerve receptors. In humans, this results in a complex response including a burning sensation of the eyes, nose, and throat. Other notable symptoms are coughing, nasal congestion, rhinorrhea, sinus and Eustachian tube dysfunction, and worsening of lower airway function in some asthmatics (the so-called "naso-bronchial reflex") (Widdicombe, 1990; Raphael et al., 1991). The response in the rodent is simpler, consisting primarily of a reflex depression of the breathing rate. When a mouse is exposed to an irritant, the decrease in respiratory rate is proportional to the concentration of the airborne chemical. Also, a minimum respiratory rate is reached and remains at a plateau, or fades in response during exposure. This has been used as the basis for a bioassay of sensory irritant properties (Alarie, 1966), in which irritant potency is expressed as the concentration producing a 50% depression in respiratory rate (RD₅₀).

Although the receptors have not been fully characterized, receptor binding has been found to follow the classic Michaelis-Menten receptor kinetics. There is evidence that many chemicals bind to a common receptor, sometimes referred to as the common "chemical sense" receptor (Cometto-Muniz et al., 1997; Bryant and Silver, 2000). There is also evidence of multiple receptor types on the trigeminal nerve (Nielsen and Vinggaard, 1988). The irritant response can be described by the Michaelis-Menten equation in an animal model (Kristiansen et al., 1986; Nielsen and Vinggaard, 1988). Competitive agonism has been demonstrated in the mouse RD₅₀ bioassay (Bos et al., 1991). This is additional evidence for a receptor mediated mechanism, with a common receptor for these two chemicals.

The degree of receptor binding is mediated by the tissue concentration of the toxicant, not the duration of exposure once equilibrium is reached, which generally occurs relatively quickly. At equilibrium, at a constant exposure concentration, a constant level of receptor binding would be expected presumably leading to a constant effect level, independent of the duration (the "T" factor in the Haber's Law equation). Michaelis-Menten kinetics also predicts that receptors would be saturated at higher irritant chemical concentrations and therefore additional trigeminal transmitted irritation response with increased exposure concentration would not be expected in this situation.

Thus, irritation should be more a function of the air concentration of the irritant than of the total dose. Often these chemicals are non-reactive volatile organic compounds (VOCs), although in some cases they may be reactive. This simple picture is complicated by additional factors such

as desensitization of receptors that can cause a decline in perceived irritation over time for some chemicals (Nielsen, 1991; Shusterman et al., 2006).

The trigeminal system is distinct from odor perception. Persons lacking a functional sense of smell (anosmics) still perceive chemical irritants in a similar fashion to people with a normal sense of smell. Odor perception occurs at a lower threshold than irritation, and in some cases at a much lower threshold. In both odor perception and trigeminal irritation from a chemical, there can be wide variability in threshold air concentrations in the general population.

If the irritation reaction is a function of the concentration, then the fact that children have higher breathing rates than adults should not influence the health impact of a particular concentration. There is no evidence that infants and children have different or more irritation receptors than adults. Therefore, OEHHA has not assumed that children are more sensitive than adults to the sensory effects of eye, nasal or respiratory irritants. However, it must be considered that many irritants, especially those that are chemically reactive, may have the potential to exacerbate or induce asthma, which is a special concern for children's health.

OEHHA will consider trigeminally-transmitted sensory irritation endpoints to be independent of the duration of exposure over the one-hour timescale, unless data indicate such time dependence. Data establishing time dependency should be in a concentration range relevant for trigeminal nerve transmitted effects and not at considerably higher concentrations. Higher concentrations may cause irritation through tissue damage, and thus show time dependence because of accumulating tissue damage. The National Academy of Science Subcommittee on Acute Exposure Guideline Levels made the same determination for their Acute Exposure Guideline Levels (AEGs) (NRC, 2001). Sometimes trigeminally-transmitted irritation is difficult to distinguish (based on available data for a chemical) from tissue damage mechanisms, or there may be mixed mechanisms. Empirical determination of an "n" value, indicating that duration of exposure for a particular chemical influences toxicity, will be accepted as an adequate basis for Haber's Law adjustments in these cases.

5.4.1.3 Strong Irritants Causing Tissue Damage and/or Hyperplasia

Some chemicals cause irritation through tissue damage that can result in hyperplasia or other nasal, eye or respiratory tissue damage. The tissue damage resulting from exposure to these chemicals may be both time and concentration dependent and in some cases be dependent on the total cumulative dose or the concentration. For example, formaldehyde-induced hyperplasia appears to be more concentration dependent than exposure duration dependent according to an analysis of several studies cited in the development of OEHHA's chronic REL (OEHHA, 2000a). Triginally-transmitted irritation may occur at a lower concentration, while tissue damage or hyperplasia may occur at a higher concentration. Tissue damage or hyperplasia may also occur with longer exposure to the same concentration (Barrow et al., 1986). This is particularly evident with highly reactive chemicals such as chlorine which have both sensory irritant and direct tissue-damaging properties in the upper respiratory tract (Jiang et al., 1983; Bos et al., 1991). Chemicals which cause sensory irritation in the upper respiratory tract as a result of lower short-term exposures may also cause pathological changes in the lower respiratory tract, especially following more extended or more intense exposures (Shusterman, 1999). However, persistent histological changes may not always be seen with the isolated one-

hour exposures against which acute RELs are intended to be protective. In such cases, the one-hour REL would likely be different from a chronic REL.

If such tissue damage in the nose or other parts of the respiratory tract accumulates over time, then the toxic effect would be dependent upon both time and concentration. Such damage could trigger pain receptors, and needs to be distinguished from trigeminally-transmitted irritation. In contrast to the case of pure sensory irritation, the use of Haber's Law where tissue damage is a factor in the response is appropriate.

The higher breathing rates of children may need to be considered for chemicals causing cumulative damage at the point of entry, for which either total dose or AUC is the determinant of toxicity. An analysis of the mechanism of toxicity may help to determine whether children are more sensitive than adults to irritants that cause tissue damage or hyperplasia.

5.4.2 Time Extrapolation for Acute RELs Based on Developmental Studies

In the previous guidelines, OEHHA (1999) considered that extrapolation to one hour using Haber's law was not appropriate in the case of repeated dose studies for developmental endpoints. OEHHA chose a single day's exposure for each chemical (ranged from 1 to 8 hours) as the exposure duration for which the REL is to be applied. Thus, no time extrapolation was used for developmental toxicants. Several of the acute RELs derived using these earlier guidelines based on developmental studies have averaging times longer than one hour. These averaging times include six hours for benzene, carbon disulfide, EGEE, EGEEA, and EGME, and seven hours for carbon tetrachloride and chloroform (OEHHA, 1999).

OEHHA has developed a different underlying methodology in the present version of these guidelines, which has been described in Section 4.4.6.3. As in the cases noted above, the time extrapolation used when deriving acute RELs will most often be from a longer experimental duration to a shorter one-hour reference period for the REL. In these cases, the revised methodology treats the experimentally applied concentration as the basis for the acute REL, *i.e.* the concentration present during the experiment is not to be exceeded during any 1-hour period. The revised methodology will, in these cases, result in an acute REL which is numerically the same as that obtained by the previous method, although the previous complication of having a non-standard averaging time is avoided.

5.5 LOAEL to NOAEL Extrapolation

As noted in the general discussion of REL methodology, there are some cases where a benchmark concentration approach will not work because of data constraints. The studies may not have identified a NOAEL, but only a LOAEL, and it may be necessary to extrapolate from the LOAEL to a NOAEL using a default UF_L of 10. We have developed criteria for when the UF_L can be less than the default of 10.

Following acute exposure, health effects of varying severity may be observed, depending on the extent of exposure, or dose, and the toxic properties of the compound. Although the relationship between exposure and health outcome is a continuous one, effects may be categorized into discrete severity levels, particularly for acute exposures (Table 5.7.1). The purpose of acute

RELs for the preparation of risk assessments under the Hot Spots Program is to evaluate impacts of short-term exposure from non-emergency releases. Thus the RELs are generally protective against mild adverse effects, although in a few cases the most sensitive endpoint, which was used in development of the REL, is severe (e.g., a reproductive/developmental endpoint).

Mild effects are defined as those with severity of grade 5 or below, as described in Table 5.5.1.

Based on an analysis of LOAELs and NOAELs reported in various acute toxicological studies, we found that when extrapolating from a LOAEL to a NOAEL for mild effects, UFs less than 10 are justified (Alexeeff et al., 1997; Alexeeff et al., 2002). In the case of the mild adverse effect, an analysis by Alexeeff et al. (1997) of LOAEL to NOAEL ratios for over 100 datasets indicated that the 95th percentile of that ratio is 6.2. The distribution was skewed to the right; for some chemicals, a UF of 10 may not be adequate. OEHHHA has chosen a UF of 6 to extrapolate from the LOAEL to the NOAEL where the effect is mild, based on this analysis. Recommended default values of UF_L for acute REL derivations are therefore as follows:

- 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.
- For 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.
- For a LOAEL where the observed effect is moderate to severe, the value of UF_L is 10.

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.

TABLE 5.5.1. RELATIONSHIP BETWEEN EFFECT CATEGORIES AND SEVERITY.

Severity Level	Effect Category	Effect
0	NOEL	No observed effects.
1	NOAEL	Enzyme induction or other biochemical change (excluding signal transduction effects), consistent with possible mechanism of action, with no pathologic changes, no change in organ weights, and no downstream adverse developmental effects.
2	NOAEL/LOAEL	Enzyme induction and subcellular proliferation or other changes in organelles, consistent with possible mechanism of action, but no other apparent effects.
3	NOAEL/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; developmental dysfunction including biochemical changes affecting signal transduction that result in developmental defects or dysfunction.
10	FEL	Life-shortening or death.

(Adapted and expanded from U.S. EPA, 1994a)

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.

5.6 Pre-Existing Acute Exposure Guidelines

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

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

5.6.1 The California Ambient Air Quality Standards (CAAQS)

CAAQSs are promulgated by the California Air Resources Board (CARB) based on recommendations from OEHHA, and are specified concentrations and durations of exposure to air pollutants which reflect the relationship between the intensity and composition of air pollution to undesirable effects. The CAAQS for a criteria air pollutant has in the past been adopted as the acute REL. If necessary, a one-hour value was derived using time extrapolation (described below). The CARB on April 28, 2005 reviewed the current one-hour ozone standard and left it unchanged, but promulgated a new eight-hour ozone standard. The two together are meant to provide adequate protection of sensitive populations including children.

5.6.1.1 Ambient Air Quality Standards as Acute RELs

Almost all acute RELs were developed *de novo*. However, the California Ambient Air Quality Standards for Criteria Air Pollutants were reviewed. If they were found to be appropriate, they were adopted as the relevant acute toxicity RELs. For the six criteria air pollutants carbon monoxide, nitrogen dioxide, sulfates, ozone, hydrogen sulfide, and sulfur dioxide, the CAAQS for short-term (one-hour) exposure is used as the REL, or one-hour values were derived by extrapolation from the 24-hour standard.

5.6.2 The Threshold Limit Value-Time Weighted Average (TLV-TWA) and Short-Term Exposure Limit (STEL)

The TLV-TWAs and STELs are developed by the American Conference of Governmental Industrial Hygienists (ACGIH) and updated annually (ACGIH, 2006); similarly, the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits also exist (NIOSH, 2005). The TLV-TWA is defined as the time-weighted average concentration for a normal eight-hour workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. The STEL is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday.

Occupational exposure limits have sometimes been used to derive chemical exposure guidelines for the general public (NATICH and McCullough, 1991; Robinson and Paxman, 1992; U.S. EPA, 1994a). More than 600 ACGIH TLVs and NIOSH RELs are available. These values have been attractive because of the large number of accessible values and the concept that they are intended to protect a human population from inhalation exposures. However, these values are not designed for or recommended for protection of the general public, and in many cases may not prevent adverse health effects among workers (Roach and Rappaport, 1990). OEHHA has therefore not taken the TLV-TWAs and STELs directly into account in developing acute RELs, but has taken advantage of the data identified and evaluations offered by ACGIH when relevant.

5.6.3 *Various Emergency Exposure Guidance Levels*

A variety of guidance levels have been developed to assist in dealing with accidental chemical releases. As such, these values focus on emergency planning and response, not on the routine emissions and exposure which are the focus of this document. Thus NRC (2001) described the objective of U.S. EPA's AEGL program (see below) as *"to develop guideline levels for once-in-a-lifetime, short-term exposures to airborne concentrations of acutely toxic, high-priority chemicals."* Emergency guidelines are typically defined as predicted thresholds above which some level of adverse health effect is anticipated: standard margins of safety are not incorporated. Also, in many cases these guidelines are designed to identify tolerable conditions for emergency first responders such as firefighters or military personnel, rather than to protect the general population. Such guidance values are seldom comparable to the acute RELs, and are not suitable for protecting the health of the general public from routine emissions. However they may incorporate relevant information as to the type of effects to be expected and the dose response for exposure to compounds of interest.

Emergency Exposure Guidance Levels (EEGLs) are designed to provide guidelines for military personnel operating under emergency conditions that are peculiar to military operations and for which regulatory agencies have not set standards, and are defined by the NAS as the ceiling concentrations of substances in air that may be judged by the Department of Defense to be acceptable for the performance of specific tasks during rare emergency conditions lasting for periods of 1 to 24 hours (NRC, 1986a). "Emergency" connotes an unexpected situation with potential for loss of life. The Short-term Public Emergency Guidance Level (SPEGL) is defined by the NAS as a suitable concentration for unpredicted, single, short-term, emergency exposure of the general public (NRC, 1986a). In contrast to the EEGL, the SPEGL takes into account the wide range of susceptibility of the general public, but it is not designed for repeated or multiple exposures.

The American Industrial Hygiene Association (AIHA) has defined Emergency Response Planning Guidelines (ERPGs) as concentration ranges where adverse health effects could be observed (AIHA, 2006). ERPGs have a specific emphasis on responding to accidental releases.

The U.S. EPA has developed Acute Emergency Guidance Levels (AEGLs) to provide information to incident commanders in an emergency. The NRC has published a methodology for developing AEGLs (NRC, 2001). As of April 2007, AEGLs for 31 chemicals have been finalized (U.S. EPA, 2007a).

5.7 Areas for Further Research

5.7.1 Acute Toxicity Data

Many chemicals lack adequate data on acute toxicity. There are approximately 450 chemicals on the Air Toxics Hot Spots list of substances to be quantified (Appendix C). This is the list of substances, which facilities must report in their emissions inventories. We have to date only developed acute RELs for 51 of these compounds, six of which have so far been revised according to these new guidelines. While not all of the 450 chemicals have reported emissions in California, more work needs to be done in analyzing available literature for the remaining compounds and in revising existing RELs to take explicit account of children's health issues.

5.7.2 LOAEL to NOAEL Uncertainty Factor

The application of UFs to account for extrapolation from a LOAEL to a NOAEL warrants further analysis (see Section 4.4.5). When evaluating dose-response relationships, the slope of the dose-response curve determines the distance between the LOAEL and the NOAEL from a particular study. Some endpoints tend to have steep dose-response slopes and may not warrant a 10-fold UF to extrapolate from a LOAEL to a NOAEL; other endpoints have a shallow dose-response slope and may warrant a 10-fold (or higher) UF for extrapolating from the LOAEL to the NOAEL. An analysis of the distribution of the LOAEL to NOAEL ratios for 112 datasets (Gift et al., 1993; Kadry et al., 1995; Alexeeff et al., 1997; Almstrup et al., 2002) suggested an intermediate UF of 6 to extrapolate from the LOAEL to a NOAEL for mild effects. Further analysis of 215 data sets for 36 pollutants yielded LOAEL to NOAEL ratios of 2.0, 5.0, 6.3, and 10.0 for the 50th, 90th, 95th, and 99th percentile, respectively (Alexeeff et al., 2002). The 90% confidence interval for the 95th percentile was 5.0-7.5. Thus, the LOAEL to NOAEL UF of 6 would be protective for 95% of the responses, and a value of 10 for 99%. However, the 99th percentile value was considered unstable. For this reason the 95th percentile value is chosen for extrapolation of the LOAEL to a NOAEL for mild effects.

Little variability was noted among species, particularly at the median. This analysis is based on toxicity data from mild acute inhalation studies and may not be applicable to other exposure routes, exposure durations, or more severe toxicity. (A value of 10 should be used by default for effects considered severe.) In addition, this analysis did not focus specifically on children.

5.7.3 Interspecies Uncertainty Factor

An interspecies UF of 10 is commonly used to extrapolate from animal studies to the human response (UF_A) (Section 4.4.7.3). The available analyses supporting use of the 10-fold interspecies UF_A were conducted on studies of toxicity by the oral route of administration (Dourson and Stara, 1983). Further analysis of available data on chemicals for which there is both human and animal data for the same endpoints by the inhalation route of exposure is warranted.

In some cases, there may be a reason that a different UF could be used. Some part of the uncertainty encompassed by this factor may be replaced by species-specific models of

deposition, distribution or metabolism where data exist to support these models. In certain cases there may be specific reasons for concluding that the toxicodynamic component of this variability may be smaller or larger than the $\sqrt{10}$ assumed by default. For example, in lethality studies, the exposure to irritant chemicals producing lung edema may have very similar dose-response slopes because the basic loss of cellular integrity at high doses may not be a phenomenon that would vary substantially from one species to another. However, in general data on the extent of toxicodynamic differences between species are limited, although the situation for acute exposures may be simpler than for the case of chronic exposures. The existing analyses are limited in terms of toxicological endpoints examined. Interspecies variability may differ significantly for different toxicological endpoints. This is another area where more research is warranted.

5.7.4 Uncertainty Factor for Database Deficiencies

An additional UF may be used in cases where there are identifiable deficiencies in the data (Section 4.4.8.3). For example, a database deficiency factor of $\sqrt{10}$ (UF_D) may be applied to protect developing infants and children if no developmental data are available. Judgment is still needed when some developmental data are available. The ideal dataset for evaluating developmental endpoints would include studies in two species in which exposure occurs during gestation and a two-generation reproductive study in each of two species. In practice such a large database is unusual. Available mechanistic data will be considered when deciding when to apply the database deficiency factor and what its value should be. The more robust the database, the less likely that the factor will be needed. Other types of data deficiency besides developmental toxicity may also be addressed with this factor.

5.7.5 Time Extrapolation for Acute RELs

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

5.7.6 Additivity of Adverse Effects

We currently use an additive approach to assess the impacts of multiple chemicals on a target organ (Sections 2.2; 5.3). Some interactions may be synergistic and others antagonistic. Additivity has generally been accepted as health-protective at low environmental concentrations. However, there is a need for key studies on the additivity or synergism of chemicals at low concentrations that act on the same target organ. Further literature evaluation would also be helpful to elucidate whether the additive approach is the most valid approach for all scenarios (DeVito et al., 2000; Crofton et al., 2005; U.S. EPA, 2007b).

6 Eight-Hour Reference Exposure Levels

This section presents additional information for deriving eight-hour inhalation Reference Exposure Levels (RELs) for toxic air contaminants (TACs). Eight-hour RELs are concentrations at or below which adverse health effects are not likely to occur in the general human population with intermittent exposures of eight hours per day, up to 7 days per week.

6.1 Populations at Risk

The Air Toxics Hot Spots Program Guidance Manual for Preparation of Health Risk Assessments (OEHHA, 2003) calls for evaluation of sensitive receptors such as daycare centers and schools as well as offsite workers. Onsite workers are under the jurisdiction of the California Occupational Safety and Health Administration. Current occupational standards such as threshold level values (TLVs) and permissible exposure levels (PELs) are usually expressed as a time weighted average (TWA) over an eight-hour shift. Noncancer health impacts for children at schools have been evaluated using either the chronic or acute RELs. Acute RELs are only useful for evaluating impacts of estimated maximum one-hour air concentrations when such exposures occur infrequently. Exposure duration for children and offsite workers will vary, but an eight-hour exposure duration assumption would be reasonable, particularly if children and offsite workers are exposed to facility emissions at their school or place of work and not at their residential locations. It is not intended that applications of 8-hour RELs will be confined to five days per week. Many facilities operate seven days a week, and the exposed individuals include categories besides workers on a standard daily shift. This means that it cannot simply be assumed that cumulative impacts and bioconcentration issues are covered by the timing of exposures for a typical occupational exposure.

Chronic RELs are designed to be protective against long term 24-hour a day exposure and thus may overestimate some noncancer chemical risks associated with shorter, daily exposure (e.g., eight-hour exposures). Alternatively, chronic RELs may underestimate the noncancer risk where facility operation and emissions occur only 8 hours per day but coincide with the presence of nearby offsite workers and attendance at daycares and schools. Many facilities operate five days a week, eight hours per day. Such facilities have been modeled as if the total emissions were occurring twenty-four hours a day, seven days a week, three hundred sixty five days a year. The annual average ground level concentration (GLC) could then be compared to the chronic REL to determine noncancer chronic health risk. This approach has the advantage of simplicity but is a less accurate modeling approach because of diurnal meteorological variation and non-continuous facility emissions. This approach assumes that a higher eight-hour pollutant concentration followed by a sixteen-hour period of no exposure is toxicologically equivalent to the twenty-four hour average concentration (with two days of non-operation). Development of eight-hour RELs would allow more accurate evaluation of the impacts of exposure to modeled eight-hour ground level concentrations by comparison with noncancer health standards specifically tailored to actual exposure duration.

6.2 Characterization of 8-Hour Exposures

An eight-hour REL, designed to protect against periodic exposure that could occur as often as daily, may share characteristics of both acute and chronic exposure. Frequent eight-hour exposures to a chemical with a short half-life in the body that does not cause tissue damage or accumulate may resemble a series of acute exposures. The previous exposures may have little or no impact on the current-day exposure. In these cases, acute exposure methodology would be employed for derivation of the eight-hour REL. Frequent eight-hour exposures to a chemical that accumulates in the body, or causes cumulative tissue damage, and/or activating or deactivating enzyme induction is considered a chronic exposure, requiring chronic exposure methodology for derivation of the eight-hour REL. The REL for an eight-hour period would need to be adjusted in such cases to reflect cumulative dose from previous eight-hour exposures. Pharmacokinetic modeling may be appropriate to determine the cumulative dose from serial eight-hour exposures.

6.2.1 Eight-Hour Averaging Period based on Chronic Toxicity

In cases where the evidence shows that an eight-hour REL should be derived based on chronic exposure, a modification of the default approach adopted for the chronic RELs is used (see Section 7.2.1). The default approach to estimating an equivalent time-weighted average concentration (C_{AVG}) from the observed concentration (C_{OBS}) in non-occupational, continuous exposure studies may be summarized as:

$$C_{AVG} = C_{OBS} \times (H \text{ hours per } 8 \text{ hours}) \times (D \text{ days per week})$$

Based on the assumption that half of the 20 m³ of air breathed in any 24-hour period is breathed while active at work, the default approach to estimating an equivalent inhalation-weighted average concentration (C_{AVG}) for an eight-hour period of elevated activity (such as at work) from the observed concentration (C_{OBS}) for continuously exposed humans or experimental animals is:

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

Commonly encountered exposure scenarios in both worker studies and experimental animal toxicology studies involve exposures of 6 to 8 hours per day for 5 days per week. Less time adjustment, and associated uncertainty, occurs applying an eight-hour REL under these exposure scenarios relative to applying a chronic REL.

For simplicity, it may be desirable in some cases to use the chronic REL as a health guidance value for repeated eight-hour exposures. This might be appropriate for substances where the response is concentration rather than time dependent, and for substances that accumulate in the body and have long internal half-lives, such as dioxins and some metals, or substances that demonstrate cumulative toxicity, where large pharmacokinetic uncertainties exist. Thus, in these cases the chronic and eight-hour REL may be the same.

6.2.2 Eight-Hour Averaging Period for Acute Recurrent Toxicity

There are some acute RELs that have used single health studies with six- or eight-hour human exposures to derive NOAELs or LOAELs. It may be appropriate to use such studies to derive eight-hour RELs using acute REL methodology if the data show that the chemical is quickly eliminated and does not cause cumulative tissue damage. Similarly, intermittent exposure studies in experimental animals, often with daily exposures at or near six hours, may exhibit toxicity that reflects a daily recurrent acute effect rather than a chronic cumulative-type injury. In some cases, that daily recurrent acute effect may consist of sensory irritation, in which case no concentration adjustment is applied to extrapolate to an eight-hour REL (see Section 5.8.1). A cautious interpretation of such situations is necessary, however, since a number of agents shown to cause sensory irritation during a single one-hour (acute) exposure have also been shown to cause persistent (and therefore to some degree cumulative) histological damage in various parts of the respiratory tract following repeated (chronic) exposures.

In cases where daily intermittent exposure shows a recurrent acute effect other than sensory irritation, acute REL methodology is applied for time extrapolation to an eight-hour exposure employing a modification of Haber's Law as follows:

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

In this equation, (C) is concentration, (T) is time of exposure, and n is a chemical-specific parameter greater than zero. When the value of n is unknown, default exponents are used by OEHHA for extrapolation to 8 hours. When extrapolating from an experimental exposure duration of less than 8 hours to an eight-hour level, the value of $n=1$ was used. A value of $n = 1$ results in a relatively rapid decrease in the derived REL when extrapolations are made from shorter to longer exposures and is considered an appropriate health-protective approach. Most human worker and experimental animal studies with daily intermittent exposures have time durations at or near 6-8 hours per day, which are well-suited for extrapolating to an eight-hour REL. Data on experimental or workplace exposures longer than 8 hours are less likely to be encountered, but if this were the case a value of $n = 3$ would be used as for the acute RELs. Daily exposures considerably less than 6 hours are not as preferable and may be more practical for acute REL derivation.

6.2.3 Eight-Hour REL Exposure Duration Adjustments for Developmental Toxicants

Because the timing and duration of the sensitive period of gestation is usually unknown, time extrapolation to an eight-hour REL must take into account two principal toxicokinetic issues to prevent, in particular, underestimation of developmental toxicity - peak tissue concentration and total tissue dose (e.g., area under the concentration-time curve, or AUC). Additionally, for those developmental toxicants where there is a suspicion that the chemical or its metabolites may accumulate with daily eight-hour exposures, a duration adjustment from discontinuous to continuous exposures based on equivalent multiples of concentration (C) and duration (T) is recommended (See Section 4.4.6.1). This C x T approach avoids possible underestimation of risk when adjusting the exposure duration from a shorter period to a longer period of exposure.

As more information becomes available on PBPK modeling of developmental toxicants for interspecies extrapolation from the exposed animal species to humans, modeling of blood and tissue levels may confirm the C x T adjustments on the REL exposure durations to ensure they do not exceed the peak tissue concentration or total tissue dose at the NOAEL.

For developmental studies in which the daily exposures are greater than eight-hours, a “not to be exceeded” health guidance is recommended in which no adjustment is applied to the duration with extrapolation down to 8 hours. This procedure avoids underestimation of risk when the pharmacokinetic nature of the developmental toxicant is unknown.

For bioaccumulating toxicants such as dioxins and some metals, developmental exposure studies in which exposure occurred only during gestation is not sufficient for establishing an eight-hour REL based on developmental toxicity. These types of toxicants can accumulate in body tissues over extended periods of time prior to gestation, leading to maternal body burdens that may be detrimental to the fetus during gestation. Lack of sufficient chronic-exposure and multi-generation studies, and adequate pharmacokinetic modeling information that can predict body tissue burdens, may require application of a modifying UF for pharmacokinetic deficiencies in calculating the REL.

6.3 Human Equivalent Concentration (HEC) and Uncertainty Factor Applications

Application of HEC adjustments and UFs for eight-hour REL derivation uses the same formulae as are used for the acute and chronic RELs. For eight-hour RELs based on chronic effects, the UFs used for chronic exposure are applied; for eight-hour RELs based on acute recurrent effects, the UFs used for acute exposures are applied.

6.4 Hazard Index Calculation

In calculating the HI, the same standardized target organ categories are used for the eight-hour RELs as for acute and chronic RELs (see Section 4.3.4). Calculation of the HI is described in Section 2.2.

7 Chronic Reference Exposure Levels

This section presents additional information for deriving chronic inhalation Reference Exposure Levels (RELs) for hazardous airborne substances. Chronic exposure is evaluated using ambient air concentrations of emitted chemicals averaged over a year. The annualized average air concentration forms the basis for both chronic noncancer and cancer risk evaluation. In reality, exposure over a 24-hour period does not occur at a continuous level. Chronic RELs are concentrations at or below which adverse health effects are not likely to occur in the general human population exposed continuously over a lifetime.

7.1 Priority for Evaluation of Chemicals

Chronic noncancer RELs have been developed for 80 substances as of May, 2005; these are described in Appendix B of this Technical Support Document and in OEHHA (OEHHA, 2000a). Substances were selected for chronic REL development primarily based on (1) the magnitude of current known emissions in California, (2) the availability of a strong scientific database on which to estimate a chronic REL, and (3) toxicity. We include impacts on children's health or other sensitive subpopulations in prioritizing chemicals for chronic REL development.

The amount of data and the quality of the information will ultimately determine whether a chronic REL can be derived for a specific chemical. Margins of safety or UFs can be used to address the common data gaps encountered in risk assessment, but in some cases, chronic RELs cannot be developed because the data are not relevant to inhalation exposure, or because too much uncertainty exists in the database and subsequent derivations. As more data become available over time, chronic RELs may be added or re-evaluated.

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 D individual summaries of acute, eight-hour, and chronic RELs.

7.2 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.

7.2.1 Effects of Exposure Continuity and Duration

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 six to eight hours per day for five days per week. OEHHA's chronic 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, 1994a). It is similar to modified Haber's law approach used for acute and 8-hour RELs in the special case where $n = 1$. Values of n greater than 1 have not been shown to be applicable in chronic exposure situations, although toxicokinetic effects such as extensive bioaccumulation may require other types of special treatment.

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

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

For studies of occupationally exposed humans, based on the assumption that half of the 20 m³ of air breathed in any 24-hour period is breathed while active at work, the default approach to estimating an equivalent inhalation-weighted average concentration (C_{AVG}) from the observed concentration (C_{OBS}) is:

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

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 \geq 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.

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	\leq 364
Baboon	55	\leq 286
Cat	15	\leq 78
Dog	15	\leq 78
Guinea pig	6	\leq 31
Hamster	2.5	\leq 13 ³
Mouse	2	\leq 13 ³
Rabbit	6	\leq 31
Rat	2	\leq 13
Rhesus monkey	35	\leq 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.

7.3 Human Equivalent Concentration (HEC) Procedure for Chronic RELs

As previously noted for the acute and 8 hour RELs, the preferred method of adjustment for interspecies toxicokinetic differences when animal studies are used for chronic REL development is the application of a compound- and species-specific toxicokinetic model. However, there will be many case where the data to support such a model are not available. If no model-based correction can be developed the default $UF_{H-k} = \sqrt{10}$ would apply. Where suitable parameters are available for the test species (*e.g.* for rats and mice), the U.S. EPA HEC procedure (described in Appendix F) may be used as a partial adjustment for interspecies toxicokinetic differences, in which case $UF_{H-k} = 2$ (thus the 10-fold overall interspecies UF is reduced to 6 if UF_{H-d} has the default value of $\sqrt{10}$). The modifications of the HEC procedure to account for children may also be used to address concerns for human intraspecies variability and to fulfill the mandates of SB 25 to account for potentially greater vulnerability of children when setting health standards.

7.4 LOAEL to NOAEL Extrapolation

There are some instances where the data are not available to identify a NOAEL for a chronic exposure to a chemical, and are not suitable for a benchmark concentration approach. In these cases, we are left with a LOAEL upon which to base a chronic REL. It should be noted that use of a LOAEL is a last resort, as it is frequently not clear how close one is to the NOAEL for a particular effect. In developing chronic RELs, OEHHA will use a default value for the LOAEL to NOAEL UF of 10. There may be cases where a smaller value can be used where the data indicate that the LOAEL is fairly close to an expected NOAEL. For acute effects, OEHHA has used the severity of effect concept developed by U.S. EPA as an indicator of proximity to a NOAEL (see Section 5.5). However, this does not work well for chronic effects, where there are disparate types of response, which are difficult to compare. Many chronic effects could reasonably be considered “serious” even if they occurred rarely or to a low degree, and the concept of reversibility (an important criterion of severity for acute effects) is ambiguous in the context of continuous exposures over extended periods up to and including a complete lifetime. Therefore, for chronic effects, indicators of the proximity or otherwise of a LOAEL to the presumed NOAEL will be described on a case-by-case basis in the toxicity summary of a specified chemical. OEHHA may use an intermediate uncertainty factor where an effect was observed in $\leq 30\%$ of subjects, since for many endpoints a low response rate suggests that the exposure is likely to be relatively nearer to the NOAEL. Similar arguments may be applied for

continuous endpoints, where low intensity of response and/or low frequency of responses above control values suggest proximity to a NOAEL.

7.5 Hyperplasia

The use of hyperplasia as a toxicological endpoint for setting chronic RELs should consider whether the hyperplasia may progress to dysplasia and neoplasia. In a chronic study, if hyperplasia was the most sensitive endpoint for that chemical, it was used as an endpoint for REL development. Hyperplasia can be seen as a normal response (e.g., to hormones), and is also seen in response to a number of sensory irritants which are not carcinogens. When hyperplasia was used as the toxicological endpoint and as a mild effect, the histological grade was low (e.g., one on a scale of one to five) and there was no increase in organ weight noted.

7.6 Pre-Existing Chronic Exposure Guidelines

Chronic exposure levels have been derived using several different approaches, but inhalation exposure values estimated using a consistent basis to protect the general public are only available for certain chemicals. The U.S. EPA RfCs, now published for 72 chemicals, are a notable example. Other values designed for the protection of the general public, such as the U.S. EPA reference doses (RfDs), are available for more chemicals but are intended primarily to deal with non-inhalation exposures to chemicals and are usually based on toxicity data obtained following oral exposure. It is likely that the oral and dermal routes would underestimate the health effects of inhalation exposure, unless the health effect is an identifiable systemic effect and not affected by first-pass metabolism. If the effect is systemic, then appropriate adjustments for absorption can be made.

7.6.1 U.S. EPA Reference Concentrations

The U.S. EPA developed an inhalation reference concentration (RfC) method (Jarabek et al., 1989; U.S. EPA, 1994a; 2002). The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extra-respiratory effects). The RfC is comparable to earlier Acceptable Daily Intake (ADI) and RfD methods but addresses inhalation specific issues such as respiratory dynamics and delivered doses by inhalation. Dosimetry models are used to extrapolate the internal dose metric across species and to estimate the human equivalent concentration (HEC), as described in Appendix F.

7.6.2 U.S. EPA Reference Doses

The U.S. EPA developed an oral reference dose (RfD) concept in 1987 (Barnes and Dourson, 1988). This provides a protocol for study selection, identifying NOAELs, applying UFs, and assessing the weight of evidence. As of September 2005, U.S. EPA RfDs were available for more than 350 substances (U.S. EPA, 2007a). The major limitation of these values for application to inhalation REL development is that they are almost entirely based on studies of exposures by routes other than inhalation. However, they have utility for substances treated as multi-pathway chemicals in the Air Toxics Hot Spots Program's risk assessments. Additionally, route-to-route extrapolation is sometimes possible, depending on the compound's toxicity and pharmacokinetics.

7.6.3 Occupational Threshold Limit Values

Occupational exposure limits have been used to derive chemical exposure guidelines for the general public (NATICH and McCullough, 1991; Robinson and Paxman, 1992). As of May, 2005, more than 600 American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) (ACGIH, 2005) and National Institute for Occupational Safety and Health (NIOSH) Permissible Exposure Limits (PELs) (NIOSH, 2005) were available. The California Occupational Safety and Health Administration also has approximately 600 occupational PELs. 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 workers (Roach and Rappaport, 1990). 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, which often included risk management and feasibility considerations specific to industrial facilities, in addition to health-based criteria, and have not always incorporated recently available data. Most importantly, occupational exposure guidelines are designed to protect healthy adult workers, and do not allow for possibly more sensitive members of the general population such as children and the elderly, or those with genetically predetermined sensitivities. Thus, OEHHA does not use occupational guidelines for chronic RELs, which are intended to protect the general public.

7.6.4 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.

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Appendix A. List of Acronyms

A.1 List of Acronyms

σ	geometric standard deviation
AAQS	Ambient Air Quality Standards
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
AEGL	Acute Emergency Guidance Level
AEL	adverse effect level
AHH	aryl hydrocarbon hydroxylase
AICE	American Institute of Chemical Engineers
AIHA	American Industrial Hygiene Association
ALL	acute lymphoblastic leukemia
ARB	Air Resources Board
ATS	American Thoracic Society
AUC	area under the (blood or tissue concentration x time) curve
AV_A	alveolar ventilation (animal)
AV_H	alveolar ventilation (human)
BMC	benchmark concentration
$BMCL_{05}$	lower 95% confidence interval of the benchmark concentration
BMD	benchmark dose
BW	body weight
$C \times T$	concentration multiplied by time
C_A	applied concentration in an animal experiment.
CAAQS	California Ambient Air Quality Standards
CalEPA	California Environmental Protection Agency
CalOSHA	California Occupational Safety and Health Administration
CAPCOA	California Air Pollution Control Officer's Association
C_{AVG}	average concentration
CFT	computational fluid dynamics
CIIT	Chemical Industry Institute of Toxicology
C_{max}	peak concentrations
C_{OBS}	observed concentration
Cr^{VI}	hexavalent chromium
CYP	cytochrome P450
DAF	dosimetric adjustment factor
DCM	dichloromethane
DES	diethylstilbestrol

D _{H-d}	dose of compound or active metabolite at site of action in default human
D _L	diffusing capacity
DOD	Department of Defense
DPR	Department of Pesticide Regulation (State of California, CalEPA)
DPX	DNA-protein cross-links
EC ₀₅	5% effective concentration (expected to produce a 5% toxic response rate)
EEGL	Emergency Exposure Guidance Level
ERPG	Emergency Response Planning Guidelines
ET	extrathoracic
ETS	environmental tobacco smoke
FAS	Fetal Alcohol Syndrome
FDA	Food and Drug Administration
FEL	frank effect level
FEV ₁	forced expiratory volume in one second
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Federal Food Quality Protection Act
FVC	forced vital capacity
GFR	glomerular filtration rate
GLC	ground level concentration
GLPs	Good Laboratory Practices
GSH	glutathione
GSTs	Glutathione sulfotransferases
H&SC	Health & Safety Code
HARP	Air Resources Board's Hot Spots Analysis and Reporting Program
HEC	Human Equivalent Concentration
Hg	mercury
HI	hazard index
IARC	International Agency for Research on Cancer
IBT	Industrial Bio-Test Laboratories Inc.
ICRP	International Commission on Radiological Protection
IRDC	International Research and Development Corporation
LCL	lower confidence limit
LD ₅₀	lethal dose to 50% of test animals in a given experiment
LOAEL	lowest-observed-adverse-effect-level
LOEL	lowest-observed-effect-level
MLE	maximum likelihood estimate
MMAD	mean mass aerodynamic diameter
MPPD	multiple path particle deposition model

MV	minute volume
NAC	National Advisory Committee
NAS	National Academy of Sciences
NATICH	National Air Toxics Information Clearinghouse
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect-level
NOEL	no observed effect level
NRC	National Research Council
NTP	National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment
OP	organophosphate
OR	odds ratio
PAH	polycyclic aromatic hydrocarbon
Pb	lead
PBPK	physiologically based pharmacokinetic modeling
PCE	perchloroethylene
PEL	Permissible Exposure Limits
PK UF	pharmacokinetic uncertainty factors
PU	pulmonary region
RD50	respiratory dose 50 (dose of gas causing 50% decrease in respiration rate)
RDDR _s	regional deposited dose ratios
REL	Reference Exposure Level
R _f C	Reference Concentration
R _f D	Reference Dose
RFLP	restriction fragment length polymorphism
RGDR	regional gas dose ratio
RIVM	The Netherlands National Institute for Public Health and the Environment
RR	relative risk
RSA _A	regional surface area (animal)
RSA _H	regional surface area (human)
RT	respiratory tracts
SA	surface area
SB	Senate Bill
SG _{aw}	specific airway conductance
SMR	standardized mortality ratios
SPEGL	Short-term Public Emergency Guidance Level
SR _{AW}	specific airway resistance
SRP	Scientific Review Panel

STEL	Short-term Exposure Limit
TACs	Toxic Air Contaminants
TB	tracheobronchial region
TCA	trichloroacetic acid
TCE	trichloroethylene
TD	toxicodynamic
TK	toxicokinetic
TLV-TWA	Threshold Limit Value-Time Weighted Average
TSDs	Technical Support Documents
UCL	upper confidence limit
UF _A	interspecies uncertainty factor
UF _{A-d}	interspecies uncertainty factor toxicodynamic component
UF _{A-k}	interspecies uncertainty factor toxicokinetic component
UF _D	database deficiency uncertainty factor
UF _H	intraspecies uncertainty factor
UF _{H-d}	intraspecies uncertainty factor toxicodynamic component
UF _{H-k}	intraspecies uncertainty factor toxicokinetic component
UF _L	LOAEL uncertainty factor
UF _S	subchronic uncertainty factor
UFs	uncertainty factors
U.S. DHHS	United States Department of Health and Human Services
U.S. EPA	United States Environmental Protection Agency
Val	valine
Vd	volume of distribution
VOCs	volatile organic compounds
WHO	World Health Organization
χ^2	chi-squared

Appendix B. Acute, 8-Hour, and Chronic Reference Exposure Levels (RELs) Summary Table

Current Reference Exposure Levels can be found at http://www.oehha.ca.gov/air/hot_spots/index.html.

RELs for acrolein, acetaldehyde, arsenic, formaldehyde, manganese, and mercury are in the final process of revision, and the new RELs will be posted here following SRP approval of the summaries. Risk assessors should continue to use the existing values until the new values are approved and posted at this web page.

Appendix C. Substances for which Emissions Must Be Quantified

SUBSTANCES FOR WHICH EMISSIONS MUST BE QUANTIFIED

CAS number	Substance name
75070	Acetaldehyde
60355	Acetamide
75058	Acetonitrile
98862	Acetophenone
53963	2-Acetylaminofluorene [PAH-Derivative, POM]
107028	Acrolein
79061	Acrylamide
79107	Acrylic acid
107131	Acrylonitrile
107051	Allyl chloride
7429905	Aluminum
1344281	Aluminum oxide (fibrous forms)
117793	2-Aminoanthraquinone [PAH-Derivative, POM]
92671	4-Aminobiphenyl [POM]
61825	Amitrole
7664417	Ammonia
6484522	Ammonium nitrate
7783202	Ammonium sulfate
62533	Aniline
90040	o-Anisidine
-	Anthracene [PAH, POM], (see PAH)
7440360	Antimony
*	Antimony compounds including but not limited to:
1309644	Antimony trioxide
7440382	Arsenic
1016	Arsenic compounds (inorganic) including but not limited to:
7784421	Arsine
1017	Arsenic compounds (other than inorganic)
-	Asbestos (see Mineral fibers)
7440393	Barium
*	Barium Compounds
-	Benz[a]anthracene [PAH, POM], (see PAH)
71432	Benzene
92875	Benzidine (and its salts) [POM]
1020	Benzidine-based dyes [POM] including but not limited to:
1937377	Direct Black 38 [PAH-Derivative, POM]
2602462	Direct Blue 6 [PAH-Derivative, POM]
16071866	Direct Brown 95 (technical grade) [POM]
-	Benzo[a]pyrene [PAH, POM], (see PAH)
-	Benzo[b]fluoranthene [PAH, POM], (see PAH)
271896	Benzofuran
98077	Benzoic trichloride {Benzotrichloride}
-	Benzo[j]fluoranthene [PAH, POM] (see PAH)
-	Benzo[k]fluoranthene [PAH, POM] (see PAH)
98884	Benzoyl chloride
94360	Benzoyl peroxide
100447	Benzyl chloride

CAS number	Substance name
7440417	Beryllium
*	Beryllium compounds
92524	Biphenyl [POM]
111444	Bis(2-chloroethyl) ether {DCEE}
542881	Bis(chloromethyl) ether
103231	Bis(2-ethylhexyl) adipate
7726956	Bromine
*	Bromine compounds (inorganic) including but not limited to:
7789302	Bromine pentafluoride
10035106	Hydrogen bromide
7758012	Potassium bromate
75252	Bromoform
106990	1,3-Butadiene
540885	t-Butyl acetate
141322	Butyl acrylate
71363	n-Butyl alcohol
78922	sec-Butyl alcohol
75650	tert-Butyl alcohol
85687	Butyl benzyl phthalate
7440439	Cadmium
*	Cadmium compounds
156627	Calcium cyanamide
105602	Caprolactam
2425061	Captafol
133062	Captan
63252	Carbaryl [PAH-Derivative, POM]
1050	Carbon black extracts
75150	Carbon disulfide
56235	Carbon tetrachloride
463581	Carbonyl sulfide
1055	Carrageenan (degraded)
120809	Catechol
133904	Chloramben
57749	Chlordane
108171262	Chlorinated paraffins (average chain length, C12; approximately 60% Chlorine by weight)
7782505	Chlorine
10049044	Chlorine dioxide
79118	Chloroacetic acid
532274	2-Chloroacetophenone
106478	p-Chloroaniline
1058	Chlorobenzenes including but not limited to:
108907	Chlorobenzene
25321226	Dichlorobenzenes (mixed isomers) including:
95501	1,2-Dichlorobenzene
541731	1,3-Dichlorobenzene
106467	p-Dichlorobenzene {1,4-Dichlorobenzene}
120821	1,2,4-Trichlorobenzene
510156	Chlorobenzilate [POM] {Ethyl-4,4'-dichlorobenzilate}
67663	Chloroform

CAS number	Substance name
107302	Chloromethyl methyl ether (technical grade)
1060	Chlorophenols including but not limited to:
95578	2-Chlorophenol
120832	2,4-Dichlorophenol
87865	Pentachlorophenol
25167833	Tetrachlorophenols including but not limited to:
58902	2,3,4,6-Tetrachlorophenol
95954	2,4,5-Trichlorophenol
88062	2,4,6-Trichlorophenol
95830	4-Chloro-o-phenylenediamine
76062	Chloropicrin
126998	Chloroprene
95692	p-Chloro-o-toluidine
7440473	Chromium
*	Chromium compounds (other than hexavalent)
18540299	Chromium, hexavalent (and compounds) including but not limited to:
10294403	Barium chromate
13765190	Calcium chromate
1333820	Chromium trioxide
7758976	Lead chromate
10588019	Sodium dichromate
7789062	Strontium chromate
-	Chrysene [PAH, POM], (see PAH)
7440484	Cobalt
*	Cobalt compounds
1066	Coke oven emissions
7440508	Copper
*	Copper compounds
1070	Creosotes
120718	p-Cresidine
1319773	Cresols (mixtures of) {Cresylic acid} including:
108394	m-Cresol
95487	o-Cresol
106445	p-Cresol
4170303	Crotonaldehyde
98828	Cumene
80159	Cumene hydroperoxide
135206	Cupferron
1073	Cyanide compounds (inorganic) including but not limited to:
74908	Hydrocyanic acid
110827	Cyclohexane
108930	Cyclohexanol
66819	Cycloheximide
	Decabromodiphenyl oxide [POM] (see Polybrominated diphenyl ethers)
1075	Dialkylnitrosamines including but not limited to:
924163	N-Nitrosodi-n-butylamine
1116547	N-Nitrosodiethanolamine
55185	N-Nitrosodiethylamine
62759	N-Nitrosodimethylamine
621647	N-Nitrosodi-n-propylamine

CAS number	Substance name
10595956	N-Nitrosomethylethylamine
615054	2,4-Diaminoanisole
1078	Diaminotoluenes (mixed isomers) including but not limited to:
95807	2,4-Diaminotoluene {2,4-Toluene diamine}
334883	Diazomethane
226368	Dibenz[a,h]acridine [POM]
224420	Dibenz[a,j]acridine [POM]
-	Dibenz[a,h]anthracene [PAH, POM], (see PAH)
194592	7H-Dibenzo[c,g]carbazole
-	Dibenzo[a,e]pyrene [PAH, POM], (see PAH)
-	Dibenzo[a,h]pyrene [PAH, POM], (see PAH)
-	Dibenzo[a,i]pyrene [PAH, POM], (see PAH)
-	Dibenzo[a,l]pyrene [PAH, POM], (see PAH)
132649	Dibenzofuran [POM]
96128	1,2-Dibromo-3-chloropropane {DBCP}
96139	2,3-Dibromo-1-propanol
84742	Dibutyl phthalate
-	p-Dichlorobenzene (1,4-Dichlorobenzene) (see Chlorobenzenes)
91941	3,3'-Dichlorobenzidine [POM]
72559	Dichlorodiphenyldichloroethylene {DDE} [POM]
75343	1,1-Dichloroethane {Ethylidene dichloride}
94757	Dichlorophenoxyacetic acid, salts and esters {2,4-D}
78875	1,2-Dichloropropane {Propylene dichloride}
542756	1,3-Dichloropropene
62737	Dichlorovos {DDVP}
115322	Dicofol [POM]
--	Diesel engine exhaust
9901	Diesel engine exhaust, particulate matter {Diesel PM}
9902	Diesel engine exhaust, total organic gas
#	Diesel fuel (marine)
111422	Diethanolamine
117817	Di(2-ethylhexyl) phthalate {DEHP}
64675	Diethyl sulfate
119904	3,3'-Dimethoxybenzidine [POM]
60117	4-Dimethylaminoazobenzene [POM]
121697	N,N-Dimethylaniline
57976	7,12-Dimethylbenz[a]anthracene [PAH-Derivative, POM]
119937	3,3'-Dimethylbenzidine {o-Tolidine} [POM]
79447	Dimethyl carbamoyl chloride
68122	Dimethyl formamide
57147	1,1-Dimethylhydrazine
131113	Dimethyl phthalate
77781	Dimethyl sulfate
534521	4,6-Dinitro-o-cresol (and salts)
51285	2,4-Dinitrophenol
42397648	1,6-Dinitropyrene [PAH-Derivative, POM]
42397659	1,8-Dinitropyrene [PAH-Derivative, POM]
25321146	Dinitrotoluenes (mixed isomers) including but not limited to:
121142	2,4-Dinitrotoluene
606202	2,6-Dinitrotoluene

CAS number	Substance name
123911	1,4-Dioxane
-	Dioxins (Chlorinated dibenzodioxins) (see Polychlorinated dibenzo-p-dioxins) [POM]
630933	Diphenylhydantoin [POM]
122667	1,2-Diphenylhydrazine {Hydrazobenzene} [POM]
1090	Environmental Tobacco Smoke
106898	Epichlorohydrin
106887	1,2-Epoxybutane
1091	Epoxy resins
140885	Ethyl acrylate
100414	Ethyl benzene
75003	Ethyl chloride {Chloroethane}
-	Ethyl-4,4'-dichlorobenzilate (see Chlorobenzilate)
74851	Ethylene
106934	Ethylene dibromide {EDB, 1,2-Dibromoethane}
107062	Ethylene dichloride {EDC, 1,2-Dichloroethane}
107211	Ethylene glycol
151564	Ethyleneimine {Aziridine}
75218	Ethylene oxide
96457	Ethylene thiourea
1101	Fluorides and compounds including but not limited to:
7664393	Hydrogen fluoride
1103	Fluorocarbons (brominated)
1104	Fluorocarbons (chlorinated) including but not limited to:
76131	Chlorinated fluorocarbon {CFC-113} {1,1,2-Trichloro-1,2,2-trifluoroethane}
75456	Chlorodifluoromethane {Freon 22}
75718	Dichlorodifluoromethane {Freon 12}
75434	Dichlorofluoromethane {Freon 21}
75694	Trichlorofluoromethane {Freon 11}
50000	Formaldehyde
110009	Furan
--	Gasoline engine exhaust including but not limited to:
--	Gasoline engine exhaust (condensates & extracts)
9910	Gasoline engine exhaust, particulate matter
9911	Gasoline engine exhaust, total organic gas
1110	Gasoline vapors
111308	Glutaraldehyde
1115	Glycol ethers and their acetates including but not limited to:
111466	Diethylene glycol
111966	Diethylene glycol dimethyl ether
112345	Diethylene glycol monobutyl ether
111900	Diethylene glycol monoethyl ether
111773	Diethylene glycol monomethyl ether
25265718	Dipropylene glycol
34590948	Dipropylene glycol monomethyl ether
629141	Ethylene glycol diethyl ether
110714	Ethylene glycol dimethyl ether
111762	Ethylene glycol monobutyl ether
110805	Ethylene glycol monoethyl ether

CAS number	Substance name
111159	Ethylene glycol monoethyl ether acetate
109864	Ethylene glycol monomethyl ether
110496	Ethylene glycol monomethyl ether acetate
2807309	Ethylene glycol monopropyl ether
107982	Propylene glycol monomethyl ether
108656	Propylene glycol monomethyl ether acetate
112492	Triethylene glycol dimethyl ether
76448	Heptachlor
118741	Hexachlorobenzene
87683	Hexachlorobutadiene
608731	Hexachlorocyclohexanes (mixed or technical grade) including but not limited to:
319846	alpha-Hexachlorocyclohexane
319857	beta-Hexachlorocyclohexane
58899	Lindane {gamma-Hexachlorocyclohexane}
77474	Hexachlorocyclopentadiene
67721	Hexachloroethane
680319	Hexamethylphosphoramide
110543	Hexane
302012	Hydrazine
7647010	Hydrochloric acid
-	Hydrocyanic acid (see Cyanide compounds)
7783064	Hydrogen sulfide
123319	Hydroquinone
-	Indeno[1,2,3-cd]pyrene [PAH, POM], (see PAH)
13463406	Iron pentacarbonyl
1125	Isocyanates including but not limited to:
822060	Hexamethylene-1,6-diisocyanate
101688	Methylene diphenyl diisocyanate {MDI} [POM]
624839	Methyl isocyanate
-	Toluene-2,4-diisocyanate (see Toluene diisocyanates)
-	Toluene-2,6-diisocyanate (see Toluene diisocyanates)
78591	Isophorone
78795	Isoprene, except from vegetative emission sources
67630	Isopropyl alcohol
80057	4,4'-Isopropylidenediphenol [POM]
7439921	Lead
1128	Lead compounds (inorganic) including but not limited to:
301042	Lead acetate
-	Lead chromate (see Chromium, hexalent)
7446277	Lead phosphate
1335326	Lead subacetate
1129	Lead compounds (other than inorganic)
108316	Maleic anhydride
7439965	Manganese
*	Manganese compounds
7439976	Mercury
*	Mercury compounds including but not limited to:
7487947	Mercuric chloride
593748	Methyl mercury {Dimethylmercury}

CAS number	Substance name
67561	Methanol
72435	Methoxychlor [POM]
75558	2-Methylaziridine {1,2-Propyleneimine}
74839	Methyl bromide {Bromomethane}
74873	Methyl chloride {Chloromethane}
71556	Methyl chloroform {1,1,1-Trichloroethane}
56495	3-Methylcholanthrene [PAH-Derivative, POM]
3697243	5-Methylchrysene [PAH-Derivative, POM]
101144	4,4'-Methylene bis(2-chloroaniline) {MOCA} [POM]
75092	Methylene chloride {Dichloromethane}
101779	4,4'-Methylenedianiline (and its dichloride) [POM]
78933	Methyl ethyl ketone {2-Butanone}
60344	Methyl hydrazine
74884	Methyl iodide {Iodomethane}
108101	Methyl isobutyl ketone {Hexone}
75865	2-Methylactonitrile {Acetone cyanohydrin}
80626	Methyl methacrylate
109068	2-Methylpyridine
1634044	Methyl tert-butyl ether
90948	Michler's ketone [POM]
1136	Mineral fibers (fine mineral fibers which are man-made, and are airborne particles of a respirable size greater than 5 microns in length, less than or equal to 3.5 microns in diameter, with a length to diameter ratio of 3:1) including but not limited to:
1056	Ceramic fibers
1111	Glasswool fibers
1168	Rockwool
1181	Slagwool
1135	Mineral fibers (other than man-made) including but not limited to:
1332214	Asbestos
12510428	Erionite
1190	Talc containing asbestiform fibers
1313275	Molybdenum trioxide
-	Naphthalene [PAH, POM], (see PAH)
7440020	Nickel
*	Nickel compounds including but not limited to:
373024	Nickel acetate
3333673	Nickel carbonate
13463393	Nickel carbonyl
12054487	Nickel hydroxide
1271289	Nickelocene
1313991	Nickel oxide
12035722	Nickel subsulfide
1146	Nickel refinery dust from the pyrometallurgical process
7697372	Nitric acid
139139	Nitrilotriacetic acid
602879	5-Nitroacenaphthene [PAH-Derivative, POM]
98953	Nitrobenzene
92933	4-Nitrobiphenyl [POM]
7496028	6-Nitrochrysene [PAH-Derivative, POM]

CAS number	Substance name
607578	2-Nitrofluorene [PAH-Derivative, POM]
302705	Nitrogen mustard N-oxide
100027	4-Nitrophenol
79469	2-Nitropropane
5522430	1-Nitropyrene [PAH-Derivative, POM]
57835924	4-Nitropyrene [PAH-Derivative, POM]
86306	N-Nitrosodiphenylamine
156105	p-Nitrosodiphenylamine [POM]
684935	N-Nitroso-N-methylurea
59892	N-Nitrosomorpholine
100754	N-Nitrosopiperidine
930552	N-Nitrosopyrrolidine
*	Oleum (see Sulfuric acid and oleum)
--	PAHs (Polycyclic aromatic hydrocarbons) [POM] including but not limited to:
1151	PAHs, total, w/o individ. components reported [PAH, POM]
1150	PAHs, total, with individ. components also reported [PAH, POM]
83329	Acenaphthene [PAH, POM]
208968	Acenaphthylene [PAH, POM]
120127	Anthracene [PAH, POM]
56553	Benz[a]anthracene [PAH, POM]
50328	Benzo[a]pyrene [PAH, POM]
205992	Benzo[b]fluoranthene
192972	Benzo[e]pyrene [PAH, POM]
191242	Benzo[g,h,i]perylene [PAH, POM]
205823	Benzo[j]fluoranthene [PAH, POM]
207089	Benzo[k]fluoranthene [PAH, POM]
218019	Chrysene [PAH, POM]
53703	Dibenz[a,h]anthracene [PAH, POM]
192654	Dibenzo[a,e]pyrene [PAH, POM]
189640	Dibenzo[a,h]pyrene [PAH, POM]
189559	Dibenzo[a,i]pyrene [PAH, POM]
191300	Dibenzo[a,l]pyrene [PAH, POM]
206440	Fluoranthene [PAH, POM]
86737	Fluorene [PAH, POM]
193395	Indeno[1,2,3-cd]pyrene [PAH, POM]
91576	2-Methyl naphthalene [PAH, POM]
91203	Naphthalene [PAH, POM]
198550	Perylene [PAH, POM]
85018	Phenanthrene [PAH, POM]
129000	Pyrene [PAH, POM]
#	PAH-Derivatives (Polycyclic aromatic hydrocarbon derivatives) [POM] (including but not limited to those substances listed in Appendix A with the bracketed designation [PAH-Derivative, POM])
56382	Parathion
1336363	PCBs (Polychlorinated biphenyls), total [POM] including but not limited to:
32598133	3,3',4,4'-Tetrachlorobiphenyl (PCB 77)
70362504	3,4,4',5-Tetrachlorobiphenyl (PCB 81)
32598144	2,3,3',4,4'-Pentachlorobiphenyl (PCB 105)
74472370	2,3,4,4',5-Pentachlorobiphenyl (PCB 114)

CAS number	Substance name
31508006	2,3',4,4',5-Pentachlorobiphenyl (PCB 118)
65510443	2,3',4,4',5'-Pentachlorobiphenyl (PCB 123)
57465288	3,3',4,4',5-Pentachlorobiphenyl (PCB 126)
38380084	2,3,3',4,4',5-Hexachlorobiphenyl (PCB 156)
69782907	2,3,3',4,4',5'-Hexachlorobiphenyl (PCB 157)
52663726	2,3',4,4',5,5'-Hexachlorobiphenyl (PCB 167)
32774166	3,3',4,4',5,5'-Hexachlorobiphenyl (PCB 169)
39635319	2,3,3',4,4',5,5'-Heptachlorobiphenyl (PCB 189)
82688	Pentachloronitrobenzene {Quintobenzene}
79210	Peracetic acid
127184	Perchloroethylene {Tetrachloroethene}
2795393	Perfluorooctanoic acid {PFOA} and its salts, esters, and sulfonates
108952	Phenol
106503	p-Phenylenediamine
90437	2-Phenylphenol [POM]
75445	Phosgene
7723140	Phosphorus
--	Phosphorus compounds:
7803512	Phosphine
7664382	Phosphoric acid
10025873	Phosphorus oxychloride
10026138	Phosphorus pentachloride
1314563	Phosphorus pentoxide
7719122	Phosphorus trichloride
126738	Tributyl phosphate
78400	Triethyl phosphine
512561	Trimethyl phosphate
78308	Triorthocresyl phosphate [POM]
115866	Triphenyl phosphate [POM]
101020	Triphenyl phosphite [POM]
85449	Phthalic anhydride
2222	Polybrominated diphenyl ethers {PBDEs}, including but not limited to:
1163195	Decabromodiphenyl oxide [POM]
--	Polychlorinated dibenzo-p-dioxins {PCDDs or Dioxins} [POM] including but not limited to:
1086	Dioxins, total, w/o individ. isomers reported {PCDDs} [POM]
1085	Dioxins, total, with individ. isomers also reported {PCDDs} [POM]
1746016	2,3,7,8-Tetrachlorodibenzo-p-dioxin {TCDD} [POM]
40321764	1,2,3,7,8-Pentachlorodibenzo-p-dioxin [POM]
39227286	1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin [POM]
57653857	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin [POM]
19408743	1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin [POM]
35822469	1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin [POM]
3268879	1,2,3,4,6,7,8,9-Octachlorodibenzo-p-dioxin [POM]
41903575	Total Tetrachlorodibenzo-p-dioxin [POM]
36088229	Total Pentachlorodibenzo-p-dioxin [POM]
34465468	Total Hexachlorodibenzo-p-dioxin [POM]
37871004	Total Heptachlorodibenzo-p-dioxin [POM]
--	Polychlorinated dibenzofurans {PCDFs or Dibenzofurans} [POM] including but not limited to:

CAS number	Substance name
1080	Dibenzofurans (Polychlorinated dibenzofurans) {PCDFs} [POM]
51207319	2,3,7,8-Tetrachlorodibenzofuran [POM]
57117416	1,2,3,7,8-Pentachlorodibenzofuran [POM]
57117314	2,3,4,7,8-Pentachlorodibenzofuran [POM]
70648269	1,2,3,4,7,8-Hexachlorodibenzofuran [POM]
57117449	1,2,3,6,7,8-Hexachlorodibenzofuran [POM]
72918219	1,2,3,7,8,9-Hexachlorodibenzofuran [POM]
60851345	2,3,4,6,7,8-Hexachlorodibenzofuran [POM]
67562394	1,2,3,4,6,7,8-Heptachlorodibenzofuran [POM]
55673897	1,2,3,4,7,8,9-Heptachlorodibenzofuran [POM]
39001020	1,2,3,4,6,7,8,9-Octachlorodibenzofuran [POM]
55722275	Total Tetrachlorodibenzofuran [POM]
30402154	Total Pentachlorodibenzofuran [POM]
55684941	Total Hexachlorodibenzofuran [POM]
38998753	Total Heptachlorodibenzofuran [POM]
#	POM (Polycyclic organic matter) (including but not limited to those substances listed in Appendix A with the bracketed designation of [POM], [PAH, POM], or [PAH-Derivative, POM])
1120714	1,3-Propane sultone
57578	beta-Propiolactone
123386	Propionaldehyde
114261	Propoxur {Baygon}
115071	Propylene
75569	Propylene oxide
-	1,2-Propyleneimine (see 2-Methylaziridine)
110861	Pyridine
91225	Quinoline
106514	Quinone
1165	Radionuclides including but not limited to:
24267569	Iodine-131
1166	Radon and its decay products
50555	Reserpine [POM]
#	Residual (heavy) fuel oils
7782492	Selenium
*	Selenium compounds including but not limited to:
7783075	Hydrogen selenide
7446346	Selenium sulfide
1175	Silica, crystalline (respirable)
7440224	Silver
*	Silver compounds
1310732	Sodium hydroxide
100425	Styrene
96093	Styrene oxide
*	Sulfuric acid and oleum
8014957	Oleum
7446719	Sulfur trioxide
7664939	Sulfuric acid
100210	Terephthalic acid
79345	1,1,2,2-Tetrachloroethane
-	Tetrachlorophenols (see Chlorophenols)

CAS number	Substance name
7440280	Thallium
	* Thallium compounds
62555	Thioacetamide
62566	Thiourea
7550450	Titanium tetrachloride
108883	Toluene
	- 2,4-Toluenediamine (see 2,4-Diaminotoluene)
26471625	Toluene diisocyanates including but not limited to:
584849	Toluene-2,4-diisocyanate
91087	Toluene-2,6-diisocyanate
95534	o-Toluidine
8001352	Toxaphene {Polychlorinated camphenes}
	- 1,1,1-Trichloroethane (see Methyl chloroform)
79005	1,1,2-Trichloroethane {Vinyl trichloride}
79016	Trichloroethylene
	- 2,4,6-Trichlorophenol (see Chlorophenols)
96184	1,2,3-Trichloropropane
121448	Triethylamine
1582098	Trifluralin
25551137	Trimethylbenzenes including but not limited to:
95636	1,2,4-Trimethylbenzene
540841	2,2,4-Trimethylpentane
51796	Urethane {Ethyl carbamate}
7440622	Vanadium (fume or dust)
1314621	Vanadium pentoxide
108054	Vinyl acetate
593602	Vinyl bromide
75014	Vinyl chloride
100403	4-Vinylcyclohexene
75025	Vinyl fluoride
75354	Vinylidene chloride
1206	Wood preservatives (containing arsenic and chromate)
1330207	Xylenes (mixed) including:
108383	m-Xylene
95476	o-Xylene
106423	p-Xylene
7440666	Zinc
	* Zinc compounds including but not limited to:
1314132	Zinc oxide

Appendix D. Individual Acute, 8-Hour, and Chronic Reference Exposure Level Summaries

D.1 Summaries using this version of the Hot Spots Risk Assessment guidelines for the following chemicals will be posted upon approval by the SRP. Risk assessors should continue to use the previous values until the revised values are posted.

**Acetaldehyde
Acrolein
Arsenic
Formaldehyde
Manganese
Mercury**

Appendix E. Application of Toxicokinetic Modeling and Analysis of Toxicokinetic Differences by Age at Exposure.

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E.1 Applications of Toxicokinetic Analysis and PBPK Modeling

Physiologically based pharmacokinetic (PBPK) models consist of a series of equations representing bodily compartments (e.g., liver, lung, highly perfused tissues, less perfused tissues), fluid flows, and biotransformation reactions that represent real biological tissues and physiological processes in the body. The models simulate the time course of absorption, distribution, metabolism, and excretion (ADME) of chemicals that enter the body.

PBPK models may also provide a scientific methodology for determining duration adjustments, and for making interspecies extrapolations, while evaluating additional uncertainty related to interspecies differences and intraspecies variability. PBPK modeling can be used to support route-to-route extrapolation, as in the situation where it is necessary to predict the toxicity of a substance from an inhaled dose from the results of an experiment in which a test species was exposed by the oral route in order to develop an inhalation REL.

A range of modeling approaches can be used to characterize exposures and resulting delivered doses to target tissues. The dose of the parent compound or of a toxic metabolite at a target tissue, rather than the applied dose, may provide a better basis for determining a NOAEL or point of departure (POD) in a benchmark dose assessment, especially where toxicokinetic features such as saturation of metabolism complicate and obscure the underlying toxicodynamic dose-response relationship. The relevance of a specific modeling approach depends on the physical and chemical characteristics of the material (e.g., stable or reactive gases, particulate matter, lipophilic or water-soluble compounds), the method and route of exposure or delivery, and the toxicities under consideration (e.g., contact site or systemic toxic effects) (U.S.EPA, 1994a; Andersen and Jarabek, 2001; Overton et al., 2001; U.S.EPA, 2004). All of these approaches attempt to improve the understanding of the dose-response relationship by describing and estimating the dose delivered to the relevant areas of the body, and can provide a reduction in uncertainty and an improved scientific basis for the risk value.

In the ideal case, where sufficient data are available, OEHHA will apply PBPK modeling to the dose-response assessment, instead of the default application of the pharmacokinetic portions of the intraspecies and interspecies uncertainty factors, and in preference to the default human equivalent concentration (HEC) procedure for applying interspecies dosimetric adjustments, as described in section 4 of this document. However, it must be recognized that in most cases sufficient data are not available to allow PBPK modeling to be used in developing a REL. Even when pharmacokinetic models for a compound and route of interest are identified it may not always be advisable to rely on these, for example, when independent data separate from those used to calibrate a model are not available to check that model's predictive validity.

OEHHA has explored PBPK modeling to evaluate the adequacy of default uncertainty factors, in particular the previously applied default of 10 for intraspecies variability, i.e. interindividual variability in the human population. We have used PBPK modeling to gain insight into the range of interindividual variability, focusing on the differences among infants, children and adults. Such information is useful in determining whether risk assessment procedures are sufficiently protective of infants and children. We also review available studies that have examined kinetic differences at age of exposure using information on pharmaceuticals. (For ethical reasons

studies of kinetics in children are largely confined to pharmaceuticals, where the subjects may receive some benefit from the exposure to the drug.) These studies demonstrate differences in clearance of chemicals by age, which in several cases exceed the previously used default factor of $\sqrt{10}$ for toxicokinetic variability in the human population.

The purposes of this appendix are:

1. To document published literature, and present our investigations using modeling approaches, which inform the selection of a default value for the intraspecies toxicokinetic uncertainty factor (UF_{H-k}) which is reasonably protective of members of the general population, specifically including infants and children.
2. To explore the use of toxicokinetic models for interspecies extrapolation, when sufficient data are available to use this approach as an alternative to the existing HEC adjustment for dosimetry (US EPA, 1994) and/or the application of an uncertainty factor (UF_{A-k}) to allow for the uncertainty in interspecies extrapolation of toxicokinetics.
3. To explore and present various toxicokinetic models as examples which may be useful in REL development in those cases where sufficient data are available to use this approach rather than merely applying assumed (default) uncertainty factors. Detailed results and model codes are presented to facilitate the application of these examples.

E.2 Published Summaries of Age-Dependent Toxicokinetics

OEHHA has reviewed published pharmacokinetic analyses which may be of interest in illustrating the applicability of these methods to specific problems in risk assessment identified in the main part of this document, and in particular to the question of how different the kinetics of toxicants may be in infants and children relative to adults (e.g., Renwick and Lazarus, 1998; Dorne et al., 2001). This is a subset of the larger question of how extensive is the inter-individual variability in kinetics for the human population as a whole, but one which is of particular concern in relation to the mandate under SB 25 to determine whether existing risk assessment practices (which have previously focused primarily on effects in adults) are sufficiently protective of the young. The objectives of this literature review were both to identify examples of successful analyses relevant to noncancer risk assessment, and secondly to assess whether a sufficient number and range of examples have been studied to inform the selection of uncertainty factor values in the general case where compound-specific and age-specific information or kinetic models are not available.

E.2.1 Age-dependent Toxicokinetic Parameters.

The following tables show published values, excerpted from kinetic studies of pharmaceuticals, of a variety of kinetic parameters where age-dependent differences have been observed. The examples in the literature of analyses of the effects of age on disposition of chemicals deal with drugs; ethical concerns generally rule out clinical studies of the effect of toxic pollutants or industrial chemicals on juvenile subjects. But the pharmacokinetics of drugs are studied as part of the requirements for registration by the US FDA (and similar regulatory authorities in other countries). In addition, the use of drugs in pediatrics has resulted in information on their disposition in younger patients. These data provide a foundation for evaluating chemical disposition by age at exposure for airborne toxicants as well as drugs, since the metabolic pathways responsible for activation and clearance of these toxicants are in general the same as those responsible for handling drugs. Some discussion of these data and age-specific characteristics of the underlying processes of absorption, distribution, metabolism and excretion appears in Section 3.1 of the main document. The principal pharmacokinetic terms used are: clearance (CL) the quantity of blood from which the chemical has been removed or cleared per unit body weight or surface area per unit time; the half-life ($T_{1/2}$) of the chemical in the blood or the time required to reduce the chemical blood concentration by half as a result of excretion, metabolism etc.; the area under the chemical blood concentration times time curve (AUC), a measure of the duration of internal dosimetry; and the maximum chemical concentration in the blood (C_{max}), a measure of the intensity of exposure. Depending on the mode of action (MOA) either duration or intensity may be more closely related to the toxic effects observed. Similar metrics may also apply to key metabolites.

TABLE E.2.1. COMPOUNDS SHOWING REDUCED ELIMINATION IN INFANTS AND/OR CHILDREN¹.

Compound	Parameter	Age	Value
Morphine	CL (mL/kg-min)	<7 d	8.7 ± 5.8
		7d – 2 mo	11.9 ± 5.1
		2 – 6 mo	28.0 ± 8.9
Paracetamol	CL (L/kg-hr)	< 10 d	0.15
		1-12 mo	0.37
Pipecuronium	CL (mL/kg-min)	6.8 mo	1.5
		4.6 yr	2.3
		Adult (42 yr)	2.5
Desacetylcefotaxime	T _{1/2} (hr)	Neonate	9.4
		Infant	2.1
		Adult	1.6
Ganciclovir	CL (mL/kg-min)	2-50 d	3.4
		Adult	4.2
Alfentanil	CL (mL/kg-min)	Newborn	3.2
		Newborn	1.5-1.7
		Adult	6.0
Trichloroethanol (from chloral hydrate)	T _{1/2} (hr)	Neonate	35
		Adult	8
Trichloroethanol glucuronide	T _{1/2} (hr)	Neonate	30
		Adult	7
Digoxin	CL renal (mL/1.73 m ² -min)	1 week	32 ± 7
		3 mo	66 ± 30
		12 mo	88 ± 43

¹ Adapted from Renwick and Lazarus (1998): CL = Clearance; T_{1/2} = Half life.

TABLE E.2.2. CYP1A2 MEDIATED METABOLIC PARTIAL CLEARANCES IN HEALTHY VOLUNTEERS

Drug	CYP1A2 Pathway	Number of subjects	Weighted Mean mL/kg-min	Weighted SD	CV
<i>p.o. administration</i>					
Caffeine	1-N-Demethylation	5	0.24	0.07	29.2
Caffeine	3-N-Demethylation	5	1.84	1.08	58.7
Caffeine	7-N-Demethylation	5	0.08	0.02	25.0
Theophylline	1-N-Demethylation	13	0.21	0.11	52.4
Theophylline	3-N-Demethylation	13	0.16	0.10	62.5
Theobromine	1-N-Demethylation	23	0.20	0.09	42.5
Paraxanthine	7-N-Demethylation	6	0.89	0.26	29.2
<i>i.v. administration</i>					
Theophylline	1-N-Demethylation	22	0.16	0.06	37.4
Theophylline	3-N-Demethylation	6	0.19	0.06	31.1
R-Warfarin	6-Hydroxylation	6	0.26 mL/min	0.15	59.1

¹ Adapted from Dorne et al. (2001): p.o. = oral; i.v. = intravenous; SD = standard deviation; CV = coefficient of variation. Weighted SD = standard deviation weighted by coefficient of variation

TABLE E.2.3. INTER-INDIVIDUAL VARIATION IN TOXICOKINETICS OF CAFFEINE IN HEALTHY VOLUNTEERS¹.

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV
<i>p.o. administration</i>				
CL mL/kg-min	163	1.20	0.43	35.7
CL mL/min	10	142	79.1	55.7
AUC/dose ng/mL-hr	15	17,200	9,490	55.2
Cmax/dose ng/mL	67	1,780	435	24.1
<i>i.v. administration</i>				
CL mL/kg-min	20	1.97	0.92	46.8
AUC/dose ng/mL-hr	8	14,050	5,760	41.0

¹ Adapted from (Dorne et al., 2001). P.o. = oral; i.v. = intravenous; CL = Clearance; AUC = area under the blood concentration x time curve; Cmax = maximum blood concentration; SD = Standard Deviation; CV = Coefficient of Variation.

TABLE E.2.4. TOXICOKINETICS OF CAFFEINE: COMPARISONS BETWEEN HEALTHY ADULTS AND DIFFERENT SUBGROUPS.¹

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV	Ratio S/H	Ratio CV
<i>Smokers</i>						
CL mL/kg-min p.o.	38	2.62	0.93	35.5	0.46	0.99
Cmax/dose ng/mL	6	1,750	610	34.9	0.98	1.43
<i>Pregnant women</i>						
CL mL/kg-min p.o. 36 wk	6	0.72	0.38	52.8	1.67	1.48
CL mL/kg-min p.o. 38 wk	8	0.39	0.18	46.2	3.08	1.29
Cmax/dose ng/mL	8	2,018	1,460	72.3	1.13	2.95
<i>Elderly</i>						
CL mL/kg-min i.v.	18	1.43	0.50	35.2	1.96	0.75
AUC/dose ng/mL-hr p.o.	8	12,400	5,920	47.9	0.78	0.90
Cmax/dose ng/mL	8	370.4	64.5	17.4	0.21	0.71
<i>Children</i>						
CL mL/kg-min p.o.	3	1.79	0.57	31.8	0.67	0.89
<i>Infants</i>						
CL mL/kg-min p.o.	4	1.00	1.04	104	1.20	2.91
<i>Neonates</i>						
CL mL/kg-min p.o.	5	0.127	0.023	18.1	9.45	0.51
CL mL/kg-min i.v.	31	0.14	0.06	42.2	13.9	0.90
Cmax/dose ng/mL	16	1280	1000	7.8	0.72	0.32
<i>Liver disease</i>						
CL mL/kg-min p.o.	81	0.62	0.61	98.9	1.96	2.77
CL mL/kg-min i.v.	45	1.00	0.48	48.3	1.96	1.03
Cmax/dose ng/mL	27	1700	283	16.6	0.96	0.68
<i>Renal disease</i>						
CL mL/kg-min i.v.	5	0.78	0.35	44.6	2.53	0.95

¹ Adapted from (Dorne et al., 2001): p.o. = oral; CL = Clearance; Cmax = maximum blood concentration; AUC = area under the blood concentration x time curve; SD = standard deviation; CV = coefficient of variation; Ratio S/H = ratio between subgroup and healthy volunteers; Ratio CV= ratio between the variability of the subgroup and the healthy volunteers..

TABLE E.2.5. INTERINDIVIDUAL VARIATION IN TOXICOKINETICS OF THEOPHYLLINE IN HEALTHY VOLUNTEERS¹

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV
<i>p.o. administration</i>				
CL mL/kg-min	106	0.60	0.38	41.4
AUC/dose ng/mL-hr	22	24,300	5,790	23.8
Cmax/dose ng/mL	32	4,600	842	18.2
<i>i.v. administration</i>				
CL mL/kg-min	100	1.00	0.29	29.2
AUC/dose ng/mL-hr	14	51,900	9,840	19.0

¹ Adapted from (Dorne et al., 2001): p.o = oral; i.v. = intravenous; CL = clearance; AUC = area under the blood concentration x time curve; Cmax = maximum blood concentration; SD = standard deviation; CV = coefficient of variation.

TABLE E.2.6. TOXICOKINETICS OF THEOPHYLLINE: COMPARISONS BETWEEN HEALTHY ADULTS AND DIFFERENT SUBGROUPS

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV	Ratio S/H	Ratio CV
<i>Smokers</i>						
CL mL/kg-min p.o.	15	1.15	0.30	25.9	0.79	0.63
AUC/dose ng/mL-hr p.o.	6	12,200	4,850	39.8	0.50	1.67
CL mL/kg-min i.v.	8	0.72	0.17	23.6	1.39	0.81
AUC/dose ng/mL-hr i.v.	14	32,900	10,300	31.3	1.58	1.65
<i>Pregnant women</i>						
CL mL/kg-min p.o.	14	0.83	0.22	25.8	1.20	0.88
<i>Elderly non-smokers</i>						
CL mL/kg-min p.o.	19	0.73	0.11	15.0	1.24	0.36
CL mL/kg-min i.v.	41	0.72	0.32	45.2	1.39	1.55
C _{max} /dose ng/mL	19	2,700	408	14.3	0.59	0.79
<i>Children</i>						
CL mL/kg-min p.o.	3	1.79	0.57	31.8	0.67	0.89
<i>Infants</i>						
CL mL/kg-min p.o.	33	1.00	0.58	58.1	0.90	1.40
C _{max} ng/mL	20	2,610	990	37.9	0.57	2.08
CL mL/kg-min i.v.	43	0.46	0.17	36.1	2.16	1.24
<i>Neonates</i>						
CL mL/kg-min i.v.	220	0.35	0.11	31.1	2.87	0.94

TABLE E.2.6. TOXICOKINETICS OF THEOPHYLLINE: COMPARISONS BETWEEN HEALTHY ADULTS AND DIFFERENT SUBGROUPS

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV	Ratio S/H	Ratio CV
<i>Liver disease</i>						
CL mL/kg-min p.o.	35	0.38	0.16	42.7	2.36	1.03
CL mL/kg-min i.v.	68	0.52	0.40	78.4	1.94	2.69
<i>Renal disease</i>						
CL mL/kg-min i.v.	31	0.97	0.33	34.3	1.03	1.18

¹ Adapted from (Dorne et al., 2001): p.o = oral; i.v. intravenous; CL = clearance; AUC = area under the blood concentration x time curve; Cmax = the maximum blood concentration; SD = standard deviation; CV = coefficient of variation; Ratio S/H = ratio between subgroup and healthy volunteers; Ratio CV = ratio between the variability of the subgroup and the healthy volunteers.

TABLE E.2.7. INTERINDIVIDUAL VARIATION IN TOXICOKINETICS OF THEOBROMINE AND PARAXANTHINE IN HEALTHY VOLUNTEERS AFTER ORAL ADMINISTRATION¹

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV
<i>Theobromine</i>				
CL mL/kg-min	45	1.02	0.33	42.8
AUC/dose ng/mL-hr	6	12,738	5,474	43.0
Cmax/dose ng/mL	3	1,478	378	21.4
<i>Paraxanthine</i>				
CL mL/kg-min	6	1.71	0.30	17.6

¹ Adapted from (Dorne et al., 2001): SD = standard deviation; CV = coefficient of variation; CL = Clearance; AUC = area under the blood concentration x time curve; Cmax = maximum blood concentration.

TABLE E.2.8. PATHWAY-SPECIFIC TOXICOKINETIC UNCERTAINTY FACTORS FOR CHILDREN AFTER ORAL EXPOSURE AND NEONATES AFTER INTRAVENOUS EXPOSURE¹.

Pathway	Nc	Ns	N	LN 95%	LN97.5%	LN99%
<i>Children</i>						
CYP1A2	1	12	195	1.4	1.6	1.8
CYP2C19	1	1	25	5.4	6.9	9.0
CYP2D6	1	2	173	22	31	45
CYP3A4	3	3	16	1.4	1.6	1.8
Hydrolysis	3	3	43	1.5	1.7	2.0
Glucuronidation	5	13	131	1.3	1.4	1.5
Glycine conjugation	1	1	20	1.5	1.6	1.8
NAT	1	1	25	2.0	2.2	2.5
NAT	1	1	25	2.2	2.3	2.4
Renal excretion	6	9	126	1.2	1.3	1.5
<i>Neonates</i>						
CYP1A2	2	7	251	11	12	14
CYP3A4	2	5	35	8.1	9.7	12
Glucuronidation	4	14	94	8.6	10	12
Glycine conjugation	2	1	10	25	26	28
Renal excretion	7	33	656	2.8	3.0	3.4

¹ Adapted from (Dorne et al., 2005). Nc = number of compounds; Ns = number of studies; N = number of subjects; LN = pathway related uncertainty factors for upper percentiles of the lognormal distributions. These potential uncertainty factors would be equated with the UF_{H-k} described in the main document. In this case the pharmacokinetic component of the interindividual variability is presented as upper percentiles of lognormal distributions of fitted data by metabolic pathway. It illustrates that a given percentile may not give an adequate level of protection depending upon the pathway critical to the toxic effect.

The studies summarized above in addition to those discussed in the text of the main document indicate that the uncertainty sub-factor to account for toxicokinetic variability in the human population is not sufficient to protect neonates and possibly infants and children. For example, in Table E2.8 above Dorne *et al.* (2005) analyze data on kinetic variability in neonates and healthy adults for five metabolic pathways (CYP1A2, CYP3A4, glucuronidation, glycine conjugation, and renal excretion). In all cases except renal excretion, uncertainty factors derived to cover 95 percent of the population, based on lognormal distributions of the study data, exceeded the default value of 3.16. The 95% values ranged from 2.8 to 25. If a more health protective criterion of 99% coverage is adopted, the range of factors would be 3.4 to 28. Even older children showed a significant lack of coverage at the 95% level with the CYP2C19 and CYP2D6 pathways with factors of 5.4 and 22, respectively, albeit with limited data. While not listed in Table E2.8, Dorne *et al.* (2005) note that limited data for CYP2D6 in two neonates showed internal doses 19- and 33-fold higher than in healthy adults. Taken together with the data in older children this may indicate a general greater susceptibility of infants and children to toxicants using the CYP2D6 pathway.

E.2.2 Published PBPK Models of Inter-individual Variability

The following section describes and reviews a selection of specific published models that have been used to address the sources and extent of inter-individual variability (between variously sensitive subpopulations of adults and between adults and children).

Pelekis *et al.* (2001) used a physiological model to derive adult and child pharmacokinetic uncertainty factors for selected volatile organic compounds (VOCs). The chemicals modeled were dichloromethane (DCM), tetrachloroethylene (PCE), toluene (TOL), m-xylene (XYL), styrene (ST), carbon tetrachloride (CATE), chloroform (CHLO), and trichloroethylene (TCE). Adult models of low (50 kg) and high (90 kg) body weight were compared with a 10 kg-based child model. Fat contents varied from 51 percent for the 90 kg adult model to 17 percent for the 10 kg child. Ventilation:perfusion ratios varied from 0.76 (50 kg) to 1.38 (10 kg). Fractional liver flows (of cardiac output) ranged from 0.11 (50 kg) to 0.34 (90 kg). All PBPK models were flow-limited with exposure by inhalation, arterial circulation to Fat, Slowly Perfused, Rapidly Perfused and Liver model compartments, metabolism in the Liver, and combination of compartment outputs in venous blood. The arterial and venous bloods were not explicitly modeled. Also no VOC metabolites were specifically modeled. A range of physiological parameters (blood:air and tissue:blood) were used for each body model and the eight VOC chemicals based on literature values.

Simulations involved exposure to one ppm VOC and estimation of arterial and venous blood concentrations (C_A , C_V), and tissue concentrations (C_i) after 30 days continuous exposure. A comparison of the two adult models (Adult high body weight and fat content versus Adult low body weight and fat content) shows relatively few significant departures from unity for the dose metrics estimated. CATE ratios ranged from 2.85 ($C_{\text{rapidly perfused}}$) to 1.71 (C_{liver}). DCM ranged from 0.29 (C_{liver}) to 1.04 ($C_{\text{arterial blood}}$). Comparisons of the Adult high/Child average from the PBPK model show some larger differences. For the C_{liver} dose metric the PBPK models predicted the following Adult/Child values: ST (0.033), XYL (0.037), TCE (0.061), DCM (0.092), CHLO (0.11). These model predictions would indicate up to a 30-fold higher concentration of the VOC chemicals in child liver than in adult liver via the inhalation route.

This is a useful approach, involving important environmental toxicants and a relevant exposure route. However, it is limited since the models and dose metrics employed address only the parent compounds. Relevant toxic effects may in fact be more closely related to the tissue dosimetry of metabolites, which were not specifically modeled. In addition, the use of a single child body weight is probably insufficient to assess the full range of physiological variability throughout development, particularly in the neonatal period. It is worth noting, however, that the higher concentrations of the VOCs in a child's liver might be expected to result in higher peak concentrations of metabolites of those compounds in the liver, and possibly also in other tissues.

Jonsson and Johanson (2001) used a PBPK model of DCM to study the influence of metabolic polymorphism on cancer risk estimates. A flow-limited PBPK model was comprised of lung, perirenal fat, subcutaneous fat, working muscle, resting muscle, rapidly perfused tissue, and liver. Exposure was by inhalation; metabolism by glutathione *S*-transferase T1 (GSTT1) and mixed function oxidases (MFO) occurred in lung and liver. The model was fitted to published toxicokinetic data on 27 male volunteers exposed to 250-1000 ppm DCM. Excess cancer risk resulting from lifelong exposures to 1-1000 ppm DCM was estimated using Bayesian and Monte Carlo methods. The relevant dose metric used was DNA-protein cross-links (DPX) in liver, which was derived from the amount of DCM metabolized via the GSTT1 pathway. Data on the frequencies of the three GSTT1 genotypes (0/0, +/0, +/+) in the Swedish population were used in the analysis. The results indicated large inter-individual variability in estimated risk, even within the two metabolizing groups (+/0, +/+). The mean risk in +/+ individuals was 50 –71 percent higher than for the general population. The results also indicate that the 3.16 factor for PK human variability may not be adequately protective for noncancer endpoints. The authors estimated that five percent of the individuals in the Swedish population would not be covered by a factor of 2.7-3.3 away from the mean (calculated from the 95 percent upper confidence limit in Table 7 of Jonsson and Johanson. One percent of individuals would not be covered by a 4.2-7.1 factor (from 99 percent upper confidence interval (UCL) in Table 7 of the published paper) and 0.1 percent by a 7.3-14.5 factor (99.9 percent UCL in Table 7 of the published paper).

These investigators noted that:

“These results support the cautionary point of Renwick and Lazarus (1998) that an intraspecies uncertainty factor higher than 3.16 should be considered for substances that, like DCM, have pronounced bioactivation polymorphism and therefore a flatter distribution than expected from unimodal log-normal distribution.”

They also note that the most sensitive individuals possess a combination of high GSTT1 activity and low metabolic capacity for the competing MFO pathway, which is likely mediated by CYP2E1. CYP2E1 is highly inducible, a factor that would contribute to inter-individual variability. While this paper addresses risk of DCM exposures in adults, the conclusions may apply even more strongly to infants and young children where inhalation may result in greater exposures per unit body weight and metabolic systems, particularly the MFO enzymes, are still under varying stages of development.

Ginsberg et al. (2004b) used PBPK modeling to evaluate the difference between neonates and adults in the pharmacokinetic handling of theophylline and caffeine. Both chemicals are largely metabolized by CYP1A2: caffeine to theophylline, theobromine, and paraxanthine; and

theophylline to 3-methylxanthine, 1-methyluric acid, and 1,3-dimethyluric acid. In neonates theophylline is also “back” methylated to caffeine. Caffeine is cleared much more slowly in neonates than in adults (0.15 vs. 1.57 mL/kg-min, respectively); theophylline is also cleared somewhat more slowly in neonates (0.35 vs. 0.86 mL/kg-min, respectively). The PBPK models, which used biochemical parameters scaled up from *in vitro* data, were able to simulate the large differences in half-life and clearance rates between adults and neonates for these chemicals. This included the faster clearance of theophylline versus caffeine in neonates. It was concluded that the extra “back” methylation path in neonates, while relatively small in percentage terms (i.e., percent of theophylline metabolite excreted in urine), could largely account for the differences seen between adults and neonates. The results emphasize the importance of different metabolic pathways operating in neonates and infants during development.

Price et al. (2003) used age-specific regressions for physiological parameters in a PBPK model for inhaled furan. The model contained compartments for brain, slowly perfused tissues, fat, liver, and the remainder of the body. The ages modeled were six, ten, 14 years and adult. It was assumed that furan was a rapidly metabolized VOC in all age-specific models in that the rate of metabolism was limited by blood flow to the liver. In 36-hour simulations involving a 30-hour exposure to 1 µg/L furan, the authors observed up to 50% higher concentrations of furan in the blood and of furan metabolites in the liver of children compared with adults. These are relatively small differences. Younger ages, which show larger differences in metabolic enzyme profiles and other kinetic factors, were not modeled. It is also questionable whether or not metabolism is truly flow-limited at the younger ages.

Gentry et al. (2003) evaluated the impact of pharmacokinetic differences on tissue dosimetry during pregnancy and lactation with a PBPK modeling approach. Six chemicals representing a variety of physiochemical properties were selected for study: isopropanol, vinyl chloride, methylene chloride, tetrachloroethylene, nicotine and TCDD. These chemicals not only provided differences in volatility, lipophilicity, and water solubility, but also different pharmacokinetic features including metabolic production of stable or reactive metabolites in the liver and competing pathways of metabolism. Model predicted changes in dosimetry during pregnancy were largely the result of the development of metabolic pathways in the fetus or changes in the tissue composition in the mother and fetus. For example, the fetal activity of alcohol dehydrogenase (ADH) was undetectable prior to three months gestation but rose to 0.23 of the adult value at birth. Generally, predicted blood concentrations were lower in the neonate during lactation than in the fetus during gestation. This decrease was relatively slight for TCDD but four orders of magnitude for vinyl chloride. Predicted fetal/neonatal exposures versus maternal exposures ranged from two fold greater (TCDD) to several orders of magnitude lower (isopropanol). The results of this study are in general agreement with reports on pharmaceuticals indicating that the greatest child/adult pharmacokinetic differences are seen in the perinatal period (Renwick et al., 2000; Ginsberg et al., 2002).

Pelekis et al. (2003) estimated intraspecies adult and child pharmacokinetic uncertainty factors using a probabilistic framework applied to a PBPK model of dichloromethane. A number of variates were included as distributions in the analysis including: age, body weight, inhalation rate, activity level, liver weight, fat weight, blood volume and blood flow to the liver and biochemical parameters. The authors found that the tissue dose ratios (UF_{H-TK} , the ratio of the 95th percentile to the 50th percentile) varied only between 1.88 and 1.98 within the population

depending on age and tissue. Many of the assumptions employed in this study are open to question, particularly the assumption that both Phase I and Phase II metabolic elimination paths are ten times greater in adults than in infants on a body weight basis. First order elimination by Phase II metabolism usually scales to the -0.3 power of body weight, which gives an adult:infant difference closer to two-fold than ten-fold on a body weight basis. Without specific data on metabolic elimination of DCM in infants and children a health protective assumption should be used.

Sarangapani et al. (2003) used a PBPK model to evaluate the impact of age- and gender-specific lung morphology and ventilation rate on the inhalation dosimetry of model toxicants. The toxicants were selected to represent category one (irreversibly reactive; ozone), category two (nonreactive water soluble; isopropanol) and category three (nonreactive water insoluble; styrene, vinyl chloride, perchloroethylene) gases. Ten PBPK models were run for males and females from 1 month of age to 75 years. Model structure was similar to Sarangapani et al. (2002) but simplified to three main respiratory tract compartments of extra thoracic (ET), tracheobronchial (TB), and pulmonary (PU) with the ET and TB each divided into three subcompartments from airway lumen to circulating blood. In addition to different anatomical and physiological values for the age and gender models, biochemical parameters were also varied with age (e.g., relative activity of CYP2E1 26.1% at 1 month to 90% at 15 yr; and alcohol dehydrogenase (ADH) 24.9% at 1 month to 83.6% at 25 yr). Dose metrics evaluated included parent and metabolite concentrations in blood, liver and lung. According to the author's analysis, only two chemicals showed higher dose metrics in children than in adults (25 yr model). For the isopropanol model with CYP2E1 and ADH metabolism, the blood concentration of the metabolite acetone was 8-fold higher in 1 month male and 11-fold higher in 1 month female than in respective 25 yr models. Ozone PU extraction per unit surface area was 8.6- to 12.5-fold higher in 1 month male and female models than in respective 25 yr models. The results of this study are in general agreement with other PBPK studies of children. "The age of greatest concern is clearly the perinatal period. The most important factor appears to be the potential for decreased clearance of toxic chemicals in the perinatal period due to immature metabolic enzyme systems, although this same factor can also reduce risk from the reactive metabolites during the same period." Although this model is simpler in structure than the Sarangapani et al. (2002), it is less well described and it has been difficult to verify the predictions for styrene, isopropanol and ozone. In our hands the ozone model gave the closest agreement of child/adult values of 13.1 and 19.4 for PU Cmax in one month/25 yr males and females, respectively.

Clewell et al. (2004) evaluated age- and gender-specific differences in tissue dosimetry with a predictive PBPK life-stage model. The model was implemented for six environmental chemicals with various physicochemical and biochemical properties and modes of toxic action. Isopropanol was studied by oral, dermal and inhalation routes of exposure with blood concentrations of parent and acetone metabolite as dose metrics of interest. The other chemicals studied were vinyl chloride, dichloromethane, tetrachloroethylene, TCDD, and nicotine. Each of these was evaluated by the oral route with dose metrics of blood concentrations of parent and either concentration of metabolite in blood or rate of parent metabolism/kg of liver volume. The dose metrics at external exposure levels of 1 ppb (inhalation) and/or 1 $\mu\text{g}/\text{kg}\cdot\text{d}$ were estimated continuously, as well as at specific ages of 1, 3, and 6 months, and 1, 5, 10, 15, 25, 50, and 75 years. The results were summarized in age-group ranges of birth to 6 months, 6 months to 5

years, 5 to 25 years, and 25 to 75 years. In general, predictions of average pharmacokinetic dose metrics for a chemical across the life stages were within two-fold, although larger transient variations were predicted, especially during the neonatal period. For the sole chemical investigated by the inhalation route, isopropanol, the highest dose ratio relative to 25 year old was 2.0 for the parent and 3.9 for the metabolite, both in the birth to 6 months of age grouping. The respective ratios for oral (drinking water) and dermal isopropanol exposures were equal or lower than those for the inhalation route for all groups up to 25 years of age. The authors concluded that the most important age-dependent pharmacokinetic factor was the potential for decreased clearance of a toxic chemical in the perinatal period due to the immaturity of xenobiotic metabolism. They note that this same factor may also reduce the production of reactive metabolites. A limitation of this study is that only one compound was evaluated by inhalation. Vinyl chloride, dichloromethane, and tetrachloroethylene could also have been evaluated by the inhalation route.

A preliminary conclusion based on this limited modeling was that a PK UF of 10 would account for inter-individual differences including infants and children for this set of compounds. This is larger than the standard assumption that an uncertainty factor of $\sqrt{10}$ is sufficient to account for inter-individual differences in human pharmacokinetics.

E.3 OEHHA Studies using PBPK Modeling to Assess Interindividual and Interspecies Differences:

Pilot study of ethylbenzene, vinyl chloride, toluene, styrene/styrene oxide, naphthalene/naphthalene oxides and ten aliphatic aldehydes.

As noted previously, OEHHA has an interest in applying PBPK modeling, when data permit, to replace the pharmacokinetic portion of the intraspecies safety factor. The approach used in applying PBPK modeling to assessing children's environmental health risks has been similar to that of Pelekis et al. (2001) noted above. We have used a case study approach using published PBPK models of selected environmental toxicants, adjusted anatomical and physiological parameters to simulate infant and child ages from newborn to 18 years, and compared these with adult models. In these models we have scaled metabolic parameters as a function of body weight. In addition to modeling age-related differences in human pharmacokinetics, the models were run with age-appropriate parameter values for rats in order to explore interspecies comparisons and, specifically, the extent to which age-related differences in the rat resemble those anticipated in humans. A low and high concentration was modeled for each chemical, and tissue doses were compared between rodent and human models for several of the chemicals.

Where possible we have focused on dose metrics involving toxicologically relevant metabolites. The chemicals selected for this pilot study were: ethylbenzene, vinyl chloride, toluene, styrene/styrene oxide, naphthalene/naphthalene oxides, and formaldehyde. There are PBPK models available for these chemicals for both the rat and human. Several aliphatic aldehydes have been measured in ambient air monitoring studies (Uebori and Imamura, 2004). We modeled the straight chain aliphatic aldehydes from acetaldehyde to decanal ($R_n\text{CHO}$, $n = 1-9$). The model output in these investigations is the animal to human ratios for blood concentrations. PBPK estimates are bound to be highly chemical dependent and strongly influenced by the metric chosen, blood/air and fat/blood partition coefficients, fractional tissue flows, metabolic parameters, and other factors.

Initial findings by this approach were given at the Children's Environmental Health Symposium (Brown, 2001). Of the seven chemicals studied with oral and inhalation exposures (vinyl chloride, DCM, TCE, chloroform, arsenic, butadiene, and naphthalene) three chemicals showed greater internal doses in children compared to adults: DCM, TCE, and butadiene, all via the inhalation route. A preliminary conclusion based on this limited modeling was that a UF_{H-k} of 10 would account for inter-individual differences including infants and children for this set of compounds.

In follow up work we have attempted to standardize the modeling approach for different chemicals as much as possible and focus on inhalation exposures only. For example, we have employed several of the age specific regressions for model parameters suggested by Price et al. (2003). Also in a few cases we have used more elaborate lung modeling, for example as proposed by Sarangapani et al. (2002) for styrene and styrene oxide, as opposed to the simpler lung modeling of Evelo et al. (1993) for butadiene. Two or three similar child models were used with differing fractional tissue flows more heavily weighted towards rapidly perfused tissues than in adults. A summary of the results obtained using this modified approach is given in Table E.3.13. Child/adult values around two are due solely to scaling and indicate little difference. In Table E.3.13 chloroform and furan exhibited little difference under the modeling conditions employed. The other chemicals showed child/adult differences for various metrics ranging from about three to 120. They appeared to be in increasing order as follows: naphthalene/naphthalene oxide; PCE; styrene/styrene oxide; vinyl chloride; MTBE; TCE; BaP; DCM; and butadiene.

It should be emphasized that this analysis focuses on those metrics that show increases in child/adult values and the highest of these across the age-specific models simulated, since we are trying to test whether the traditional UF_H is adequate across all chemicals. In a few cases, metrics showed lower values in children than in adults, i.e. child/adult values < 1 . These metrics have not been included in the tables below.

E.3.1 Materials and Methods

Prior to our simulation study, we evaluated the purpose, structure, mathematical representation, parameter estimation (calibration), computer implementation and predictive validity of PBPK models to be used in health risk assessment.

E.3.1.1 Mathematical representation

Model structures were chosen to represent the category of gas (1, 2 or 3) traditionally used in dosimetric adjustments across species. The type of PBPK model used by OEHHA is dependent on the physicochemical characteristics and toxicokinetic properties of the agent in question. Broadly speaking, gaseous agents fall into one of three categories, based on solubility or reactivity with tissues, which affects how deep into the respiratory tract (RT) the chemicals penetrate, and where toxicity occurs (local or systemic).

- Category 1 gases interact mainly at the site of contact: either the nasal or respiratory tracts (RT) as portals of entry.

- Category 2 gases have effects both locally, on the RT, and systemically.
- Category 3 gases mainly have remote systemic effects.

E.3.1.2 Parameter estimation (calibration)

Initial comparisons were limited to rat/human data and in the absence of parameter values, scaled for adults and immature animals/children. Immature rats and human children were modeled following the recommendations of Clewell et al. (2004) and Price et al. (2003), respectively. Metabolic parameters (V_{max}) were scaled to the $3/4$ power of body weight. Note that known differences in cytochrome P450 and Phase II enzymes (beyond those described by body weight scaling), which are broadest when comparing the neonate with an adult, are not included in this modeling (see discussion above of Sarangapani et al. 2003 where metabolic differences during development are incorporated into PBPK modeling for CYP2E1 and ADH mediated chemicals). All simulations were for resting animals with alveolar ventilation equaling cardiac output.

E.3.1.3 Computer implementation

Each model was constructed from published code or equations and transcribed into Berkeley Madonna code and model performance was tested for accuracy. Model simulations were conducted using Berkeley Madonna software (www.berkeleymadonna.com, version 8.0.1).

E.3.1.4 Predictive validity

For agents in Category 1, OEHHA has examined a 4-compartment RT model of the type described by Sarangapani et al. (2004) that is similar to a 3-compartment default model of the RT recommended by Hanna et al. (2001), with uptake defined by regional mass transfer coefficients. Depending on the agent being studied, for some Category 1 gases, OEHHA explored nasal models as described by Frederick et al. (1998) and Georgieva et al. (2003).

E.3.1.4.1 Category 1: nasal model for formaldehyde

- A version of a published rat nasal model for formaldehyde was adjusted to accommodate human conditions (Georgieva et al., 2003). This is a nose only model with no body. The nasal region is divided into two parts, essentially anterior and posterior, and each compartment consists of about 25 layers from air to bone. This is a diffusion-limited model using average flux values determined by computational fluid dynamics (CFD) methods (Georgieva et al., 2003). The endpoint is DPX (DNA-protein cross-links pmol/mg DNA), but HCHO tissue concentrations (pM) and DPX-AUC (pmol min/mg DNA) are also available. Diffusivity parameters are for the hydrated form of formaldehyde, methylene glycol. DPX values with this whole nose model for the rat are about one-fourth those which focus on flux hot spots within the nasal region.

In order to extend the adult model to immature rats and children we assumed:

- (1) that the mucosal nasal surface was directly proportional to body weight;
- (2) that saturable metabolism V_{max} scaled with the $3/4$ power of body weight;

- (3) that the first order rates of binding, loss, and DPX loss scaled with the -0.25 power of body weight; and
- (4) that the average flux vs. air flow rate could be interpolated from the tables and figures in Kimbell et al. (2001b). The following relations were used to determine the formaldehyde average flux in units of $\text{pmol}/\text{mm}^2/\text{hr}/\text{ppm HCOH}$ (y in the equations below):

Human: $y = 5.0 \times \text{IF}^{1.7281}$, where IF = inspiratory flow rate in L/min;
 Rat: $y = 0.7 \times \text{IF}^{1.05}$, where IF is in mL/min

IF is 2 x minute volume, and hence a function of body weight (BW).

MODEL STRUCTURE: Georgieva et al. (2003) (rat model)

- Rat and human data sets/parameter values (Georgieva et al, 2003) were obtained by interpolation of data for average flux versus air flow rate (Kimbell et al., 2001a; 2001b).for neonatal and immature rats and human children, scaled with $\text{BW}^{0.75}$. First order rates were scaled with $\text{BW}^{0.25}$ (Clewell et al., 2003a).

E.3.1.4.2 Models for Category 2 gases

For Category 2 gases, OEHHA has examined RT-PBPK models of the type described by Sarangapani et al., (2004). These models include both RT compartments and body compartments for remote distribution and metabolism as recommended by Hanna (2001). These are complex hybrid diffusion-limited, flow-limited, “Respiratory Tract” models consisting of a 16 compartment lung (upper RT, conducting airways, terminal bronchioles, and alveoli; each times lumen, mucus, epithelial cell, and blood exchange sub-compartments) and a five compartment body (liver, fat, muscle, vessel rich group, and blood). The models predict the concentrations of both the parent and a metabolite (usually an oxide).

The model structure (Sarangapani et al., 2004) was used with rat and human data sets/parameter values for styrene and styrene oxide obtained from Sarangapani et al. (2002) and Csanady et al. (2003). Human and rat parameters for naphthalene and naphthalene oxides were obtained from Sarangapani et al. (2002) and Willems et al. (2001)

E.3.1.4.3 Models for Category 3 gases

For Category 3 gases, with mainly remote effects, OEHHA has explored either a one-compartment or, alternatively, a two-compartment lung model as described by Evelo et al. (1993), consisting of a high-perfusion alveolar exchange compartment and a low-perfusion bronchial compartment. During our exploratory analysis, we discovered that in some instances flow-limited model components may be augmented or replaced with diffusion-limited components based on physicochemical/kinetic properties and improved model performance (e.g., dioxin).

A simple flow-limited model was used, with compartments for liver, fat, muscle, and lung where the lung is divided into bronchiolar and alveolar sub-compartments (Evelo et al., 1993). Model

parameters were derived from quantitative structure parameter relations (QSPR) or published models/data. Rat body weight was 0.25 kg, and human 70 kg. While metabolic parameters were available for the aliphatic series of aldehydes in both humans and rats, chemical parameters were not available and had to be estimated.

Model predictions are based on chemical property estimation methods for partition coefficients (Lyman, 1982; Paterson and Mackay, 1989; Haddad et al., 2000). The metabolic parameters of the straight chain aliphatic aldehydes (Vmax, Km) were from Mitchell and Petersen (1989) for rats and Kelson et al. (1997) for humans.

For ethylbenzene, the model structure (Evelo et al., 1993) was used with rat flow parameters from Tardif et al. (1997), and with human parameters scaled from rat according to $BW^{0.75}$ (Haddad et al., 2001). Metabolic parameters were scaled from adult rat and human (Sams et al., 2004); rat metabolic parameters were scaled with $BW^{0.75}$ (Clewell et al., 2003a)

For vinyl chloride the same model was used with human and rat metabolic parameters scaled to $BW^{0.75}$ (Chen and Blancato, 1989) and with rat parameters from Clewell et al. (2003a). For toluene, human and rat parameters were obtained from Tardif et al. (1995), with other rat parameters from Chen and Blancato (1989)

The model (Evelo et al., 1993) was applied to the aliphatic aldehyde group (Ethanal – Decanal) using human and rat parameters from Haddad et al. (2001), Paterson and Mackay (1989), Mitchell and Petersen (1989), and Kelson et al. (1997).

Values of chronic and acute reference exposure levels for the six test chemicals ranged between four and five orders of magnitude ($3.0 \mu\text{g}/\text{m}^3$ for formaldehyde to $1.8 \times 10^{+5} \mu\text{g}/\text{m}^3$ for vinyl chloride). The chemicals were simulated at 8-hour exposures ranging from $1 \mu\text{g}/\text{m}^3$ to $10 \text{mg}/\text{m}^3$. Within this range, the models exhibited linearity of response. For the remainder of the study, we simulated low-level exposures of $1 \mu\text{g}/\text{m}^3$ for 8 hours within a 24-hour observation period. The internal dose metrics we examined were Cmax (parent and metabolite peak concentration in the blood), AUC (parent and metabolite concentration in blood at the end of the exposure period), and AMET (amount of parent compound metabolized/kg body weight /day in tissue). For ethylbenzene, vinyl chloride, toluene, styrene, naphthalene and formaldehyde, we examined the ratio of human to rat chemical concentration or amount of metabolite among adults. We also calculated a dosimetric adjustment factor (DAF), which is simply the reciprocal of the human/rat ratios, tabulated below, which can be used to derive a human equivalent concentration (HEC), i.e., animal exposure concentration (mg/m^3) x DAF = HEC. We also compared young humans and animals for simulations for the same set of chemicals. Since the human ages and rat body weights do not correspond exactly in terms of developmental stage, chemical concentrations and metabolite amounts are compared for the youngest and averaged over all. The average human to rat values for the two human parameter sets were then averaged as well.

E.3.2 Results

E.3.2.1 Ethylbenzene, Vinyl Chloride, Toluene, Styrene, Naphthalene, Formaldehyde

E.3.2.1.1 Interspecies comparisons for adults

The dose predictions for C_{max}, AUC and AMET resulting from an exposure to 1 µg/m³ and 10 mg/m³ for 8 h during a 24-hour exposure time, are shown in Table E.3.1 and Table E.3.2, respectively. For the most part, the model predictions are quite linear in this exposure range. Models with differing sets of metabolic parameters for a particular chemical predict different amounts of the chemical metabolite in tissue compartments, e.g., styrene oxide. For example, the model for styrene and styrene oxide (SO) shows much larger values for SO concentration metrics with the metabolic parameter set from Csanady et al. (2003) than with the parameter set of Sarangapani et al. (2002). With the exception of toluene (about four-fold) the human/animal maximum values were less than two-fold for the dose metrics examined for low and high exposure levels.

TABLE E.3.1. PBPK MODEL PREDICTIONS FOR SELECTED CHEMICALS: LOW END OF RANGE (1 $\mu\text{g}/\text{m}^3 \times 8 \text{ hr}/\text{d}$, 24 hr SIMULATIONS)

Chemical Species	Cmax blood pM	AUC blood pMhr/d	Amount metabolized ² pmol/kg-d	Model basis and source of metabolic parameters
Ethylbenzene ¹ Human	55.9	560	870	Scaled from rat (Haddad et al., 2001)
Ethylbenzene Rat	38.2	290	900	Tardiff et al. (1997)
Ethylbenzene Human/rat	1.46	1.93	0.97	
Vinyl Chloride Human	15.4	126.3	106.45	Chen & Blancato (1989)
Vinyl Chloride Rat	21.9	172.4	519.36	Chen & Blancato (1989)
Vinyl Chloride Human/Rat	0.70	0.73	0.20	
Toluene Human	32.5	274.2	365.7	Tardif et al. (1995)
Toluene Rat	7.3	62.0	736.0	Tardif et al. (1995); Chen & Blancato (1989)
Toluene Human/Rat	4.45	4.42	0.50	
Styrene(ST)/Styrene Oxide (SO) Human	ST = 0.15 SO = 5.1	ST = 72.2 SO = 2.4	STp450 = 1.9 SOeh = 1.75 SOgst = 0.053	Sarangapani et al. (2002)
Styrene/SO Rat	ST = 0.38 SO = 0.065	ST = 181.2 SO = 0.031	STp450 = 22.6 SOeh = 9.32 SOgst = 9.24	Sarangapani et al. (2002)
Styrene/SO Human	ST = 0.15 SO = 0.024	ST = 73.8 SO = 11.3	STp450 = 1.77 SOeh = 0.82 SOgst = 0.29	Metabolic parameters (Sarangapani et al., 2002; Csanady et al., 2003)
Styrene/SO Rat	ST = 0.42 SO = 0.021	ST = 200.1 SO = 10.3	STp450 = 14.6 SOeh = 10.4 SOgst = 1.36	Metabolic parameters (Sarangapani et al., 2002; Csanady et al., 2003)
Styrene/SO Human/Rat Mean	ST = 0.38 SO = 39.8	ST = 0.38 SO = 39.2	STp450 = 0.10	

TABLE E.3.1. PBPK MODEL PREDICTIONS FOR SELECTED CHEMICALS: LOW END OF RANGE (1 $\mu\text{g}/\text{m}^3 \times 8 \text{ hr}/\text{d}$, 24 hr SIMULATIONS)

Chemical Species	Cmax blood pM	AUC blood pMhr/d	Amount metabolized ² pmol/kg-d	Model basis and source of metabolic parameters
Naphthalene (NAP)/Naphthalene Oxide (NPO) Human	NAP = 0.24 NPO = 0.0026	NAP = 117.5 NO = 1.29	NAPp450 = 0.012 NPOeh = 0.12 NPOgst = 1.55	Sarangapani et al. (2002); Willems et al. (2001)
Naphthalene/NPO Rat	NAP = 0.24 NPO = 0.0085	NAP = 115.3 NPO = 4.07	NAPp450 = 0.68 NPOeh = 1.24 NPOgst = 9.86	Sarangapani et al. (2002); Willems et al. (2001)
Naphthalene/NPO Human/Rat	NAP = 1.0 NPO = 0.31	NAP = 1.0 NPO = 0.32	NAPp450 = 0.02	

Chemical Species	Nasal Cmax pM	Nasal DPXmax pmol/mg DNA (/mm ² nasal surface area)	Nasal AUCDPX pmol min/mg DNA/d	Model basis and source of metabolic parameters
Formaldehyde Human surface area (SA) = 21411 mm ²	2800	1.4E-3 (6.5E-8)	0.72	Georgieva et al. (2003); (Kimbell et al., 2001a) (Kimbell et al., 2001b)
Formaldehyde Rat SA = 1777 mm ²	1600	2.1E-3 (1.2E-6)	1.92	Georgieva et al. (2003); Kimbell et al. (2001b); Kimbell et al. (2001a)
Formaldehyde Human/Rat	1.75	0.67	0.38	

¹ Ethylbenzene simulations were 48 hr.

² p450 = cytochrome p450 epoxidation reaction, eh = epoxide hydrolase, gst = glutathione S-transferase.

**TABLE E.3.2. PBPK MODEL PREDICTIONS FOR SELECTED CHEMICALS:
HIGHEND OF RANGE (10 mg/m³ x 8 hr/d, 24 hr SIMULATIONS)**

Chemical Species	Cmax blood nM	AUC blood nMhr/d	Amount metabolized ¹ nmol/kg-d	Model basis
Ethylbenzene Human	290	2690	4690	Scaled from rat (Haddad et al., 2001)
Ethylbenzene, Rat	430	3240	9480	Tardif et al. (1997)
Ethylbenzene Human/Rat	0.67	0.83	0.49	
Vinyl Chloride Human	0.15	1260	1060	Chen & Blancato (1989)
Vinyl Chloride, Rat	0.10	812	4874	Chen & Blancato (1989)
Vinyl Chloride Human/Rat	1.5	1.6	0.22	
Toluene, Human	0.31	2570	3640	Tardif et al. (1995)
Toluene, Rat	0.073	620	7360	Tardif et al. (1995); (Chen and Blancato, 1989)
Toluene, Human/Rat	4.24	4.14	0.36	
Styrene/SO, Human	ST = 1.49 SO = 0.050	ST = 12.0 SO = 0.41	STp450 = 18.6 SOeh = 17.1 SOgst = 0.53	Sarangapani et al. (2002)
Styrene/SO, Rat	ST = 3.8 SO = 0.64	ST = 30.0 SO = 5.2	STp450 = 227 SOeh = 93.4 SOgst = 92.4	Sarangapani et al. (2002)
Styrene/SO, Human	ST = 1.53 SO = 0.24	ST = 12.3 SO = 1.88	STp450 = 17.7 SOeh = 8.1 SOgst = 2.9	Metabolic parameters (Sarangapani et al., 2002; Csanady et al., 2003)
Styrene/SO, Rat	ST = 4.2 SO = 0.22	ST = 33.3 SO = 1.67	STp450 = 144 SOeh = 104 SOgst = 13.6	Metabolic Parameters (Sarangapani et al. 2002; Csanady et al., 2003)
ST/SO Human/Rat, Mean	ST = 0.38 SO = 0.35	ST = 0.39 SO = 0.33		

**TABLE E.3.2. PBPK MODEL PREDICTIONS FOR SELECTED CHEMICALS:
HIGHEND OF RANGE (10 mg/m³ x 8 hr/d, 24 hr SIMULATIONS)**

Chemical Species	Cmax blood nM	AUC blood nMhr/d	Amount metabolized ¹ nmol/kg-d	Model basis
Naphthalene/NPO, Human	NAP = 2.41 NPO = 0.026	NAP = 19.7 NPO = 0.22	NAPp450 = 1.18 NPOeh = 1.21 NPOgst = 15.4	Sarangapani et al. (2002); Willems et al. (2001)
Naphthalene/NPO, Rat	NAP = 2.36 NPO = 0.085	NAP = 19.2 NO = 0.68	NAPp450 = 6.92 NPOeh = 12.5 NPOgst = 98.6	Sarangapani et al. (2002); Willems et al. (2001)
Naphthalene/NPO, Human/Rat	NAP = 1.0 NPO = 0.3	NAP = 1.0 NPO = 0.3		

Chemical Species	Nasal Cmax μ M	Nasal DPXmax pmol/mg DNA	Nasal AUC DPX nmol min/mg DNA/d	Model basis and source of metabolic parameters
Formaldehyde Human SA = 21411 mm ²	29	6.66	7.65	Georgieva et al. (2003); Kimbell et al. (2001a) Kimbell et al. (2001b)
Formaldehyde Rat SA = 1777 mm ²	16	9.67	19.24	Georgieva et al. (2003); Kimbell et al. (2001a) Kimbell et al. (2001b)
Formaldehyde Human/Rat	1.8	0.7	0.4	

¹ p450 = cytochrome p450 epoxidation reaction, eh = epoxide hydrolase, gst = glutathione S-transferase; DPX = DNA-protein cross-links.

E.3.2.1.2 Intraspecies comparisons for young humans and animals

In Table E.3.3, the results of PBPK model predictions of low-level exposure to ethylbenzene for human children with two sets of metabolic parameters are presented. Sams et al. (2004) investigated the enzyme kinetics of the initial hydroxylation of ethylbenzene to form 1-phenylethanol. Human liver microsomes were obtained from TCS Cellworks. The production of 1-phenylphenol with the human microsomes exhibited biphasic kinetics with a high affinity, low K_m , component (mean $K_m = 8 \mu\text{M}$; $V_{\text{max}} = 689 \text{ pmol/min/mg protein}$; $n = 6$ livers) and a low affinity, high K_m , component ($K_m = 391 \mu\text{M}$; $V_{\text{max}} = 3039 \text{ pmol/min/mg protein}$; $n = 6$). Experiments with inhibitors and recombinant CYP isoforms indicated that CYP2E1 was the major form of the high affinity component and that CYP1A2 was very likely involved in the low affinity component. Haddad et al. (2001) investigated PBPK modeling of chemical mixtures including ethylbenzene. The biochemical parameters were based on studies in rats: $V_{\text{maxC}} = 6.39 \text{ mg/hr/kg bw}$; $K_m = 1.04 \text{ mg/L}$. For human PBPK models the V_{max} was scaled, i.e., $V_{\text{max}} = V_{\text{maxC}} \times \text{BW}^{0.75} = \text{mg/hr}$.

With the parameters from Sams et al. (2004) the concentration metrics are higher and the metabolism (AMET) is lower than with the values from Haddad et al. (2001). While the differences appear large it should be appreciated that the Sams values are based on analysis of isolated microsomes in vitro. Extrapolating these values to a whole body PBPK model probably involves greater uncertainty than extrapolating from rat to human. Table E.3.4 gives the corresponding values for the immature rat. Also presented in this table are the human/rat ratios for children and adults. Since the human ages and rat body weights do not correspond exactly in terms of developmental stage, they are compared for the youngest and averaged over all. If the average immature values for human/rat for the two parameter sets are used with the blood C_{max} metric, the corresponding dosimetric adjustment factor (DAF) for ethylbenzene would be 0.21. If only the neonate values are used, the DAF would be 0.22.

TABLE E.3.3. PBPK MODEL PREDICTIONS FOR ETHYLBENZENE WITH HUMAN AGE-SPECIFIC REGRESSIONS AND ALTERNATIVE METABOLIC PARAMETERS (1 $\mu\text{g}/\text{m}^3$ x 8 hr/d, 24-48 hr SIMULATIONS)

Age Group	Cmax blood pM	AUC blood pMhr/d	Amount Metabolized pmol/kg-d	Model basis
<i>Ethyl Benzene, Human</i> Age 1 yr	100	1300	13	Metabolic parameters scaled from adult (Sams et al., 2004)
Age 3 yr	110	1450	11	
Age 5 yr	120	1620	10	
Age 10 yr	120	1580	8.2	
Age 14 yr	120	1420	6.3	
Age 18 yr	110	1510	5.9	
Adult	110	1750	7.2	
<i>Ethyl Benzene, Human</i> Age 1 yr	55.9	570	370	Parameters scaled to $\text{BW}^{0.75}$ (Haddad et al., 2001)
Age 3 yr	58.6	570	370	
Age 5 yr	62.2	660	475	
Age 10 yr	53.9	550	500	
Age 14 yr	48.6	470	390	
Age 18 yr	35.0	330	380	
Adult	55.9	560	870	
Rat Mature	38.2	290	900	

TABLE E.3.4. PBPK MODEL PREDICTIONS FOR ETHYLBENZENE WITH AGE-SPECIFIC PARAMETERS FROM CLEWELL ET AL. 2003 MODELING OF NEONATAL RAT (1 $\mu\text{g}/\text{m}^3$ x 8 hr/d, 24-48 hr SIMULATIONS)

Age Group	Cmax blood pM	AUC blood pMhr/d	Amount metabolized pmol/kg-d	Model basis
<i>Ethylbenzene, Rat Neonate</i> BW = 0.0075 kg	17.0	130	450	Scaled BW ^{0.75} (Haddad et al., 2001; Clewell et al., 2003a)
BW = 0.015 kg	17.0	135	450	
BW = 0.03 kg	17.0	138	440	
BW = 0.06 kg	17.2	140	430	
BW = 0.12 kg	17.1	140	420	
BW = 0.20 kg	17.4	145	420	
<i>Human neonate/Rat neonate</i>	5.88	10.0	0.029	Parameters (Sams et al., 2004)
<i>Human neonate/Rat neonate</i>	3.29	4.38	0.82	Parameters (Haddad et al., 2001)
<i>Human/Rat Immature Mean</i>	6.61	9.19	0.018	Parameters (Sams et al., 2004)
<i>Human/Rat Immature Mean</i>	3.06	3.61	0.97	Parameters (Haddad et al., 2001)
Mean DAF Immature	0.21	0.16	6.79 (G _{mean})	

Note: Human neonate/Rat neonate = 100pM/17.0pM = 5.88 (Sams Cmax); Human/Rat Immature Mean = (5.88+6.47+7.06+6.98+7.01+6.32)/6 = 6.61 (Sams Cmax); G_{mean} = geometric mean; DAF = dosimetric adjustment factor; human/rat values in this table were calculated using human values from Table E3.3. Mean DAF based on immature values i.e. 1/((6.61 + 3.06)/2).

Table E.3.5 gives PBPK simulation values for toluene for both immature rats and human children. As above, the individual human/rat ratios are given for neonates and the mean is based on all immature ages (i.e., all except adult) simulated. The mean DAFs are given at the bottom of the table. In this case the DAFs are close to unity for both concentration based metrics. Similarly Table E.3.6 gives the corresponding values for vinyl chloride. In this case the mean DAF based on blood concentration (Cmax) and average immature values was 1.19. The human/rat ratios for the three chemicals with similar model structures (Table E.3.5 to Table E.3.8) are quite similar with blood Cmax and AUC based DAFs averaging 1.62, 0.96, and 1.17, respectively for children. For adults the concentration-based ratios were very similar, averaging 1.12 for ethylbenzene and 1.47 for vinyl chloride. For toluene, the adult ratios differed substantially: 3.1 for Cmax and 0.31 for AUC.

TABLE E.3.5. PBPK MODEL PREDICTIONS FOR TOLUENE WITH AGE-SPECIFIC REGRESSIONS (1 $\mu\text{g}/\text{m}^3$ X 8 hr/d, 24 hr SIMULATIONS)

Age Group	Cmax blood pM	AUC blood pMhr/d	Amount metabolized pmol/kg-d	Model basis
<i>Toluene, Human:</i>				
Age 1 yr	83.2	771	551	Metabolic parameters scaled to BW ^{0.75} (Haddad et al., 2001)
Age 3 yr	85.6	825	637	
Age 5 yr	90.0	899	754	
Age 10 yr	61.3	580	684	
Age 15 yr	52.9	472	486	
Age 18 yr	51.7	483	440	
Adult	30.0	255	365	
<i>Toluene, Rat</i>				
Neonate, 0.0075 kg	108.7	873	33201	Parameters scaled to BW ^{0.75} (Haddad et al., 2001)
BW = 0.015 kg	86.1	688	16409	
BW = 0.03 kg	72.6	579	8149	
BW = 0.06 kg	65.0	516	4058	
BW = 0.12 kg	58.7	478	2024	
BW = 0.20 kg	52.8	457	1206	
BW = 0.25 Adult	92.4	80.2	375	
<i>Human/Neonate/Rat</i>				
<i>Neonate</i>	0.76	0.88	0.016	
<i>Human/Rat</i>				
<i>Immature Mean</i>	0.97	1.13	0.15	
Mean DAF	1.03	0.88	6.7	

Note: Human neonate/Rat neonate = 83.2 pM/108.7 pM = 0.76 (Cmax); Human/Rat Immature Mean = (0.76+0.99+1.24+0.94+0.90+0.98)/6 = 0.97 (Cmax); DAF = dosimetric adjustment factor. Mean DAF = 1/0.97 = 1.03 (Cmax).

TABLE E.3.6. PBPK MODEL PREDICTIONS FOR VINYL CHLORIDE WITH AGE-SPECIFIC REGRESSIONS (1 $\mu\text{g}/\text{m}^3$ x 8 hr/d, 24 hr SIMULATIONS)

Age Group	Cmax blood pM	AUC blood pMhr/d	Amount Metabolized pmol/kg-d	Model basis
<i>Vinyl Chloride, Human,</i>				Metabolic parameters scaled as $\text{BW}^{0.75}$ (Chen & Blancato 1989)
Age 1 yr	16.5	137.2	101.3	
Age 3 yr	17.0	138.7	108.2	
Age 5 yr	17.4	140.0	116.6	
Age 10 yr	16.3	132.3	137.2	
Age 15 yr	16.0	131.9	102.5	
Age 18 yr	16.5	133.9	87.7	
Adult	14.4	117.6	101.0	
<i>Vinyl Chloride, Rat</i>				Parameters scaled to $\text{BW}^{0.75}$ (Clewel et al., 2003a; Chen & Blancato 1989)
Neonate, 0.0075 kg	18.9	149.6	424.4	
BW = 0.015 kg	19.0	150.3	421.3	
BW = 0.03 kg	19.2	151.9	414.7	
BW = 0.06 kg	19.7	155.5	397.8	
BW = 0.12 kg	20.7	162.9	363.8	
BW = 0.20 kg	21.7	172.2	321.5	
BW = 0.25 adult	21.6	169.4	511.4	
<i>Human/Rat Neonate</i>	0.89	0.92	0.24	
<i>Human/Rat Immature Mean</i>	0.84	0.87	0.28	
Mean DAF	1.19	1.15	3.6	

Note: Human neonate/Rat neonate = $16.5 \text{ pM}/18.9 \text{ pM} = 0.87$ (Cmax); Human/Rat Immature Mean = $(0.87+0.89+0.91+0.83+0.77+0.76)/6 = 0.84$ (Cmax); DAF = dosimetric adjustment factor. Mean DAF = $1/0.84 = 1.19$ (Cmax).

In Table E.3.7 are summarized the results obtained with the respiratory tract (RT) model with naphthalene. This model predicts concentrations of both parent (NP) and oxidative metabolite naphthalene oxide (NPO). The predicted values for the latter are shown in parentheses. Also included is an average lung concentration of the naphthalene oxides. In this model the isomeric naphthalene oxides are grouped together for simplicity. For the usual concentration metrics of Cmax and AUC in the blood the DAFs range from 8 to 14 for parent and oxide metabolite in the child and 8 to 6, respectively in the adult. For the predicted lung oxide concentration the DAF is 0.17 for the child and 0.07 for the adult.

TABLE E.3.7. PBPK MODEL PREDICTIONS FOR NAPHTHALENE/NAPHTHALENE OXIDES (NPO) WITH AGE-SPECIFIC REGRESSIONS (NAPHTHALENE $1 \mu\text{g}/\text{m}^3 \times 8 \text{ hr}/\text{d}$, 24 hr SIMULATIONS)

Age Group	Cmax blood pM NP (NPO)	AUC blood pMhr/d NP (NPO)	Amount Naphthalene Metabolized pmol/kg-d	Avg. NPO Conc. in Lung pM*
Human,				
Age 1 yr	0.22 (0.0032)	1.83 (0.027)	1.5	0.057
Age 3 yr	0.22 (0.003)	1.83 (0.025)	1.6	0.062
Age 5 yr	0.22 (0.0033)	1.83 (0.026)	1.8	0.064
Age 10 yr	0.19 (0.0031)	1.5 (0.025)	5.2	0.065
Age 15 yr	0.18 (0.0026)	1.48 (0.022)	3.8	0.07
Age 18 yr	0.18 (0.0026)	1.49 (0.021)	3.3	0.07
Adult	0.18 (0.0019)	1.49 (0.016)	4.6	0.073
Rat				
Neonate, 0.0075 kg	1.7 (0.3)	13.8 (2.3)	1.97	0.07
BW = 0.015 kg	1.7 (0.16)	13.7 (1.3)	2.26	0.037
BW = 0.03 kg	1.7 (0.08)	13.5 (0.65)	2.7	0.020
BW = 0.06 kg	1.68 (0.04)	13.2 (0.33)	3.17	0.011
BW = 0.12 kg	1.7 (0.023)	13.3 (0.18)	3.75	0.0072
BW = 0.20 kg	1.67 (0.016)	13.3 (0.12)	4.3	0.0050
BW = 0.25 kg (adult)	1.5 (0.012)	12.2 (0.095)	4.56	0.0048
Human/Rat Neonate	0.13 (0.011)	0.13 (0.012)	0.76	0.81
Human/Rat Immature Mean	0.10 (0.07)	0.12 (0.072)	0.92	5.88
Mean DAF Immature	10 (14.3)	8.3 (13.9)	1.1	0.17
Human/Rat Adult	0.12 (0.16)	0.12 (0.17)	1.01	15.2
DAF Adult	8.3 (6.2)	8.3 (5.9)	0.99	0.066

Note: (*)Average of upper respiratory tract and terminal bronchiole model compartments Cmax for naphthalene oxides; NP = naphthalene; NPO = oxidative metabolite; models based on Sarangapani et al. (2002); Willems et al. (2001); and Clewell et al. (2003a). Human neonate/Rat neonate = $0.22\text{pM}/1.7\text{pM} = 0.13$ (NP Cmax); Human/Rat Immature Mean = $(0.13+0.13+0.13+0.11+0.11+0.11)/6 = 0.103$ (NP Cmax); DAF = dosimetric adjustment factor. Mean DAF = $1/0.10 = 10$ (NP Cmax). HEC = DAF x Animal Exposure Concentration

The predicted values obtained with styrene exposure in a similar RT model are shown in Table E.3.8. For children, the average DAF (based on the immature values, i.e. all values except adult) for the concentration-based metrics was 0.42 $((0.41 + 0.42) / 2)$ for the parent compound (ST) and 0.18 $((0.17 + 0.20) / 2)$ for the oxide metabolite (SO). For the adult these values were 1.07 and 0.18, respectively. To recap if we were to calculate the human equivalent concentration (HEC) based on these values we might consider multiplying an immature rat exposure concentration by 0.42 or an adult rat value by 1.07 if the toxic effect were due to the parent compound (i.e., $HEC = DAF * \text{Animal Exposure Concentration}$).

TABLE E.3.8. PBPK MODEL PREDICTIONS FOR STYRENE/ STYRENE OXIDE WITH AGE-SPECIFIC REGRESSIONS ($1 \mu\text{g}/\text{m}^3 \times 8 \text{ hr}/\text{d}$, 24 hr SIMULATIONS)

Age group	Cmax blood pM ST (SO)	AUC blood pMhr/d ST (SO)	Amount of Styrene Metabolized pmol/kg-d	Average SO Conc. in Lung pM*
Human				
Age 1 yr	0.27 (0.0027)	2.23 (0.022)	1.34	1E-5
Age 3 yr	0.28 (0.0032)	2.25 (0.026)	1.34	1E-5
Age 5 yr	0.28 (0.0037)	2.30 (0.030)	1.34	8E-6
Age 10 yr	0.27 (0.012)	2.22 (0.094)	1.94	9E-6
Age 15 yr	0.27 (0.012)	2.18 (0.095)	1.53	8E-6
Age 18 yr	0.27 (0.026)	2.20 (0.095)	1.39	8E-6
Adult	0.15 (0.024)	1.23 (0.18)	1.77	2.4E-5
Rat				
Neonate, 0.0075 kg	0.09 (3.7E-4)	0.73 (0.003)	6.5	8.7E-3
BW = 0.015 kg	0.097 (5.4E-4)	0.76 (0.004)	8.1	7.5E-3
BW = 0.03 kg	0.10 (0.0084)	0.83 (0.0067)	10.0	7.0E-3
BW = 0.06 kg	0.12 (0.0014)	0.93 (0.011)	13.8	6.5E-3
BW = 0.12 kg	0.14 (0.0024)	1.08 (0.018)	19.0	7.0E-3
BW = 0.20 kg	0.16 (0.0036)	1.26 (0.029)	25.0	7.5E-3
BW = 0.25 kg (adult)	0.16 (0.0041)	1.32 (0.033)	28.0	7.5E-3
Human/Rat Neonate	3.0 (7.3)	3.05 (7.3)	0.21	0.0011
Human/Rat Immature Mean	2.42 (5.74)	2.40 (5.0)	0.11	0.0012
Child Mean DAF	0.41 (0.17)	0.42 (0.2)	9.1	833
Adult DAF	1.07 (0.17)	1.07 (0.18)	15.8	3.12

*Average styrene oxide concentration of upper respiratory tract and terminal bronchiole model compartments; Cmax = maximum blood concentration for styrene (ST) and styrene oxide (SO); AUC = blood concentration x time for styrene and styrene oxide; models based on Sarangapani et al. (2002); and Clewell et al. (2003a). Human neonate/Rat neonate = 0.27 pM/0.09 pM = 3.00 (ST Cmax); Human/Rat Immature Mean = $(3.00+2.87+2.80+2.25+1.93+1.69)/6 = 2.42$ (ST Cmax); DAF = dosimetric adjustment factor. Mean DAF = $1/2.42 = 0.41$ (ST Cmax). Human Equivalent Concentration (HEC) = DAF x Animal Concentration.

TABLE E.3.9. PBPK MODEL PREDICTIONS FOR FORMALDEHYDE WITH AGE-SPECIFIC PARAMETERS FROM CLEWELL *et al.*, 2003a: MODELING OF NEONATAL AND IMMATURE RAT (1 $\mu\text{g}/\text{m}^3$ x 8 hr/d, 24 hr SIMULATIONS)

Age Group	Nasal Cmax pM	Nasal DPXmax pmol/mg DNA	Nasal AUCDPX pmol min/mg DNA-d	Model basis
Rat				
Neonate, BW = 0.0075 kg	53	3.2×10^{-5}	0.033	Scaled BW ^{0.75} and first order rates BW ^{-0.25} Georgieva et al. (2003); Clewell et al. (2003a)
BW = 0.015 kg	110	7.8×10^{-5}	0.080	
BW = 0.03 kg	220	1.8×10^{-4}	0.184	
BW = 0.06 kg	430	4.1×10^{-4}	0.406	
BW = 0.12 kg	820	9.4×10^{-4}	0.872	
BW = 0.20 kg	1320	1.8×10^{-3}	1.57	
Adult: BW = 0.25 kg	1600	2.1×10^{-3}	1.92	

Note: Cmax = maximum concentration; DPXmax = maximum DNA-protein crosslinks concentration; AUCDPX = the area under the DPX x time curve per day.

TABLE E.3.10. PBPK MODEL PREDICTIONS FOR FORMALDEHYDE WITH AGE-SPECIFIC PARAMETERS: MODELING OF HUMAN CHILDREN (1 µg/m³ x 8 hr/d, 24 hr SIMULATIONS).

Age Group	Nasal C _{max} pM	Nasal DPX _{max} pmol/mg DNA	Nasal AUCDPX pmol min/mg DNA-d	Model basis
Human 3 month Neonate, BW = 5.7 kg	150	6.2 x 10 ⁻⁵	0.035	Scaled BW ^{0.75} and first order rates BW ^{-0.25} (Georgieva et al., 2003; Clewell <i>et al.</i> 2003a)
1 yr, BW = 10.1 kg	390	1.7 x 10 ⁻⁴	0.094	
3 yr, BW = 14.6 kg	860	3.9 x 10 ⁻⁴	0.215	
5 yr, BW = 19.4 kg	1400	6.5 x 10 ⁻⁴	0.348	
10 yr, BW = 32.6 kg	1700	8.4 x 10 ⁻⁴	0.437	
15 yr, BW = 54.5 kg	2360	1.2 x 10 ⁻³	0.603	
18 yr, BW = 63.1 kg	2700	1.4 x 10 ⁻³	0.682	
Human/Rat Neonate	2.83	1.94	1.10	
DAF Neonate	0.35	0.52	0.91	
Human/Rat Immature Mean	2.90	1.47	0.80	
DAF Immature Mean	0.34	0.68	1.25	
Adult, BW = 70 kg	2700	1.4 x 10 ⁻³	0.684	
Human/Rat Adult	1.69	0.67	0.36	
DAF Adult	0.59	1.49	2.78	

Note: C_{max} = maximum concentration; DPX_{max} = maximum DNA-protein crosslinks concentration; AUCDPX = the area under the DPX x time curve per day. Human neonate/Rat neonate = 150 pM/53 pM = 2.83 (C_{max}); Human/Rat Immature Mean = (2.83+3.54+3.91+3.26+2.07+1.79)/6 = 2.90 (C_{max}); DAF = dosimetric adjustment factor. Mean DAF = 1/2.78 = 0.36 (C_{max}). Human Equivalent Concentration (HEC) = DAF x Animal Concentration.

E.3.2.1.3 Summary of HEC factors for Adults and Children/pups

TABLE E.3.11. DAFs SUMMARY BASED ON PBPK MODELING OF INTERNAL DOSIMETRY

Chemical Species	Cmax blood (range)	AUC blood (range)	Amount Metabolized /kg-d	Other
Ethyl Benzene Child Average	0.21	0.16	6.79	
Ethyl Benzene Adult	0.52	0.34	11.37	
Naphthalene/NPO Child Average.	(8-14)	(8-14)	1.1	0.17 Cmax NPO lung
Naphthalene/NPO Adult	(6-8)	(6-8)	0.99	0.065 Cmax NPO lung
Toluene Child Average.	1.03	0.88	6.7	
Toluene Adult	3.1	0.31	2.0	
Vinyl Chloride (VCl) Child Average.	1.19	1.15	3.6	
VCl Adult	1.50	1.44	5.1	
Styrene Child Average	0.41	0.42	9.1	833 (child/rat pup)
SO Child Average	0.17	0.2		
Styrene Adult Average	1.07	1.07	15.8	3.12 (human/rat)
SO Adult Average	0.17	0.18		
Child Gmean	1.94	1.63	6.1	
Adult Gmean	1.85	1.30	3.9	
	Nasal Cmax	Nasal DPXmax	Nasal AUCDPX	
Formaldehyde Child Mean	0.34	0.68	1.25	
Formaldehyde Adult	0.59	1.49	2.78	

Note: Note: Cmax = maximum concentration; DPXmax = maximum DNA-protein crosslinks concentration; AUCDPX = the area under the DPX x time curve per day. Human Equivalent Concentration (HEC) = DAF x Animal Exposure Concentration.

Table E.3.11 provides a summary of Table E.3.3 - Table E.3.10. For the five test compounds that provide blood concentration metrics (Cmax, AUC), the child DAFs have geometric means of 1.94 and 1.63, respectively. Adult values were only slightly lower at 1.85 and 1.30, respectively. The results of the formaldehyde nasal model, which differs significantly in

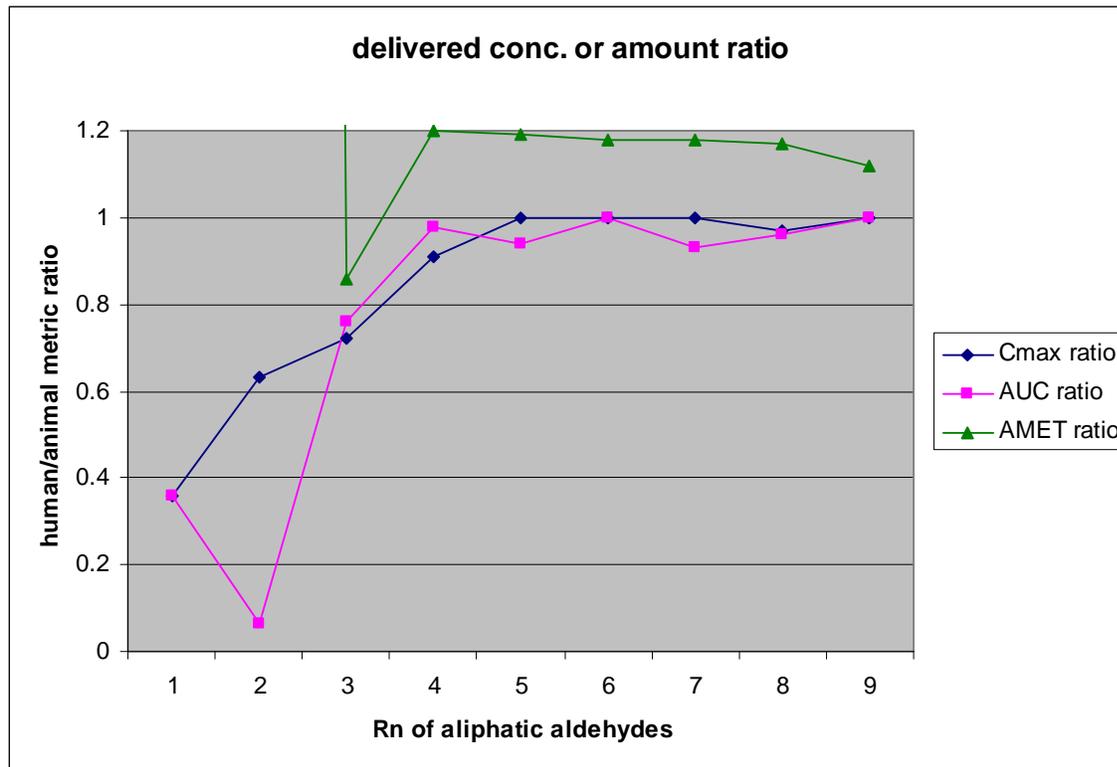
structure from the previous five chemicals, are presented in Table E.3.9 and Table E.3.10. For the child the DAFs for nasal tissue C_{max} and DPX_{max} were 0.34 and 0.68. The value for the AUC DPX was 1.25. For the adult these DAFs were higher at 0.59, 1.49, and 2.78, respectively. The predicted formaldehyde DAFs are also given at the bottom of Table E.3.11 with separate column headings.

E.3.2.2 Aliphatic Aldehydes

The body of Table E.3.12 gives the ratio of Human/Rat metric values (unitless). The reciprocals of the mean (bottom) represent a factor (i.e., the DAF) by which to multiply the respective animal toxicity criteria in order to calculate the HEC. The models were formulated for adults only. There appears to be a clear difference between the shorter chain length, water-soluble aldehydes and the longer chain length, fat-soluble aldehydes. This difference is reflected in the metabolic parameters where both acetaldehyde and propionaldehyde have two saturable metabolic paths: a high-capacity, low-affinity and a low-capacity, high-affinity, as opposed to the single saturable path for the fatty aldehydes. Overall the HEC factors for the aliphatic aldehydes appear similar to the other compounds studied in adults with blood concentration ratios for each metric averaging 1.3 vs. 1.3 to 1.85 for the geometric means of the models for the five test compounds which give similar metrics. If the values for acetaldehyde and propionaldehyde are removed from the mean, the C_{max} HEC factor is reduced to 1.06. This PBPK series approach may also be applicable to the straight chain aliphatic hydrocarbons and acids.

TABLE E.3.12. HUMAN/RAT PBPK MODEL PREDICTIONS FOR ALIPHATIC ALDEHYDES: (1 µg/m³ x 8 hr/d, 24 hr SIMULATIONS)

Chemical Species	C _{max} blood	AUC blood	Amount Metabolized	Model Basis
Acetaldehyde	0.36	0.36	11.4	Haddad et al. (2000); Paterson & MacKay (1989); Mitchell & Petersen (1989); Kelson et al. (1997)
Propionaldehyde	0.63	0.065	24.1	
Butyraldehyde	0.72	0.76	0.86	
Pentanal	0.91	0.98	1.20	
Hexanal	1.0	0.94	1.19	
Heptanal	1.0	1.0	1.18	
Octanal	1.0	0.93	1.18	
Nonanal	0.97	0.96	1.17	
Decanal	1.0	1.0	1.12	
Mean	0.84	0.78	4.82	
DAF	1.18	1.28	0.21	

FIGURE E.3-1 HUMAN/ANIMAL METRIC RATIOS FOR ALIPHATIC ALDEHYDES.

E.3.3 Discussion

The rat neonatal PBPK values in Tables E.3.4 to E.3.8 and Table E.3.10 are derived from the Clewell et al. (2003a) paper on neonatal perchlorate dosimetry. The values range from body weights of 0.0075 kg to 0.1985 kg. Except for fat and slowly perfused compartments, which vary inversely with each other and body weight, the tissues are a fixed percentage of body weight. Blood flows are also a fixed percentage of cardiac output, which itself is a fixed percent of body weight (14 L/hr/kg). This scheme differs from that of Price et al. (2003) and their age-specific regressions for human neonates and children. In the latter paper fractional blood flows, specifically those for liver, vary by much more than do tissue volumes. The rat values may vary more with respect to developmental age than indicated by Clewell et al. (2003a). These physiological differences may have influenced the results in Table E.3.5 and the human/rat comparisons.

In general the DAFs based on PBPK model-predicted blood concentration for adults seem lower and those for children seem higher than those produced by the current HEC methodology, which is not chemical specific but based on ventilation rates and lung surface area. Thus if we credit the chemical specific PBPK approach, the current methodology may underestimate the HEC for children and overestimate it for adults. However, these interim conclusions are based on a very limited number of chemicals and on many assumptions. HECs based on internal dosimetry PBPK estimates are bound to be highly chemical dependent and strongly influenced by the dose

metric chosen, blood/air and fat/blood partition coefficients, fractional tissue flows, metabolic parameters, and other factors.

This report also estimated values for immature rats where the examples are given in the tables, as well as for adult rat and human child, to assist in derivation of a DAF. It is anticipated that future laboratory studies will more often involve immature animals to assess accurately the toxicity of environmental agents throughout the postnatal development period.

TABLE E.3.13. SUMMARY OF INFANTS' AND CHILDREN'S PBPK MODELING BY OEHA WITH SELECTED ENVIRONMENTAL TOXICANTS BY INHALATION

Chemical and Exposure	Tissue and Dose Metric	Age at Maximum Child/Adult	Child/Adult Maximum	Basis for the Model
Chloroform 1 ppm x 24 hr	Liver AMET	Newborn	2.3	Corley et al. (1990); Price et al. (2003)
	Kidney AMET	Newborn	2.3	
TCE 1 ppm x 24 hr	Lung C _{maxCH}	Newborn	9.6	Abbas & Fisher (1997); Fisher et al. (1998); Price et al. (2003)
	Venous blood AUC _{TCE}	3 yr	10.6	
	AUC _{CH}	Newborn	12.5	
	Lung AUC _{CH}	1.5 mo	12.9	
	Liver AUC _{TCA}	3 yr	10.3	
	Liver AMET	Newborn	15.7	
Vinyl chloride 1 ppm x 24 hr	Liver Risk M	Newborn	10.2	Clewell et al. (1995); Price et al. (2003)
	Liver Risk G	Newborn	11.0	
Dichloromethane 1 ppm x 24 hr	Liver MFO AMET	Newborn	2.1	OSHA (1997); Price et al. (2003)
	Lung MFO AMET	Newborn	2.1	
	Liver GST AMET	Newborn	43.3	
	Lung GST AMET	Newborn	11.6	
DCM 1 ppm x 24 hr respiratory tract model	Liver MFO AMET	Newborn	3.0	OSHA (1997); Sarangapani et al., (2002); Price et al. (2003)
	Lung MFO AMET	Newborn	60.7	
	MFO AMET total	Newborn	3.0	
	Liver GST AMET	Newborn	42.7	
	Lung GST AMET	Newborn	65.9	
Styrene/styrene (ST/SO) oxide 1 ppm x 24 hr	Lung MFOAMET/L tissue-d	Newborn	9.3	Sarangapani et al., (2002; Price et al., (2003)
	Lung EH AMET/Ltissue-d	Newborn	9.2	
	Lung GST AMET/Ltissue -d	Newborn	4.7	
ST/SO 1 ppm x 24 hr respiratory tract model	Lung MFOAMET/L tissue-d	0.5 mo	2.7	Sarangapani et al. (2002); Price et al. (2003)
	Lung EH AMET/Ltissue-d	0.5 mo	2.6	
	Lung GST AMET/Ltissue-d	0.5 mo	2.7	
ST/SO 50 ppm x 2 hr respiratory tract model, Csanady et al. biochemical parameters	Lung MFO AMET/Ltissue-d	0.5 mo	2.7	Sarangapani et al. (2002); Csanady et al. (2003); Price et al. (2003)
	Lung EH AMET/Ltissue-d	0.5 mo	2.8	
	Lung GST AMET/Ltissue-d	0.5 mo	2.9	
	Liver + Lung AMET/Ltissue-d	Newborn	3.5	
ST/SO 50 ppm x 2 hr respiratory tract model, Sarangapani et al. biochemical parameters	Lung MFOAMET/L tissue-d	0.5 mo	2.5	Sarangapani et al. (2002); Price et al. (2003)
	Lung EH AMET/Ltissue-d	0.5 mo	3.0	
	Lung GST AMET/Ltissue-d	Newborn	6.0	
	Liver + Lung AMET/Ltissue-d	Newborn	6.5	

TABLE E.3.13. SUMMARY OF INFANTS' AND CHILDREN'S PBPK MODELING BY OEHA WITH SELECTED ENVIRONMENTAL TOXICANTS BY INHALATION

Chemical and Exposure	Tissue and Dose Metric	Age at Maximum Child/Adult	Child/Adult Maximum	Basis for the Model
ST/SO 1 ppm x 24 hr respiratory tract model of Csanady et al.	Lung MFOAMET/Ltissue-d	0.5 mo	7.3	Csanady et al. (2003); Price et al. (2003)
	Venous Blood SO Cmax	3.5 mo to 1 yr	5.1	
	Lung alveoli SO Cmax	3.5 mo	4.3	
	Lung alveoli AUC _{SO}	Newborn to 5 yr	4.2	
ET/EO 1 ppm x 24 hr PBPK model of Csanady et al.	Clearance of ET and EO by liver, Venous blood Cmax, AUC EO in liver, blood, Hb and DNA adducts	Newborn (AMET EO $\mu\text{mol/kg-d}$)	32.1	Csanady et al. (2000); Price et al. (2003)
Butadiene (BD) 1 ppm x 24 hr BD/BMO/DEB model	Liver + Lung DEB AMET $\mu\text{mol/kg-d}$	Newborn	7.1	Kohn & Melnick (1993); Johanson & Filser (1993); Price et al. (2003)
	Venous blood AUC _{BMO} $\mu\text{M hr}$	Newborn	71	
	Venous blood AUC _{DEB} $\mu\text{M hr}$	Newborn	16.2	
	Liver AUC _{DEB} $\mu\text{M hr}$	Newborn	20.7	
	Lung AUC _{BMO} $\mu\text{M hr}$	Newborn	32.8	
	Lung AUC _{DEB} $\mu\text{M hr}$	Newborn	17.2	
BD/BMO 1 ppm x 24 hr respiratory tract model	Lung BMO→DEB AMET $\mu\text{mol/Llung-d}$	Newborn	33.8	Sarangapani et al. (2002); Kohn & Melnick (1993); Price et al. (2003)
	Liver BMO→DEB AMET $\mu\text{mol/Lliver-d}$	Newborn	19.2	
BD/BMO 1 ppm x 24 hr respiratory tract model	Lung alveoli BMO→DEB AMET $\mu\text{mol/Lalveoli-d}$	Newborn	120	Sarangapani et al. (2002); Kohn & Melnick (1993); Price et al. (2003)
	Lung bronchi BMO→DEB AMET $\mu\text{mol/Lbronchi-d}$	Newborn	33.8	
MTBE 1 ppm x 24 hr; 10 ppm x 8 hr VPs 0.8, 1.25	Blood, brain Cmaxs μM , AUCs $\mu\text{M hr}$, AMET $\mu\text{mol/kg-d}$	3-8 yr	1.2 to 12.4 highly dependent on VP	(Licata et al., 2001); Price et al. 2003; Evelo et al. (1993)
PCE 1ppm x 24 hr; 10 ppm x 8 hr VP = 1	AUC ^{PCE} blood, liver, brain, AMET, AUC ^{TCA} , TCAurine/kg-d	Newborn	1.1 to 4.6	Gearhart et al. (1993); Loizou (2001); Price et al. (2003)
Furan 1 ppm x 24 hr 0-13yr + adult Flow-limited liver metabolism	Liver AMET $\mu\text{mol/kg-d}$ Brain AUC μMhr	13 yr	2.2	Price et al. (2003)
Carbon tetrachloride 1 ppm x 24 hr, 10 ppm x 8 hr	Liver AMET $\mu\text{mol/kg-d}$, Blood or liver AUC μMhr , blood or liver Cmax	Newborn	1.6	Thrall et al. (2000); Price et al. (2003)

TABLE E.3.13. SUMMARY OF INFANTS' AND CHILDREN'S PBPK MODELING BY OEHA WITH SELECTED ENVIRONMENTAL TOXICANTS BY INHALATION

Chemical and Exposure	Tissue and Dose Metric	Age at Maximum Child/Adult	Child/Adult Maximum	Basis for the Model
Toluene 1 ppm x 24 hr	Liver AMET $\mu\text{mol/kg-d}$, Blood or liver AUC μMhr , blood or liver Cmax	5 yr	3.6	Tardiff et al. (1995); Price et al. (2003)
Xylene 1 ppm x 24 hr	Liver AMET $\mu\text{mol/kg-d}$, Blood or liver AUC μMhr , blood or liver Cmax	5 yr	4.5	Tardif et al. (1995); Price et al. (2003)
Toluene/Xylene mixed model with competitive inhibition, 10/10, 1/10, 10/1 ppm x 8 hr	Liver AMET $\mu\text{mol/kg-d}$, Blood or liver AUC μMhr , blood or liver Cmax	5 yr	5.2	Tardif et al. (1995); Price et al. (2003)
Benzo[a]pyrene vapor 10 ppb x 24 hr; Hybrid diffusion-limited-lung flow-limited-body model	Lung alveoli, bronchi. Liver AMET $\mu\text{mol/kg-d}$. AUC ^{BaP} $\mu\text{M min}$; V _{max} S scaled from uninduced and 3-MC induced rats	Newborn	4.3 to 31.9 uninduced 3.7 to 26.1 induced	Wiersma and Roth (1983); Gerde et al. (1991); Moir et al. (1998); Price et al. (2003); and others
Benzo[a]pyrene particle 1 $\mu\text{g/m}^3$ x 24 hr; hybrid model as above	Lung alveoli, bronchi. Liver AMET $\mu\text{mol/kg-d}$. AUC ^{BaP} $\mu\text{M min}$; V _{max} S scaled from uninduced and 3-MC induced rats	Newborn to 1 yr	9.7 to 18.6 uninduced 10.8 to 22.0 induced	As above and Sun et al. (1982); Sun et al. (1984); ICRP (1994); Gerde et al. (2001); Ramiesh et al. (2001)
NAP/NO 1 ppm x 24 hr respiratory tract model	Lung AMET $\mu\text{mol/L}_{\text{alveoli-d}}$	Newborn	2.4	Sweeney et al. (1996); Willems et al. (2001); Price et al. (2003)
	AMET ^{NO} GST $\mu\text{mol/kg-d}$	Newborn	3.1	

Notes: AMET = amount metabolized; Cmax = maximum concentration in blood or tissue; CH = chloral hydrate; TCA = trichloroacetic acid; AUC = area under the concentration x time curve; Risk M = μmol metabolites DNA bound/L liver/d; Risk G = μmol metabolites conjugated with glutathione/L liver/d; MFO = mixed function oxidase (P450) pathway; EH = epoxide hydrolase pathway; GST = glutathione sulfotransferase pathway; BMO = butadiene monoxide; DEB = diepoxybutane; AMET DEB amount of BMO oxidized to DEB. Model based on [Kohn & Melnick (1993)], Evelo et al. (1993), Sarangapani et al. (2002), Jonsson, (2001). Exposure for 24 hr, simulations 48 hr. respiratory tract model = model with diffusion limited lung (upper airways, conducting airways, transitional bronchioles, and alveoli) and flow limited body (fat muscle, vessel rich group and liver) based on Sarangapani et al. (2002) with BD/BMO parameters from [Kohn and Melnick (1993)]. VP = ventilation:perfusion ratio (alveolar ventilation/cardiac output). MTBE = methyl *tert*-butyl ether; PCE = tetrachloroethylene; TCA = trichloroacetic acid.

E.3.4 Uncertainty Factor for Variability within the Human Population

- Traditional application and previously published analyses.

A 10-fold uncertainty factor (UF_H) has traditionally been used by risk assessors to account for variability within the human population. As understanding of the sources of interindividual variability has evolved, this uncertainty factor has been regarded as consisting of two components, both with a value of $\sqrt{10}$, attributed to differences in toxicokinetics and toxicodynamics, respectively. The overall uncertainty factor is intended to account for the greater susceptibility to chemical toxicity of various sensitive subpopulations, including infants and children. Intraspecies variability in toxicokinetics can be better quantified now because of better data and advances in modeling techniques.

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

OEHHA has, like U.S.EPA (1994a), generally applied a 10-fold uncertainty factor to address the greater susceptibility of sensitive individuals. In accordance with U.S.EPA guidelines, when an exposure level is estimated from a study that includes the assessment of a sensitive human subpopulation, an intraspecies factor of 1 is used (U.S.EPA, 1994a). 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.

As noted by Dourson and Stara (1983), the steepness of the dose-response relationship affects the adequacy of the uncertainty factor for sensitive individuals. They summarized the range of dose response slopes reported by Weil (1972), indicating that, based on studies of acute lethality, a 10-fold factor was health-protective in most cases (Weil, 1972). However, in our experience, dose response curves for acute lethality exposures are generally steeper than those for non-lethal acute or chronic exposures (Table E.14).

TABLE E.3.14. COMPARISON OF SLOPES OF MILD AND LETHAL EFFECTS^A.

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

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

^b Human data for mild effects include: (Hine et al., 1961; Lester et al., 1963; MacEwen et al., 1970; Verberk, 1977).

^c Animal LC₅₀ studies include: (Silver and McGrath, 1948; Champeix and Catilina, 1967; Philipin et al., 1970; Prodan et al., 1975; Appelman et al., 1982; Kapeghian et al., 1982; U.S.EPA, 1992a; 1992b)

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.

E.3.5 Adequacy of the UF_{H-k} for younger ages – newer analyses.

Dorne et al. (2001) evaluated the validity of the 10^{0.5} (3.16) human toxicokinetic subfactor in relation to CYP1A2 metabolism using published data on clearance (CL), AUC and peak plasma concentrations (C_{max}) for caffeine, theophylline, theobromine, paraxanthine, and R-warfarin in human volunteers. After oral dosing, the variation (coefficient of variation, CV) in metabolic clearance in healthy adults of the first four compounds ranged from 25 to 63 percent (mean = 42 percent) in nine studies of 70 subjects. For i.v. dosing the variability of theophylline and R-warfarin ranged from 31 to 59 percent (mean = 43 percent) in four studies of 34 subjects. The authors concluded that in the case of kinetics of compounds metabolized by CYP1A2 “essentially the whole of the healthy adult population would be covered by the 3.16 kinetic default for both steady state (CL and AUC) and acute exposures (C_{max}) assuming a normal distribution, while between <0.01 to 1.8% would be outside the default factor of 3.16 assuming a log-normal distribution”. The authors identified population subgroups for which the default UF of 3.16 would be less protective. These included about one-half of pregnant women at term (based on caffeine at 38 weeks gestation), neonates (99-100 percent not covered), 13 percent of infants, but only 0.1 percent of children, who would have internal doses falling outside the default. It should be noted that these conclusions are based on a relatively few drugs administered orally or parenterally.

Ginsberg et al. (2002) also evaluated child/adult pharmacokinetic differences by analyzing the therapeutic drug literature. The authors identified about 100 chemicals with some pharmacokinetic (PK) data in children and a subset of 45 of these was selected for further study. Of the 45 chemicals, eight were excreted unchanged in urine, 18 had some form of CYP metabolism, six were unclassified, six were subject to glucuronidation, two to alcohol dehydrogenase, two to sulfation and one to glutathione conjugation. The subjects were classified as premature neonates (≤ 1 week, 7 chemicals), full-term neonates (≤ 1 week, 19 chemicals),

newborns (1 week-2 months, 14 chemicals), early infants (2-6 months, 7 chemicals), toddlers (6 mo-2 yr, 14 chemicals), preadolescents (2-12 yr, 26 chemicals), adolescents (12-18 yr, 7 chemicals) and adults (42 chemicals). The kinetic parameters evaluated (number of chemicals) were AUC (9), clearance (27), C_{max} (5), half-life ($t_{1/2}$, 41), and volume of distribution (V_d, 25).

Multiple regression analysis was used to evaluate relationships between age groups and the log mean PK parameter value across chemicals. In general, for many chemicals, early life stages (premature and full-term neonates, newborns 1 week to 2 months) appeared to be different from adults in terms of clearance, $t_{1/2}$, and V_d. For 40 chemicals with half-life data, the analysis showed that half-lives in premature neonates were about four-fold longer than in adults ($P < 0.001$) and about two-fold longer in full term neonates to two months of age ($P < 0.001$). For 27 chemicals with clearance data, premature to two months of age infants showed significantly lower clearance ($P < 0.01$) and six months to 12-year-old children significantly higher clearance ($P < 0.0001$) than adults. For the CYP1A2 substrates caffeine and theophylline, neonates to infants two months of age showed about four to nine-fold longer half-lives than adults while older age groups six months-12 years had significantly shorter half-lives than adults. A similar pattern was observed with the CYP3A substrates (e.g., alfentanil, carbamazepine, fentanyl, lignocaine).

The overall study results indicate that premature and full-term neonates tend to have three to nine times longer half-lives than adults for the drugs studied. Like the previous work of Renwick et al. (2000) and Dorne et al. (2001) noted above, the drugs studied were administered orally or parenterally and not via inhalation. While some of the same metabolic pathways are no doubt involved, it is difficult to make direct extrapolations from drugs to environmental toxicants. The authors note that three of the included chemicals, chloral hydrate, dichloroacetic acid and trichloroacetic acid, are major metabolites of trichloroethylene (TCE) and tetrachloroethylene (PCE), both important environmental contaminants.

Dorne et al. (2005a) estimated intraspecies pharmacokinetic uncertainty factors based on analysis of a database on human variability in phase I metabolism (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, hydrolysis, alcohol dehydrogenase (ADH)), phase II metabolism (N-acetyltransferases (NAT), glucuronidation, glycine conjugation, sulfation) and renal excretion. The authors derived pathway-specific UF_{H-k} s covering 95%, 97.5%, and 99% of the population of healthy adults, and other subgroups. For healthy adults exposed to toxicants metabolized by monomorphic pathways (CYP1A2, CYP2A6, CYP2E1, CYP3A4, ADH, hydrolysis, glucuronidation, sulfation, glycine conjugation) the UF_{H-k} of 3.16 was adequate to cover more than 99% of the population. However, for toxicants subject to polymorphic pathways, particularly CYP2C19 (99% - UF of 52) and CYP2D6 (99% - UF of 26) poor metabolizers and NAT slow acetylators (99% - UF of 5.2), these subpopulations were not adequately covered by a 3.16 UF_{H-k} . Children and neonates were among the subgroups analyzed. Children exposed to toxicants metabolized by CYP2C19 (99% - UF of 9.0) and CYP2D6 (99% - UF of 45) were not adequately protected by a UF of 3.16. Neonates were not adequately protected by the CYP1A2 (99% - UF of 14), CYP3A4 (99% - UF of 12), glucuronidation (99% - UF of 12), and glycine conjugation (99% - UF of 28) pathways and only marginally by the renal excretion path (99% - UF of 3.4). All of the compounds in the database evaluated were administered by the oral or intravenous routes. In addition, the UFs are estimated from internal dose metrics (AUCs or C_{max}s) for the parent compounds assuming that it is the toxicant of

concern. This may not be the case with many environmental toxicants of concern. The authors argue for the use of pathway-specific UFs in risk assessment instead of defaults. This may be feasible in some instances where metabolism, modes of action, and potential polymorphisms are well understood. However, there will still be a need for adequately protective defaults for sensitive subgroups when this is not the case. In view of the results of the authors' analysis it is apparent the UF_{H-k} of 3.16 is not adequately protective for infants and many children.

PBPK models can give useful predictions of how the body handles a particular chemical and its metabolites. The models address issues of internal body or tissue dosimetry, route to route extrapolation, and, in some cases, interspecies extrapolation. To date relatively few published models for various environmental pollutants address infant and child exposure in a systematic fashion. This is parallel to the bulk of toxicity testing in animals which is usually initiated in young adult animals.

Pelekis et al. (2001) used a physiological model to derive adult and child pharmacokinetic UFs for selected volatile organic compounds (VOCs). The chemicals modeled were dichloromethane (DCM), tetrachloroethylene (PCE), toluene (TOL), m-xylene (XYL), styrene (ST), carbon tetrachloride (CATE), chloroform (CHLO), and trichloroethylene (TCE). Adult models of low (50 kg) and high (90 kg) body weight were compared with a 10 kg-based child model. Fat contents varied from 51 percent for the 90 kg adult model to 17 percent for the 10 kg child. Ventilation:perfusion ratios varied from 0.76 (50 kg) to 1.38 (10 kg). Fractional liver flows (of cardiac output) ranged from 0.11 (50 kg) to 0.34 (90 kg). All PBPK models were flow-limited with exposure by inhalation, arterial circulation to Fat, Slowly Perfused, Rapidly Perfused and Liver model compartments, metabolism in the Liver, and combination of compartment outputs in venous blood. The arterial and venous bloods were not explicitly modeled, nor were VOC metabolites specifically modeled. A range of physiological parameters (blood:air and tissue:blood) was used for each body model and the eight VOC chemicals based on literature values.

Simulations involved exposure to one ppm VOC and estimation of arterial and venous blood concentrations (CA , CV), and tissue concentrations (C_i) after 30 days continuous exposure. A comparison of the two adult models (Adult high/Adult low) shows relatively few significant departures from unity for the dose metrics estimated. CATE ratios ranged from 2.85 ($C_{\text{rapidly perfused}}$) to 1.71 (C_{liver}). DCM ranged from 0.29 (C_{liver}) to 1.04 ($C_{\text{arterial blood}}$). Comparisons of the Adult high/Child average from the PBPK model show some larger differences. For the C_{liver} dose metric the PBPK models predicted the following Adult/Child values: ST (0.033), XYL (0.037), TCE (0.061), DCM (0.092), CHLO (0.11). These model predictions would indicate up to a 30-fold higher concentration of the VOC chemicals in child liver than in adult liver via the inhalation route.

While this is a useful approach involving important environmental toxicants and a relevant exposure route, the models and dose metrics employed address only the parent compounds where relevant toxic effects may be more closely related to the tissue dosimetry of metabolites, which were not specifically modeled. The use of a single child body weight is insufficient to assess the full range of physiological variability throughout development, particularly in the neonatal period. It is worth noting, however, that the higher concentrations of the VOCs in a child's liver

might be expected to result in higher peak concentrations of metabolites of those compounds in the liver.

E.3.6 Adequacy of the UF_{H-k} for Younger Ages – Indications from PBPK Modeling

The results of limited PBPK modeling with age-specific parameters and a range of about 20 chemicals are summarized in Table E3.13. For a variety of dose metrics for parent chemicals and metabolites it appears that a UF_{H-k} of $\sqrt{10}$ may be inadequate for one or more of the age-group models evaluated. Most frequently the newborn models showed the greatest child/adult ratios. It is important to note that the large majority of the studies and PBPK modeling exercises described above involve relatively short-term exposures that represent environmental, occupational, or therapeutic scenarios. Extreme situations of short-term high exposures or very long-term low level exposures were not simulated. Also considerable variation in child breathing rates was not modeled in a systematic fashion. Despite these limitations the results are considered indicative of the types of exposures of greatest concern with respect to infants and children.

E.4 Toxicokinetic Model Parameters for Individual Chemicals

This section provides a sampling of the parameters used in the PBPK modeling (Table E.3.13). Not all the chemical or all the age-specific parameters are given but the early age groups (ages 0-6 yr) have been emphasized.

TABLE E.4.1. PBPK MODEL PARAMETERS FOR FURAN: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
0-6 yr Model				
Fat, f	(1)	0.053*Qtot	33.39	
Liver l	(2)	0.0795*Qtot	4.69	Cart*Ql
Muscle, m	(3)	0.03*Qtot	3.24	
Brain, brain	(4)	(8)	8.82	
Lung, Vlu	(5)	Qtot	4.69	
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	4.69	
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot	4.69	
Other body	BW-(Vf + Vl + Vlu + Vbrain + Vm)	Qtot – (Qf + Ql + Qm + Qbrain)	4.69	
Alveolar ventilation, Qalv		0.8*Qtot		
Cardiac Output, Qtot		(6)		
Blood:Air, Pb			2.47	
Body weight, BW	(7)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age⁵ – 1.9784*Age⁴ + 51.963*Age³ – 459.38*Age² + 1566.8*Age + 1004.2)/1000; (2) Vl = (0.0072*Age⁵ – 0.3975*Age⁴ + 7.9052*Age³ – 65.624*Age² + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age⁵ + 2.3433*Age⁴ – 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2)/1000; (4) Vbrain = (1E4*((Age + 0.213)/(6.030 + 6.895*Age)))/1000; (5) Vlu = (-0.0346*Age⁴ + 1.5069*Age³ – 20.31*Age² + 123.99*Age + 59.213)/1000; (6) Qtot = 0.012*Age³ – 1.2144*Age² + 40.324*Age + 44.414; (7) BW = (-1.9*Age⁴ + 72.8*Age³ – 813.1*Age² + 5535.6*Age + 4453.7)/1000; (8) Qbrain = -0.0024*Age⁴ + 0.1305*Age³ – 2.4822*Age² + 18.025*Age + 15.197. For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qbrain = 0.159*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qbrain = 0.116*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qbrain = 0.1148Qtot. (Price, 2003)

TABLE E.4.2. PBPK MODEL PARAMETERS FOR MTBE: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
0-6 yr Model				
Fat, f	(1)	0.053*Qtot	4.79	
Liver, l	(2)	0.0795*Qtot	0.723	Vmax1, Km1 Vmax2, Km2
Muscle, m	(3)	0.03*Qtot	1.181	
VRG, vrg	(4)	0.674*Qtot	0.723	
Lung, Vlu	(5)	Qtot	0.723	
Kidneys, kid		0.164*Qtot		
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	0.723	
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot	0.723	
Alveolar ventilation, Qalv		0.8*Qtot		
Cardiac Output, Qtot		(6)		
Blood:Air, Pb			17.7	
Body weight, BW	(7)			

Age (yr)-specific regressions : (1) $V_f = (0.0162*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000$; (2) $V_l = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000$; (3) $V_m = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000$; (4) $V_{kid} = (9.373E-4*Age^5 - 0.0569*Age^4 + 1.1729*Age^3 - 10.34*Age^2 + 44.604*Age + 28.291)/1000$; (5) $V_{lu} = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000$; (6) $Q_{tot} = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414$; (7) $BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000$; For 7-10 yr model $Q_f = 0.05*Q_{tot}$; $Q_l = 0.118*Q_{tot}$; $Q_m = 0.045*Q_{tot}$; $Q_{kid} = 0.12*Q_{tot}$; For 11-18yr model $Q_f = 0.044*Q_{tot}$; $Q_l = 0.136*Q_{tot}$; $Q_m = 0.068*Q_{tot}$; $Q_{kid} = 0.136*Q_{tot}$. For adult $Q_f = 0.052*Q_{tot}$; $Q_l = 0.26*Q_{tot}$; $Q_m = 0.1648Q_{tot}$; $Q_{kid} = 0.26Q_{tot}$. $V_{max1} = 3.38E-5*BW^{0.75}$; $V_{max2} = 6.2E-6*BW^{0.75}$ mol/hr; $K_{m1} = 6.17E-5M$; $K_{m2} = 3.8E-6M$.

TABLE E.4.3. PBPK MODEL PARAMETERS FOR PCE: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat 1, f1	(1) $0.8 \cdot V_f$	$0.615 \cdot 0.053 \cdot Q_{tot}$	125.2	
Fat 2, f2	(1) $0.2 \cdot V_f$	$0.385 \cdot 0.053 \cdot Q_{tot}$	125.2	
Liver l	(2)	$0.0795 \cdot Q_{tot}$	5.28	Vmax1, Km1,K2
Muscle, m	(3)	$0.03 \cdot Q_{tot}$	6.11	
VRG, vrg	BW – ($V_f + V_l + V_m + V_{lu}$)	$0.674 \cdot Q_{tot}$	5.06	
Lung, Vlu	(4)	Q_{tot}	5.06	
Lung Alveoli, Valv	$0.9 \cdot V_{lu}$	$0.93 \cdot Q_{tot}$	5.06	
Lung bronchi, Vbr	$0.1 \cdot V_{lu}$	$0.07 \cdot Q_{tot}$	5.06	
Alveolar ventilation, Qalv		Q_{tot}		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			11.58	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) $V_f = (0.0162 \cdot \text{Age}^5 - 1.9784 \cdot \text{Age}^4 + 51.963 \cdot \text{Age}^3 - 459.38 \cdot \text{Age}^2 + 1566.8 \cdot \text{Age} + 1004.2)/1000$; (2) $V_l = (0.0072 \cdot \text{Age}^5 - 0.3975 \cdot \text{Age}^4 + 7.9052 \cdot \text{Age}^3 - 65.624 \cdot \text{Age}^2 + 262.02 \cdot \text{Age} + 157.52)/1000$; (3) $V_m = (-0.0623 \cdot \text{Age}^5 + 2.3433 \cdot \text{Age}^4 - 26.559 \cdot \text{Age}^3 + 144.75 \cdot \text{Age}^2 + 339.84 \cdot \text{Age} + 1648.2)/1000$; (4) $V_{lu} = (-0.0346 \cdot \text{Age}^4 + 1.5069 \cdot \text{Age}^3 - 20.31 \cdot \text{Age}^2 + 123.99 \cdot \text{Age} + 59.213)/1000$; (5) $Q_{tot} = 0.012 \cdot \text{Age}^3 - 1.2144 \cdot \text{Age}^2 + 40.324 \cdot \text{Age} + 44.414$; (6) $BW = (-1.9 \cdot \text{Age}^4 + 72.8 \cdot \text{Age}^3 - 813.1 \cdot \text{Age}^2 + 5535.6 \cdot \text{Age} + 4453.7)/1000$; For 7-10 yr model $Q_f = 0.05 \cdot Q_{tot}$; $Q_l = 0.118 \cdot Q_{tot}$; $Q_m = 0.045 \cdot Q_{tot}$; $Q_{kid} = 0.12 \cdot Q_{tot}$; For 11-18yr model $Q_f = 0.044 \cdot Q_{tot}$; $Q_l = 0.136 \cdot Q_{tot}$; $Q_m = 0.068 \cdot Q_{tot}$; $Q_{kid} = 0.136 \cdot Q_{tot}$. For adult $Q_f = 0.052 \cdot Q_{tot}$; $Q_l = 0.26 \cdot Q_{tot}$; $Q_m = 0.1648 \cdot Q_{tot}$; $Q_{kid} = 0.26 \cdot Q_{tot}$. $V_{max1} = 1.69E-6 \cdot BW^{0.75}$ mol/hr; $K_{m1} = 4.6E-5M$; $K_2 = 2.0 \cdot BW^{-0.25}$.

TABLE E.4.4. PBPK MODEL PARAMETERS FOR BAP: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat, f	(1)	0.053*Qtot	294.7	
Liver, l	(2)	0.0795*Qtot	7.0	Vmax1, Km1, Vmaxlu Kmlu
Muscle, m	(3)	0.03*Qtot	4.0	
KVRG, kvrg	BW – (Vf+Vl+Vm+Vlu)	Qtot – (Qf + Ql + Qm)	4.0	
Lung, Vlu	(4)	Qtot		
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	1.3	
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot	2.3	
Alveolar ventilation, Qalv		Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			10	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) $V_f = (0.0162 \cdot \text{Age}^5 - 1.9784 \cdot \text{Age}^4 + 51.963 \cdot \text{Age}^3 - 459.38 \cdot \text{Age}^2 + 1566.8 \cdot \text{Age} + 1004.2)/1000$; (2) $V_l = (0.0072 \cdot \text{Age}^5 - 0.3975 \cdot \text{Age}^4 + 7.9052 \cdot \text{Age}^3 - 65.624 \cdot \text{Age}^2 + 262.02 \cdot \text{Age} + 157.52)/1000$; (3) $V_m = (-0.0623 \cdot \text{Age}^5 + 2.3433 \cdot \text{Age}^4 - 26.559 \cdot \text{Age}^3 + 144.75 \cdot \text{Age}^2 + 339.84 \cdot \text{Age} + 1648.2)/1000$; (4) $V_{lu} = (-0.0346 \cdot \text{Age}^4 + 1.5069 \cdot \text{Age}^3 - 20.31 \cdot \text{Age}^2 + 123.99 \cdot \text{Age} + 59.213)/1000$; (5) $Q_{tot} = 0.012 \cdot \text{Age}^3 - 1.2144 \cdot \text{Age}^2 + 40.324 \cdot \text{Age} + 44.414$; (6) $BW = (-1.9 \cdot \text{Age}^4 + 72.8 \cdot \text{Age}^3 - 813.1 \cdot \text{Age}^2 + 5535.6 \cdot \text{Age} + 4453.7)/1000$; For 7-10 yr model $Q_f = 0.05 \cdot Q_{tot}$; $Q_l = 0.118 \cdot Q_{tot}$; $Q_m = 0.045 \cdot Q_{tot}$; $Q_{kid} = 0.12 \cdot Q_{tot}$; For 11-18yr model $Q_f = 0.044 \cdot Q_{tot}$; $Q_l = 0.136 \cdot Q_{tot}$; $Q_m = 0.068 \cdot Q_{tot}$; $Q_{kid} = 0.136 \cdot Q_{tot}$. For adult $Q_f = 0.052 \cdot Q_{tot}$; $Q_l = 0.26 \cdot Q_{tot}$; $Q_m = 0.1648 \cdot Q_{tot}$; $Q_{kid} = 0.26 \cdot Q_{tot}$. $V_{max1} = 1.7E-9 \cdot (BW/0.25)^{0.75}$ mol/hr; $K_{m1} = 5.5E-6M$; $V_{maxlu} = 1.2E-11 \cdot (BW/0.25)^{0.75}$ mol/hr, $K_{mlu} = 2.2E-7M$.

TABLE E.4.5. PBPK-RT MODEL PARAMETERS FOR NAP/NO: 0-5 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood NAP/NO	Metabolism
Fat, f	(1)	0.053*Q _{tot}	160/22.9	
Liver, l	(2)	0.0795*Q _{tot}	7.0/7.0	V _{max1} , K _{m1} , V _{max2} , K _{m2} , K _{m2ih} , V _{max3} , K _{m3GSH} , K _{m3NO}
Muscle, m	(3)	0.03*Q _{tot}	4.0/4.0	
VRG, vrg	BW – (V _f +V _l +V _m +V _{lu} +V _{blood})	Q _{tot} – (Q _f + Q _l + Q _m)	4.0/4.0	
V _{blood} , blood	0.075*BW			
Lung, V _{lu}	(4)	Q _{tot}		V _{maxlu} , K _{mlu} , V _{max2lu} , K _{m2} , K _{m2ih} , V _{max3} , K _{m3GSH} , K _{m3NO}
Lung URT, V _{ua}	0.0026*V _{lu}	0.0025*Q _{tot}		
Lung CA, V _{ca}	0.018*V _{lu}	0.0075*Q _{tot}		
Lung TB, V _{tb}	0.043*V _{lu}	0.0067*Q _{tot}		
Lung PU, V _{pu}	0.9378V _{lu}	0.983*Q _{tot}		
Alveolar ventilation, Q _{alv}		0.82*Q _{tot}		
Cardiac Output, Q _{tot}		(5)		
Blood:Air, P _b			571/571	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) $V_f = 0.0162*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2$; (2) $V_l = 0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52$; (3) $V_m = -0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2$; (4) $V_{lu} = -0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213$; (5) $Q_{tot} = (0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414)*(1000/60)$; (6) $BW = -1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7$; For 7-10 yr model $Q_f = 0.05*Q_{tot}$; $Q_l = 0.118*Q_{tot}$; $Q_m = 0.045*Q_{tot}$; $Q_{kid} = 0.12*Q_{tot}$; For 11-18yr model $Q_f = 0.044*Q_{tot}$; $Q_l = 0.136*Q_{tot}$; $Q_m = 0.068*Q_{tot}$; $Q_{kid} = 0.136*Q_{tot}$. For adult $Q_f = 0.052*Q_{tot}$; $Q_l = 0.26*Q_{tot}$; $Q_m = 0.1648*Q_{tot}$; $Q_{kid} = 0.26*Q_{tot}$. V_{max1} (P450) = $2.46E-2*MPI*V_l/(BW/250)^{0.25}$ $\mu\text{mol}/\text{min}$; $K_{m1} = 0.003\text{mM}$; V_{maxlu} (P450) = $2.45E-3*MPlu*V_{lu}/(BW/250)^{0.25}$ $\mu\text{mol}/\text{min}$, $K_{mlu} = 0.006\text{mM}$. V_{max2l} (Epoxide Hydrolase) = $4.0E-3*MPI*V_l/(BW/250)^{0.25}$ $\mu\text{mol}/\text{min}$, $K_{m2} = 0.001\text{mM}$, $K_{m2ih} = 2.0E-4\text{mM}$, $V_{max2lu} = 9.0E-3*MPlu*V_{lu}/(BW/250)^{0.25}$ $\mu\text{mol}/\text{min}$, $K_{m2lu} = 0.001\text{mM}$, $K_{m2luh} = 2E-4\text{mM}$. V_{max3} (GST) = $0.5*CPI*V_l/(BW/250)^{0.25}$ $\mu\text{mol}/\text{min}$, K_{m3} (GSH) = 3.3mM , K_{m3} (NO) = 0.05mM , $V_{max3lu} = 0.4*CPlu*V_{lu}/(BW/250)^{0.25}$ $\mu\text{mol}/\text{min}$. $MPI = 14.5\text{mg}/\text{mL}$, $MPlu = 3.0\text{mg}/\text{mL}$, $CPI = 58\text{mg}/\text{mL}$, $CPlu = 54\text{mg}/\text{mL}$ tissue.

TABLE E.4.6. PBPK-RT MODEL PARAMETERS FOR BD/BMO: 0-5 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood BD/BMO	Metabolism
Fat, f	(1)	0.053*Qtot	118.2/1.808	
Liver, l	(2)	0.0795*Qtot	5.49/0.654	Vmax1, Km1, Vmax2, Km2, Km2ih, VmaxG, KmG _{GSH} , KmG _{BMO} , Vmax3, Km3
Muscle, m	(3)	0.03*Qtot	5.26/0.653	
VRG, vrg	BW – (Vf+Vl+Vm +Vlu+Vblood)	Qtot – (Qf + Ql + Qm)	5.34/0.635	
Vblood, blood	0.075*BW			
Lung, Vlu	(4)	Qtot		Vmaxlu, Kmlu, K1, K2, Vmax3lu
Lung URT, Vua	0.0026*Vlu	0.0025*Qtot		
Lung CA, Vca	0.018*Vlu	0.0075*Qtot		
Lung TB, Vtb	0.043*Vlu	0.0067*Qtot		
Lung PU, Vpu	0.9378Vlu	0.983*Qtot		
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			1.5/60	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) $V_f = 0.0162*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2$; (2) $V_l = 0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52$; (3) $V_m = -0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2$; (4) $V_{lu} = -0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213$; (5) $Q_{tot} = (0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414)8(1000/60)$; (6) $BW = -1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7$; For 7-10 yr model $Q_f = 0.05*Q_{tot}$; $Q_l = 0.118*Q_{tot}$; $Q_m = 0.045*Q_{tot}$; $Q_{kid} = 0.12*Q_{tot}$; For 11-18yr model $Q_f = 0.044*Q_{tot}$; $Q_l = 0.136*Q_{tot}$; $Q_m = 0.068*Q_{tot}$; $Q_{kid} = 0.136*Q_{tot}$. For adult $Q_f = 0.052*Q_{tot}$; $Q_l = 0.26*Q_{tot}$; $Q_m = 0.1648*Q_{tot}$; $Q_{kid} = 0.26*Q_{tot}$. $V_{max1} (P450) = 7.08E-2*MP1*V_l*(7E4/BW)^{0.25}/60 \mu\text{mol}/\text{min}$; $K_{m1} = 0.00514\text{mM}$; $V_{maxlu} (P450) = 9.09E-3*MPlu*V_{lu}*(7E4/BW)^{0.25}/60 \mu\text{mol}/\text{min}$, $K_{mlu} = 0.002\text{mM}$. V_{max2} (Epoxide Hydrolase) = $1.1*MP1*V_l*(7E4/BW)^{0.25}/60 \mu\text{mol}/\text{min}$, $K_{m2} = 0.58 \text{mM}$, $K_{m2ih} = 0.116 \text{mM}$, $K_1 = 0.1914*V_{lu}*Mplu*(7E4/BW)^{0.25}/60 \mu\text{mol}/\text{min}$. V_{maxG1} (GST) = $2.71*CPlu*V_l*(7E4/BW)^{0.25}/60 \mu\text{mol}/\text{min}$, K_{m3G} (GSH) = 0.1mM , K_{mG} (BMO) = 10.4mM , K_2 (GST) = $0.1536*V_{lu}*Cplu*(7E4/BW)^{0.25}/60 \mu\text{mol}/\text{min}$. V_{max3} (P450) = $14.8*V_l*MP1*(7E4/BW)^{0.25}/60 \mu\text{mol}/\text{min}$, $V_{max3lu} = 1.7*V_{lu}*Cplu*(7E4/BW)^{0.25}/60 \mu\text{mol}/\text{min}$. $MP1 = 14.5 \text{mg}/\text{mL}$, $Mplu = 3.0 \text{mg}/\text{mL}$, $CPlu = 58 \text{mg}/\text{mL}$, $CPlu = 54 \text{mg}/\text{mL}$ tissue.

TABLE E.4.7. PBPK MODEL PARAMETERS FOR BD/BMO/DEB: 0-5 YEARS OF AGE

Tissue/ Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood BD/BMO/DEB	Metabolism
Fat, f	(1)	0.053*Qtot	118.2/1.808/0.715	
Liver, l	(2)	0.0795*Qtot	5.49/0.6545/0.7	Vmax1, Km,Vmax1l Km1, Km1ih, Vmax12, Km2 _{GSH} , Km2 _{BMO} Vmax13, Km3, Km3ih, Ke
Muscle, m	(3)	0.03*Qtot	5.26/0.6533/0.697	
VRG, kvrg	BW – (Vf+Vl+Vm+Vlu)	Qtot – (Qf + Ql + Qm)	5.34/0.6348/0.6	
Lung, Vlu	(4)	Qtot	4.02/0.4725/0.6	Vmaxlu, Kmlu, K1, K2,Ke
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot		Vmax3pu
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot		Vmax3br
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			1.5/60/300	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age⁵ – 1.9784*Age⁴ + 51.963*Age³ – 459.38*Age² + 1566.8*Age + 1004.2)/1000; (2) V1 = (0.0072*Age⁵ – 0.3975*Age⁴ + 7.9052*Age³ – 65.624*Age² + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age⁵ + 2.3433*Age⁴ – 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age⁴ + 1.5069*Age³ – 20.31*Age² + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age³ – 1.2144*Age² + 40.324*Age + 44.414; (6) BW = (-1.9*Age⁴ + 72.8*Age³ – 813.1*Age² + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 (P450) = 7.08E-8*(70/BW)^{0.25} mol/hr/mg MPI/Ltissue; Km1 = 5.14E-6M; Vmaxlu = 9.0E-9*(70/BW)^{0.25} mol/hr/mg MPlu/Ltissue, Kmlu = 2.0E-6M. Vmax1l(EH) = 1.1E-6*(70/BW)^{0.25} mol/hr/mg MPI/Ltissue, Km1 = 5.8E-4 M, Km1ih = 1.16E-4 M, K1 = 0.1914*(70/BW)^{-0.25} mol/hr/mg MPlu/Ltissue. Vmax12 = 2.71E-6*(70/BW)^{0.25} mol/hr/mg CPI/Ltissue, Km2_{GST} = 1.04E-2M. Km2_{BMO} = 1.0E-4M, K2 = 0.1536*(70/BW)^{-0.25} mol/hr/mg CPlu/Ltissue. Vmax13 (P450) = 1.48E-5*(70/BW)^{0.25} mol/hr, Km3 = 1.56E-5M, Km3ih = 3.12E-6M, Vmax3pu = 1.7E-6*(70/BW)^{0.25} mol/hr, Vmax3br = 2.0E-7*(70/BW)^{0.25} mol/hr. Ke(DEB elimination) = 0.6*(70/BW)^{-0.25}/hr

**TABLE E.4.8. PBPK-RT MODEL PARAMETERS FOR STYRENE/SO:
0-5 YEARS OF AGE**

Tissue/ Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood ST/SO	Metabolism
Fat, f	(1)	0.053*Qtot	93.8/6.1	
Liver, l	(2)	0.0795*Qtot	2.71/2.6	Vmax1, Km, Vmax2, Km2, VmaxG, KmG _{GSH} , KmG _{SO}
Muscle, m	(3)	0.0304*Qtot	1.96/1.5	
VRG, vrg	BW – (Vf+Vl+Vm+ Vlu+Vblood)	Qtot – (Qf + Ql + Qm)	2.60/0.6	
Vblood, blood	0.075*BW			
Lung, Vlu	(4)	Qtot		
Lung URT, Vua	0.0026*Vlu	0.0025*Qtot		Vmaxua, Kmlu, Vmaxua2, Kmlu2, VmaxGua, KmG _{GSH} , KmG _{SO}
Lung CA, Vca	0.018*Vlu	0.0075*Qtot		
Lung TB, Vtb	0.043*Vlu	0.0067*Qtot		Vmaxtb, Kmlu, Vmaxtb2, Kmlu2, VmaxGtb, KmG _{GSH} , KmG _{SO}
Lung PU, Vpu	0.9378Vlu	0.983*Qtot		
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			48/2000	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) $V_f = 0.0162*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2$; (2) $V_l = 0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52$; (3) $V_m = -0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2$; (4) $V_{lu} = -0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213$; (5) $Q_{tot} = (0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414)8(1000/60)$; (6) $BW = -1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7$; For 7-10 yr model $Q_f = 0.05*Q_{tot}$; $Q_l = 0.118*Q_{tot}$; $Q_m = 0.045*Q_{tot}$; $Q_{kid} = 0.12*Q_{tot}$; For 11-18yr model $Q_f = 0.044*Q_{tot}$; $Q_l = 0.136*Q_{tot}$; $Q_m = 0.068*Q_{tot}$; $Q_{kid} = 0.136*Q_{tot}$. For adult $Q_f = 0.052*Q_{tot}$; $Q_l = 0.26*Q_{tot}$; $Q_m = 0.1648*Q_{tot}$; $Q_{kid} = 0.26*Q_{tot}$. $V_{max1} (P450) = 0.033*(7E4/BW)^{0.25}$ $\mu\text{mol}/\text{min}/\text{mLtissue}$; $K_{mlu} = 0.01\text{mM}$; $V_{maxua} = V_{maxtb} (P450) = 4.17E-5*(7E4/BW)^{0.25}$ $\mu\text{mol}/\text{min}/\text{mLtissue}$, $K_{mlu2} = 0.0175\text{mM}$. $V_{max2} (\text{Epoxide Hydrolase}) = 0.075*(7E4/BW)^{0.25}$ $\mu\text{mol}/\text{min}/\text{mLtissue}$, $K_{m2} = 0.01\text{mM}$. $V_{maxua2} = V_{maxtb2} = 0.0112*(7E4/BW)^{0.25}$ $\mu\text{mol}/\text{min}/\text{mLtissue}$, $K_{mlu2} = 0.0156\text{mM}$. $V_{maxG} (\text{GST}) = 0.467*(7E4/BW)^{0.25}$ $\mu\text{mol}/\text{min}/\text{mLtissue}$, $K_{mG_{SH}} = 0.1\text{mM}$, $K_{mG_{SO}} = 2.5\text{mM}$, $V_{maxGua} = V_{maxGtb} = 1.36*(7E4/BW)^{0.25}$ $\mu\text{mol}/\text{min}/\text{mLtissue}$.

**TABLE E.4.9. PBPK MODEL PARAMETERS FOR VINYL CHLORIDE:
0-5 YEARS OF AGE**

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat, f	(1)	0.053*Qtot	20.7	
Liver, l	(2)	0.0795*Qtot	1.45	Vmax1, Km1, Vmax2 Km2
Muscle, m	(3)	0.03*Qtot	0.83	
VRG, kvrg	BW – (Vf+Vl+Vm +Vlu)	Qtot – (Qf + Ql + Qm)	1.45	
Lung, Vlu	(4)	Qtot		
Lung alveoli, Valv	0.9*Vlu	0.93*Qtot	1.45	
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot	1.45	
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			1.16	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age⁵ – 1.9784*Age⁴ + 51.963*Age³ – 459.38*Age² + 1566.8*Age + 1004.2)/1000; (2) Vl = (0.0072*Age⁵ – 0.3975*Age⁴ + 7.9052*Age³ – 65.624*Age² + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age⁵ + 2.3433*Age⁴ – 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age⁴ + 1.5069*Age³ – 20.31*Age² + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age³ – 1.2144*Age² + 40.324*Age + 44.414; (6) BW = (-1.9*Age⁴ + 72.8*Age³ – 813.1*Age² + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 = 4.0*BW^{0.75} mg/hr; Km1 = 1.0 mg/L; Vmax2 = 0.1*BW^{0.75} mg/hr, Km2 = 10 mg/L .

**TABLE E.4.10. PBPK MODEL PARAMETERS FOR TCE AND METABOLITES:
0-5 YEARS OF AGE**

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood TCE/CH/TCA/ TCOH/TCOG	Metabolism
Fat, f	(1)	0.053*Qtot	36.38/	
Liver, l	(2)	0.0795*Qtot	1.73/1.42/1.18/ 1.30/0.56	Vmax1, Km1 PTCA, PTCOH, KTCA, Vmax2,Km2
Muscle, m	(3)	0.03*Qtot	2.36/	
VRG, vrg	(4)	0.674*Qtot	1.73/	
Lung, Vlu	(5)	Qtot	2.61/1.65/0.54/ 0.78/1.06	
Kidneys, kid	(6)	0.164*Qtot	2.07/0.98/0.74/ 1.02/1.44	
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	2.61/1.65/0.54/ 0.78/1.06	
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot	2.61/1.65/0.54/ 0.78/1.06	
Body (metabolite submodels)			/1.35/0.88/1.11/ 1.11	
Alveolar ventilation, Qalv		0.8*Qtot		
Cardiac Output, Qtot		(7)		
Blood:Air, Pb			15.91/	
Body weight, BW	(8)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age⁵ - 1.9784*Age⁴ + 51.963*Age³ - 459.38*Age² + 1566.8*Age + 1004.2)/1000; (2) V1 = (0.0072*Age⁵ - 0.3975*Age⁴ + 7.9052*Age³ - 65.624*Age² + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age⁵ + 2.3433*Age⁴ - 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2)/1000; (4) Vkid = (9.373E-4*Age⁵ - 0.0569*Age⁴ + 1.1729*Age³ - 10.34*Age² + 44.604*Age + 28.291)/1000; (5) Vlu = (-0.0346*Age⁴ + 1.5069*Age³ - 20.31*Age² + 123.99*Age + 59.213)/1000; (6) Vkid = (9.373E-4*Age⁵ - 0.0569*Age⁴ + 1.1729*Age³ - 10.34*Age² + 44.604*Age + 28.291)/1000 (7) Qtot = 0.012*Age³ - 1.2144*Age² + 40.324*Age + 44.414; (8) BW = (-1.9*Age⁴ + 72.8*Age³ - 813.1*Age² + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 (TCE→CH) = 2.49E-4*BW^{0.75} mol/hr, Km1 = 3.51E-5M; Vmax2 (TCOH→TCOG) = 1.11E-4*BW^{0.75} mol/hr, Km2 = 1.06E-4M. PTCA(CH→TCA) = 115*BW /hr; PTCOH (CH→TCOH) = 309*BW /hr; KTCA (TCOH→TCA) = 10 /hr. Urinary excretion rates /hr: KU_{TCA} = 1.55*BW; KU_{TCOH} = 1.14*BW; KU_{TCOG} = 32.8*BW. CH = chloral hydrate; TCA = trichloroacetic acid; TCOH = trichloroethanol; TCOG = trichloroethanol glucuronide.

TABLE E.4.11. PBPK MODEL PARAMETERS FOR DCM: 0-5 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat, f	(1)	0.053*Qtot	7.239	
Liver, l	(2)	0.0795*Qtot	0.824	Vmaxl, Km, Kfl
Muscle, m	(3)	0.03*Qtot	1.09	
VRG, vrg	(4)	0.674*Qtot	0.788	
Lung, Vlu	(5)	Qtot	0.552	
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	0.552	Vmaxpu, Km, Kfpu
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot	0.552	Vmaxbr, Km, Kfbr
Alveolar ventilation, Qalv		0.8*Qtot		
Cardiac Output, Qtot		(6)		
Blood:Air, Pb			9.09	
Body weight, BW	(7)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age⁵ - 1.9784*Age⁴ + 51.963*Age³ - 459.38*Age² + 1566.8*Age + 1004.2)/1000; (2) Vl = (0.0072*Age⁵ - 0.3975*Age⁴ + 7.9052*Age³ - 65.624*Age² + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age⁵ + 2.3433*Age⁴ - 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2)/1000; (4) Vkid = (9.373E-4*Age⁵ - 0.0569*Age⁴ + 1.1729*Age³ - 10.34*Age² + 44.604*Age + 28.291)/1000; (5) Vlu = (-0.0346*Age⁴ + 1.5069*Age³ - 20.31*Age² + 123.99*Age + 59.213)/1000; (6) Qtot = 0.012*Age³ - 1.2144*Age² + 40.324*Age + 44.414; (7) BW = (-1.9*Age⁴ + 72.8*Age³ - 813.1*Age² + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmaxl (P450) = 8.58E-5*BW^{0.7} mol/hr; Vmaxpu = 0.9*1.46E-3*Vmaxl; Vmaxbr = 0.1*1.46E-3*Vmaxl, Km = 8.7E-6M; Kfl (GST) = 1.26*BW^{-0.3}, Kfpu = 0.9*0.242*Kfl, Kfbr = 0.1*0.242*Kfl

**TABLE E.4.12. PBPK MODEL PARAMETERS FOR ETHYLENE/EO:
0-6 YEARS OF AGE**

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood ET/EO	Metabolism
Fat, f	(1)	0.053*Qtot	8.73/0.70	
Liver, l	(2)	0.0795*Qtot	2.05/0.89	ClrET ClrEO L/hr
Muscle, m	(3)	0.0304*Qtot	2.95/1.08	
VRG, vrg	BW – (Vf+Vl+Vm +Vlu+Vblood)	Qtot – (Qf + Ql + Qm)	2.18/1.03	
Vlubd, lung blood	0.0079*BW			
Vart, arterial blood	0.0178*BW			
Vven, venous blood	0.0533*BW			
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(4)		
Blood:Air, Pb			0.22/61	
Body weight, BW	(5)			

Age (yr)-specific regressions : (1) $V_f = (0.0162 \cdot \text{Age}^5 - 1.9784 \cdot \text{Age}^4 + 51.963 \cdot \text{Age}^3 - 459.38 \cdot \text{Age}^2 + 1566.8 \cdot \text{Age} + 1004.2)/1000$; (2) $V_l = (0.0072 \cdot \text{Age}^5 - 0.3975 \cdot \text{Age}^4 + 7.9052 \cdot \text{Age}^3 - 65.624 \cdot \text{Age}^2 + 262.02 \cdot \text{Age} + 157.52)/1000$; (3) $V_m = (-0.0623 \cdot \text{Age}^5 + 2.3433 \cdot \text{Age}^4 - 26.559 \cdot \text{Age}^3 + 144.75 \cdot \text{Age}^2 + 339.84 \cdot \text{Age} + 1648.2)/1000$; (4) $Q_{tot} = 0.012 \cdot \text{Age}^3 - 1.2144 \cdot \text{Age}^2 + 40.324 \cdot \text{Age} + 44.414$; (5) $BW = (-1.9 \cdot \text{Age}^4 + 72.8 \cdot \text{Age}^3 - 813.1 \cdot \text{Age}^2 + 5535.6 \cdot \text{Age} + 4453.7)/1000$; For 7-10 yr model $Q_f = 0.05 \cdot Q_{tot}$; $Q_l = 0.118 \cdot Q_{tot}$; $Q_m = 0.045 \cdot Q_{tot}$; For 11-18yr model $Q_f = 0.044 \cdot Q_{tot}$; $Q_l = 0.136 \cdot Q_{tot}$; $Q_m = 0.068 \cdot Q_{tot}$; $Q_{kid} = 0.136 \cdot Q_{tot}$. For adult $Q_f = 0.052 \cdot Q_{tot}$; $Q_l = 0.26 \cdot Q_{tot}$; $Q_m = 0.1648 \cdot Q_{tot}$; $Q_{kid} = 0.26 \cdot Q_{tot}$. Metabolic clearance by liver: $Clr_{ET} (P450) = 74.9 \cdot (70/BW)^{0.25}$ L/hr; $Clr_{EO} (EH+GST) = 1.53 \cdot (70/BW)^{0.25}$ L/hr. (Csanady et al., 2000; Price et al., 2003)

TABLE E.4.13. PBPK-RT MODEL PARAMETERS FOR STYRENE/SO ADULT

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood ST/SO	Metabolism
Fat, f	0.19*BW	0.05*Qtot	93.8/6.1	
Liver, l	0.026*BW	0.26*Qtot	2.71/2.6	Vmax11, Kml1, Vmax12, Kml2eh, Kml2app, Vmax13, Kml3 _{GSH} , Kml3 _{SO} , Kdl
Muscle, m	0.541*BW	0.25*Qtot	1.96/1.5	
VRG, vrg	BW – (Vf+Vl+Vm +Vlu+Vblood)	Qtot – (Qf + Ql + Qm)	2.60/2.6	
Vlubld, lung blood	0.0079*BW			
Vart, arterial blood	0.0178*BW			
Vven, venous blood	0.0533*BW			
Lung tissue, Vlu	0.0076*BW			
Vluc, conducting zone, fs = 0.1	fs*Vlu			Vmaxlu1, Kmlu1, Vmaxlu2, Kmlu2, Vmaxlu3, Kmlu3 _{GSH} , Kmlu3, Kdlu _{SO}
Vlua, alveolar zone	(1-fs)*Vlu			Vmaxlu1, Kmlu1, Vmaxlu2, Kmlu2, Vmaxlu3, Kmlu3 _{GSH} , Kmlu3, Kdlu _{SO}
Alveolar ventilation, Qalv, L/hr		300		
Cardiac Output, Qtot, L/hr		372		
Blood:Air, Pb			70/2370	
Body weight, BW kg	70			

Vmax1 = 0.002 mmol/hr/mL tissue, Kml1 = 0.01 mM; Vmax12 = 0.0045, Kml2eh = 0.001, Kml2app = 0.01; Vmax13 = 0.028, Kml3G = 0.1, Kml3so = 2.5, Kdl = 0.2; Vmaxlu1 = 2.5E-6, Kmlu1 = 0.0175; Vmaxlu2 = 6.73E-4, Kmlu2 = 0.0156; Vmaxlu3 = 0.082, Kmlu3 = 0.082; Kmlu3G = 0.1, Kmlu3so = 2.5, Kdlu = 2.0. (Csanady et al., 2003)

**TABLE E.4.14. PBPK MODEL PARAMETERS FOR CARBON TETRACHLORIDE:
0-6 YEARS OF AGE**

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat, f	(1)	0.053*Qtot	79.4	
Liver, l	(2)	0.0795*Qtot	3.14	Vmaxl, Km
Muscle, m	(3)	0.03*Qtot	1.00	
VRG, vrg	BW – (Vf+Vl+Vm+Vlu)	Qtot – (Qf + Ql + Qm)	1.00	
Lung, Vlu	(4)	Qtot		
Lung alveoli, Valv	0.9*Vlu	0.93*Qtot	1.00	
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot	1.00	
Alveolar ventilation, Qalv		Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			4.52	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age⁵ – 1.9784*Age⁴ + 51.963*Age³ – 459.38*Age² + 1566.8*Age + 1004.2)/1000; (2) Vl = (0.0072*Age⁵ – 0.3975*Age⁴ + 7.9052*Age³ – 65.624*Age² + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age⁵ + 2.3433*Age⁴ – 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age⁴ + 1.5069*Age³ – 20.31*Age² + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age³ – 1.2144*Age² + 40.324*Age + 44.414; (6) BW = (-1.9*Age⁴ + 72.8*Age³ – 813.1*Age² + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmaxl = 1.35E-7*BW^{0.75} mol/hr; Km = 5.68E-5 mol/L. 23.0 mg MP/mL liver tissue. (Thrall et al., 2000; Price et al., 2003)

TABLE E.4.15: PBPK MODEL PARAMETERS FOR TOLUENE 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat, f	(1)	0.053*Qtot	65.8	
Liver, l	(2)	0.0795*Qtot	2.98	Vmax1, Km, Ki
Muscle, m	(3)	0.03*Qtot	1.37	
VRG, vrg	BW – (Vf+Vl+Vm+Vlu)	Qtot – (Qf + Ql + Qm)	2.66	
Lung, Vlu	(4)	Qtot		
Lung alveoli, Valv	0.9*Vlu	0.93*Qtot	2.66	
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot	2.66	
Alveolar ventilation, Qalv		Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			15.6	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) $V_f = (0.0162 \cdot \text{Age}^5 - 1.9784 \cdot \text{Age}^4 + 51.963 \cdot \text{Age}^3 - 459.38 \cdot \text{Age}^2 + 1566.8 \cdot \text{Age} + 1004.2)/1000$; (2) $V_l = (0.0072 \cdot \text{Age}^5 - 0.3975 \cdot \text{Age}^4 + 7.9052 \cdot \text{Age}^3 - 65.624 \cdot \text{Age}^2 + 262.02 \cdot \text{Age} + 157.52)/1000$; (3) $V_m = (-0.0623 \cdot \text{Age}^5 + 2.3433 \cdot \text{Age}^4 - 26.559 \cdot \text{Age}^3 + 144.75 \cdot \text{Age}^2 + 339.84 \cdot \text{Age} + 1648.2)/1000$; (4) $V_{lu} = (-0.0346 \cdot \text{Age}^4 + 1.5069 \cdot \text{Age}^3 - 20.31 \cdot \text{Age}^2 + 123.99 \cdot \text{Age} + 59.213)/1000$; (5) $Q_{tot} = 0.012 \cdot \text{Age}^3 - 1.2144 \cdot \text{Age}^2 + 40.324 \cdot \text{Age} + 44.414$; (6) $BW = (-1.9 \cdot \text{Age}^4 + 72.8 \cdot \text{Age}^3 - 813.1 \cdot \text{Age}^2 + 5535.6 \cdot \text{Age} + 4453.7)/1000$; For 7-10 yr model $Q_f = 0.05 \cdot Q_{tot}$; $Q_l = 0.118 \cdot Q_{tot}$; $Q_m = 0.045 \cdot Q_{tot}$; $Q_{kid} = 0.12 \cdot Q_{tot}$; For 11-18yr model $Q_f = 0.044 \cdot Q_{tot}$; $Q_l = 0.136 \cdot Q_{tot}$; $Q_m = 0.068 \cdot Q_{tot}$; $Q_{kid} = 0.136 \cdot Q_{tot}$. For adult $Q_f = 0.052 \cdot Q_{tot}$; $Q_l = 0.26 \cdot Q_{tot}$; $Q_m = 0.1648 \cdot Q_{tot}$; $Q_{kid} = 0.26 \cdot Q_{tot}$. $V_{max1} = 5.2E-5 \cdot BW \cdot (70/BW)^{0.25}$ mol/hr; $K_m = 5.97E-6$ M, $K_i = 3.8E-6$ M. (Tardif et al., 1995; Price et al., 2003)

TABLE E.4.16. PBPK MODEL PARAMETERS FOR XYLENE: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat, f	(1)	0.053*Qtot	77.8	
Liver, l	(2)	0.0795*Qtot	3.02	Vmax1, Km, Ki
Muscle, m	(3)	0.03*Qtot	3.00	
VRG, vrg	BW – (Vf+Vl+Vm+ Vlu)	Qtot – (Qf + Ql + Qm)	4.42	
Lung, Vlu	(4)	Qtot		
Lung alveoli, Valv	0.9*Vlu	0.93*Qtot	4.42	
Lung bronchi, Vbr	0.1*Vlu	0.07*Qtot	4.42	
Alveolar ventilation, Qalv		Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			26.4	
Body weight, BW	(6)			

Age (yr)-specific regressions: (1) $V_f = (0.0162 \cdot \text{Age}^5 - 1.9784 \cdot \text{Age}^4 + 51.963 \cdot \text{Age}^3 - 459.38 \cdot \text{Age}^2 + 1566.8 \cdot \text{Age} + 1004.2)/1000$; (2) $V_l = (0.0072 \cdot \text{Age}^5 - 0.3975 \cdot \text{Age}^4 + 7.9052 \cdot \text{Age}^3 - 65.624 \cdot \text{Age}^2 + 262.02 \cdot \text{Age} + 157.52)/1000$; (3) $V_m = (-0.0623 \cdot \text{Age}^5 + 2.3433 \cdot \text{Age}^4 - 26.559 \cdot \text{Age}^3 + 144.75 \cdot \text{Age}^2 + 339.84 \cdot \text{Age} + 1648.2)/1000$; (4) $V_{lu} = (-0.0346 \cdot \text{Age}^4 + 1.5069 \cdot \text{Age}^3 - 20.31 \cdot \text{Age}^2 + 123.99 \cdot \text{Age} + 59.213)/1000$; (5) $Q_{tot} = 0.012 \cdot \text{Age}^3 - 1.2144 \cdot \text{Age}^2 + 40.324 \cdot \text{Age} + 44.414$; (6) $BW = (-1.9 \cdot \text{Age}^4 + 72.8 \cdot \text{Age}^3 - 813.1 \cdot \text{Age}^2 + 5535.6 \cdot \text{Age} + 4453.7)/1000$; For 7-10 yr model $Q_f = 0.05 \cdot Q_{tot}$; $Q_l = 0.118 \cdot Q_{tot}$; $Q_m = 0.045 \cdot Q_{tot}$; $Q_{kid} = 0.12 \cdot Q_{tot}$; For 11-18yr model $Q_f = 0.044 \cdot Q_{tot}$; $Q_l = 0.136 \cdot Q_{tot}$; $Q_m = 0.068 \cdot Q_{tot}$; $Q_{kid} = 0.136 \cdot Q_{tot}$. For adult $Q_f = 0.052 \cdot Q_{tot}$; $Q_l = 0.26 \cdot Q_{tot}$; $Q_m = 0.1648 \cdot Q_{tot}$; $Q_{kid} = 0.26 \cdot Q_{tot}$. $V_{max1} = 7.9E-5 \cdot BW \cdot (70/BW)^{0.25}$ mol/hr; $K_m = 1.88E-6$ M, $K_i = 5.6E-6$. (Tardif et al., 1995; Price et al., 2003)

E.5 Toxicokinetics: Berkeley Madonna Model Codes

This section provides PBPK model code for a selection of the chemicals studied. The models follow a standard format although the order is not critical for Berkeley Madonna (A = mass, Q = flow rate, V = volume, P = partition coefficient, Cv = concentration leaving the tissue, f= fat, l = liver, m = muscle (vessel poor tissues), vrg = vessel rich group of tissues, lu = lung, br = bronchi, pu = alveoli, BW = body weight = volume at 1 kg/L, Amet = amount metabolized)

E.5.1 Model Code for Furan 0-5 yr child

METHOD Stiff

STARTTIME = 0

STOPTIME= 48

DT = 0.001

{furan moles}

init Af = 0

init Al = 0

init Am = 0

init Avrg = 0

init Abr = 0

init Apu = 0

init Abrain = 0

{moles furan metabolized}

init Ametl = 0

init Ametlg = 0

Init AUCbrain = 0

{tissue flows L/hr}

Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414

Qalv = 0.8*Qtot

Qf = 0.053*Qtot

Ql = 0.0795*Qtot

Qm = 0.03*Qtot

Qvrg = Qtot - (Qf + Ql + Qm + Qbrain)

Qpu = 0.93*Qtot

Qbr = 0.07*Qtot

Qbrain = -0.0024*Age^4 + 0.1305*Age^3 - 2.4822*Age^2 + 18.025*Age + 15.197

{tissue volumes L}

Vf = (0.0162*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000

Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000

Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000

Vvrg = BW - (Vf + Vl + Vlu + Vbrain + Vm)

Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000

Vpu = 0.90*Vlu

$$V_{br} = 0.10 * V_{lu}$$

$$V_{brain} = (1E4 * ((Age + 0.213) / (6.030 + 6.895 * Age))) / 1000$$

$$BW = (-1.9 * Age^4 + 72.8 * Age^3 - 813.1 * Age^2 + 5535.6 * Age + 4453.7) / 1000$$

$$Age = 3.0$$

{blood/air and tissue/blood partition coefficients}

$$P_b = 2.47$$

$$P_l = 4.69$$

$$P_f = 33.39$$

$$P_m = 3.24$$

$$P_{brain} = 8.82$$

$$P_{vrg} = 4.69$$

$$P_{pu} = 4.69$$

$$P_{br} = 4.69$$

{metabolic parameters, E }

$$E = 1.0$$

{exposure in ppm converted to moles/L}

$$C_{air} = \text{IF TIME} \leq 24 \text{ THEN } 1 * (1E-6 / 25.45) \text{ ELSE } 0$$

{calculated concentrations of furan}

$$C_{art} = (Q_{pu} * C_{vpu} + Q_{br} * C_{vbr}) / Q_{tot}$$

$$C_{vf} = A_f / (V_f * P_f)$$

$$C_{vbrain} = A_{brain} / (V_{brain} * P_{brain})$$

$$C_{vl} = A_l / (V_l * P_l)$$

$$C_{vm} = A_m / (V_m * P_m)$$

$$C_{vrg} = A_{vrg} / (V_{vrg} * P_{vrg})$$

$$C_{vpu} = A_{pu} / (V_{pu} * P_{pu})$$

$$C_{vbr} = A_{br} / (V_{br} * P_{br})$$

$$C_{vtot} = (Q_l * C_{vl} + Q_f * C_{vf} + Q_m * C_{vm} + Q_{vrg} * C_{vrg} + Q_{brain} * C_{vbrain}) / Q_{pu}$$

$$C_{vipu} = (Q_{alv} * C_{air} + Q_{pu} * C_{vtot}) / ((Q_{alv} / P_b) + Q_{pu})$$

$$C_{exh} = C_{vipu} / P_b$$

{differential equations for furan uptake and metabolism}

$$d/dt(A_{brain}) = Q_{brain} * (C_{art} - C_{vbrain})$$

$$d/dt(A_{pu}) = Q_{pu} * (C_{vipu} - C_{vpu})$$

$$d/dt(A_{br}) = Q_{br} * (C_{art} - C_{vbr})$$

$$d/dt(A_l) = Q_l * (C_{art} - C_{vl}) - C_{art} * Q_l * E$$

$$d/dt(A_f) = Q_f * (C_{art} - C_{vf})$$

$$d/dt(A_m) = Q_m * (C_{art} - C_{vm})$$

$$d/dt(A_{vrg}) = Q_{vrg} * (C_{art} - C_{vrg})$$

{amount of furan metabolized in the liver and AUC in brain}

$$d/dt(A_{metl}) = C_{art} * Q_l * E$$

$$d/dt(A_{metlg}) = C_{art} * Q_l * E / BW$$

$$d/dt(AUC_{brain}) = C_{vbrain}$$

*E.5.2 Model Code for MTBE 0-6 Yr Child***METHOD Stiff****STARTTIME = 0****STOPTIME= 48****DT = 0.001**

{mtbe moles}

init Af = 0**init AI = 0****init Am = 0****init Avrg = 0****init Akid = 0****init Abr = 0****init Apu = 0**

{moles mtbe metabolized}

init Amet1 = 0**init Amet2 = 0**

{area under the venous blood concn x time curve, mtbe}

init AUCvtot = 0**init AUCvl = 0****init AUCvpu = 0****init AUCvbr = 0****init AUCvkid = 0****init AUCvvrg = 0**

{tissue flows L/hr}

Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414**Qalv = 0.8*Qtot****Qf = 0.053*Qtot****Ql = 0.0795*Qtot****Qm = 0.03*Qtot****Qkid = 0.164*Qtot****Qvrg = 0.674*Qtot****Qpu = 0.93*Qtot****Qbr = 0.07*Qtot**

{tissue volumes L}

BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000**Vf = (0.0162*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000****VI = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000****Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000****Vvrg = BW - (Vf + VI + Vkid + Vm + Vlu)****Vkid = (9.737E-4*Age^5 - 0.0561*Age^4 + 1.1729*Age^3 - 10.34*Age^2 + 44.604*Age + 28.291)/1000****Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000****Vpu = 0.9*Vlu****Vbr = 0.1*Vlu**

{blood/air and tissue/blood partition coefficients, mtbe}

$$\mathbf{Pb = 17.7}$$

$$\mathbf{PI = 0.723}$$

$$\mathbf{Pf = 4.79}$$

$$\mathbf{Pm = 1.181}$$

$$\mathbf{Pkid = 0.723}$$

$$\mathbf{Pvrg = 0.723}$$

$$\mathbf{Ppu = 0.723}$$

$$\mathbf{Pbr = 0.723}$$

{mtbe metabolic parameters, mol/hr, mol/L}

$$\mathbf{Vmax1 = 3.38E-5 * BW^{0.75}}$$

$$\mathbf{Vmax2 = 6.2E-6 * BW^{0.75}}$$

$$\mathbf{Km1 = 6.17E-5}$$

$$\mathbf{Km2 = 3.8E-6}$$

{exposure in ppm converted to moles}

$$\mathbf{Cair = IF TIME \leq 24 THEN 1 * (1E-6 / 24.45) ELSE 0}$$

$$\mathbf{Age = 0.0}$$

{calculated concentrations of mtbe}

$$\mathbf{Cart = (Qpu * Cvpu + Qbr * Cvbr) / Qtot}$$

$$\mathbf{Cvf = Af / (Vf * Pf)}$$

$$\mathbf{Cvl = Al / (Vl * Pl)}$$

$$\mathbf{Cvkid = Akid / (Vkid * Pkid)}$$

$$\mathbf{Cvm = Am / (Vm * Pm)}$$

$$\mathbf{Cvrg = Avrg / (Vvrg * Pvrg)}$$

$$\mathbf{Cvpu = Apu / (Vpu * Ppu)}$$

$$\mathbf{Cvbr = Abr / (Vbr * Pbr)}$$

$$\mathbf{Cvtot = (Ql * Cvl + Qf * Cvf + Qm * Cvm + Qvrg * Cvrg + Qkid * Cvkid) / Qpu}$$

$$\mathbf{Cvipu = (Qalv * Cair + Qpu * Cvtot) / ((Qalv / Pb) + Qpu)}$$

$$\mathbf{Cexh = Cvipu / Pb}$$

{differential equations for mtbe uptake and metabolism}

$$\mathbf{d/dt(Apu) = Qpu * (Cvipu - Cvpu)}$$

$$\mathbf{d/dt(Abr) = Qbr * (Cart - Cvbr)}$$

$$\mathbf{d/dt(Al) = Ql * (Cart - Cvl) - Vmax1 * Cvl / (Km1 + Cvl) - Vmax2 * Cvl / (Km2 + Cvl)}$$

$$\mathbf{d/dt(Af) = Qf * (Cart - Cvf)}$$

$$\mathbf{d/dt(Akid) = Qkid * (Cart - Cvkid)}$$

$$\mathbf{d/dt(Am) = Qm * (Cart - Cvm)}$$

$$\mathbf{d/dt(Avrg) = Qvrg * (Cart - Cvrg)}$$

{amount of mtbe metabolized in liver by high and low affinity pathways}

$$\mathbf{d/dt(Amet1) = Vmax1 * (Al / Vl) / (Km1 + (Al / Vl))}$$

$$\mathbf{d/dt(Amet2) = Vmax2 * (Al / Vl) / (Km2 + (Al / Vl))}$$

{AUCs for mtbe}

$$\mathbf{d/dt(AUCvtot) = Cvtot}$$

$$\mathbf{d/dt(AUCvl) = Cvl}$$

$$\mathbf{d/dt(AUCvpu) = Cvpu}$$

$$\begin{aligned}d/dt(\text{AUCvbr}) &= \text{Cvbr} \\d/dt(\text{AUCvkid}) &= \text{Cvkid} \\d/dt(\text{AUCvvrg}) &= \text{Cvvrg}\end{aligned}$$

E.5.3 Model Code for PCE 0-6 yr Child

METHOD Stiff

```

STARTTIME = 0
STOPTIME= 240
DT = 0.001
{PCE moles}
init Af1 = 0
init Af2 = 0
init AI = 0
init Am = 0
init Abrain = 0
init Akid = 0
init Avrg = 0
init Abr = 0
init Apu = 0
init TCA = 0
init TCAurine = 0
{moles PCE metabolized}
init Amet1 = 0
{area under the venous blood concn x time curve, pce, TCA}
init AUCvtot = 0
init AUCvl = 0
init AUCTCA = 0
init AUCvbrain = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = K*Qtot
K = 0.8
Qf1 = 0.043*Qtot
Qf2 = 0.01*Qtot
QI = 0.0795*Qtot
Qm = 0.03*Qtot
Qkid = 0.08*Qtot
Qbrain = -0.0024*Age^4 + 0.1305*Age^3 - 2.4822*Age^2 + 18.025*Age + 15.197
Qvrg = Qtot - (Qf1 + Qf2 + QI + Qm + Qkid + Qbrain)
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot

```

{tissue volumes L}

$$BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000$$

$$Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000$$

$$Vf1 = 0.8*Vf$$

$$Vf2 = 0.2*Vf$$

$$VI = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000$$

$$Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000$$

$$Vbrain = (1E4*(Age + 0.213)/(6.030 + 6.895*Age))/1000$$

$$Vkid = (9.737E-4*Age^5 - 0.0561*Age^4 + 1.1729*Age^3 - 10.34*Age^2 + 44.604*Age + 28.291)/1000$$

$$Vvrg = BW - (Vf + VI + Vm + Vkid + Vbrain + Vlu)$$

$$Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000$$

$$Vpu = 0.9*Vlu$$

$$Vbr = 0.1*Vlu$$

{blood/air and tissue/blood partition coefficients, PCE}

$$Pb = 11.6$$

$$PI = 5.27$$

$$Pf1 = 125.0$$

$$Pf2 = 125.0$$

$$Pbrain = 125.0$$

$$Pkid = 5.05$$

$$Pm = 6.1$$

$$Pvrg = 5.27$$

$$Ppu = 5.27$$

$$Pbr = 5.27$$

{PCE metabolic parameters, mol/hr, mol/L}

$$Vmax1 = 1.69E-6*BW^0.75$$

$$Km1 = 4.6E-5$$

$$KeC = 0.05$$

$$Ke = KeC/BW^0.25$$

$$Ku = 0.5$$

{exposure in ppm converted to moles}

$$Cair = IF TIME <= 24 THEN 1*(1E-6/24.45) ELSE 0$$

$$Age = 0$$

{calculated concentrations of PCE}

$$Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot$$

$$Cvf1 = Af1/(Vf1*Pf1)$$

$$Cvf2 = Af2/(Vf2*Pf2)$$

$$Cvl = Al/(VI*PI)$$

$$Cvbrain = Abrain/(Vbrain*Pbrain)$$

$$Cvkid = Akid/(Vkid*Pkid)$$

$$Cvm = Am/(Vm*Pm)$$

$$Cvvrg = Avrg/(Vvrg*Pvrg)$$

$$Cvpu = Apu/(Vpu*Ppu)$$

$$Cvbr = Abr/(Vbr*Pbr)$$

$$Cvtot = (Ql * Cv_l + Qf1 * Cv_{f1} + Qm * Cvm + Qvrg * Cvvrg + Qf2 * Cv_{f2} + Qbrain * Cv_{brain} + Qkid * Cv_{kid}) / Qpu$$

$$Cvipu = (Qalv * Cair + Qpu * Cvtot) / ((Qalv / Pb) + Qpu)$$

$$Cexh = Cvipu / Pb$$

$$Ctca = TCA / (BW * 0.1)$$

{differential equations for pce uptake and metabolism}

$$d/dt(Apu) = Qpu * (Cvipu - Cvp_u)$$

$$d/dt(Abr) = Qbr * (Cart - Cvbr)$$

$$d/dt(AI) = Ql * (Cart - Cv_l) - Vmax1 * Cv_l / (Km1 + Cv_l)$$

$$d/dt(Af1) = Qf1 * (Cart - Cv_{f1})$$

$$d/dt(Af2) = Qf2 * (Cart - Cv_{f2})$$

$$d/dt(Akid) = Qkid * (Cart - Cv_{kid})$$

$$d/dt(Abrain) = Qbrain * (Cart - Cv_{brain})$$

$$d/dt(Am) = Qm * (Cart - Cvm)$$

$$d/dt(Avrg) = Qvrg * (Cart - Cvvrg)$$

$$d/dt(TCA) = 0.15 * Vmax1 * Cv_l / (Km1 + Cv_l) - Ke * TCA - Ku * TCA$$

$$d/dt(TCAurine) = TCA * Ku$$

{amount of PCE metabolized in liver }

$$d/dt(Amet1) = Vmax1 * (AI / VI) / (Km1 + (AI / VI))$$

$$\text{init Ametg} = 0$$

$$d/dt(Ametg) = Amet1 / BW$$

{AUCs for PCE}

$$d/dt(AUCvtot) = Cvtot$$

$$d/dt(AUCv_l) = Cv_l$$

$$d/dt(AUCTCA) = Ctca$$

$$d/dt(AUCv_{brain}) = Cv_{brain}$$

E.5.4 Model Code for BaP vapor 0-6 yr Child

METHOD Stiff

$$\text{STARTTIME} = 0$$

$$\text{STOPTIME} = 2880$$

$$\text{DT} = 0.001$$

{Alveolar compartments, moles}

$$\text{init AAP} = 0$$

$$\text{init AAVA} = 0$$

$$\text{init AAV1} = 0$$

$$\text{limit AAV1} \geq 0$$

$$\text{init AAV2} = 0$$

$$\text{limit AAV2} \geq 0$$

$$\text{init AAVE} = 0$$

$$\text{limit AAVE} \geq 0$$

```

init AAVB = 0
limit AAVE >= 0
init Ameta1 = 0
init Ameta2 = 0
init LNth = 0
init AUCCalv = 0
{Bronchiolar compartments, moles}
init ABP = 0
init ABM = 0
init ABL1 = 0
init ABL2 = 0
init ABL3 = 0
init ABBL = 0
init Ametb1 = 0
init Ametb2 = 0
init Ametb3 = 0
init AUCCbron = 0
{Venous and arterial blood, moles}
init Aven = 0
init Aart = 0
{Body compartments, input, output, moles}
init Af = 0
init Am = 0
init Akvrg = 0
init Aliv = 0
init Aurine = 0
init Aet = 0
init Ametliv = 0
init AUCCliv = 0
{Model parameters, constants}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vkvrg = BW - (Vf + Vm + Vliv + Vlu + Vart + Vven)
Vliv = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Valv = 0.9*Vlu
Vbron = 0.1*Vlu
Vart = BW*0.05/3
Vven = BW*0.05*2/3
Ka = 1.0E-3
Kb = 100
Kbln = 6.9E-6
Kaln = 6.9E-7
Kln = 1.16E-5

```

DL = 2.14E-11
SF = 1.04
Vmaxlu = 1.2E-11*(BW/.25)^0.75
Vmaxliv = 1.7E-9*(BW/.25)^0.75
Kmliv = 5.5E-6
Kmlu = 2.2E-7
Pf = 294.7
Pm = 4.0
Pkvrg = 4.0
Pliv = 7.0
Pb = 10
Palv = 1.3
Pbron = 2.3
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
Qtot = (0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414)/60
Qvent = ((17.874*Age) + 39.785)/60
Qalv = 0.93*Qtot
Qbron = 0.07*Qtot
Qf = 0.053*Qtot
Qm = 0.03*Qtot
Qkvrg = Qtot - (Qf + Qliv + Qm)
Qliv = 0.0795*Qtot
MPliv = 5.8E4
MPlu = 3E3
 {Concentrations, mol/L, ppm}
Cairex = Exposure
Exposure = IF TIME < 1440 THEN 1E-2*(1E-6/25.45) ELSE 0 {ppm to mol/L}
Age = 0
Cair = AAVA/(0.5*Vlu)
Calv = (AAV1+AAV2+AAVE)/Valv
Cbron = (ABL1+ABL2+ABL3)/Vbron
Cart = Aart/Vart
Cven = Aven/Vven
Cliv = Aliv/Vliv
 {differential equations, alveoli moles, L, min}
d/dt(AAVA) = Qvent*(AAV1/Valv) - Qvent*(AAVA/0.5) + Cairex*Qvent
d/dt(AAP) = - AAP*0.9*4.8E-4 - AAP*0.1*4.8E-4
d/dt(AAV1) = AAP*0.9*4.8E-4 - Ka*((AAV1/(Valv*0.25*0.9)) - (AAVE/(Valv*0.75))) + Qvent*(AAVA/0.5)
- Qvent*(AAV1/Valv) - SF*Vmaxlu*MPlu*AAV1/(Kmlu + (AAV1/(Valv*0.9*0.25)))
d/dt(AAV2) = AAP*0.1*4.8E-4
- Ka*((AAV2/(Valv*0.25*0.1)) - (AAVE/(Valv*0.75))) - SF*Vmaxlu*MPlu*AAV2/(Kmlu +
(AAV2/(Valv*0.1*0.25)))
d/dt(AAVE) = Ka*((AAV1/(Valv*0.25*0.9)) - (AAVE/(Valv*0.75))) + Ka*((AAV2/(Valv*0.25*0.1)) -
(AAVE/(Valv*0.75))) - Ka*((AAVE/(Valv*0.75)) - (AAVB/(Vven*Palv))) + Kln*LNth - Kaln*AAVE

$$d/dt(AAVB) = Ka*((AAVE/(Valv*0.75)) - (AAVB/(Vven*Palv))) + (Aven/Vven)*Qalv - AAVB*Qalv/(Vven*Palv)$$

$$d/dt(Ameta1) = SF*Vmaxlu*MPlu*AAV1/(Kmlu + (AAV1/(Valv*0.9*0.25)))$$

$$d/dt(Ameta2) = SF*Vmaxlu*MPlu*AAV2/(Kmlu + (AAV2/(Valv*0.1*0.25)))$$

$$d/dt(LNth) = Kbln*ABL1 + Kbln*ABL2 + Kbln*ABL3 + Kaln*AAVE - Kln*LNth$$

$$d/dt(AUCCalv) = Calv$$

{differential equations, bronchi}

$$d/dt(ABP) = - ABP*4.8E-4$$

$$d/dt(ABM) = ABP*4.8E-4 - Ka*Kb*((ABM/0.06) - (ABL1/(Vbron*0.333)))$$

$$d/dt(ABL1) = Ka*Kb*((ABM/0.06) - (ABL1/(Vbron*0.333))) - Ka*(ABL1/(Vbron*0.333) - ABL2/(Vbron*0.333)) + DL*Kb*(ABL1/(Vbron*0.333) - ABL3/(Vbron*0.333)) - SF*Vmaxlu*MPlu*ABL1/(Kmlu + (ABL1/(Vbron*0.333))) - Kbln*ABL1 + Kln*LNth$$

$$d/dt(ABL2) = Ka*(ABL1/(Vbron*0.333) - ABL2/(Vbron*0.333)) + DL*Kb*(ABL1/(Vbron*0.333) - ABL3/(Vbron*0.333)) - Ka*Kb*(ABL2/(Vbron*0.333) - ABL3/(Vbron*0.333)) - SF*Vmaxlu*MPlu*ABL2/(Kmlu + (ABL2/(Vbron*0.333))) - Kbln*ABL2 + Kln*LNth$$

$$d/dt(ABL3) = Ka*Kb*(ABL2/(Vbron*0.333) - ABL3/(Vbron*0.333)) - Ka*ABL3/(Vbron*0.333) - SF*Vmaxlu*MPlu*ABL3/(Kmlu + (ABL3/(Vbron*0.333))) - Kbln*ABL3 + Kln*LNth$$

$$d/dt(ABBL) = Ka*ABL3/(Vbron*0.333) + Qbron*(Aven/Vven) - ABBL*Qbron/(Vven*Pbron)$$

$$d/dt(Ametb1) = SF*Vmaxlu*MPlu*ABL1/(Kmlu + (ABL1/(Vbron*0.333)))$$

$$d/dt(Ametb2) = SF*Vmaxlu*MPlu*ABL2/(Kmlu + (ABL2/(Vbron*0.333)))$$

$$d/dt(Ametb3) = SF*Vmaxlu*MPlu*ABL3/(Kmlu + (ABL3/(Vbron*0.333)))$$

$$d/dt(AUCCbron) = Cbron$$

{differential equations, body}

$$d/dt(Aart) = AAVB*Qalv/(Vven*Palv) + ABBL*Qbron/(Vven*Pbron) - (Aart/Vart)*(Qf + Qm + Qkvrg + Qliv)$$

$$d/dt(Aven) = Af*Qf/(Vf*Pf) + Am*Qm/(Vm*Pm) + Akvrg*Qkvrg/(Vkvrg*Pkvrg) + Aliv*Qliv/(Vliv*Pliv) - (Aven/Vven)*Qalv - (Aven/Vven)*Qbron$$

$$d/dt(Af) = Cart*Qf - Af*Qf/(Vf*Pf)$$

$$d/dt(Am) = Cart*Qm - Am*Qm/(Vm*Pm)$$

$$d/dt(Akvrg) = Cart*Qkvrg - Akvrg*Qkvrg/(Vkvrg*Pkvrg) - Akvrg*0.2$$

$$d/dt(Aliv) = Cart*Qliv - Aliv*Qliv/(Vliv*Pliv) - SF*Vmaxliv*MPliv*Aliv/(Kmliv + (Aliv/Vliv)) + Aet*0.01$$

$$d/dt(Aet) = - Aet*0.01$$

$$d/dt(Aurine) = Akvrg*0.2$$

$$d/dt(Ametliv) = SF*Vmaxliv*MPliv*Aliv/(Kmliv + (Aliv/Vliv))$$

$$d/dt(AUCCliv) = Cliv$$

E.5.5 Model Code for NAP/NO RT 0-6 yr Child

METHOD Stiff

STARTTIME = 0

STOPTIME= 2880

DT = 0.0001

{Naphthalene (NAP) in upper respiratory tract compartment (URT) umoles}

init ANURTa = 0
init ANURTmuc = 0
init ANURTepi = 0
Limit ANURTepi >= 0
init ANURTex = 0
Limit ANURTex >= 0
init AMETua = 0
 {NAP oxide (NO) in upper respiratory compartment (URT) umoles}
init ABURTa = 0
init ABURTmuc = 0
init ABURTepi = 0
init GSHua = 1.0*VURTepi
init ABURTex = 0
Limit ABURTex >= 0
init ABMET2ua = 0
init ABMETGua = 0
 {NAP in conducting airways compartment (CA), umoles}
init ANCAa = 0
init ANCAmuc = 0
init ANCAepi = 0
init ANCAex = 0
Limit ANCAex >= 0
init AMETca = 0
 {NO in conducting airways compartment (CA), umoles}
init ABCAa = 0
init ABCAmuc = 0
init ABCAepi = 0
init ABCAex = 0
Limit ABCAex >= 0
init GSHca = 1.0*VCA
init ABMET2ca = 0
init ABMETGca = 0
 {NAP in transitional bronchioles compartment (TB), umoles}
init ANTBa = 0
init ANTBmuc = 0
init ANTBepi = 0
init ANTBex = 0
Limit ANTBex >= 0
init AMETtb = 0
 {NO in transitional bronchioles compartment (TB), umoles}
init ABTBa = 0
init ABTBmuc = 0
init ABTBepi = 0
init GSHtb = 1.0*VTBepi

init ABTBex = 0
Limit ABTBex >= 0
init ABMET2tb = 0
init ABMETGtb = 0
 {NAP in pulmonary compartment (PU), umoles}
init ANPUa = 0
init ANPUmuc = 0
init ANPUepi = 0
init ANPUex = 0
Limit ANPUex >= 0
init ANex = 0
Limit ANex >= 0
init AMETpu = 0
 {NO in pulmonary compartment (PU), umoles}
init ABPUa = 0
init ABPUmuc = 0
init ABPUepi = 0
init ABPUex = 0
init ABex = 0
Limit ABex >= 0
init GSHpu = 1.0*VPU
init ABMET2pu = 0
init ABMETGpu = 0
 {model equations}
Q = RPM*TVOL
Cairin = exposure/(24.36*1E3)
VURTepi = SAURT*WUA
VURTmuc = SAURT*WSMua
VURTex = SAURT*WUAs
VCAmuc = SACA*WSMca
VCAepi = SACA*WCA
VCAex = SACA*WCAs
VTBmuc = SATB*WSMtb
VTBepi = SATB*WTA
VTBex = SATB*WTAs
VPUmuc = SAPU*WSMpu
VPUepi = SAPU*WPA
VPUex = SAPU*WTAs
Vlu = 59.213 + 123.99*Age - 20.31*Age^2 + 1.5069*Age^3 - 0.0346*Age^4
VURT = 0.0026*Vlu
VCA = 0.018*Vlu
VTB = 0.043*Vlu
VPU = 0.937*Vlu
 {calculated concentrations of NAP umol/mL}

Curtepil = (ANURTEpi/VURTEpi)
Ccaepil = (ANCAepi/VCAepi)
Ctbepil = (ANTBepi/VTBepi)
Cpuepil = (ANPUepi/VPUEpi)
Cvurtex = (ANURTex/(VURTex*Pvrg))
Cvcaex = (ANCAex/(VCAex*Pvrg))
Cvtbex = (ANTBex/(VTBex*Pvrg))
Cvpuex = (ANPUex/(VPUex*Pvrg))
Cvex = (ANURTex+ANCAex+ANTBex+ANPUex)/((VURTex+VCAex+VTBex+VPUex)*Pvrg)
 {calculated concentrations of NO umol/mL}
CBurtepil = (ABURTEpi/VURTEpi)
CBcaepil = (ABCAepi/VCAepi)
CBtbepil = (ABTBepi/VTBepi)
CBpuepil = (ABPUepi/VPUEpi)
CBvurtex = (ABURTex/(VURTex*PBvrg))
CBvcaex = (ABCAex/(VCAex*PBvrg))
CBvtbex = (ABTBex/(VTBex*PBvrg))
CBvpuex = (ABPUex/(VPUex*PBvrg))
CBvex = (ABURTex+ABCAex+ABTBex+ABPUex)/((VURTex+VCAex+VTBex+VPUex)*PBvrg)
 {concentrations of GSH, mM}
CGSHuab = 2.5
CGSHua = GSHua/VURT
CGSHcab = 2.0
CGSHca = GSHca/VCA
CGSHtbb = 1.0
CGSHtb = GSHtb/VTB
CGSHpub = 1.0
CGSHpu = GSHpu/VPU
init inhaleddose = 0
d/dt(Inhaleddose) = Cairin*Qalv
Exposure = IF TIME <= 1440 THEN 1 ELSE 0
ExposureB = IF TIME <= 1440 THEN 0 ELSE 0
Age = 3.0
 {upper respiratory tract constants}
PMA = 30 {mucus:air partition coeff}
KOURT = 198.0 {mass transfer coeffs., cm/min}
KTRURT = 1.92
KBOURT = 0.192
KOCA = 18.1
KTRCA = 1.92
KBOCA = 0.192
KOTB = 15.8
KTRTB = 1.92
KBOTB = 0.192

$$\text{KOPU} = 15.8$$

$$\text{KTRPU} = 1.92$$

$$\text{KBOPU} = 0.192$$

$$\text{KMUC} = 0.001 \text{ \{diffusion constants, cm}^2\text{/min\}}$$

$$\text{KSQM} = 0.0002$$

$$\text{KG} = 6.0$$

$$\text{SAURT} = \text{VURT}/\text{WUA} \text{ \{surface areas, cm}^2\text{\}}$$

$$\text{SACA} = \text{VCA}/\text{WCA}$$

$$\text{SATB} = \text{VTB}/\text{WTA}$$

$$\text{SAPU} = \text{VPU}/\text{WPA}$$

$$\text{VURTa} = 0.00035 * \text{TLC} \text{ \{luminal volumes, cm}^3\text{\}}$$

$$\text{VCAa} = 0.0105 * \text{TLC}$$

$$\text{VTBa} = 0.042 * \text{TLC}$$

$$\text{VPUa} = 0.944 * \text{TLC}$$

$$\text{TLC} = 236.5 + 282 * \text{Age} - 4.775 * \text{Age}^2 + 0.285 * \text{Age}^3 \text{ \{mL\}}$$

$$\text{RPM} = 53.5 * (\text{BW}/1\text{E}3)^{-0.26} \text{ \{breaths/min\}}$$

$$\text{TVOL} = 35.45 + 33.56 * \text{Age} - 1.47 * \text{Age}^2 + 0.0793 * \text{Age}^3 \text{ \{tidal volume mL/breath\}}$$

\{thicknesses (W) of upper airways epithelium (UA), submucosa (UAs); mucus (SM); conducting airways epi (CA), submucosa (CAs); transitional airways epi (TA), submucosa (TAs); and pulmonary airways epi (PA), cm\}

$$\text{WUA} = 0.005$$

$$\text{WSMua} = 0.001$$

$$\text{WSMca} = 0.0005$$

$$\text{WSMtb} = 0.0002$$

$$\text{WSMpu} = 0.0001$$

$$\text{WCA} = 0.0025$$

$$\text{WTA} = 0.001$$

$$\text{WPA} = 0.0005$$

$$\text{WUAs} = 0.01$$

$$\text{WCAs} = 0.005$$

$$\text{WTAs} = 0.002$$

$$\text{Qua} = 0.0025 * \text{Qtot} \text{ \{blood flow to the URT region\}}$$

$$\text{Qca} = 0.0075 * \text{Qtot} \text{ \{blood flow to the CA\}}$$

$$\text{Qta} = 0.0067 * \text{Qtot} \text{ \{blood flow to the TA\}}$$

\{metabolic constants umol/min, umol/mL, based on Sweeny et al. 1996, Willems et al. 2001 rat values scaled to larger BWs, 2 = EH, G = conj\}

$$\text{Vmaxua} = 2.45\text{E-}3 * 3.0 * \text{VURTepi}/(\text{BW}/250)^{0.25}$$

$$\text{Vmaxca} = 2.45\text{E-}3 * 3.0 * \text{VCAepi}/(\text{BW}/250)^{0.25}$$

$$\text{Vmaxtb} = 2.45\text{E-}3 * 3.0 * \text{VTBepi}/(\text{BW}/250)^{0.25}$$

$$\text{Vmaxpu} = 2.45\text{E-}3 * 3.0 * \text{VPUepi}/(\text{BW}/250)^{0.25}$$

$$\text{VmaxI} = 2.46\text{E-}2 * 14.5 * \text{VI}/(\text{BW}/250)^{0.25}$$

$$\text{Km} = 0.003 \text{ \{umol/mL\}}$$

$$\text{Kmlu} = 0.006$$

$$\text{VmaxI2} = 4.0\text{E-}3 * 14.5 * \text{VI}/(\text{BW}/250)^{0.25} \text{ \{EH\}}$$

$$\text{Vmax2ua} = 9.0\text{E-}3 * 3.0 * \text{VURTepi}/(\text{BW}/250)^{0.25}$$

$V_{max2ca} = 9.0E-3 \cdot 3.0 \cdot VCA_{epi} / (BW/250)^{0.25}$
 $V_{max2tb} = 9.0E-3 \cdot 3.0 \cdot VT_{Bepi} / (BW/250)^{0.25}$
 $V_{max2pu} = 9.0E-3 \cdot 3.0 \cdot VPU_{epi} / (BW/250)^{0.25}$
 $Km2lu = 0.001$
 $Km2 = 0.001$
 $Km2ih = 2E-4$
 $Kec = 400$
 $init\ Kgshl = 0.003 \cdot VI \{GSH / min\}$
 $d/dt(Kgshl) = (2.4E-4 \cdot ((CGSHIb + 2.0) / (CGSHI + 2.0)) - 0.005 \cdot 0.003) / 58$
 $Kgshua = 0.003 \cdot VURT$
 $Kgshca = 0.003 \cdot VCA$
 $Kgshtb = 0.003 \cdot VT_{B}$
 $Kgshpu = 0.003 \cdot VPU$
 $Kge = 2.5E-3$
 $V_{maxG1} = 0.5 \cdot 58 \cdot VI / (BW/250)^{0.25} \{umol/min/liver, GST\}$
 $V_{maxGua} = 0.4 \cdot 54.0 \cdot VUR_{Tepi} / (BW/250)^{0.25}$
 $V_{maxGca} = 0.4 \cdot 54.0 \cdot VCA_{epi} / (BW/250)^{0.25}$
 $V_{maxGtb} = 0.4 \cdot 54.0 \cdot VT_{Bepi} / (BW/250)^{0.25}$
 $V_{maxGpu} = 0.4 \cdot 54.0 \cdot VPU_{epi} / (BW/250)^{0.25}$
 $KmG1 = 3.3 \{GSH\}$
 $KmG2 = 0.05 \{NO\}$
 $MPI = 14.5 \{mg\ microsomal\ protein / mL\ tissue\}$
 $MPIu = 3.0 \{mg\ microsomal\ protein / mL\ tissue\}$
 $CPI = 58 \{mg\ cytosolic\ protein / mL\ tissue\}$
 $CPIu = 54 \{mg\ cytosolic\ protein / mL\ tissue\}$
 $KNOH = 0.25 \{naphthol\ fomatation\}$
 {differential equations for NAP in URT compartment, URT}
 $d/dt(ANURTa) = Q \cdot (Cairin - (ANURTa / VURTa)) - KOURT \cdot SAURT \cdot ((ANURTa / VURTa) - (ANURTmuc / (PMA \cdot VURTmuc)))$
 $d/dt(ANURTmuc) = KOURT \cdot SAURT \cdot ((ANURTa / VURTa) - (ANURTmuc / (PMA \cdot VURTmuc))) - KTRURT \cdot SAURT \cdot ((ANURTmuc / (VURTmuc \cdot PMA)) - (ANUR_{Tepi} / (VUR_{Tepi} \cdot Pvrg)))$
 $d/dt(ANUR_{Tepi}) = KTRURT \cdot SAURT \cdot ((ANURTmuc / (VURTmuc \cdot PMA)) - (ANUR_{Tepi} / (VUR_{Tepi} \cdot Pvrg))) - KBOURT \cdot SAURT \cdot ((ANUR_{Tepi} / (VUR_{Tepi} \cdot Pvrg)) - (ANUR_{Tex} / (VUR_{Tex} \cdot Pvrg))) - V_{maxua} \cdot (ANUR_{Tepi} / (VUR_{Tepi} \cdot Pvrg)) / (Kmlu + (ANUR_{Tepi} / (VUR_{Tepi} \cdot Pvrg)))$
 $d/dt(ANUR_{Tex}) = KBOURT \cdot SAURT \cdot ((ANUR_{Tepi} / VUR_{Tepi}) - (ANUR_{Tex} / VUR_{Tex})) + Qua \cdot (Cart - (ANUR_{Tex} / (VUR_{Tex} \cdot Pvrg)))$
 $d/dt(AMETua) = V_{maxua} \cdot (ANUR_{Tepi} / (VUR_{Tepi} \cdot Pvrg)) / (Kmlu + (ANUR_{Tepi} / (VUR_{Tepi} \cdot Pvrg)))$
 $d/dt(GSHua) = Kgshua \cdot (CGSHuab - (GSHua / VUR_{Tepi})) - Kge \cdot GSHua - V_{maxGua} \cdot (ABUR_{Tepi} / (VUR_{Tepi} \cdot PBvrg)) \cdot CGSHua / (KmG1 \cdot (ABUR_{Tepi} / (VUR_{Tepi} \cdot PBvrg))) + KmG2 \cdot CGSHua + CGSHua \cdot (ABUR_{Tepi} / (VUR_{Tepi} \cdot PBvrg))$
 {differential equations for NO in URT compartment, URT}
 $d/dt(ABURTa) = Q \cdot (CBairin - (ABURTa / VURTa)) - KOURT \cdot SAURT \cdot ((ABURTa / VURTa) - (ABURTmuc / (PMA \cdot VURTmuc)))$
 $d/dt(ABURTmuc) = KOURT \cdot SAURT \cdot ((ABURTa / VURTa) - (ABURTmuc / (PMA \cdot VURTmuc))) - KTRURT \cdot SAURT \cdot ((ABURTmuc / (VURTmuc \cdot PMA)) - (ABUR_{Tepi} / (VUR_{Tepi} \cdot PBvrg)))$

$$\begin{aligned} d/dt(ABURTepi) &= KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - \\ &(ABURTepi/(VURTepi*PBvrg))) - KBOURT*SAURT*((ABURTepi/(VURTepi*PBvrg)) - \\ &(ABURTex/(VURTex*PBvrg))) + Vmaxua*(ANURTepi/(VURTepi*PBvrg))/(Kmlu + \\ &(ANURTepi/(VURTepi*PBvrg))) - Vmax2ua*(ABURTepi/(VURTepi*PBvrg))/(Km2lu + \\ &(ABURTepi/VURTepi)) - \\ &VmaxGua*(ABURTepi/(VURTepi*PBvrg))*CGSHua/(KmG1*(ABURTepi/(VURTepi*PBvrg)) + \\ &KmG2*CGSHua + CGSHua*(ABURTepi/(VURTepi*PBvrg))) - \\ &KNOH*(ABURTepi/(VURTepi*PBvrg))*1E3 \\ d/dt(ABMET2ua) &= (Vmax2ua*ABURTepi/(VURTepi*PBvrg))/(Km2lu + (ABURTepi/VURTepi))/2 \\ d/dt(ABMETGua) &= \\ &(VmaxGua*(ABURTepi/(VURTepi*PBvrg))*CGSHua/(KmG1*(ABURTepi/(VURTepi*PBvrg)) + \\ &KmG2*CGSHua + CGSHua*(ABURTepi/(VURTepi*PBvrg)))/2 \\ d/dt(ABNOHua) &= KNOH*(ABURTepi/(VURTepi*PBvrg))*1E3 \\ init ABNOHua &= 0 \\ d/dt(ABURTex) &= KBOURT*SAURT*((ABURTepi/VURTepi) - (ABURTex/(VURTex*PBvrg))) + \\ &Qua*(CBart - (ABURTex/(VURTex*PBvrg))) \\ \{differential equations for NAP in CA compartment, CA\} \\ d/dt(ANCAa) &= Q*(Cairin - (ANCAa/VCAa)) - KOCA*SACA*((ANCAa/VCAa)- \\ &(ANCAmuc/(PMA*VCAmuc))) \\ d/dt(ANCAmuc) &= KOCA*SACA*((ANCAa/VCAa) - (ANCAmuc/(PMA*VCAmuc))) - \\ &KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg))) \\ d/dt(ANCAepi) &= KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg))) - \\ &KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) - \\ &Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg))) \\ d/dt(ANCAex) &= KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) + Qca*(Cart - \\ &(ANCAex/(VCAex*Pvrg))) \\ d/dt(AMETca) &= Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg))) \\ d/dt(GSHca) &= Kgshca*(CGSHcab - (GSHca/VCAepi)) - Kge*GSHca - \\ &VmaxGca*(ABCAepi/(VCAepi*PBvrg))*CGSHca/(KmG1*(ABCAepi/(VCAepi*PBvrg)) + \\ &KmG2*CGSHca + CGSHca*(ABCAepi/(VCAepi*PBvrg))) \\ \{differential equations for NO in CA compartment, CA\} \\ d/dt(ABCAa) &= Q*(CBairin - (ABCAa/VCAa)) - KOCA*SACA*((ABCAa/VCAa)- \\ &(ABCAmuc/(PMA*VCAmuc))) \\ d/dt(ABCAmuc) &= KOCA*SACA*((ABCAa/VCAa) - (ABCAmuc/(PMA*VCAmuc))) - \\ &KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg))) \\ d/dt(ABCAepi) &= KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg))) \\ &+ Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg))) - \\ &KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) - \\ &Vmax2ca*ABCAepi/(VCAepi*PBvrg)/(Km2lu + (ABCAepi/VCAepi)) - \\ &VmaxGca*(ABCAepi/(VCAepi*PBvrg))*CGSHca/(KmG1*(ABCAepi/(VCAepi*PBvrg)) + \\ &KmG2*CGSHca + CGSHca*(ABCAepi/(VCAepi*PBvrg))) - KNOH*(ABCAepi/(VCAepi*PBvrg))*1E3 \\ d/dt(ABCAex) &= KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) + \\ &Qca*(CBart - (ABCAex/(VCAex*PBvrg))) \\ d/dt(ABMET2ca) &= (Vmax2ca*ABCAepi/(VCAepi*PBvrg))/(Km2lu + (ABCAepi/VCAepi))/2 \\ d/dt(ABMETGca) &= \\ &(VmaxGca*(ABCAepi/(VCAepi*PBvrg))*CGSHca/(KmG1*(ABCAepi/(VCAepi*PBvrg)) + \\ &KmG2*CGSHca + CGSHca*(ABCAepi/(VCAepi*PBvrg)))/2 \\ d/dt(ABNOHca) &= KNOH*(ABCAepi/(VCAepi*PBvrg))*1E3 \\ init ABNOHca &= 0 \\ \{differential equations for NAP in TB compartment umoles, TB\} \end{aligned}$$

$$d/dt(ANTBa) = Q*(Cairin - (ANTBa/VTBa)) - KOTB*SATB*((ANTBa/VTBa) - (ANTBmuc/(PMA*VTBmuc)))$$

$$d/dt(ANTBmuc) = KOTB*SATB*((ANTBa/VTBa) - (ANTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBmuc/(VTBmuc*PMA)))$$

$$d/dt(ANTBepi) = KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBepi/(VTBepi*Pvrg))) - KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) - Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg)))$$

$$d/dt(ANTBex) = KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) + Qta*(Cart - (ANTBex/(VTBex*Pvrg)))$$

$$d/dt(AMETtb) = Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg)))$$

$$d/dt(GSHtb) = Kgshtb*(CGSHtbb - (GSHtb/VTBepi)) - Kge*GSHtb - VmaxGtb*(ABTBepi/(VTBepi*PBvrg))*CGSHtb/(KmG1*(ABTBepi/(VTBepi*PBvrg)) + KmG2*CGSHtb + CGSHtb*(ABTBepi/(VTBepi*PBvrg)))$$

{differential equations for NO in TB compartment umoles, TB}

$$d/dt(ABTBa) = Q*(CBairin - (ABTBa/VTBa)) - KOTB*SATB*((ABTBa/VTBa) - (ABTBmuc/(PMA*VTBmuc)))$$

$$d/dt(ABTBmuc) = KOTB*SATB*((ABTBa/VTBa) - (ABTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg)))$$

$$d/dt(ABTBepi) = KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg))) - KBOTB*SATB*((ABTBepi/(VTBepi*PBvrg)) - (ABTBex/(VTBex*PBvrg))) +$$

$$Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg))) - Vmax2tb*ABTBepi/(VTBepi*PBvrg)/(Km2lu + (ABTBepi/VTBepi)) - VmaxGtb*(ABTBepi/(VTBepi*PBvrg))*CGSHtb/(KmG1*(ABTBepi/(VTBepi*PBvrg)) + KmG2*CGSHtb + CGSHtb*(ABTBepi/(VTBepi*PBvrg))) - KNOH*(ABTBepi/(VTBepi*PBvrg))*1E3$$

$$d/dt(ABMET2tb) = (Vmax2tb*(ABTBepi/(VTBepi*PBvrg))/(Km2lu + (ABTBepi/VTBepi)))/2$$

$$d/dt(ABMETGtb) = (VmaxGtb*(ABTBepi/(VTBepi*PBvrg))*CGSHtb/(KmG1*(ABTBepi/(VTBepi*PBvrg)) + KmG2*CGSHtb + CGSHtb*(ABTBepi/(VTBepi*PBvrg))))/2$$

$$d/dt(ABNOHtb) = KNOH*(ABTBepi/(VTBepi*PBvrg))*1E3$$

$$\text{init ABNOHtb} = 0$$

$$d/dt(ABTBex) = KBOTB*SATB*(ABTBepi/(VTBepi*PBvrg) - (ABTBex/(VTBex*PBvrg))) + Qta*(CBart - (ABTBex/(VTBex*PBvrg)))$$

{differential equations for NAP in PU compartment umoles, PU}

$$d/dt(ANPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc)))$$

$$d/dt(ANPUmuc) = KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ANPUmuc/VPUmuc) - (ANPUepi/(VPUepi*Pvrg)))$$

$$d/dt(ANPUepi) = KTRPU*SAPU*((ANPUmuc/(VPUmuc*PMA)) - (ANPUepi/(VPUepi*Pvrg))) - KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) -$$

$$Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg)))$$

$$d/dt(ANPUex) = KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) + Qtot*(Cart - (ANPUex/(VPUex*Pvrg)))$$

$$d/dt(GSHpu) = Kgshtb*(CGSHpub - (GSHpu/VPUepi)) - Kge*GSHpu - VmaxGpu*(ABPUepi/(VPUepi*PBvrg))*CGSHpu/(KmG1*(ABPUepi/(VPUepi*PBvrg)) + KmG2*CGSHpu + CGSHpu*(ABPUepi/(VPUepi*PBvrg)))$$

$$d/dt(AMETpu) = Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg)))$$

{differential equations for NO in PU compartment umoles, PU}

$$d/dt(ABPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc)))$$

$$\frac{d}{dt}(\text{ABPUmuc}) = \text{KOPU} * \text{SAPU} * ((\text{ABPUa}/\text{VPUa}) - (\text{ABPUmuc}/(\text{PMA} * \text{VPUmuc}))) - \text{KTRPU} * \text{SAPU} * ((\text{ABPUmuc}/(\text{VPUmuc} * \text{PMA})) - (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})))$$

$$\frac{d}{dt}(\text{ABPUepi}) = \text{KTRPU} * \text{SAPU} * ((\text{ABPUmuc}/(\text{VPUmuc} * \text{PMA})) - (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg}))) - \text{KBOPU} * \text{SAPU} * ((\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})) - (\text{ABPUex}/(\text{VPUex} * \text{PBvrg}))) + \text{Vmaxpu} * (\text{ANPUepi}/(\text{VPUepi} * \text{Pvrg})) / (\text{Kmlu} + (\text{ANPUepi}/(\text{VPUepi} * \text{Pvrg}))) - \text{Vmax2pu} * \text{ABPUepi}/(\text{VPUepi} * \text{PBvrg}) / (\text{Km2lu} + (\text{ABPUepi}/\text{VPUepi})) - \text{VmaxGpu} * (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})) * \text{CGSHpu} / (\text{KmG1} * (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})) + \text{KmG2} * \text{CGSHpu} + \text{CGSHpu} * (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg}))) - \text{KNOH} * (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})) * 1\text{E}3$$

$$\frac{d}{dt}(\text{ABPUex}) = \text{KBOPU} * \text{SAPU} * ((\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})) - (\text{ABPUex}/(\text{VPUex} * \text{PBvrg}))) + \text{Qtot} * (\text{CBart} - (\text{ABPUex}/(\text{VPUex} * \text{PBvrg})))$$

$$\frac{d}{dt}(\text{ABMET2pu}) = (\text{Vmax2pu} * (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})) / (\text{Km2lu} + (\text{ABPUepi}/\text{VPUepi}))) / 2$$

$$\frac{d}{dt}(\text{ABMETGpu}) = (\text{VmaxGpu} * (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})) * \text{CGSHpu} / (\text{KmG1} * (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})) + \text{KmG2} * \text{CGSHpu} + \text{CGSHpu} * (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})))) / 2$$

$$\frac{d}{dt}(\text{ABNOHpu}) = \text{KNOH} * (\text{ABPUepi}/(\text{VPUepi} * \text{PBvrg})) * 1\text{E}3$$

init ABNOHpu = 0
 {Sum of Lung NAP}

d/dt(ANex) = Qtot * ((Cart-Cvurtex) + (Cart-Cvcaex) + (Cart-Cvtbex) + (Cart-Cvpuex))
 {Sum of Lung NO}

d/dt(ABex) = Qtot * ((CBart-CBvurtex) + (CBart-CBvcaex) + (CBart-CBvtbex) + (CBart-CBvpuex))
 {NAP ex respiratory tract, umoles}

init Af = 0
init AI = 0
Limit AI >= 0
init Am = 0
Limit Am >= 0
init Avrg = 0
Limit Avrg >= 0
init Ablood = 0
init GSHI = 6.0*VI
 {NO oxide ex respiratory tract, umoles}

init ABf = 0
init ABler = 0
Limit ABler >= 0
init ABlcy = 0
Limit ABlcy >= 0
init ABm = 0
Limit ABm >= 0
init ABvrg = 0
Limit ABvrg >= 0
init ABblood = 0
 {umoles NAP metabolized}

init AMETI = 0
 {umoles NO ex rt metabolized EH, GST and P450 pathways}

init ABMETI2 = 0
init ABMETGI = 0

{AUCs NAP}**init AUCvtot = 0****init AUCvl = 0****{AUCs NO}****init AUCBvtot = 0****init AUCBvl = 0**

{tissue flows mL/min}

Qtot = (0.012*Age³ - 1.2144*Age² + 40.32*Age + 44.144)*1000/60**Qalv = 0.82*Qtot****Qf = 0.0528*Qtot****Ql = 0.0795*Qtot****Qm = 0.0304*Qtot****Qvrg = 0.837*Qtot**

{tissue volumes mL}

BW = -1.9*Age⁴ + 72.8*Age³ - 813.1*Age² + 5535.6*Age + 4453.7**Vf = 0.0165*Age⁵ - 1.9784*Age⁴ + 51.963*Age³ - 459.38*Age² + 1566.8*Age + 1004.2****VI = 0.0072*Age⁵ - 0.3975*Age⁴ + 7.9052*Age³ - 65.625*Age² + 262.02*Age + 157.2****Vm = -0.0623*Age⁵ + 2.3433*Age⁴ - 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2****Vvrg = BW - (Vf + VI + Vm + Vlu + Vblood)****Vblood = 0.075*BW**

{blood/air and tissue/blood partition coefficients, NAP}

Pb = 571**PI = 7.0****Pf = 160.0****Pm = 4.0****Pvrg = 4.0**

{blood/air and tissue/blood partition coefficients, NO}

PBb = 571**PBI = 7.0****PBf = 22.9****PBm = 4.0****PBvrg = 4.0**

{calculated concentrations of NAP umol/mL}

Cblood = Ablood/Vblood**Cart = Cvex****Cvf = Af/(Vf*Pf)****Cvl = Al/(VI*PI)****Cvm = Am/(Vm*Pm)****Cvrg = Avrg/(Vvrg*Pvrg)****Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvrg)/Qtot****Cairin = exposure/(24.45*1E3)****CGSHI = GSHI/VI****CGSHIb = 6.0**

{calculated concentrations of NO umol/mL}

$$\text{CBblood} = \text{ABblood}/\text{Vblood}$$

$$\text{CBart} = \text{CBvex}$$

$$\text{CBvf} = \text{ABf}/(\text{Vf}*\text{PBf})$$

$$\text{CBvler} = \text{ABler}/(\text{VI}*\text{PBI})$$

$$\text{CBvlcy} = \text{ABlcy}/(\text{VI}*\text{PBI})$$

$$\text{CBvm} = \text{ABm}/(\text{Vm}*\text{PBm})$$

$$\text{CBvvr} = \text{ABvrg}/(\text{Vvrg}*\text{PBvrg})$$

$$\text{CBvtot} = (\text{Ql}*\text{CBvlcy} + \text{Qf}*\text{CBvf} + \text{Qm}*\text{CBvm} + \text{Qvrg}*\text{CBvvr})/\text{Qtot}$$

$$\text{CBairin} = \text{exposureB}/(24.45*1\text{E}3)$$

{differential equations for NAP uptake and metabolism, umoles}

$$\text{d/dt(Al)} = \text{Ql}*(\text{Cart} - \text{Cvl}) - \text{Vmaxl}*\text{Cvl}/(\text{Km} + \text{Cvl})$$

$$\text{d/dt(Af)} = \text{Qf}*(\text{Cart} - \text{Cvf})$$

$$\text{d/dt(Am)} = \text{Qm}*(\text{Cart} - \text{Cvm})$$

$$\text{d/dt(Avrg)} = \text{Qvrg}*(\text{Cart} - \text{Cvvr})$$

$$\text{d/dt(ABlood)} = \text{Ql}*\text{Cvl} + \text{Qf}*\text{Cvf} + \text{Qm}*\text{Cvm} + \text{Qvrg}*\text{Cvvr} + \text{Qtot}*\text{Cvex}$$

{differential equations for NO uptake and metabolism, umoles}

$$\text{d/dt(ABf)} = \text{Qf}*(\text{CBart} - \text{CBvf})$$

$$\text{d/dt(ABm)} = \text{Qm}*(\text{CBart} - \text{CBvm})$$

$$\text{d/dt(ABvrg)} = \text{Qvrg}*(\text{CBart} - \text{CBvvr})$$

$$\text{d/dt(ABblood)} = \text{Ql}*\text{CBvlcy} + \text{Qf}*\text{CBvf} + \text{Qm}*\text{CBvm} + \text{Qvrg}*\text{CBvvr} + \text{Qtot}*\text{CBvex}$$

$$\text{d/dt(ABler)} = \text{Vmaxl}*\text{Cvl}/(\text{Km} + \text{Cvl}) - \text{Kec}*(\text{CBvler} - \text{CBvlcy}) - \text{Vmaxl}2*\text{CBvler}/(\text{Km}2\text{ih} + \text{CBvler})$$

$$\text{d/dt(ABlcy)} = \text{Kec}*(\text{CBvler} - \text{CBvlcy}) + \text{Ql}*(\text{CBart} - \text{CBvlcy}) - \text{VmaxG1}*\text{CBvlcy}*\text{CGSHI}/(\text{KmG}2*\text{CBvlcy} + \text{KmG}1*\text{CGSHI} + \text{CBvlcy}*\text{CGSHI})$$

$$\text{d/dt(GSHI)} = \text{Kgshl}*(\text{CGSHIb} - (\text{GSHI}/\text{VI})) - \text{Kge}*\text{GSHI} - \text{VmaxG1}*\text{CBvlcy}*\text{CGSHI}/(\text{KmG}1*\text{CBvlcy} + \text{KmG}2*\text{CGSHI} + \text{CBvlcy}*\text{CGSHI}) - \text{KNOH}*\text{CBvlcy}*\text{1E}3$$

{amount of BD metabolized in liver to NO, umoles}

$$\text{d/dt(AMETI)} = \text{Vmaxl}*\text{Cvl}/(\text{Km} + \text{Cvl})$$

{amount of NO metabolized in liver and lung to diol, umoles}

$$\text{d/dt(ABMETI2)} = (\text{Vmaxl}2*\text{CBvler}/(\text{Km}2\text{ih} + \text{CBvler}))/2$$

{amount of NO metabolized in liver and lung to GSH conjugate, umoles}

$$\text{d/dt(ABMETGI)} = (\text{VmaxG1}*\text{CBvlcy}*\text{CGSHI}/(\text{KmG}1*\text{CBvlcy} + \text{KmG}2*\text{CGSHI} + \text{CGSHI}*\text{CBvlcy}))/2$$

{amount of NO rearranged to NOH, umoles}

$$\text{d/dt(ABNOHI)} = \text{KNOH}*\text{CBvlcy}*\text{1E}3$$

$$\text{init ABNOHI} = 0$$

{AUCs for NAP, umolmin/mL}

$$\text{d/dt(AUCvtot)} = \text{Cvtot}$$

$$\text{d/dt(AUCvl)} = \text{Cvl}$$

{AUCs for NO, umolmin/mL}

$$\text{d/dt(AUCBvtot)} = \text{CBvtot}$$

$$\text{d/dt(AUCBvl)} = \text{CBvlcy}$$

E.5.6 Model Code for BD/BMO RT 0-5 yr Child**METHOD Stiff****STARTTIME = 0****STOPTIME= 2880****DT = 0.0001**

{Butadiene (BD) in upper respiratory tract compartment (URT) umoles}

init ANURTa = 0**init ANURTmuc = 0****init ANURTepi = 0****Limit ANURTepi >= 0****init ANURTex = 0****init AMETua = 0**

{Butadienemonoxide (BMO) in upper respiratory compartment (URT) umoles}

init ABURTa = 0**init ABURTmuc = 0****init ABURTepi = 0****init GSHua = 1.0*VURTepi****init ABURTex = 0****init ABMET2ua = 0****init ABMETGua = 0****init ABMET3ua = 0****Limit ABMET3ua >= 0**

{BD in conducting airways compartment (CA), umoles}

init ANCAa = 0**init ANCAmuc = 0****init ANCAepi = 0****init ANCAex = 0****init AMETca = 0**

{BMO in conducting airways compartment (CA), umoles}

init ABCAa = 0**init ABCAmuc = 0****init ABCAepi = 0****init ABCAex = 0****init GSHca = 1.0*VCA****init ABMET2ca = 0****init ABMETGca = 0****init ABMET3ca = 0**

{BD in transitional bronchioles compartment (TB), umoles}

init ANTBa = 0**init ANTBmuc = 0****init ANTBepi = 0****init ANTBex = 0**

init AMETtb = 0
 {BMO in transitional bronchioles compartment (TB), umoles}
init ABTBa = 0
init ABTBmuc = 0
init ABTBepi = 0
init GSHtb = 1.0*VTBepi
init ABTBex = 0
init ABMET2tb = 0
init ABMETGtb = 0
init ABMET3tb = 0
 {BD in pulmonary compartment (PU), umoles}
init ANPUa = 0
init ANPUmuc = 0
init ANPUepi = 0
init ANPUex = 0
init ANex = 0
init AMETpu = 0
 {BMO in pulmonary compartment (PU), umoles}
init ABPUa = 0
init ABPUmuc = 0
init ABPUepi = 0
init ABPUex = 0
init ABex = 0
init GSHpu = 1.0*VPU
init ABMET2pu = 0
init ABMETGpu = 0
init ABMET3pu = 0
 {model equations}
Q = RPM*TVOL
Cairin = exposure/(24.36*1E3)
VURTEpi = SAURT*WUA
VURTmuc = SAURT*WSMua
VURTex = SAURT*WUAs
VCAmuc = SACA*WSMca
VCAepi = SACA*WCA
VCAex = SACA*WCAs
VTBmuc = SATB*WSMtb
VTBepi = SATB*WTA
VTBex = SATB*WTAs
VPUmuc = SAPU*WSMpu
VPUepi = SAPU*WPA
VPUex = SAPU*WTAs
Vlu = 59.213 + 123.99*Age - 20.31*Age^2 + 1.5069*Age^3 - 0.0346*Age^4
VURT = 0.0026*Vlu

VCA = 0.018*Vlu
VTB = 0.043*Vlu
VPU = 0.937*Vlu
Curtepil = (ANURTEpi/VURTEpi)
Ccaepil = (ANCAepi/VCAepi)
Ctbepil = (ANTBepi/VTBepi)
Cpuepil = (ANPUepi/VPUepi)
Cvurtex = (ANURTex/(VURTex*Pvrg))
Cvcaex = (ANCAex/(VCAex*Pvrg))
Cvtbex = (ANTBex/(VTBex*Pvrg))
Cvpuex = (ANPUex/(VPUex*Pvrg))
Cvex = (ANURTex+ANCAex+ANTBex+ANPUex)/((VURTex+VCAex+VTBex+VPUex)*Pvrg)
CBurtepil = (ABURTEpi/VURTEpi)
CBcaepil = (ABCAepi/VCAepi)
CBtbepil = (ABTBepi/VTBepi)
CBpuepil = (ABPUepi/VPUepi)
CBvurtex = (ABURTex/(VURTex*PBvrg))
CBvcaex = (ABCAex/(VCAex*PBvrg))
CBvtbex = (ABTBex/(VTBex*PBvrg))
CBvpuex = (ABPUex/(VPUex*PBvrg))
CBvex = (ABURTex+ABCAex+ABTBex+ABPUex)/((VURTex+VCAex+VTBex+VPUex)*PBvrg)
CGSHuab = 2.5
CGSHcab = 2.0
CGSHtbb = 1.0
CGSHpub = 1.0
Exposure = IF TIME <= 1440 THEN 1 ELSE 0
ExposureB = IF TIME <= 1440 THEN 0 ELSE 0
Age = 3.0
 {upper respiratory tract constants}
PMA = 30 {mucus:air partition coeff}
KOURT = 1980 {mass transfer coeffs., cm/min}
KTRURT = 19.2
KBOURT = 19.2
KOCA = 181
KTRCA = 19.2
KBOCA = 19.2
KOTB = 158
KTRTB = 19.2
KBOTB = 19.2
KOPU = 158
KTRPU = 19.2
KBOPU = 19.2
KMUC = 0.001 {diffusion constants, cm²/min}
KSQM = 0.0002

$$KG = 6.0$$

$$SAURT = VURT/WUA \text{ \{surface areas, cm}^2\}$$

$$SACA = VCA/WCA$$

$$SATB = VTB/WTA$$

$$SAPU = VPU/WPA$$

$$VURTa = 0.00035 * TLC \text{ \{luminal volumes, cm}^3\}$$

$$VCAa = 0.0105 * TLC$$

$$VTBa = 0.042 * TLC$$

$$VPUa = 0.944 * TLC$$

$$TLC = 236.5 + 282 * Age - 4.775 * Age^2 + 0.285 * Age^3$$

$$RPM = 53.5 * (BW/1000)^{-0.26} \text{ \{breaths/min}\}$$

$$TVOL = 35.45 + 33.56 * Age - 1.47 * Age^2 + 0.0793 * Age^3 \text{ \{tidal volume mL/ breath}\}$$

\{thicknesses (W) of upper airways epithelium (UA), submucosa (UAs); mucus (SM); conducting airways epi (CA), submucosa (CAs); transitional airways epi (TA), submucosa (TAs); and pulmonary airways epi (PA), cm\}

$$WUA = 0.005$$

$$WSMua = 0.001$$

$$WSMca = 0.0005$$

$$WSMtb = 0.0002$$

$$WSMpu = 0.0001$$

$$WCA = 0.0025$$

$$WTA = 0.001$$

$$WPA = 0.0005$$

$$WUAs = 0.01$$

$$WCAs = 0.005$$

$$WTAs = 0.002$$

$$Qua = 0.0025 * Qtot \text{ \{blood flow to the URT region}\}$$

$$Qca = 0.0075 * Qtot \text{ \{blood flow to the CA}\}$$

$$Qta = 0.0067 * Qtot \text{ \{blood flow to the TA}\}$$

\{metabolic constants umol/min, umol/mL, based on Csanady et al. 2003 scaled to smaller BWs, 1 = EH, 2 = conj, 3 = oxid\}

$$Vmaxua = 9.09E-3 * 3.0 * VURTepi * (7E4/BW)^{0.25/60}$$

$$Vmaxca = 9.09E-3 * 3.0 * VCAepi * (7E4/BW)^{0.25/60}$$

$$Vmaxtb = 9.09E-3 * 3.0 * VTBepi * (7E4/BW)^{0.25/60}$$

$$Vmaxpu = 9.09E-3 * 3.0 * VPUepi * (7E4/BW)^{0.25/60}$$

$$Vmaxl = 7.08E-2 * 14.5 * VI * (7E4/BW)^{0.25/60}$$

$$Vmaxl2 = 1.1 * 14.5 * VI * (7E4/BW)^{0.25/60} \text{ \{EH}\}$$

$$K1ua = 0.1914 * 3.0 * VURTepi * (7E4/BW)^{-0.25/60}$$

$$K1ca = 0.1914 * 3.0 * VCAepi * (7E4/BW)^{-0.25/60}$$

$$K1tb = 0.1914 * 3.0 * VTBepi * (7E4/BW)^{-0.25/60}$$

$$K1pu = 0.1914 * 3.0 * VPUepi * (7E4/BW)^{-0.25/60}$$

$$Kgsh = 0.012 \text{ \{GSH /min}\}$$

$$Kge = 0.15/60$$

$$VmaxGl = 2.71 * 58 * VI * (7E4/BW)^{0.25/60} \text{ \{umol/min/liver, GST}\}$$

$$K2ua = 0.1536 * 54 * VURTepi * (7E4/BW)^{-0.25/60} \text{ \{umol/min/URT}\}$$

$$K2ca = 0.1536*54*VCAepi*(7E4/BW)^{-0.25/60} \text{ {umol/min/CA}}$$

$$K2tb = 0.1536*54*VTBepi*(7E4/BW)^{-0.25/60} \text{ {umol/min/TB}}$$

$$K2pu = 0.1536*54*VPUepi*(7E4/BW)^{-0.25/60} \text{ {umol/min/PU}}$$

$$MPI = 14.5 \text{ {mg microsomal protein /mL tissue}}$$

$$MPIu = 3.0 \text{ {mg microsomal protein/mL tissue}}$$

$$CPI = 58 \text{ {mg cytosolic protein/mL tissue}}$$

$$CPIu = 54 \text{ {mg cytosolic protein/mL tissue}}$$

$$Km = 0.00514 \text{ {umol/mL}}$$

$$Kmlu = 0.002$$

$$Km2 = 0.58$$

$$Km2ih = 0.116$$

$$KmG1 = 0.1 \text{ {GSH}}$$

$$KmG2 = 10.4 \text{ {BMO}}$$

$$Kec = 400$$

$$Vmaxua3 = 0.0066*0.2/(7E4/BW)^{0.25/60}$$

$$Vmaxca3 = 0.1986*0.2/(7E4/BW)^{0.25/60}$$

$$Vmaxtb3 = 0.7947*0.2/(7E4/BW)^{0.25/60}$$

$$Vmaxpu3 = 1.7/(7E4/BW)^{0.25/60}$$

$$VmaxI3 = 14.8/(7E4/BW)^{0.25/60}$$

$$Km3 = 0.0156$$

{differential equations for BD in URT compartment, URT}

$$d/dt(ANURTa) = Q*(Cairin - (ANURTa/VURTa)) - KOURT*SAURT*((ANURTa/VURTa) - (ANURTmuc/(PMA*VURTmuc)))$$

$$d/dt(ANURTmuc) = KOURT*SAURT*((ANURTa/VURTa) - (ANURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTEpi/(VURTEpi*Pvrg)))$$

$$d/dt(ANURTEpi) = KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTEpi/(VURTEpi*Pvrg))) - KBOURT*SAURT*((ANURTEpi/(VURTEpi*Pvrg)) - (ANURTex/(VURTex*Pvrg))) - Vmaxua*(ANURTEpi/(VURTEpi*Pvrg))/(Kmlu + (ANURTEpi/(VURTEpi*Pvrg)))$$

$$d/dt(ANURTex) = KBOURT*SAURT*((ANURTEpi/VURTEpi) - (ANURTex/VURTex)) + Qua*(Cart - (ANURTex/(VURTex*Pvrg)))$$

$$d/dt(AMETua) = Vmaxua*(ANURTEpi/(VURTEpi*Pvrg))/(Kmlu + (ANURTEpi/(VURTEpi*Pvrg)))$$

$$d/dt(GSHua) = Kgsh*(CGSHuab - (GSHua/VURTEpi)) - Kge*GSHua - K2ua*ABURTEpi$$

{differential equations for BMO in URT compartment, URT}

$$d/dt(ABURTa) = Q*(CBairin - (ABURTa/VURTa)) - KOURT*SAURT*((ABURTa/VURTa) - (ABURTmuc/(PMA*VURTmuc)))$$

$$d/dt(ABURTmuc) = KOURT*SAURT*((ABURTa/VURTa) - (ABURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTEpi/(VURTEpi*PBvrg)))$$

$$d/dt(ABURTEpi) = KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTEpi/(VURTEpi*PBvrg))) - KBOURT*SAURT*((ABURTEpi/(VURTEpi*PBvrg)) - (ABURTex/(VURTex*PBvrg))) + Vmaxua*(ANURTEpi/(VURTEpi*PBvrg))/(Kmlu + (ANURTEpi/(VURTEpi*PBvrg))) - K1ua*ANURTEpi - K2ua*ANURTEpi - Vmaxua3*(ABURTEpi/(VURTEpi*PBvrg))/(Km3 + (ABURTEpi/(VURTEpi*PBvrg)))$$

$$d/dt(ABMET2ua) = K1ua*ANURTEpi$$

$$d/dt(ABMETGua) = K2ua*ANURTEpi$$

$$d/dt(ABMET3ua) = Vmaxua3*(ABURTEpi/(VURTEpi*PBvrg))/(Km3 + (ABURTEpi/(VURTEpi*PBvrg)))$$

$$d/dt(ABURTex) = KBOURT*SAURT*((ABURTEpi/VURTEpi) - (ABURTex/(VURTex*PBvrg))) + Qua*(CBart - (ABURTex/(VURTex*PBvrg)))$$

{differential equations for BD in CA compartment, CA}

$$d/dt(ANCAa) = Q*(Cairin - (ANCAa/VCAa)) - KOCA*SACA*((ANCAa/VCAa) - (ANCAmuc/(PMA*VCAmuc)))$$

$$d/dt(ANCAmuc) = KOCA*SACA*((ANCAa/VCAa) - (ANCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg)))$$

$$d/dt(ANCAepi) = KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg))) - KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) - Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg)))$$

$$d/dt(ANCAex) = KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) + Qca*(Cart - (ANCAex/(VCAex*Pvrg)))$$

$$d/dt(AMETca) = Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg)))$$

$$d/dt(GSHca) = Kgsh*(CGSHcab - (GSHca/VCAepi)) - Kge*GSHca - K2ca*ABCAepi$$

{differential equations for BMO in CA compartment, CA}

$$d/dt(ABCAa) = Q*(CBairin - (ABCAa/VCAa)) - KOCA*SACA*((ABCAa/VCAa) - (ABCAmuc/(PMA*VCAmuc)))$$

$$d/dt(ABCAmuc) = KOCA*SACA*((ABCAa/VCAa) - (ABCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg)))$$

$$d/dt(ABCAepi) = KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg))) + Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg))) - KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) - K1ca*ABCAepi - K2ca*ABCAepi - Vmaxca3*(ABCAepi/(VCAepi*PBvrg))/(Km3 + (ABCAepi/(VCAepi*PBvrg)))$$

$$d/dt(ABCAex) = KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) + Qca*(CBart - (ABCAex/(VCAex*PBvrg)))$$

$$d/dt(ABMET2ca) = K1ca*ABCAepi$$

$$d/dt(ABMETGca) = K2ca*ABCAepi$$

$$d/dt(ABMET3ca) = Vmaxca3*(ABCAepi/(VCAepi*PBvrg))/(Km3 + (ABCAepi/(VCAepi*PBvrg)))$$

{differential equations for BD in TB compartment umoles, TB}

$$d/dt(ANTBa) = Q*(Cairin - (ANTBa/VTBa)) - KOTB*SATB*((ANTBa/VTBa) - (ANTBmuc/(PMA*VTBmuc)))$$

$$d/dt(ANTBmuc) = KOTB*SATB*((ANTBa/VTBa) - (ANTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBmuc/(VTBmuc*PMA)))$$

$$d/dt(ANTBepi) = KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBepi/(VTBepi*Pvrg))) - KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) - Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg)))$$

$$d/dt(ANTBex) = KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) + Qta*(Cart - (ANTBex/(VTBex*Pvrg)))$$

$$d/dt(AMETtb) = Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg)))$$

$$d/dt(GSHtb) = Kgsh*(CGSHtbb - (GSHtb/VTBepi)) - Kge*GSHtb - K2tb*ABTBepi$$

{differential equations for BMO in TB compartment umoles, TB}

$$d/dt(ABTBa) = Q*(CBairin - (ABTBa/VTBa)) - KOTB*SATB*((ABTBa/VTBa) - (ABTBmuc/(PMA*VTBmuc)))$$

$$d/dt(ABTBmuc) = KOTB*SATB*((ABTBa/VTBa) - (ABTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg)))$$

$$d/dt(ABTBepi) = KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg))) - KBOTB*SATB*((ABTBepi/(VTBepi*PBvrg)) - (ABTBex/(VTBex*PBvrg))) + Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg))) - K1tb*ABTBepi - K2tb*ABTBepi - Vmaxtb3*(ANTBepi/(VTBepi*Pvrg))/(Km3 + (ANTBepi/(VTBepi*Pvrg)))$$

$$d/dt(ABMET2tb) = K1tb*ABTBepi$$

$$d/dt(ABMETGtb) = K2tb*ABTBepi$$

$$d/dt(ABMET3tb) = Vmaxtb3*(ANTBepi/(VTBepi*Pvrg))/(Km3 + (ANTBepi/(VTBepi*Pvrg)))$$

$$d/dt(ABTBex) = KBOTB*SATB*(ABTBepi/(VTBepi*PBvrg) - (ABTBex/(VTBex*PBvrg))) + Qta*(CBart - (ABTBex/(VTBex*PBvrg)))$$
 {differential equations for BD in PU compartment umoles, PU}

$$d/dt(ANPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc)))$$

$$d/dt(ANPUmuc) = KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ANPUmuc/VPUmuc) - (ANPUepi/(VPUepi*Pvrg)))$$

$$d/dt(ANPUepi) = KTRPU*SAPU*((ANPUmuc/(VPUmuc*PMA)) - (ANPUepi/(VPUepi*Pvrg))) - KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) - Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg)))$$

$$d/dt(ANPUex) = KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) + Qtot*(Cart - (ANPUex/(VPUex*Pvrg)))$$

$$d/dt(GSHpu) = Kgsh*(CGSHpub - (GSHpu/VPUepi)) - Kge*GSHpu - K2pu*ABPUepi$$

$$d/dt(AMETpu) = Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg)))$$
 {differential equations for BMO in PU compartment umoles, PU}

$$d/dt(ABPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc)))$$

$$d/dt(ABPUmuc) = KOPU*SAPU*((ABPUa/VPUa) - (ABPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg)))$$

$$d/dt(ABPUepi) = KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg))) - KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg))) + Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg))) - K1pu*ABPUepi - K2pu*ABPUepi - Vmaxpu3*(ABPUepi/(VPUepi*Pvrg))/(Km3 + (ABPUepi/(VPUepi*Pvrg)))$$

$$d/dt(ABPUex) = KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg))) + Qtot*(CBart - (ABPUex/(VPUex*PBvrg)))$$

$$d/dt(ABMET2pu) = K1pu*ABPUepi$$

$$d/dt(ABMETGpu) = K2pu*ABPUepi$$

$$d/dt(ABMET3pu) = Vmaxpu3*(ABPUepi/(VPUepi*Pvrg))/(Km3 + (ABPUepi/(VPUepi*Pvrg)))$$
 {Sum of Lung BD}

$$d/dt(ANex) = Qtot*((Cart-Cvurtex) + (Cart-Cvcaex) + (Cart-Cvtbex) + (Cart-Cvpueex))$$
 {Sum of Lung BMO}

$$d/dt(ABex) = Qtot*((CBart-CBvurtex) + (CBart-CBvcaex) + (CBart-CBvtbex) + (CBart-CBvpueex))$$
 {BD ex respiratory tract, umoles}

$$\text{init Af} = 0$$

$$\text{init Al} = 0$$

$$\text{init Am} = 0$$

$$\text{init Avrg} = 0$$

$$\text{init Ablood} = 0$$

$$\text{init GSHI} = 6.0*VI$$
 {BMO oxide ex respiratory tract, umoles}

$$\text{init ABf} = 0$$

$$\text{init ABler} = 0$$

$$\text{init ABlcy} = 0$$

$$\text{init ABm} = 0$$

$$\text{init ABvrg} = 0$$

$$\text{init ABblood} = 0$$

{umoles BD metabolized}

init AMETI = 0

{umoles BMO ex rt metabolized EH, GST and P450 pathways}

init ABMETI2 = 0

init ABMETGI = 0

init ABMETI3 = 0

{AUCs BD}

init AUCvtot = 0

init AUCvl = 0

{AUCs BMO}

init AUCBvtot = 0

init AUCBvl = 0

{tissue flows mL/min}

Qtot = (0.012*Age^3 - 1.2144*Age^2 + 40.32*Age + 44.144)*(1000/60)

Qalv = (17.874*Age + 39.785)*(1000/60)

Qf = 0.0528*Qtot

QI = 0.0795*Qtot

Qm = 0.0304*Qtot

Qvrg = 0.837*Qtot

{tissue volumes mL}

BW = - 1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7

Vf = 0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2

VI = 0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.625*Age^2 + 262.02*Age + 157.52

Vm = -0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2

Vvrg = BW - (Vf + VI + Vm + Vlu + Vblood)

Vblood = 0.075*BW

{blood/air and tissue/blood partition coefficients, BD}

Pb = 1.5

PI = 5.49

Pf = 118.2

Pm = 5.26

Pvrg = 5.34

{blood/air and tissue/blood partition coefficients, BMO}

PBb = 60

PBI = 0.6545

PBf = 1.808

PBm = 0.6533

PBvrg = 0.6348

{calculated concentrations of BD umol/mL}

Cblood = Ablood/Vblood

Cart = Cvex

Cvf = Af/(Vf*Pf)

Cvl = AI/(VI*PI)

Cvm = Am/(Vm*Pm)

$$\text{Cvvr}g = \text{Avr}g / (\text{Vvr}g * \text{Pvr}g)$$

$$\text{Cvtot} = (\text{Ql} * \text{Cvl} + \text{Qf} * \text{Cvf} + \text{Qm} * \text{Cvm} + \text{Qvr}g * \text{Cvvr}g) / \text{Qtot}$$

$$\text{Cairin} = \text{exposure} / (24.45 * 1\text{E}3)$$

$$\text{CGSHI} = \text{GSHI} / \text{VI}$$

$$\text{CGSHIb} = 6.0$$

{calculated concentrations of BMO umol/mL}

$$\text{CBblood} = \text{ABblood} / \text{Vblood}$$

$$\text{CBart} = \text{CBvex}$$

$$\text{CBvf} = \text{ABf} / (\text{Vf} * \text{PBf})$$

$$\text{CBvler} = \text{ABler} / (\text{VI} * \text{PBI})$$

$$\text{CBvlcy} = \text{ABlcy} / (\text{VI} * \text{PBI})$$

$$\text{CBvm} = \text{ABm} / (\text{Vm} * \text{PBm})$$

$$\text{CBvvr}g = \text{ABvvr}g / (\text{Vvr}g * \text{PBvvr}g)$$

$$\text{CBvtot} = (\text{Ql} * \text{CBvlcy} + \text{Qf} * \text{CBvf} + \text{Qm} * \text{CBvm} + \text{Qvr}g * \text{CBvvr}g) / \text{Qtot}$$

$$\text{CBairin} = \text{exposureB} / (24.45 * 1\text{E}3)$$

{differential equations for BD uptake and metabolism, umoles}

$$d/dt(\text{Al}) = \text{Ql} * (\text{Cart} - \text{Cvl}) - \text{VmaxI} * \text{Cvl} / (\text{Km} + \text{Cvl})$$

$$d/dt(\text{Af}) = \text{Qf} * (\text{Cart} - \text{Cvf})$$

$$d/dt(\text{Am}) = \text{Qm} * (\text{Cart} - \text{Cvm})$$

$$d/dt(\text{Avr}g) = \text{Qvr}g * (\text{Cart} - \text{Cvvr}g)$$

$$d/dt(\text{Ablood}) = \text{Ql} * \text{Cvl} + \text{Qf} * \text{Cvf} + \text{Qm} * \text{Cvm} + \text{Qvr}g * \text{Cvvr}g + \text{Qtot} * \text{Cvex}$$

{differential equations for BMO uptake and metabolism, umoles}

$$d/dt(\text{ABf}) = \text{Qf} * (\text{CBart} - \text{CBvf})$$

$$d/dt(\text{ABm}) = \text{Qm} * (\text{CBart} - \text{CBvm})$$

$$d/dt(\text{ABvvr}g) = \text{Qvr}g * (\text{CBart} - \text{CBvvr}g)$$

$$d/dt(\text{ABblood}) = \text{Ql} * \text{CBvlcy} + \text{Qf} * \text{CBvf} + \text{Qm} * \text{CBvm} + \text{Qvr}g * \text{CBvvr}g + \text{Qtot} * \text{CBvex}$$

$$d/dt(\text{ABler}) = \text{VmaxI} * \text{Cvl} / (\text{Km} + \text{Cvl}) - \text{Kec} * (\text{CBvler} - \text{CBvlcy}) - \text{VmaxI}2 * \text{CBvler} / (\text{Km}2\text{ih} + \text{CBvler})$$

$$d/dt(\text{ABlcy}) = \text{Kec} * (\text{CBvler} - \text{CBvlcy}) + \text{Ql} * (\text{CBart} - \text{CBvlcy}) - \text{VmaxGI} * \text{CBvlcy} * \text{CGSHI} / (\text{KmG}2 * \text{CBvlcy} + \text{KmG}1 * \text{CGSHI} + \text{CBvlcy} * \text{CGSHI})$$

$$d/dt(\text{GSHI}) = \text{Kgsh} * (\text{CGSHIb} - (\text{GSHI} / \text{VI})) - \text{Kge} * \text{GSHI} - \text{VmaxGI} * \text{CBvlcy} * \text{CGSHI} / (\text{KmG}2 * \text{CBvlcy} + \text{KmG}1 * \text{CGSHI} + \text{CBvlcy} * \text{CGSHI}) - \text{VmaxI}3 * \text{CBvlcy} / (\text{Km}3 + \text{CBvlcy})$$

{amount of BD metabolized in liver to BMO, umoles}

$$d/dt(\text{AMETI}) = \text{VmaxI} * \text{Cvl} / (\text{Km} + \text{Cvl})$$

{amount of BMO metabolized in liver and lung to diol, umoles}

$$d/dt(\text{ABMETI}2) = \text{VmaxI}2 * \text{CBvler} / (\text{Km}2\text{ih} + \text{CBvler})$$

{amount of bmo metabolized in liver and lung to GSH conjugate, umoles}

$$d/dt(\text{ABMETGI}) = \text{VmaxGI} * \text{CBvlcy} * \text{CGSHI} / (\text{KmG}2 * \text{CBvlcy} + \text{KmG}1 * \text{CGSHI} + \text{CGSHI} * \text{CBvlcy})$$

{amount of BMO oxidized to DEB, umoles}

$$d/dt(\text{ABMETI}3) = \text{VmaxI}3 * \text{CBvlcy} / (\text{Km}3 + \text{CBvlcy})$$

{AUCs for BD, umolmin/mL}

$$d/dt(\text{AUCvtot}) = \text{Cvtot}$$

$$d/dt(\text{AUCvl}) = \text{Cvl}$$

{AUCs for BMO, umolmin/mL}

$$d/dt(\text{AUCBvtot}) = \text{CBvtot}$$

$$d/dt(\text{AUCBvl}) = \text{CBvlcy}$$

*E.5.7 Model Code for BD/BMO/DEB 0-5 Yr Child***METHOD Stiff****STARTTIME = 0****STOPTIME= 48****DT = 0.001**

{butadiene BD, moles}

init Af = 0**init AI = 0****init Am = 0****init Avrg = 0****init Abr = 0****init Apu = 0**

{butadienemonoxide BMO, moles}

init ABf = 0**init ABler = 0****init ABlcy = 0****init ABm = 0****init ABvrg = 0****init ABbr = 0****init ABpu = 0**

{diepoxybutane DEB, moles}

init ACf = 0**init ACI = 0****init ACm = 0****init ACvrg = 0****init ACbr = 0****init ACpu = 0**

{moles of GSH in liver and lung}

init GSHI = 5.9E-3*VI**GSHI0 = 5.9E-3*VI****init GSHlu = 1.12E-3*Vlu****GSHlu0 = 1.12E-3*Vlu****Kgsh = 0.72****Kge = 0.15****CGSHI = GSHI/VI****CGSHlu = GSHlu/Vlu**

{moles butadiene metabolized}

init Ametl = 0**init Ametpu = 0****init Ametbr = 0**

{moles of butadienemonoxide metabolized}

init ABmetl1 = 0**init ABmetl2 = 0**

init ABmetpu1 = 0
init ABmetpu2 = 0
init ABmetbr1 = 0
init ABmetbr2 = 0
init ABmetl3 = 0
init ABmetpu3 = 0
init ABmetbr3 = 0
 {area under the venous blood concn x time curve, butadiene}
init AUCvtot = 0
init AUCvl = 0
init AUCvpu = 0
init AUCvbr = 0
init AUCvlung = 0
 {area under the venous blood concn x time curve, butadienemonoxide}
init AUCBvtot = 0
init AUCBvl = 0
init AUCBvpu = 0
init AUCBvbr = 0
init AUCBvlung = 0
 {area under the venous blood concn x time curve, diepoxybutene}
init AUCCvtot = 0
init AUCCvl = 0
init AUCCvpu = 0
init AUCCvbr = 0
init AUCCvlung = 0
 {tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.32*Age + 44.144
Qalv = 17.874*Age + 39.785
Qf = 0.0528*Qtot
Ql = 0.0795*Qtot
Qm = 0.0304*Qtot
Qvrg = 0.837*Qtot
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
Age = 0.0
 {tissue volumes L}
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
VI = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.625*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + VI + Vm + Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu

{blood/air and tissue/blood partition coefficients, butadiene}

$$Pb = 1.5$$

$$PI = 5.49$$

$$Pf = 118.2$$

$$Pm = 5.26$$

$$Pvrg = 5.34$$

$$Ppu = 4.02$$

$$Pbr = 4.02$$

{blood/air and tissue/blood partition coefficients, butadienemonoxide}

$$PBb = 60$$

$$PBI = 0.6545$$

$$PBf = 1.8083$$

$$PBm = 0.6533$$

$$PBvrg = 0.6348$$

$$PBpu = 0.4725$$

$$PBbr = 0.4725$$

{blood/air and tissue/blood partition coefficients, diepoxybutene}

$$PCb = 300$$

$$PCI = 0.70$$

$$PCf = 0.715$$

$$PCm = 0.697$$

$$PCvrg = 0.6$$

$$PCpu = 0.6$$

$$PCbr = 0.6$$

{butadiene oxidation metabolic parameters, mol/hr, mol/L}

$$Vmaxlu = 9.0E-9*Vlu*3E3*(70/BW)^{0.25}$$

$$Vmaxbr = 0.1*Vmaxlu$$

$$Vmaxpu = 0.9*Vmaxlu$$

$$Vmaxl = 7.08E-8*VI*1.45E4*(70/BW)^{0.25}$$

$$Km = 5.14E-6$$

$$Kmlu = 2.0E-6$$

{butadienemonoxide metabolic parameters, mol/hr, mol/L, /hr; 1 = hydrolysis, 2 = conjugation, 3 = oxidation}

$$Vmaxl1 = 1.1E-6*VI*1.45E4*(70/BW)^{0.25}$$

$$Km1 = 5.8E-4$$

$$Km1ih = 0.2*Km1$$

$$Kec = 400$$

$$Vmaxl2 = 2.71E-6*VI*5.8E4*(70/BW)^{0.25}$$

$$Km2 = 1.04E-2$$

$$Km2bmo = 1E-4$$

$$k1 = 0.1914*3E3*Vlu*(70/BW)^{-0.25}$$

$$k2 = 0.1536*5.8E4*Vlu*(70/BW)^{-0.25}$$

$$Vmaxl3 = 1.48e-5*(70/BW)^{0.25}$$

$$Vmaxpu3 = 1.7E-6*(70/BW)^{0.25}$$

$$\mathbf{Vmaxbr3 = 2.0E-7*(70/BW)^{0.25}}$$

$$\mathbf{Km3 = 1.56E-5}$$

$$\mathbf{Km3ih = 0.2*Km3}$$

{diepoxybutene elimination constant, /hr}

$$\mathbf{Ke = 0.6*(70/BW)^{0.25}}$$

{exposure in ppm converted to moles}

$$\mathbf{Cair = IF TIME <= 24 THEN 1*(1E-6/25.45) ELSE 0}$$

{calculated concentrations of butadiene}

$$\mathbf{Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot}$$

$$\mathbf{Cvf = Af/(Vf*Pf)}$$

$$\mathbf{Cvl = Al/(Vl*Pl)}$$

$$\mathbf{Cvm = Am/(Vm*Pm)}$$

$$\mathbf{Cvvr = Avrg/(Vvrg*Pvrg)}$$

$$\mathbf{Cvpu = Apu/(Vpu*Ppu)}$$

$$\mathbf{Cvbr = Abr/(Vbr*Pbr)}$$

$$\mathbf{Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvr)/Qpu}$$

$$\mathbf{Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)}$$

$$\mathbf{Cexh = Cvipu/Pb}$$

{calculated concentrations of butadienemonoxide}

$$\mathbf{CBart = (Qpu*CBvpu + Qbr*CBvbr)/Qtot}$$

$$\mathbf{CBvf = ABf/(Vf*PBf)}$$

$$\mathbf{CBvler = ABler/(Vl*PBl)}$$

$$\mathbf{CBvlcy = ABlcy/(Vl*PBl)}$$

$$\mathbf{CBvm = ABm/(Vm*PBm)}$$

$$\mathbf{CBvvr = ABvrg/(Vvrg*PBvrg)}$$

$$\mathbf{CBvpu = ABpu/(Vpu*PBpu)}$$

$$\mathbf{CBvbr = ABbr/(Vbr*PBbr)}$$

$$\mathbf{CBvtot = (Ql*CBvlcy + Qf*CBvf + Qm*CBvm + Qvrg*CBvvr)/Qtot}$$

$$\mathbf{CBair = CBvtot/PBb}$$

$$\mathbf{CBvipu = (Qalv*CBair + Qpu*CBvtot)/((Qalv/PBb) + Qpu)}$$

$$\mathbf{CBexh = CBvipu/PBb}$$

{calculated concentrations of diepoxybutene}

$$\mathbf{CCart = (Qpu*CCvpu + Qbr*CCvbr)/Qtot}$$

$$\mathbf{CCvf = ACf/(Vf*PCf)}$$

$$\mathbf{CCvl = ACI/(Vl*PCI)}$$

$$\mathbf{CCvm = ACm/(Vm*PCm)}$$

$$\mathbf{CCvvr = ACvrg/(Vvrg*PCvrg)}$$

$$\mathbf{CCvpu = ACpu/(Vpu*PCpu)}$$

$$\mathbf{CCvbr = ACbr/(Vbr*PCbr)}$$

$$\mathbf{CCvtot = (Ql*CCvl + Qf*CCvf + Qm*CCvm + Qvrg*CCvvr)/Qtot}$$

$$\mathbf{CCair = CCvtot/PCb}$$

$$\mathbf{CCvipu = (Qalv*CCair + Qpu*CCvtot)/((Qalv/PCb) + Qpu)}$$

$$\mathbf{CCexh = CCvipu/PCb}$$

{differential equations for butadiene uptake and metabolism}

$$d/dt(A_{pu}) = Q_{pu} * (C_{vipu} - C_{vpu}) - V_{maxpu} * C_{vpu} / (K_{mlu} + C_{vpu})$$

$$d/dt(A_{br}) = Q_{br} * (C_{art} - C_{vbr}) - V_{maxbr} * C_{vbr} / (K_{mlu} + C_{vbr})$$

$$d/dt(A_l) = Q_l * (C_{art} - C_{vl}) - V_{maxl} * C_{vl} / (K_m + C_{vl})$$

$$d/dt(A_f) = Q_f * (C_{art} - C_{vf})$$

$$d/dt(A_m) = Q_m * (C_{art} - C_{vm})$$

$$d/dt(A_{vrg}) = Q_{vrg} * (C_{art} - C_{vvrg})$$

{amount of butadiene metabolized in liver and lung}

$$d/dt(A_{metl}) = V_{maxl} * C_{vl} / (K_m + C_{vl})$$

$$d/dt(A_{metpu}) = V_{maxpu} * C_{vpu} / (K_{mlu} + C_{vpu})$$

$$d/dt(A_{metbr}) = V_{maxbr} * C_{vbr} / (K_{mlu} + C_{vbr})$$

{AUCs for butadiene}

$$d/dt(AUC_{vtot}) = C_{vtot}$$

$$d/dt(AUC_{vl}) = C_{vl}$$

$$d/dt(AUC_{vpu}) = C_{vpu}$$

$$d/dt(AUC_{vbr}) = C_{vbr}$$

$$d/dt(AUC_{vlung}) = C_{vpu} + C_{vbr}$$

{differential equations for butadienemonoxide metabolism}

$$d/dt(AB_{pu}) = Q_{pu} * (C_{art} - C_{Bvpu}) + V_{maxpu} * C_{vpu} / (K_{mlu} + C_{vpu}) - k_1 * AB_{pu} - k_2 * AB_{pu} - V_{maxpu3} * C_{Bvpu} / (K_{m3} + C_{Bvpu})$$

$$d/dt(AB_{br}) = Q_{br} * (C_{art} - C_{Bvbr}) + V_{maxbr} * C_{vbr} / (K_{mlu} + C_{vbr}) - k_1 * AB_{br} - k_2 * AB_{br} - V_{maxbr3} * C_{Bvbr} / (K_{m3} + C_{Bvbr})$$

$$d/dt(AB_{ler}) = V_{maxl} * C_{vl} / (K_m + C_{vl}) - K_{ec} * (C_{Bvler} - C_{Bvlcy}) - V_{maxl1} * C_{Bvler} / (K_{m1ih} + C_{Bvler}) - V_{maxl3} * C_{Bvler} / (K_{m3ih} + C_{Bvler})$$

$$d/dt(AB_{lcy}) = Q_l * (C_{art} - C_{Bvlcy}) + K_{ec} * (C_{Bvler} - C_{Bvlcy}) - V_{maxl2} * C_{Bvlcy} * CGSHI / (K_{m2} * CGSHI + K_{m2bmo} * C_{Bvlcy} + CGSHI * C_{Bvlcy})$$

$$d/dt(AB_f) = Q_f * (C_{art} - C_{Bvf})$$

$$d/dt(AB_m) = Q_m * (C_{art} - C_{Bvm})$$

$$d/dt(AB_{vrg}) = Q_{vrg} * (C_{art} - C_{Bvvrg})$$

{AUCs for butadienemonoxide}

$$d/dt(AUC_{Bvtot}) = C_{Bvtot}$$

$$d/dt(AUC_{Bvl}) = C_{Bvler} + C_{Bvlcy}$$

$$d/dt(AUC_{Bvpu}) = C_{Bvpu}$$

$$d/dt(AUC_{Bvbr}) = C_{Bvbr}$$

$$d/dt(AUC_{Bvlung}) = C_{Bvpu} + C_{Bvbr}$$

{amounts of butadienemonoxide metabolized in liver and lung}

$$d/dt(AB_{metl1}) = V_{maxl1} * C_{Bvler} / (K_{m1ih} + C_{Bvler})$$

$$d/dt(AB_{metl2}) = V_{maxl2} * C_{Bvlcy} * CGSHI / (K_{m2} * CGSHI + K_{m2bmo} * C_{Bvlcy} + CGSHI * C_{Bvlcy})$$

$$d/dt(AB_{metpu1}) = k_1 * AB_{pu}$$

$$d/dt(AB_{metpu2}) = k_2 * AB_{pu}$$

$$d/dt(AB_{metbr1}) = k_1 * AB_{br}$$

$$d/dt(AB_{metbr2}) = k_2 * AB_{br}$$

$$d/dt(AB_{metl3}) = V_{maxl3} * C_{Bvler} / (K_{m3ih} + C_{Bvler})$$

$$d/dt(AB_{metpu3}) = V_{maxpu3} * C_{Bvpu} / (K_{m3} + C_{Bvpu})$$

$$d/dt(AB_{metbr3}) = V_{maxbr3} * C_{vbr} / (K_{m3} + C_{vbr})$$

{differential equations for diepoxybutene}

$$d/dt(ACpu) = Qpu*(CCart - CCvpu) + Vmaxpu3*(ABpu/Vpu)/(Km3 + (ABpu/Vpu)) - Ke*ACpu$$

$$d/dt(ACbr) = Qbr*(CCart - CCvbr) + Vmaxbr3*(ABbr/Vbr)/(Km3 + (ABbr/Vbr)) - Ke*ACbr$$

$$d/dt(ACI) = QI*(CCart - CCvl) + VmaxI3*CBvler/(Km3ih + CBvler) - Ke*ACI$$

$$d/dt(ACf) = Qf*(CCart - CCvf)$$

$$d/dt(ACm) = Qm*(CCart - CCvm)$$

$$d/dt(ACvrg) = Qvrg*(CCart - CCvrg)$$

{AUCs for diepoxybutene}

$$d/dt(AUCCvtot) = CCvtot$$

$$d/dt(AUCCvl) = CCvl$$

$$d/dt(AUCCvpu) = CCvpu$$

$$d/dt(AUCCvbr) = CCvbr$$

$$d/dt(AUCCVlung) = CCvpu + CCvbr$$

{differential equation for GSH}

$$d/dt(GSHI) = Kgsh*VI*(GSHI0 - CGSHI) - Kge*GSHI - VmaxI2*CBvlcy*CgshI/(Km2*CGSHI + Km2bmo*CBvlcy + CGSHI*CBvlcy)$$

$$d/dt(GSHlu) = Kgsh*Vlu*(GSHlu0 - CGSHlu) - Kge*GSHlu$$

E.5.8 Model Code for Styrene/SO RT (Sarangapani et al. 2002) 0-5 yr Child

METHOD Stiff

STARTTIME = 0

STOPTIME= 2880

DT = 0.0001

{Styrene in upper respiratory tract compartment (URT) umoles}

init ANURTa = 0

init ANURTmuc = 0

init ANURTepi = 0

init ANURTex = 0

init AMETurt = 0

{Styrene oxide in upper respiratory compartment (URT) umoles}

init ABURTa = 0

init ABURTmuc = 0

init ABURTepi = 0

init ABURTer = 0

init ABURTcy = 0

init GSHua = 1.0*VURTepi

init ABURTex = 0

init AMET2urt = 0

init AMET3urt = 0

{Styrene in conducting airways compartment (CA), umoles}

init ANCAa = 0

```

init ANCAmuc = 0
init ANCAepi = 0
init ANCAex = 0
{Styrene oxide in conducting airways compartment (CA), umoles}
init ABCAa = 0
init ABCAmuc = 0
init ABCAepi = 0
init ABCAex = 0
{Styrene in terminal bronchioles compartment (TB), umoles}
init ANTBa = 0
init ANTBmuc = 0
init ANTBepi = 0
init ANTBex = 0
init AMETtb = 0
{Styrene oxide in terminal bronchioles compartment (TB), umoles}
init ABTBa = 0
init ABTBmuc = 0
init ABTBepi = 0
init ABTBer = 0
init ABTBcy = 0
init GSHtb = 1.0*VTBepi
init ABTBex = 0
init AMET2tb = 0
init AMET3tb = 0
{Styrene in pulmonary compartment (PU), umoles}
init ANPUa = 0
init ANPUmuc = 0
init ANPUepi = 0
init ANPUex = 0
init ANex = 0
{Styrene oxide in pulmonary compartment (PU), umoles}
init ABPUa = 0
init ABPUmuc = 0
init ABPUepi = 0
init ABPUex = 0
init ABex = 0
{model equations}
Q = RPM*TVOL
Cairin = exposure/(24.36*1E3)
VURTepi = SAURT*WUA
VURTmuc = SAURT*WSMua
VURTex = SAURT*WUAs
VCAmuc = SACA*WSMca
VCAepi = SACA*WCA

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VCAex = SACA*WCAs
VTBmuc = SATB*WSMtb
VTBepi = SATB*WTA
VTBex = SATB*WTAs
VPUmuc = SAPU*WSMpu
VPUepi = SAPU*WPA
VPUex = SAPU*WTAs
Vlu = 59.213 + 123.99*Age - 20.31*Age^2 + 1.5069*Age^3 - 0.0346*Age^4
VURT = 0.0026*Vlu
VCA = 0.018*Vlu
VTB = 0.043*Vlu
VPU = 0.937*Vlu
Curtepil = (ANURTEpi/VURTEpi)
Ccaepil = (ANCAepi/VCAepi)
Ctbepil = (ANTBepi/VTBepi)
Cpuepil = (ANPUepi/VPUepi)
Cvurtex = (ANURTex/(VURTex*Pvrg))
Cvcaex = (ANCAex/(VCAex*Pvrg))
Cvtbex = (ANTBex/(VTBex*Pvrg))
Cvpuex = (ANPUex/(VPUex*Pvrg))
Cvex = (ANURTex+ANCAex+ANTBex+ANPUex)/((VURTex+VCAex+VTBex+VPUex)*Pvrg)
CBurtepil = (ABURTEpi/VURTEpi)
CBcaepil = (ABCAepi/VCAepi)
CBtbepil = (ABTBepi/VTBepi)
CBpuepil = (ABPUepi/VPUepi)
CBvurtex = (ABURTex/(VURTex*PBvrg))
CBvcaex = (ABCAex/(VCAex*PBvrg))
CBvtbex = (ABTBex/(VTBex*PBvrg))
CBvpuex = (ABPUex/(VPUex*PBvrg))
CBvex = (ABURTex+ABCAex+ABTBex+ABPUex)/((VURTex+VCAex+VTBex+VPUex)*PBvrg)
GSHuab = 2.5
GSHtbb = 1.0
Exposure = IF TIME <= 1440 THEN 1 ELSE 0
ExposureB = IF TIME <= 1440 THEN 0 ELSE 0
Age = 3.0
 {upper respiratory tract constants}
PMA = 30 {mucus:air partition coeff}
KOURT = 1980 {mass transfer coeffs., cm/min}
KTRURT = 19.2
KBOURT = 19.2
KOCA = 181
KTRCA = 19.2
KBOCA = 19.2
KOTB = 158

KTRTB = 19.2
KBOTB = 19.2
KOPU = 158
KTRPU = 19.2
KBOPU = 19.2
KMUC = 0.001 {diffusion constants, cm²/min}
KSQM = 0.0002
KG = 6.0
SAURT = VURT/WUA {surface areas, cm²}
SACA = VCA/WCA
SATB = VTB/WTA
SAPU = VPU/WPA
VURTa = 0.00035*TLC {luminal volumes, cm³}
VCAa = 0.0105*TLC
VTBa = 0.042*TLC
VPUa = 0.944*TLC
TLC = 236*5 + 282*Age - 4.775*Age² + 0.285*Age³
RPM = 53.5*(BW/1000)^{-0.26} {breaths/min}
TVOL = 35.45 + 33.56*Age - 1.47*Age² + 0.0793*Age³ {tidal volume mL/ breath}
 {thicknesses (W) of upper airways epithelium (UA), submucosa (UAs); mucus (SM); conducting airways epi (CA), submucosa (CAs); transitional airways epi (TA), submucosa (TAs); and pulmonary airways epi (PA), cm}
WUA = 0.005
WSMua = 0.001
WSMca = 0.0005
WSMtb = 0.0002
WSMpu = 0.0001
WCA = 0.0025
WTA = 0.001
WPA = 0.0005
WUAs = 0.01
WCAs = 0.005
WTAs = 0.002
Qua = 0.0025*Qtot {blood flow to the URT region}
Qca = 0.0075*Qtot {blood flow to the CA}
Qta = 0.0067*Qtot {blood flow to the TA}
 {metabolic constants umol/min, umol/mL, based on Csanady et al. 2003 scaled to smaller BWs}
Vmaxua = 4.17E-5*VURTepi*(70/BW)^{0.25}
Vmaxtb = 4.17E-5*VTBepi*(70/BW)^{0.25}
Vmaxl = 0.033*VI*(70/BW)^{0.25}
Vmaxl2 = 0.075*VI*(70/BW)^{0.25} {EH}
Vmaxua2 = 0.0112*VURTepi*(70/BW)^{0.25}
Vmaxtb2 = 0.0112*VTBepi*(70/BW)^{0.25}
Kgsh = 0.012 {/min}

VmaxGI = 0.467*VI*(70/BW)^0.25 {umol/min/liver, GST}
VmaxGua = 1.36*VURTepi*(70/BW)^0.25 {umol/min/URT}
VmaxGtb = 1.36*VTBepi*(70/BW)^0.25 {umol/min/TB}
MPI = 23 {mg microsomal protein /mL tissue}
MPIu = 3.8 {mg microsomal protein/mL tissue}
CPI = 45 {mg cytosolic protein/mL tissue}
CPIu = 43 {mg cytosolic protein/mL tissue}
Km1 = 0.01 {umol/mL}
Km2 = 0.01
Kmlu1 = 0.0175
Kmlu2 = 0.0156
KmG1 = 0.1 {GST}
KmG2 = 2.5 {SO}
Kec = 400

{differential equations for ST in URT compartment, URT}

d/dt(ANURTa) = Q*(Cairin - (ANURTa/VURTa)) - KOURT*SAURT*((ANURTa/VURTa) - (ANURTmuc/(PMA*VURTmuc)))

d/dt(ANURTmuc) = KOURT*SAURT*((ANURTa/VURTa) - (ANURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTepi/(VURTepi*Pvrg)))

d/dt(ANURTepi) = KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTepi/(VURTepi*Pvrg))) - KBOURT*SAURT*((ANURTepi/(VURTepi*Pvrg)) - (ANURTex/(VURTex*Pvrg))) - Vmaxua*(ANURTepi/(VURTepi*Pvrg))/(Kmlu1 + (ANURTepi/(VURTepi*Pvrg)))

d/dt(ANURTex) = KBOURT*SAURT*((ANURTepi/(VURTepi) - (ANURTex/VURTex)) + Qua*(Cart - (ANURTex/(VURTex*Pvrg))))

d/dt(AMETurt) = Vmaxua*(ANURTepi/(VURTepi*Pvrg))/(Kmlu1 + (ANURTepi/(VURTepi*Pvrg)))

d/dt(GSHua) = Kgsh*(GSHuab - (GSHua/VURTepi)) - VmaxGua*(ABURTCy/VURTepi)*(GSHua/VURTepi)/(KmG1*(ABURTCy/VURTepi) + KmG2*(GSHua/VURTepi) + (ABURTCy/VURTepi)*(GSHua/VURTepi))

{differential equations for ST oxide in URT compartment, URT}

d/dt(ABURTa) = Q*(CBairin - (ABURTa/VURTa)) - KOURT*SAURT*((ABURTa/VURTa) - (ABURTmuc/(PMA*VURTmuc)))

d/dt(ABURTmuc) = KOURT*SAURT*((ABURTa/VURTa) - (ABURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTepi/(VURTepi*PBvrg)))

d/dt(ABURTepi) = KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTepi/(VURTepi*PBvrg))) - KBOURT*SAURT*((ABURTepi/(VURTepi*PBvrg)) - (ABURTex/(VURTex*PBvrg))) + Vmaxua*(ANURTepi/(VURTepi*PBvrg))/(Kmlu1 + (ANURTepi/(VURTepi*PBvrg)))

d/dt(ABURTer) = Vmaxua*(ANURTepi/(VURTepi*PBvrg))/(Kmlu1 + (ANURTepi/(VURTepi*PBvrg))) - Kec*((ABURTer/(VURTepi*PBvrg)) - (ABURTCy/(VURTepi*PBb))) - Vmaxua2*(ABURTer/(VURTepi*PBvrg))/(Kmlu2 + (ABURTer/(VURTepi*PBvrg)))

d/dt(AMET2urt) = Vmaxua2*(ABURTer/(VURTepi*PBvrg))/(Kmlu2 + (ABURTer/(VURTepi*PBvrg)))

d/dt(ABURTCy) = Kec*((ABURTer/(VURTepi*PBvrg)) - (ABURTCy/(VURTepi*PBb))) + Qua*(CBart - ABURTCy/(VURTepi*PBvrg)) -

VmaxGua*(ABURTCy/VURTepi)*(GSHua/VURTepi)/(KmG1*(ABURTCy/VURTepi) + KmG2*(ABURTCy/VURTepi) + KmG2*(GSHua/VURTepi) + (ABURTCy/VURTepi)*(GSHua/VURTepi))

d/dt(AMET3urt) = VmaxGua*(ABURTCy/VURTepi)*(GSHua/VURTepi)/(KmG1*(ABURTCy/VURTepi) + KmG2*(ABURTCy/VURTepi) + KmG2*(GSHua/VURTepi) + (ABURTCy/VURTepi)*(GSHua/VURTepi))

$$d/dt(ABURTex) = KBOURT*SAURT*((ABURTepi/VURTEpi) - (ABURTex/(VURTex*PBvrg))) + Qua*(CBart - (ABURTex/(VURTex*PBvrg)))$$

{differential equations for ST in CA compartment, CA}

$$d/dt(ANCAa) = Q*(Cairin - (ANCAa/VCAa)) - KOCA*SACA*((ANCAa/VCAa) - (ANCAmuc/(PMA*VCAmuc)))$$

$$d/dt(ANCAmuc) = KOCA*SACA*((ANCAa/VCAa) - (ANCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg)))$$

$$d/dt(ANCAepi) = KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg))) - KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg)))$$

$$d/dt(ANCAex) = KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) + Qca*(Cart - (ANCAex/(VCAex*Pvrg)))$$

{differential equations for ST oxide in CA compartment, CA}

$$d/dt(ABCAa) = Q*(CBairin - (ABCAa/VCAa)) - KOCA*SACA*((ABCAa/VCAa) - (ABCAmuc/(PMA*VCAmuc)))$$

$$d/dt(ABCAmuc) = KOCA*SACA*((ABCAa/VCAa) - (ABCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg)))$$

$$d/dt(ABCAepi) = KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg))) - KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg)))$$

$$d/dt(ABCAex) = KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) + Qca*(CBart - (ABCAex/(VCAex*PBvrg)))$$

{differential equations for ST in TB compartment umoles, TB}

$$d/dt(ANTBa) = Q*(Cairin - (ANTBa/VTBa)) - KOTB*SATB*((ANTBa/VTBa) - (ANTBmuc/(PMA*VTBmuc)))$$

$$d/dt(ANTBmuc) = KOTB*SATB*((ANTBa/VTBa) - (ANTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBmuc/(VTBmuc*PMA)))$$

$$d/dt(ANTBepi) = KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBepi/(VTBepi*Pvrg))) - KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) - Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu1 + (ANTBepi/(VTBepi*Pvrg)))$$

$$d/dt(ANTBex) = KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) + Qta*(Cart - (ANTBex/(VTBex*Pvrg)))$$

$$d/dt(AMETtb) = Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu1 + (ANTBepi/(VTBepi*Pvrg)))$$

$$d/dt(GSHtb) = Kgsh*(GSHtbb - (GSHtb/VTBepi)) - VmaxGtb*(ABTBcy/VTBepi)*(GSHtb/VTBepi)/(KmG1*(ABTBcy/VTBepi) + KmG2*(GSHtb/VTBepi) + (ABTBcy/VTBepi)*(GSHtb/VTBepi))$$

{differential equations for ST oxide in TB compartment umoles, TB}

$$d/dt(ABTBa) = Q*(CBairin - (ABTBa/VTBa)) - KOTB*SATB*((ABTBa/VTBa) - (ABTBmuc/(PMA*VTBmuc)))$$

$$d/dt(ABTBmuc) = KOTB*SATB*((ABTBa/VTBa) - (ABTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg)))$$

$$d/dt(ABTBepi) = KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg))) - KBOTB*SATB*((ABTBepi/(VTBepi*PBvrg)) - (ABTBex/(VTBex*PBvrg))) + Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu1 + (ANTBepi/(VTBepi*Pvrg)))$$

$$d/dt(ABTBer) = Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu1 + (ANTBepi/(VTBepi*Pvrg))) - Kec*((ABTBer/(VTBepi*PBvrg)) - (ABTBcy/(VTBepi*PBvrg))) - Vmaxtb2*(ABTBer/(VTBepi*PBvrg))/(Kmlu2 + (ABTBer/(VTBepi*PBvrg)))$$

$$d/dt(AMET2tb) = Vmaxtb2*(ABTBer/(VTBepi*PBvrg))/(Kmlu2 + (ABTBer/(VTBepi*PBvrg)))$$

$$d/dt(ABTBcy) = Kec*((ABTBer/(VTBepi*PBvrg)) - (ABTBcy/(VTBepi*PBvrg))) + Qta*(CBart - (ABTBcy/(VTBepi*PBvrg))) - VmaxGtb*(ABTBcy/VTBepi)*(GSHtb/VTBepi)/(KmG1*(ABTBcy/VTBepi) + KmG2*(ABTBcy/VTBepi) + (ABTBcy/VTBepi)*(GSHtb/VTBepi))$$

$$d/dt(AMET3tb) = VmaxGtb*(ABTBcy/VTBepi)*(GSHtb/VTBepi)/(KmG1*(ABTBcy/VTBepi) + KmG2*(ABTBcy/VTBepi) + KmG2*(GSHtb/VTBepi) + (ABTBcy/VTBepi)*(GSHtb/VTBepi))$$

$$d/dt(ABTBex) = KBOTB*SATB*((ABTBepi/(VTBepi*PBvrg)) - (ABTBex/(VTBex*PBvrg))) + Qta*(CBart - (ABTBex/(VTBex*PBvrg)))$$

{differential equations for ST in PU compartment umoles, PU}

$$d/dt(ANPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc)))$$

$$d/dt(ANPUmuc) = KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ANPUmuc/VPUmuc) - (ANPUepi/(VPUepi*Pvrg)))$$

$$d/dt(ANPUepi) = KTRPU*SAPU*((ANPUmuc/(VPUmuc*PMA)) - (ANPUepi/(VPUepi*Pvrg))) - KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg)))$$

$$d/dt(ANPUex) = KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) + Qtot*(Cart - (ANPUex/(VPUex*Pvrg)))$$

{differential equations for ST oxide PU compartment umoles, PU}

$$d/dt(ABPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc)))$$

$$d/dt(ABPUmuc) = KOPU*SAPU*((ABPUa/VPUa) - (ABPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg)))$$

$$d/dt(ABPUepi) = KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg))) - KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg)))$$

$$d/dt(ABPUex) = KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg))) + Qtot*(CBart - (ABPUex/(VPUex*PBvrg)))$$

{Sum of Lung Styrene}

$$d/dt(ANex) = Qtot*((Cart-Cvurtex) + (Cart-Cvcaex) + (Cart-Cvtbex) + (Cart-Cvpueex))$$

{Sum of Lung Styrene Oxide}

$$d/dt(ABex) = Qtot*((CBart-CBvurtex) + (CBart-CBvcaex) + (CBart-CBvtbex) + (CBart-CBvpueex))$$

{ST ex respiratory tract, umoles}

$$\text{init Af} = 0$$

$$\text{init AI} = 0$$

$$\text{init Am} = 0$$

$$\text{init Avrg} = 0$$

$$\text{init Ablood} = 0$$

$$\text{init GSHI} = 6.0*VI$$

{ST oxide ex respiratory tract, umoles}

$$\text{init ABf} = 0$$

$$\text{init ABI} = 0$$

$$\text{init ABler} = 0$$

$$\text{init ABlcy} = 0$$

$$\text{init ABm} = 0$$

$$\text{init ABvrg} = 0$$

$$\text{init ABblood} = 0$$

{umoles ST metabolized}

$$\text{init AmetI} = 0$$

{umoles ST oxide ex rt metabolized by EH and GST pathways}

$$\text{init ABmetI} = 0$$

$$\text{init ABmetGI} = 0$$

{AUCs}

init AUCvtot = 0

init AUCvl = 0

{AUCs BaP oxide}

init AUCBvtot = 0

init AUCBvl = 0

{tissue flows mL/min}

Qtot = (0.012*Age³ - 1.2144*Age² + 40.32*Age + 44.144)*(1000/60)

Qalv = (17.874*Age + 39.785)*(1000/60)

Qf = 0.0528*Qtot

Ql = 0.0795*Qtot

Qm = 0.0304*Qtot

Qvrg = 0.837*Qtot

{tissue volumes mL}

BW = - 1.9*Age⁴ + 72.8*Age³ - 813.1*Age² + 5535.6*Age + 4453.7

Vf = 0.0165*Age⁵ - 1.9784*Age⁴ + 51.963*Age³ - 459.38*Age² + 1566.8*Age + 1004.2

VI = 0.0072*Age⁵ - 0.3975*Age⁴ + 7.9052*Age³ - 65.625*Age² + 262.02*Age + 157.52

Vm = -0.0623*Age⁵ + 2.3433*Age⁴ - 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2

Vvrg = BW - (Vf + VI + Vm + Vlu + Vblood)

Vblood = 0.075*BW

{blood/air and tissue/blood partition coefficients, ST}

Pb = 48

PI = 2.0

Pf = 50

Pm = 1.3

Pvrg = 1.3

{blood/air and tissue/blood partition coefficients, ST oxide}

PBb = 2000

PBI = 1.0

PBf = 14.0

PBm = 0.6

PBvrg = 0.6

{calculated concentrations of ST umol/mL}

Cblood = Ablood/Vblood

Cart = Cvex

Cvf = Af/(Vf*Pf)

Cvl = Al/(VI*PI)

Cvm = Am/(Vm*Pm)

Cvrg = Avrg/(Vvrg*Pvrg)

Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvrg)/Qtot

Cairin = exposure/(24.45*1E3)

CGSHI = GSHI/VI

GSHIb = 6.0

{calculated concentrations of ST oxide umol/mL}

$$\text{CBblood} = \text{ABblood}/\text{Vblood}$$

$$\text{CBart} = \text{CBvex}$$

$$\text{CBvf} = \text{ABf}/(\text{Vf} \cdot \text{PBf})$$

$$\text{CBvl} = \text{ABI}/(\text{VI} \cdot \text{PBI})$$

$$\text{CBler} = \text{ABler}/\text{VI}$$

$$\text{CBlcy} = \text{ABlcy}/\text{VI}$$

$$\text{CBvm} = \text{ABm}/(\text{Vm} \cdot \text{PBm})$$

$$\text{CBvrg} = \text{ABvrg}/(\text{Vvrg} \cdot \text{PBvrg})$$

$$\text{CBvtot} = (\text{Ql} \cdot \text{CBvl} + \text{Qf} \cdot \text{CBvf} + \text{Qm} \cdot \text{CBvm} + \text{Qvrg} \cdot \text{CBvrg})/\text{Qtot}$$

$$\text{CBairin} = \text{exposureB}/(24.45 \cdot 1\text{E}3)$$

{differential equations for ST uptake and metabolism, umoles}

$$\text{d/dt(Al)} = \text{Ql} \cdot (\text{Cart} - \text{Cvl}) - \text{Vmaxl} \cdot \text{Cvl}/(\text{Km1} + \text{Cvl})$$

$$\text{d/dt(Af)} = \text{Qf} \cdot (\text{Cart} - \text{Cvf})$$

$$\text{d/dt(Am)} = \text{Qm} \cdot (\text{Cart} - \text{Cvm})$$

$$\text{d/dt(Avrg)} = \text{Qvrg} \cdot (\text{Cart} - \text{Cvrg})$$

$$\text{d/dt(ABlood)} = \text{Ql} \cdot \text{Cvl} + \text{Qf} \cdot \text{Cvf} + \text{Qm} \cdot \text{Cvm} + \text{Qvrg} \cdot \text{Cvrg} + \text{Qtot} \cdot \text{Cvex}$$

{differential equations for ST oxide uptake and metabolism, umoles}

$$\text{d/dt(ABI)} = \text{Ql} \cdot (\text{CBart} - \text{CBvl}) + \text{Vmaxl} \cdot \text{Cvl}/(\text{Km1} + \text{Cvl}) - \text{Vmaxl2} \cdot \text{CBvl}/(\text{Km2} + \text{CBvl})$$

$$\text{d/dt(ABf)} = \text{Qf} \cdot (\text{CBart} - \text{CBvf})$$

$$\text{d/dt(ABm)} = \text{Qm} \cdot (\text{CBart} - \text{CBvm})$$

$$\text{d/dt(ABvrg)} = \text{Qvrg} \cdot (\text{CBart} - \text{CBvrg})$$

$$\text{d/dt(ABblood)} = \text{Ql} \cdot \text{CBvl} + \text{Qf} \cdot \text{CBvf} + \text{Qm} \cdot \text{CBvm} + \text{Qvrg} \cdot \text{CBvrg} + \text{Qtot} \cdot \text{CBvex}$$

$$\text{d/dt(ABler)} = \text{Vmaxl} \cdot \text{Cvl}/(\text{Km1} + \text{Cvl}) - \text{Kec} \cdot ((\text{ABler}/(\text{VI} \cdot \text{PBI})) - (\text{ABlcy}/(\text{VI} \cdot \text{PBI}))) - \text{Vmaxl2} \cdot (\text{ABler}/(\text{VI} \cdot \text{PBI}))/(\text{Km2} + (\text{ABler}/(\text{VI} \cdot \text{PBI})))$$

$$\text{d/dt(ABlcy)} = \text{Kec} \cdot ((\text{ABler}/(\text{VI} \cdot \text{PBI})) - (\text{ABlcy}/(\text{VI} \cdot \text{PBI}))) + \text{Ql} \cdot (\text{CBart} - \text{ABlcy}/(\text{VI} \cdot \text{PBI})) - (\text{VmaxGl} \cdot (\text{ABlcy}/\text{VI}) \cdot (\text{GSHI}/\text{VI})/(\text{KmG1} \cdot (\text{ABlcy}/\text{VI}) + \text{KmG2} \cdot (\text{ABlcy}/\text{VI}) + \text{KmG2} \cdot (\text{GSHI}/\text{VI}) + (\text{ABlcy}/\text{VI}) \cdot (\text{GSHI}/\text{VI})))$$

$$\text{d/dt(GSHI)} = \text{Kgsh} \cdot (\text{GSHIb} - (\text{GSHI}/\text{VI})) - \text{VmaxGl} \cdot (\text{ABlcy}/\text{VI}) \cdot (\text{GSHI}/\text{VI})/(\text{KmG1} \cdot (\text{ABlcy}/\text{VI}) + \text{KmG2} \cdot (\text{GSHI}/\text{VI}) + (\text{ABlcy}/\text{VI}) \cdot (\text{GSHI}/\text{VI}))$$

{amount of ST metabolized in liver to Styrene oxide, umoles}

$$\text{d/dt(Ametl)} = \text{Vmaxl} \cdot \text{Cvl}/(\text{Km1} + \text{Cvl})$$

{amount of ST oxide metabolized in liver and lung to diol, umoles}

$$\text{d/dt(ABmetl)} = \text{Vmaxl2} \cdot \text{CBvl}/(\text{Km2} + \text{CBvl})$$

{amount of ST oxide metabolized in liver and lung to GSH conjugate, umoles}

$$\text{d/dt(ABmetGl)} = \text{VmaxGl} \cdot \text{CBlcy} \cdot \text{CGSHI}/(\text{KmG1} \cdot \text{CBlcy} + \text{KmG2} \cdot \text{CBlcy} + \text{KmG2} \cdot \text{CGSHI} + \text{CGSHI} \cdot \text{CBlcy})$$

{AUCs for ST, umolmin/mL}

$$\text{d/dt(AUCvtot)} = \text{Cvtot}$$

$$\text{d/dt(AUCvl)} = \text{Cvl}$$

{AUCs for ST oxide, umolmin/mL}

$$\text{d/dt(AUCBvtot)} = \text{CBvtot}$$

$$\text{d/dt(AUCBvl)} = \text{CBvl}$$

*E.5.9 Model Code for Vinyl Chloride 0-5 yr Child***METHOD Stiff****STARTTIME = 0****STOPTIME = 48****DT = 0.005**

{vinyl chloride moles or equivalents}

init Af = 0**init AI = 0****init Am = 0****init Avrg = 0****init Abr = 0****init Apu = 0****init Areactive = 0****init ACO2 = 0****init Aconj = 0****init ADNAad = 0****init AGI = 0****init AGSH = 0.058*VI****init AMET = 0****init AUCrm = 0****init RISKM = 0****init RISKG = 0**

{tissue flows L/hr}

Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414**Qalv = 17.875*Age + 39.785****Qf = 0.0528*Qtot****Ql = 0.0795*Qtot****Qm = 0.0304*Qtot****Qvrg = 0.837*Qtot****Qpu = 0.93*Qtot****Qbr = 0.07*Qtot**

{tissue volumes L}

Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000**VI = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000****Vvrg = BW - (Vf+VI+Vm+Vlu)****Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.13*Age^2 + 123.99*Age + 59.213)/1000****Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000****Vpu = 0.90*Vlu****Vbr = 0.10*Vlu**

{blood/air and tissue/blood partition coefficients, vinyl chloride}

Pb = 1.16**PI = 1.45**

$$Pf = 20.7$$

$$Pm = 0.83$$

$$Pvrg = 1.45$$

$$Ppu = 1.45$$

$$Pbr = 1.45$$

{calculated concentrations of vinyl chloride}

$$Cart = (Qpu * Cvpu + Qbr * Cvbr) / Qtot$$

$$Cvf = Af / (Vf * Pf)$$

$$Cvl = Al / (Vl * Pl)$$

$$Cvm = Am / (Vm * Pm)$$

$$Cvvr = Avrg / (Vvrg * Pvrg)$$

$$Cvpu = Apu / (Vpu * Ppu)$$

$$Cvbr = Abr / (Vbr * Pbr)$$

$$Cvtot = (Ql * Cvl + Qf * Cvf + Qm * Cvm + Qvrg * Cvvr) / Qpu$$

$$Cvipu = (Qalv * Cair + Qpu * Cvtot) / ((Qalv / Pb) + Qpu)$$

$$Cexh = Cvipu / Pb$$

{exposure in ppm converted to moles}

$$Cair = \text{IF TIME} \leq 24 \text{ THEN } 1 * (1E-6 / 25.45) \text{ ELSE } 0$$

{constants and conversions}

$$BW = (-1.9 * Age^4 + 72.8 * Age^3 - 813.1 * Age^2 + 5535.6 * Age + 4453.7) / 1000$$

$$Age = 0.0$$

$$MW = 62.5$$

$$Vmax1c = 4.0$$

$$Vmax2c = 0.1$$

$$Km1 = 1.0$$

$$Km2 = 10.0$$

$$KGSMc = 0.13$$

$$KFEEc = 35.0$$

$$KCO2c = 1.6$$

$$KOC = 28.5$$

$$KBC = 0.12$$

$$KS = 2000$$

$$KA = 3.0$$

$$GSO = 0.058$$

$$H2O = 55.0$$

$$KGSM = KGSMc / BW^{0.25}$$

$$KFEE = KFEEc / BW^{0.25}$$

$$KO = KOC * BW^{0.75}$$

$$KB = KBC / BW^{0.25}$$

$$KCO2 = KCO2c / BW^{0.25}$$

$$Vmax1 = Vmax1c * BW^{0.75}$$

$$Vmax2 = Vmax2c * BW^{0.75}$$

$$Vmax1M = Vmax1c * (BW^{0.75}) / (1000 * MW)$$

$$Vmax2M = Vmax2c * (BW^{0.75}) / (1000 * MW)$$

$$KmM = Km1/(1000*MW)$$

$$Km2M = Km2/(1000*MW)$$

{differential equations for vinyl chloride uptake and metabolism}

$$d/dt(Apu) = Qpu*(Cvipu - Cvpu)$$

$$d/dt(Abr) = Qbr*(Cart - Cvbr)$$

$$d/dt(AI) = QI*(Cart - Cvl) - Vmax1M*(AI/VI)/(KmM + (AI/VI)) - Vmax2M*(AI/VI)/(Km2M + (AI/VI)) + KA*AGI$$

$$d/dt(Areactive) = Vmax1M*(AI/VI)/(KmM + (AI/VI)) + Vmax2M*(AI/VI)/(Km2M + (AI/VI)) - KGSM*(AGSH/VI)*(Areactive/VI) - KFEE*(Areactive/VI) - KCO2*(Areactive/VI)*H2O*VI$$

$$d/dt(AGSH) = KO*(KS + GSO)/(KS + (AGSH/VI))$$

$$d/dt(ACO2) = KCO2*(Areactive/VI)*H2O*VI$$

$$d/dt(ADNAad) = KFEE*(Areactive/VI)$$

$$d/dt(Aconj) = KGSM*(AGSH/VI)*(Areactive/VI)$$

$$d/dt(Af) = Qf*(Cart - Cvf)$$

$$d/dt(Am) = Qm*(Cart - Cvm)$$

$$d/dt(Avrg) = Qvrg*(Cart - Cvrg)$$

$$d/dt(AMET) = Vmax1M*Cvl/(KmM + Cvl) + Vmax2M*Cvl/(Km2M + Cvl)$$

$$d/dt(AUCrm) = (Areactive/VI)*TIME$$

$$d/dt(AGI) = - KA*AGI$$

$$d/dt(RISKM) = ADNAad/VI$$

$$d/dt(RISKG) = Aconj/VI$$

E.5.10 Model Code for TCE 0-5 yr child

METHOD Auto

STARTTIME = 0

STOPTIME= 120

DT = 0.001

{TCE moles}

init Af = 0

init AI = 0

init Am = 0

init Avrg = 0

init Abr = 0

init Apu = 0

init Alu = 0

init Akid = 0

init Astom = 0

init Agi = 0

init AUCvtot = 0

init Aexh = 0

{CH moles}

init ABI = 0
init ABbody = 0
init ABlu = 0
init ABkid = 0
init AUCBvtot = 0
init AUCBlu = 0
init ABurine = 0
{TCA moles}
init ACI = 0
init ACbody = 0
init AClu = 0
init ACKid = 0
init AUCCI = 0
init AUCCvtot = 0
init AUCCI = 0
init ACurine = 0
{TCOH moles}
init ADI = 0
init ADbody = 0
init ADlu = 0
init ADkid = 0
init AUCDvtot = 0
init ADurine = 0
{TCOG moles}
init AEI = 0
init AEbody = 0
init AElu = 0
init AEkid = 0
init AUCEvtot = 0
init AUCEkid = 0
init AEurine = 0
init AEfec = 0
{moles of TCE metabolized}
init Ametl1 = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = 17.875*Age + 39.785
Qf = 0.0528*Qtot
Ql = 0.0795*Qtot
Qm = 0.0304*Qtot
Qvrg = 0.687*Qtot
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
Qkid = 0.15*Qtot

$$\mathbf{Qbody = 0.24*Qtot}$$

{tissue volumes, L}

$$\mathbf{Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000}$$

$$\mathbf{VI = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000}$$

$$\mathbf{Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000}$$

$$\mathbf{Vvrg = BW - (Vf + VI + Vm + Vlu + Vkid)}$$

$$\mathbf{Vpu = 0.9*Vlu}$$

$$\mathbf{Vbr = 0.1*Vlu}$$

$$\mathbf{Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000}$$

$$\mathbf{Vkid = (0.000973*Age^5 - 0.0561*Age^4 + 1.1729*Age^3 - 10.34*Age^2 + 44.604*Age + 28.291)/1000}$$

$$\mathbf{Vbody = BW}$$

{blood/air and tissue/blood partition coefficients, TCE}

$$\mathbf{Pb = 15.91}$$

$$\mathbf{PI = 1.73}$$

$$\mathbf{Pf = 36.38}$$

$$\mathbf{Pm = 2.36}$$

$$\mathbf{Pvrg = 1.73}$$

$$\mathbf{Ppu = 2.61}$$

$$\mathbf{Pbr = 2.61}$$

$$\mathbf{Pkid = 2.07}$$

{blood/air and tissue/blood partition coefficients, CH}

$$\mathbf{PBI = 1.42}$$

$$\mathbf{PBIu = 1.65}$$

$$\mathbf{PBbody = 1.35}$$

$$\mathbf{PBkid = 0.98}$$

{tissue/blood partition coefficients, TCA}

$$\mathbf{PCI = 1.18}$$

$$\mathbf{PClu = 0.54}$$

$$\mathbf{PCbody = 0.88}$$

$$\mathbf{PCKid = 0.74}$$

{blood/air and tissue/blood partition coefficients, TCOH}

$$\mathbf{PDI = 1.30}$$

$$\mathbf{PDlu = 0.78}$$

$$\mathbf{PDbody = 1.11}$$

$$\mathbf{PDkid = 1.02}$$

{blood/air and tissue/blood partition coefficients, TCOG}

$$\mathbf{PEI = 0.56}$$

$$\mathbf{PElu = 1.06}$$

$$\mathbf{PEbody = 1.11}$$

$$\mathbf{PEkid = 1.44}$$

{TCE oxidation metabolic parameters, mol/hr, mol/L, /hr, fraction}

$$\mathbf{VmaxI1C = 3.04E-5}$$

$$\mathbf{VmaxI1 = VmaxI1C*BW^0.75}$$

$$\mathbf{Km1 = 1.37E-5}$$

{CH conversion to TCA and TCOH}

$$\text{PTCA} = 115 * \text{BW}$$

$$\text{PTCOH} = 309 * \text{BW}$$

$$\text{KUB} = 0.06 * \text{BW}$$

{TCOH conversion to TCA and TCOG}

$$\text{KTCA} = 10$$

$$\text{VmaxI2C} = 1.11\text{E-4}$$

$$\text{VmaxI2} = \text{VmaxI2C} * \text{BW}^{0.75}$$

$$\text{Km2} = 1.06\text{E-4}$$

$$\text{KUD} = 1.14 * \text{BW}$$

$$\text{KUC} = 1.55 * \text{BW}$$

$$\text{KFE} = 4.61 * \text{BW}$$

$$\text{KUE} = 32.8 * \text{BW}$$

$$\text{Age} = 5.0$$

$$\text{BW} = (-1.9 * \text{Age}^4 + 72.8 * \text{Age}^3 - 813.1 * \text{Age}^2 + 5535.6 * \text{Age} + 4453.7) / 1000$$

{exposure in ppm converted to moles}

$$\text{Cair} = \text{IF TIME} \leq 24 \text{ THEN } 1 * (1\text{E-6} / 24.45) \text{ ELSE } 0.0$$

$$\text{Cart} = (\text{Qpu} * \text{Cvpu} + \text{Qbr} * \text{Cvbr}) / \text{Qtot}$$

$$\text{Cvf} = \text{Af} / (\text{Vf} * \text{Pf})$$

$$\text{Cvl} = \text{Al} / (\text{VI} * \text{PI})$$

$$\text{Cl} = \text{Al} / \text{VI}$$

$$\text{Cvm} = \text{Am} / (\text{Vm} * \text{Pm})$$

$$\text{Cvvr} = \text{Avrg} / (\text{Vvrg} * \text{Pvrg})$$

$$\text{Cvpu} = \text{Apu} / (\text{Vpu} * \text{Ppu})$$

$$\text{Cvbr} = \text{Abr} / (\text{Vbr} * \text{Pbr})$$

$$\text{Cvkid} = \text{Akid} / (\text{Vkid} * \text{Pkid})$$

$$\text{Cvtot} = (\text{Ql} * \text{Cvl} + \text{Qf} * \text{Cvf} + \text{Qm} * \text{Cvm} + \text{Qvrg} * \text{Cvvr} + \text{Qkid} * \text{Cvkid}) / \text{Qpu}$$

$$\text{Cvipu} = (\text{Qalv} * \text{Cair} + \text{Qpu} * \text{Cvtot}) / ((\text{Qalv} / \text{Pb}) + \text{Qpu})$$

$$\text{Cexh} = \text{Cvipu} / \text{Pb}$$

$$\text{A} = \text{Sum}(\text{Alu}, \text{Al}, \text{Am}, \text{Akid}, \text{Agi}, \text{Aexh})$$

$$\text{Mass} = \text{Sum}(\text{A}, \text{B}, \text{C}, \text{D}, \text{E})$$

{calculated concentrations of CH}

$$\text{CBart} = \text{CBvlu}$$

$$\text{CBvl} = \text{ABl} / (\text{VI} * \text{PBl})$$

$$\text{CBvlu} = \text{ABlu} / (\text{Vlu} * \text{PBlu})$$

$$\text{CBlu} = \text{ABlu} / \text{Vlu}$$

$$\text{CBvbody} = \text{ABbody} / (\text{Vbody} * \text{PBbody})$$

$$\text{CBvkid} = \text{ABkid} / (\text{Vkid} * \text{PBkid})$$

$$\text{CBvtot} = (\text{Ql} * \text{CBvl} + \text{Qbody} * \text{CBvbody} + \text{Qkid} * \text{CBvkid}) / \text{Qtot}$$

$$\text{B} = \text{Sum}(\text{ABlu}, \text{ABl}, \text{ABkid}, \text{ABbody}, \text{ABurine})$$

{calculated concentrations of TCA}

$$\text{CCart} = \text{CCvlu}$$

$$\text{CCvl} = \text{ACl} / (\text{VI} * \text{PCI})$$

$$\text{CCI} = \text{ACl} / \text{VI}$$

$$CCvlu = AClu/(Vlu*PClu)$$

$$CCvbody = ACbody/(Vbody*PCbody)$$

$$CCvkid = ACKid/(Vkid*PCkid)$$

$$CCvtot = (Ql*CCvl + Qbody*CCvbody + Qkid*CCvkid)/Qtot$$

$$C = \text{Sum}(AClu, ACI, ACKid, ACbody, ACurine)$$

{calculated concentrations of TCOH}

$$CDart = CDvlu$$

$$CDvl = ADI/(VI*PDI)$$

$$CDI = ADI/VI$$

$$CDvlu = ADlu/(Vlu*PDlu)$$

$$CDvbody = ADbody/(Vbody*PDbody)$$

$$CDvkid = ADkid/(Vkid*PDkid)$$

$$CDvtot = (Ql*CDvl + Qbody*CDvbody + Qkid*CDvkid)/Qtot$$

$$D = \text{Sum}(ADlu, ADI, ADkid, ADbody, ADurine)$$

{calculated concentrations of TCOG}

$$CEart = CEvlu$$

$$CEvl = AEI/(VI*PEI)$$

$$CEvlu = AElu/(Vlu*PElu)$$

$$CEvbody = AEbody/(Vbody*PEbody)$$

$$CEvkid = AEkid/(Vkid*PEkid)$$

$$CEkid = AEkid/Vkid$$

$$CEvtot = (Ql*CEvl + Qbody*CEvbody + Qkid*CEvkid)/Qtot$$

$$E = \text{Sum}(AElu, AEI, AEkid, AEbody, AEfec, AEurine)$$

{differential equations for TCE uptake, metabolism, and excretion}

$$d/dt(Astom) = -Astom*3.09 - Astom*2.18$$

$$d/dt(Agi) = Astom*2.18 - Agi*0.044$$

$$d/dt(Apu) = Qpu*(Cvipu - Cvpv)$$

$$d/dt(Abr) = Qbr*(Cart - Cvbr)$$

$$d/dt(Alu) = Apu + Abr$$

$$d/dt(AI) = Ql*(Cart - Cvl) - Vmaxl1*Cvl/(Km1 + Cvl) + Agi*0.044 + Astom*3.09$$

$$d/dt(Af) = Qf*(Cart - Cvf)$$

$$d/dt(Am) = Qm*(Cart - Cvm)$$

$$d/dt(Avrg) = Qvrg*(Cart - Cvrg)$$

$$d/dt(Akid) = Qkid*(Cart - Cvkid)$$

{amount of TCE metabolized in liver}

$$d/dt(Ametl1) = Vmaxl1*Cvl/(Km1 + Cvl)$$

$$d/dt(AUCvtot) = Cvtot$$

$$d/dt(Aexh) = Cexh*Qalv$$

{differential equations for CH metabolism}

$$d/dt(ABlu) = Qtot*(CBvtot - CBvlu)$$

$$d/dt(ABI) = Ql*(CBart - CBvl) + Vmaxl1*Cvl/(Km1 + Cvl) - ABI*PTCA - ABI*PTCOH$$

$$d/dt(ABbody) = Qbody*(CBart - CBvbody)$$

$$d/dt(ABkid) = Qkid*(CBart - CBvkid) - ABkid*KUB$$

$$d/dt(ABurine) = ABkid*KUB$$

{AUCs for CH}

$$d/dt(\text{AUCBlu}) = \text{CBlu}$$

$$d/dt(\text{AUCBvtot}) = \text{CBvtot}$$

{differential equations for TCA}

$$d/dt(\text{AClu}) = \text{Qtot} * (\text{CCvtot} - \text{CCvlu})$$

$$d/dt(\text{ACI}) = \text{QI} * (\text{CCart} - \text{CCvl}) + \text{ABI} * \text{PTCA} + \text{ADI} * \text{KTCA}$$

$$d/dt(\text{ACbody}) = \text{Qbody} * (\text{CCart} - \text{CCvbody})$$

$$d/dt(\text{ACKid}) = \text{Qkid} * (\text{CCart} - \text{CCvkid}) - \text{ACKid} * \text{KUC}$$

$$d/dt(\text{ACurine}) = \text{ACKid} * \text{KUC}$$

{AUCs for TCA}

$$d/dt(\text{AUCCI}) = \text{CCI}$$

$$d/dt(\text{AUCCvtot}) = \text{CCvtot}$$

{differential equations for TCOH}

$$d/dt(\text{ADlu}) = \text{Qtot} * (\text{CDvtot} - \text{CDvlu})$$

$$d/dt(\text{ADI}) = \text{QI} * (\text{CDart} - \text{CDvl}) + \text{ABI} * \text{PTCOH} - \text{ADI} * \text{KTCA} - 2.73\text{E-}3 * \text{CDvl} / (\text{Km}2 + \text{CDvl})$$

$$d/dt(\text{ADbody}) = \text{Qbody} * (\text{CDart} - \text{CDvbody})$$

$$d/dt(\text{ADkid}) = \text{Qkid} * (\text{CDart} - \text{CDvkid}) - \text{ADkid} * \text{KUD}$$

$$d/dt(\text{AUCDvtot}) = \text{CDvtot}$$

$$d/dt(\text{ADurine}) = \text{ADkid} * \text{KUD}$$

{differential equations for TCOG}

$$d/dt(\text{AElu}) = \text{Qtot} * (\text{CEvtot} - \text{CEvlu})$$

$$d/dt(\text{AEI}) = \text{QI} * (\text{CEart} - \text{CEvl}) + 2.73\text{E-}3 * \text{CDvl} / (\text{Km}2 + \text{CDvl}) - \text{AEI} * \text{KFE}$$

$$d/dt(\text{AEbody}) = \text{Qbody} * (\text{CEart} - \text{CEvbody})$$

$$d/dt(\text{AEkid}) = \text{Qkid} * (\text{CEart} - \text{CEvkid}) - \text{AEkid} * \text{KUE}$$

$$d/dt(\text{AEurine}) = \text{AEkid} * \text{KUE}$$

$$d/dt(\text{AEfec}) = \text{AEI} * \text{KFE}$$

$$d/dt(\text{AUCEkid}) = \text{CEkid}$$

$$d/dt(\text{AUCEvtot}) = \text{CEvtot}$$

E.5.11 Model Code for Styrene/SO (Csanady et al. 2003) 0-6 yr Child

METHOD Stiff

STARTTIME = 0

STOPTIME= 48

DT = 0.001

{Styrene mmol}

init Aluc = 0 {conducting airways}

init Alua = 0 {alveoli}

init Alubl = 0 {lung blood}

init Aven = 0 {venous blood}

init Aart = 0 {arterial blood}

init Afat = 0
init Avrg = 0
init Amusc = 0
init AI = 0
init Amet1luc = 0
init Amet1lua = 0
init Amet1I = 0
 {Styrene oxide, mmol}
init ABluc = 0
init ABlua = 0
init ABlubld = 0
init ABven = 0
init ABart = 0
init ABfat = 0
init ABvrg = 0
init ABmusc = 0
init ABler = 0
init ABlcy = 0
init ABmet2luc = 0
init ABmet2lua = 0
init ABmet2I = 0
init ABmet3luc = 0
init ABmet3lua = 0
init ABmet3I = 0
init AUCBluc = 0
init AUCBlua = 0
init AUCBI = 0
 {Model parameters}
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000 {kg, L}
Qalv = 0.82*Qtot {L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
tcap = 7.45E-6 {dm}
Scap = 115 {dm²/kg}
Dst = 4.4E-4 {dm²/hr}
Dso = 4.3E-4
 {Flows, L/hr}
Qfat = 0.053*Qtot
QI = 0.0795*Qtot
Qvrg = Qtot - (Qfat + QI + Qmusc)
Qmusc = 0.03*Qtot
 {Volumes, L}
Vart = 0.0178*BW
Vven = 0.0533*BW
Vlubld = 0.0079*BW

$$\mathbf{Vfat = 0.19 * BW}$$

$$\mathbf{Vlu = (-0.0346 * Age^4 + 1.5069 * Age^3 - 20.31 * Age^2 + 123.99 * Age + 59.213) / 1000}$$

$$\mathbf{Vluc = fs * Vlu}$$

$$\mathbf{Vlua = (1 - fs) * Vlu}$$

$$\mathbf{VI = (0.0072 * Age^5 - 0.3975 * Age^4 + 7.9052 * Age^3 - 65.624 * Age^2 + 262.02 * Age + 157.52) / 1000}$$

$$\mathbf{Vvrg = BW - (Vfat + VI + Vart + Vven + Vlubl + Vmusc + Vlu)}$$

$$\mathbf{Vmusc = (-0.0623 * Age^5 + 2.3433 * Age^4 - 26.559 * Age^3 + 144.75 * Age^2 + 339.84 * Age + 1648.2) / 1000}$$

{Partition coeffs styrene, dimensionless}

$$\mathbf{Pb = 70.0}$$

$$\mathbf{Pfat = 93.8}$$

$$\mathbf{PI = 2.71}$$

$$\mathbf{Plu = 1.46}$$

$$\mathbf{Pvrg = 2.60}$$

$$\mathbf{Pmusc = 1.96}$$

{Partition coeffs styrene oxide, dimensionless}

$$\mathbf{PbB = 2370}$$

$$\mathbf{PBfat = 6.1}$$

$$\mathbf{PBI = 2.6}$$

$$\mathbf{PBlu = 1.9}$$

$$\mathbf{PBvrg = 2.6}$$

$$\mathbf{PBmusc = 1.5}$$

{Concentrations ST mmol/L}

$$\mathbf{Exposure = IF TIME < 24 THEN 1 * (1E-3 / 24.45) ELSE 0}$$

$$\mathbf{Age = 0.542}$$

$$\mathbf{fs = 0.1}$$

$$\mathbf{Cair = exposure}$$

$$\mathbf{Cart = Aart / Vart}$$

$$\mathbf{Cven = Aven / Vven}$$

$$\mathbf{Cfat = Afat / Vfat}$$

$$\mathbf{CI = AI / VI}$$

$$\mathbf{Cvrg = Avrg / Vvrg}$$

$$\mathbf{Cmusc = Amusc / Vmusc}$$

$$\mathbf{Clubl = Alubl / Vlubl}$$

$$\mathbf{Cluc = Aluc / (fs * Vlu)}$$

$$\mathbf{Clua = Alua / ((1 - fs) * Vlu)}$$

{Concentrations SO, mmol/L}

$$\mathbf{CBart = ABart / Vart}$$

$$\mathbf{CBven = ABven / Vven}$$

$$\mathbf{CBfat = ABfat / Vfat}$$

$$\mathbf{CBvrg = ABvrg / Vvrg}$$

$$\mathbf{CBmusc = ABmusc / Vmusc}$$

$$\mathbf{CBicy = ABicy / VI}$$

$$\mathbf{CBvlcy = ABicy / (VI * PI)}$$

$$\mathbf{CBluc = ABluc / (fs * Vlu)}$$

$$CBlua = ABlua / ((1 - fs) * Vlu)$$

$$CBlubld = ABlubld / Vlubld$$

$$Qendo = VmaxI2 * 1E3 * VI / (Kml2app - Kml2eh)$$

$$a = CBicy - Kml2eh + (VmaxI1 * 1E3 * VI * CI / (Qendo * (PI * Kml1 + CI))) - (VmaxI2 * 1E3 * VI / Qendo)$$

$$CBendo = 0.5 * (a + (a^2 + 4 * Kml2eh * (CBicy + VmaxI1 * 1E3 * VI * CI / Qendo * (PI * Kml1 + CI))))^{0.5}$$

{GSH}

$$\text{init GSHluc} = fs * GSHlu0$$

$$\text{init GSHlua} = (1 - fs) * GSHlu0$$

$$\text{init GSHI} = GSHI0$$

$$CGSHluc = GSHluc * fs / Vluc$$

$$CGSHlua = GSHlua * (1 - fs) / Vlua$$

$$CGSHI = GSHI / VI$$

$$fGSH = 0.75$$

$$GSHlu0 = 1.95 * Vlu$$

$$GSHI0 = 5.9 * VI$$

{Biochemical parameters, mmol/hr/mL, mmol/L; 1 = P450, 2 = EH, 3 = GST}

$$VmaxI1 = 0.002 * (70/BW)^{0.25}$$

$$Kml1 = 0.01$$

$$VmaxI2 = 0.0045 * (70/BW)^{0.25}$$

$$Kml2eh = 0.001$$

$$Kml2app = 0.01$$

$$VmaxI3 = 0.028 * (70/BW)^{0.25}$$

$$Kml3G = 0.1$$

$$Kml3so = 2.5$$

$$Kdl = 0.2$$

$$Vmaxlu1 = 2.5E-6 * (70/BW)^{0.25}$$

$$Kmlu1 = 0.0175$$

$$Vmaxlu2 = 6.73E-4 * (70/BW)^{0.25}$$

$$Kmlu2 = 0.0156$$

$$Vmaxlu3 = 0.082 * (70/BW)^{0.25}$$

$$Kmlu3G = 0.1$$

$$Kmlu3so = 2.5$$

$$Kdlu = 2.0$$

{Differential equations for styrene}

$$\frac{d}{dt}(Aluc) = Qalv * (Cair * fs + fs * (1 - fs) * (Clua/Pb)) - (fs + fs * (1 - fs)) * Cluc/Pb - Vmaxlu1 * 1E3 * Vlu * fs * Cluc / (Kmlu1 + Cluc)$$

$$\frac{d}{dt}(Alua) = Qalv * (Cair * (1 - fs) - (1 - fs) * Clua/Pb) - Vmaxlu1 * 1E3 * Vlu * (1 - fs) * Clua / (Kmlu1 + Clua) - (Scap * Dst / tcap) * (Clua/Plu - Clubld)$$

$$\frac{d}{dt}(Alubld) = (Scap * Dst / tcap) * (Clua/Plu - Clubld) + Qtot * (Cven - Clubld)$$

$$\frac{d}{dt}(Aart) = Qtot * (Clubld - Cart)$$

$$\frac{d}{dt}(Afat) = Qfat * (Cart - Cfat/Pfat)$$

$$\frac{d}{dt}(Avrg) = Qvrg * (Cart - Cvrg/Pvrg)$$

$$\frac{d}{dt}(Amusc) = Qmusc * (Cart - Cmusc/Pmusc)$$

$$\frac{d}{dt}(AI) = QI * (Cart - CI/PI) - VmaxI1 * 1E3 * VI * CI / (PI * Kml1 + CI)$$

$$\frac{d}{dt}(Aven) = (Qfat * Cfat/Pfat + Qvrg * Cvrg/Pvrg + QI * CI/PI + Qmusc * Cmusc/Pmusc) - Qtot * Cven$$

$$d/dt(\text{Amet1luc}) = \text{Vmaxlu1} * 1\text{E3} * \text{Vlu} * \text{fs} * \text{Cluc} / (\text{Kmlu1} + \text{Cluc})$$

$$d/dt(\text{Amet1lua}) = \text{Vmaxlu1} * 1\text{E3} * \text{Vlu} * (1-\text{fs}) * \text{Clua} / (\text{Kmlu1} + \text{Clua})$$

$$d/dt(\text{Amet1I}) = \text{VmaxI1} * 1\text{E3} * \text{VI} * \text{CI} / (\text{PI} * \text{Kml1} + \text{CI})$$

{Differential equations for styrene oxide, B}

$$d/dt(\text{ABluc}) = \text{Vmaxlu1} * 1\text{E3} * \text{Vlu} * (1-\text{fs}) * \text{Cluc} / (\text{Kmlu1} + \text{Cluc}) - \text{Vmaxlu2} * 1\text{E3} * \text{Vlu} * \text{fs} * \text{CBluc} / (\text{Kmlu2} + \text{CBluc}) - \text{Vmaxlu3} * 1\text{E3} * \text{Vlu} * \text{fs} * \text{CBluc} * \text{CGSHluc} / (\text{Kmlu3so} * \text{CGSHluc} + \text{Kmlu3G} * \text{CBluc} + \text{CBluc} * \text{CGSHluc})$$

$$d/dt(\text{ABlua}) = \text{Vmaxlu1} * 1\text{E3} * \text{Vlu} * (1-\text{fs}) * \text{Clua} / (\text{Kmlu1} + \text{Clua}) - \text{Vmaxlu2} * 1\text{E3} * \text{Vlu} * (1-\text{fs}) * \text{CBlua} / (\text{Kmlu2} + \text{CBlua}) - \text{Vmaxlu3} * 1\text{E3} * \text{Vlu} * (1-\text{fs}) * \text{CBlua} * \text{CGSHlua} / (\text{Kmlu3so} * \text{CGSHlua} + \text{Kmlu3G} * \text{CBlua} + \text{CBlua} * \text{CGSHlua}) - (\text{Scap} * \text{Dso} / \text{tcap}) * (\text{CBlua} / \text{PBlu} - \text{CBlubld})$$

$$d/dt(\text{ABlubl}) = (\text{Scap} * \text{Dso} / \text{tcap}) * (\text{CBlua} / \text{PBlu} - \text{CBlubl}) + \text{Qtot} * (\text{CBven} - \text{CBlubl})$$

$$d/dt(\text{ABart}) = \text{Qtot} * (\text{CBlubl} - \text{CBart})$$

$$d/dt(\text{ABfat}) = \text{Qfat} * (\text{CBart} - \text{CBfat} / \text{PBfat})$$

$$d/dt(\text{ABvrg}) = \text{Qvrg} * (\text{CBart} - \text{CBvrg} / \text{PBvrg})$$

$$d/dt(\text{ABmusc}) = \text{Qmusc} * (\text{CBart} - \text{CBmusc} / \text{PBmusc})$$

$$d/dt(\text{ABlcy}) = \text{QI} * (\text{CBart} - \text{CBvicy}) + \text{Qendo} * (\text{CBendo} - \text{CBlcy}) - \text{VmaxI3} * 1\text{E3} * \text{VI} * \text{CBlcy} * \text{CGSHI} / (\text{Kml3so} * \text{CGSHI} + \text{Kml3G} * \text{CBlcy} + \text{CBlcy} * \text{CGSHI})$$

$$d/dt(\text{ABler}) = \text{VmaxI1} * 1\text{E3} * \text{VI} * \text{CI} / (\text{PI} * \text{Kml1} + \text{CI}) - \text{Qendo} * (\text{CBendo} - \text{CBlcy}) - \text{VmaxI2} * \text{CBendo} * 1\text{E3} * \text{VI} / (\text{Kml2eh} + \text{CBendo})$$

$$d/dt(\text{ABven}) = (\text{Qfat} * \text{CBfat} / \text{PBfat} + \text{Qvrg} * \text{CBvrg} / \text{PBvrg} + \text{QI} * \text{CBvicy} / \text{PBI} + \text{Qmusc} * \text{CBmusc} / \text{PBmusc}) - \text{Qtot} * \text{CBven}$$

$$d/dt(\text{ABmet2luc}) = \text{Vmaxlu2} * 1\text{E3} * \text{Vlu} * \text{fs} * \text{CBluc} / (\text{Kmlu2} + \text{CBluc})$$

$$d/dt(\text{ABmet2lua}) = \text{Vmaxlu2} * 1\text{E3} * \text{Vlu} * (1-\text{fs}) * \text{CBlua} / (\text{Kmlu2} + \text{CBlua})$$

$$d/dt(\text{ABmet2I}) = \text{VmaxI2} * \text{CBendo} * 1\text{E3} * \text{VI} / (\text{Kml2eh} + \text{CBendo})$$

$$d/dt(\text{ABmet3luc}) = \text{Vmaxlu3} * 1\text{E3} * \text{Vlu} * \text{fs} * \text{CBluc} * \text{CGSHluc} / (\text{Kmlu3so} * \text{CGSHluc} + \text{Kmlu3G} * \text{CBluc} + \text{CBluc} * \text{CGSHluc})$$

$$d/dt(\text{ABmet3lua}) = \text{Vmaxlu3} * 1\text{E3} * \text{Vlu} * (1-\text{fs}) * \text{CBlua} * \text{CGSHlua} / (\text{Kmlu3so} * \text{CGSHlua} + \text{Kmlu3G} * \text{CBlua} + \text{CBlua} * \text{CGSHlua})$$

$$d/dt(\text{ABmet3I}) = \text{VmaxI3} * 1\text{E3} * \text{VI} * \text{CBlcy} * \text{CGSHI} / (\text{Kml3so} * \text{CGSHI} + \text{Kml3G} * \text{CBlcy} + \text{CBlcy} * \text{CGSHI})$$

$$d/dt(\text{AUCBluc}) = \text{CBluc}$$

$$d/dt(\text{AUCBlua}) = \text{CBlua}$$

$$d/dt(\text{AUCBI}) = \text{CBlcy}$$

{differential equations GSH, no circadian term included}

$$d/dt(\text{GSHluc}) = \text{fs} * \text{Kdlu} * \text{Vluc} * (\text{fGSH} * 1.95 - \text{CGSHluc}) - \text{Vmaxlu3} * 1\text{E3} * \text{Vlu} * \text{fs} * \text{CBluc} * \text{CGSHluc} / (\text{Kmlu3so} * \text{CGSHluc} + \text{Kmlu3G} * \text{CBluc} + \text{CBluc} * \text{CGSHluc})$$

$$d/dt(\text{GSHlua}) = (1-\text{fs}) * \text{Kdlu} * \text{Vlua} * (\text{fGSH} * 1.95 - \text{CGSHlua}) - \text{Vmaxlu3} * 1\text{E3} * \text{Vlu} * (1-\text{fs}) * \text{CBlua} * \text{CGSHlua} / (\text{Kmlu3so} * \text{CGSHlua} + \text{Kmlu3G} * \text{CBlua} + \text{CBlua} * \text{CGSHlua})$$

$$d/dt(\text{GSHI}) = \text{Kdl} * \text{VI} * (\text{fGSH} * 5.9 - \text{CGSHI}) - \text{VmaxI3} * 1\text{E3} * \text{VI} * \text{CBlcy} * \text{CGSHI} / (\text{Kml3so} * \text{CGSHI} + \text{Kml3G} * \text{CBlcy} + \text{CBlcy} * \text{CGSHI})$$

*E.5.12 Model Code for DCM 0-5 yr Child***METHOD Stiff****STARTTIME = 0****STOPTIME=48****DT = 0.001**

{dichloromethane moles}

init Af = 0**init AI = 0****init Am = 0****init Avrg = 0****init Abr = 0****init Apu = 0****init Agi = 0**

{moles dichloromethane metabolized by MFO pathway}

init Ametl1 = 0**init Ametpu1 = 0****init Ametbr1 = 0**

{moles of dichloromethane metabolized by GST pathway}

init Ametl2 = 0**init Ametpu2 = 0****init Ametbr2 = 0**

{tissue flows L/hr}

Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414**Qalv = (17.875*Age) + 39.785****Qf = 0.0528*Qtot****Ql = 0.0795*Qtot****Qm = 0.0304*Qtot****Qvrg = 0.837*Qtot****Qpu = 0.93*Qtot****Qbr = 0.07*Qtot**

{tissue volumes L}

Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000**VI = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000****Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000****Vvrg = BW - (Vf + VI + Vm + Vlu)****Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000****Vpu = 0.9*Vlu****Vbr = 0.1*Vlu****BW = (-1.9*age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.70)/1000****Age = 0**

{blood/air and tissue/blood partition coefficients, dichloromethane}

Pb = 9.09

$$PI = 0.824$$

$$Pf = 7.239$$

$$Pm = 1.09$$

$$Pvrg = 0.788$$

$$Ppu = 0.552$$

$$Pbr = 0.552$$

{dichloromethane oxidation metabolic parameters, mol/hr, mol/L}

$$Vmaxbr = 0.1 * 1.46E-3 * Vmaxl$$

$$Vmaxpu = 0.9 * 1.46E-3 * Vmaxl$$

$$Vmaxl = 8.58E-5 * BW^{0.7}$$

$$Km = 8.7E-6$$

{dichloromethane GST conjugation /hr}

$$Kfl = 1.26 * BW^{-0.3}$$

$$Kfpu = 0.9 * 0.242 * Kfl$$

$$Kfbr = 0.1 * 0.242 * Kfl$$

{uptake of DCM gfrom GI tract to liver, /hr}

$$KAI = 0.5$$

{exposure in ppm converted to moles/L}

$$Cair = IF TIME \leq 6 THEN 10 * (1E-6/25.45) ELSE 0$$

{calculated concentrations of dichloromethane}

$$Cart = (Qpu * Cvpu + Qbr * Cvbr) / Qtot$$

$$Cvf = Af / (Vf * Pf)$$

$$Cvl = Al / (Vl * Pl)$$

$$Cvm = Am / (Vm * Pm)$$

$$Cvrg = Avrg / (Vvrg * Pvrg)$$

$$Cvpu = Apu / (Vpu * Ppu)$$

$$Cvbr = Abr / (Vbr * Pbr)$$

$$Cvtot = (Ql * Cvl + Qf * Cvf + Qm * Cvm + Qvrg * Cvrg) / Qpu$$

$$Cvipu = (Qalv * Cair + Qpu * Cvtot) / ((Qalv / Pb) + Qpu)$$

$$Cexh = Cvipu / Pb$$

{differential equations for dichloromethane uptake and metabolism}

$$d/dt(Agi) = - KAI * Agi$$

$$d/dt(Apu) = Qpu * (Cvipu - Cvpu) - Vmaxpu * Cvpu / (Km + Cvpu) - Kfpu * Apu$$

$$d/dt(Abr) = Qbr * (Cart - Cvbr) - Vmaxbr * Cvbr / (Km + Cvbr) - Kfbr * Abr$$

$$d/dt(Al) = Ql * (Cart - Cvl) - Vmaxl * Cvl / (Km + Cvl) - Kfl * Al + KAI * Agi$$

$$d/dt(Af) = Qf * (Cart - Cvf)$$

$$d/dt(Am) = Qm * (Cart - Cvm)$$

$$d/dt(Avrg) = Qvrg * (Cart - Cvrg)$$

{amount of dichloromethane metabolized by MFO pathway in liver and lung}

$$d/dt(Ametl1) = Vmaxl * (Al / Vl) / (Km + (Al / Vl))$$

$$d/dt(Ametpu1) = Vmaxpu * (Apu / Vpu) / (Km + (Apu / Vpu))$$

$$d/dt(Ametbr1) = Vmaxbr * (Abr / Vbr) / (Km + (Abr / Vbr))$$

{amount of dichloromethane metabolized by GST pathway in liver and lung}

$$d/dt(Ametl2) = Kfl * Al$$

$$d/dt(\text{Ametpu2}) = \text{Kfpu} * \text{Apu}$$

$$d/dt(\text{Ametbr2}) = \text{Kfbr} * \text{Abr}$$

$$\text{Ametpu2k} = \text{Ametpu2} / \text{BW}$$

$$\text{Ametbr2k} = \text{Ametbr2} / \text{BW}$$

E.5.13 Model Code for Ethylene/Ethylene oxide 0-6 yr Child

METHOD Stiff

STARTTIME = 0

STOPTIME=48

DT = 0.001

{ethylene moles}

init Af = 0

Limit Af >= 0

init AI = 0

Limit AI >= 0

init Am = 0

Limit Am >= 0

init Avrg = 0

Limit Avrg >= 0

init Alubld = 0

Limit Alubld >= 0

init Aart = 0

Limit Aart >= 0

init Aven = 0

Limit Aven >= 0

{ethylene oxide moles}

init ABf = 0

Limit ABf >= 0

init ABI = 0

Limit ABI >= 0

init ABm = 0

Limit ABm >= 0

init ABvrg = 0

Limit ABvrg >= 0

init ABlubld = 0

Limit ABlubld >= 0

init ABart = 0

Limit ABart >= 0

init ABven = 0

Limit ABven >= 0

{adducts formed}

init Hbadd = 0

init DNAadd = 0

Khb = 4.5E-5

Kdna = 9.4E-5

Keldna = 0.0077

ter = 3024

{moles ethylene metabolized}

init Amet = 0

{moles of ethylene oxide metabolized}

init ABmet = 0

{area under the venous blood concn x time curve, ethylene}

init AUCvtot = 0

init AUCvl = 0

init AUCvlubld = 0

{area under the venous blood concn x time curve, ethylene oxide}

init AUCBvtot = 0

init AUCBvl = 0

init AUCBvlubld = 0

{tissue flows L/hr}

Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414

Qalv = 0.82*Qtot

Qf = 0.053*Qtot

Ql = 0.0795*Qtot

Qm = 0.03*Qtot

Qvrg = Qtot - (Qf + Ql + Qm)

{tissue volumes, L}

BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000

Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000

VI = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000

Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000

Vvrg = BW - (Vf + VI + Vm + Vart + Vven + Vlubld)

Vart = 0.0178*BW

Vven = 0.0533*BW

Vlubld = 0.0079*BW

t = TIME

{blood/air and tissue/blood partition coefficients, ethylene}

Pb = 0.22

PI = 2.05

Pf = 8.73

Pm = 2.95

Pvrg = 2.18

{blood/air and tissue/blood partition coefficients, ethylene oxide}

PBb = 61

$$\text{PBI} = 0.89$$

$$\text{PBf} = 0.70$$

$$\text{PBm} = 1.08$$

$$\text{PBvrg} = 1.03$$

{ethylene oxidation metabolic parameters, clearance L/hr}

$$\text{Clr} = 74.9 \cdot (70/\text{BW})^{0.25}$$

{ethylene oxide metabolic parameters, clearance L/hr}

$$\text{CBlr} = 1.53 \cdot (70/\text{BW})^{0.25}$$

$$\text{Feo} = 0.8$$

{exposure in ppm converted to, mmoles/L}

$$\text{Cair} = \text{IF TIME} \leq 24 \text{ THEN } 1 \cdot (1\text{E-}3/25.45) \text{ ELSE } 0$$

$$\text{CBair} = \text{IF TIME} \leq 24 \text{ THEN } 0.01 \cdot (1\text{E-}3/25.45) \text{ ELSE } 0$$

$$\text{Age} = 0$$

{calculated concentrations of ethylene}

$$\text{Cart} = \text{Aart}/\text{Vart}$$

$$\text{Cven} = \text{Aven}/\text{Vven}$$

$$\text{Clubld} = \text{Alubld}/\text{Vlubld}$$

$$\text{Cvlubld} = \text{Alubld}/(\text{Vlubld} \cdot \text{Pb})$$

$$\text{Cvf} = \text{Af}/(\text{Vf} \cdot \text{Pf})$$

$$\text{Cvl} = \text{Al}/(\text{Vl} \cdot \text{Pl})$$

$$\text{Cl} = \text{Al}/\text{Vl}$$

$$\text{Cvl} = \text{Al}/(\text{Vl} \cdot \text{Pl})$$

$$\text{Cvm} = \text{Am}/(\text{Vm} \cdot \text{Pm})$$

$$\text{Cvvrg} = \text{Avrg}/(\text{Vvrg} \cdot \text{Pvrg})$$

$$\text{Cvtot} = (\text{Ql} \cdot \text{Cvl} + \text{Qf} \cdot \text{Cvf} + \text{Qm} \cdot \text{Cvm} + \text{Qvrg} \cdot \text{Cvvrg})/\text{Qtot}$$

$$\text{Cexh} = \text{Cvlubld}/\text{Pb}$$

{calculated concentrations of ethylene oxide}

$$\text{CBart} = \text{ABart}/\text{Vart}$$

$$\text{CBven} = \text{ABven}/\text{Vven}$$

$$\text{CBvf} = \text{ABf}/(\text{Vf} \cdot \text{PBf})$$

$$\text{CBI} = \text{ABI}/\text{VI}$$

$$\text{CBvl} = \text{ABI}/(\text{VI} \cdot \text{PBI})$$

$$\text{CBvm} = \text{ABm}/(\text{Vm} \cdot \text{PBm})$$

$$\text{CBlubld} = \text{ABlubld}/\text{Vlubld}$$

$$\text{CBvlubld} = \text{ABlubld}/(\text{Vlubld} \cdot \text{Pb})$$

$$\text{CBvvrg} = \text{ABvrg}/(\text{Vvrg} \cdot \text{PBvrg})$$

$$\text{CBvtot} = (\text{Ql} \cdot \text{CBvl} + \text{Qf} \cdot \text{CBvf} + \text{Qm} \cdot \text{CBvm} + \text{Qvrg} \cdot \text{CBvvrg})/\text{Qtot}$$

$$\text{CBair} = \text{CBvtot}/\text{PB}$$

$$\text{Chb} = \text{Hbadd} \cdot (1 - t/(2 \cdot \text{ter})) \text{ {circulating Hb adducts}}$$

{differential equations for ethylene uptake and metabolism}

$$d/dt(\text{Alubld}) = \text{Qalv} \cdot (\text{Cair} - \text{Cvlubld}) + \text{Qtot} \cdot (\text{Cven} - \text{Cvlubld})$$

$$d/dt(\text{Aart}) = \text{Qtot} \cdot (\text{Clubld} - \text{Cart}) + 4.71\text{E-}7 \cdot \text{BW}$$

$$d/dt(\text{Aven}) = (\text{Ql} \cdot \text{Cvl} + \text{Qf} \cdot \text{Cvf} + \text{Qm} \cdot \text{Cvm} + \text{Qvrg} \cdot \text{Cvvrg}) - \text{Qtot} \cdot \text{Cven}$$

$$d/dt(\text{Al}) = \text{Ql} \cdot (\text{Cart} - \text{Cvl}) - \text{Clr} \cdot \text{Cvl}$$

$d/dt(Af) = Qf*(Cart - Cvf)$
 $d/dt(Am) = Qm*(Cart - Cvm)$
 $d/dt(Avrg) = Qvrg*(Cart - Cvrg)$
 {amount of ethylene metabolized in liver}
 $d/dt(Amet) = Clr*Cvl$
 {AUCs for ethylene}
 $d/dt(AUCvtot) = Cvtot$
 $d/dt(AUCvl) = Cvl$
 $d/dt(AUCvlubld) = Cvlubld$
 {differential equations for ethylene oxide metabolism}
 $d/dt(ABlubld) = Qalv*(CBair*Feo - CBvlubld) + Qtot*(CBven - CBvlubld)$
 $d/dt(ABart) = Qtot*(CBlubld - CBart)$
 $d/dt(ABven) = (Ql*CBvl + Qf*CBvf + Qm*CBvm + Qvrg*CBvrg) - Qtot*CBven$
 $d/dt(ABI) = Ql*(CBart - CBvl) + Clr*Cvl - CBlr*CBvl$
 $d/dt(ABf) = Qf*(CBart - CBvf)$
 $d/dt(ABm) = Qm*(CBart - CBvm)$
 $d/dt(ABvrg) = Qvrg*(CBart - CBvrg)$
 $d/dt(Hbadd) = (Vart*CBart + Vven*CBven + Vlubl*d*CBlubld)*Khb$
 $d/dt(DNAadd) = (Vart*CBart + Vven*CBven + Vlubl*d*CBlubld)*Kdna - Keldna*DNAadd$
 {AUCs for ethylene oxide}
 $d/dt(AUCBvtot) = CBvtot$
 $d/dt(AUCBvl) = CBvl$
 $d/dt(AUCBvlubld) = CBvlubld$
 {amounts of ethylene oxide metabolized in liver}
 $d/dt(ABmet) = CBlr*CBvl$

E.5.14 Model Code for Styrene/SO RT Model of Csanady et al. (2003) Adult

METHOD Stiff

STARTTIME = 0
STOPTIME= 48
DT = 0.001
 {Styrene mmol}
init Aluc = 0 {conducting airways}
init Alua = 0 {alveoli}
init Alubld = 0 {lung blood}
init Aven = 0 {venous blood}
init Aart = 0 {arterial blood}
init Afat = 0
init Avrg = 0
init Amusc = 0

init AI = 0
init Amet1luc = 0
init Amet1lua = 0
init Amet1lu = 0
init Amet1I = 0
 {Styrene oxide, mmol}
init ABluc = 0
init ABlua = 0
init ABlubld = 0
init ABven = 0
init ABart = 0
init ABfat = 0
init ABvrg = 0
init ABmusc = 0
init ABler = 0
init ABlcy = 0
init ABmet2luc = 0
init ABmet2lua = 0
init ABmet2I = 0
init ABmet3luc = 0
init ABmet3lua = 0
init ABmet3I = 0
init AUCBluc = 0
init AUCBlua = 0
init AUCBI = 0
 {Hb adduct, DNA Adduct}
Init Hbadd = 0

$$d/dt(Hbadd) = (Vart*CBart + Vven*CBven + Vlubld*CBlubld)*Kher$$
init DNAadd = 0

$$d/dt(DNAadd) = (Vart*CBart + Vven*CBven + Vlubld*CBlubld)*Kfdna - Keldna*DNAadd$$
Kher = 4.5E-5
Kfdna = 3.7E-5
Keldna = 0.0077
 {Model parameters}
BW = 70 {kg, L}
Qalv = 300 {L/hr}
Qtot = 372
tcap = 7.45E-6 {dm}
Scap = 115 {dm²/kg}
Dst = 4.4E-4 {dm²/hr}
Dso = 4.3E-4
 {Flows, L/hr}
Qfat = 0.05*Qtot
QI = 0.26*Qtot

Qvrg = 0.44*Qtot
Qmusc = 0.25*Qtot
 {Volumes, L}
Vch = 3E3
Vart = 0.0178*BW
Vven = 0.0533*BW
Vlubld = 0.0079*BW
Vfat = 0.19*BW
Vlu = 0.0076*BW
Vluc = fs*Vlu
Vlua = (1-fs)*Vlu
VI = 0.026*BW
Vvrg = 0.042*BW
Vmusc = 0.541*BW
 {Partition coeffs styrene, dimensionless}
Pb = 70.0
Pfat = 93.8
PI = 2.71
Plu = 1.46
Pvrg = 2.60
Pmusc = 1.96
 {Partition coeffs styrene oxide, dimensionless}
PbB = 2370
PBfat = 6.1
PBI = 2.6
PBlu = 1.9
PBvrg = 2.6
PBmusc = 1.5
 {Concentrations ST mmol/L}
Exposure = IF TIME < 24 THEN 1*(1E-3/24.45) ELSE 0
fs = 0.1
Cair = exposure
Cart = Aart/Vart
Cven = Aven/Vven
Cfat = Afat/Vfat
CI = AI/VI
Cvrg = Avrg/Vvrg
Cmusc = Amusc/Vmusc
Clubld = Alubld/Vlubld
Cluc = Aluc/(fs*Vlu)
Clua = Alua/((1-fs)*Vlu)
Cexalv = (fs*(2.0-fs)*(Cluc/Pb) + (1.0-fs)*(1.0-fs)*(Clua/Pb))/factor
Cexpul = (fs*(2.0-fs)*(Cluc/Pb) + (1.0-fs)*(1.0-fs)*(Clua/Pb))/factor + 1/3*Cairp
factor = 1

$$\text{Cairp} = \text{Cair} * (24.45 / 1E-3)$$

{Concentrations SO, mmol/L}

$$\text{CBart} = \text{ABart} / \text{Vart}$$

$$\text{CBven} = \text{ABven} / \text{Vven}$$

$$\text{CBfat} = \text{ABfat} / \text{Vfat}$$

$$\text{CBvrg} = \text{ABvrg} / \text{Vvrg}$$

$$\text{CBmusc} = \text{ABmusc} / \text{Vmusc}$$

$$\text{CBlcy} = \text{ABlcy} / \text{VI}$$

$$\text{CBvlcy} = \text{ABlcy} / (\text{VI} * \text{PI})$$

$$\text{CBluc} = \text{ABluc} / (\text{fs} * \text{Vlu})$$

$$\text{CBlua} = \text{ABlua} / ((1 - \text{fs}) * \text{Vlu})$$

$$\text{CBlubld} = \text{ABlubld} / \text{Vlubld}$$

$$\text{Qendo} = \text{Vmaxl2} * 1E3 * \text{VI} / (\text{Kml2app} - \text{Kml2eh})$$

$$a = \text{CBlcy} - \text{Kml2eh} + \text{Vmaxl1} * 1E3 * \text{VI} * \text{CI} / \text{Qendo} * (\text{PI} * \text{Kml1} + \text{CI}) - \text{Vmaxl2} * 1E3 * \text{VI} / \text{Qendo}$$

$$\text{CBendo} = 0.5 * (a + (a^2 + 4 * \text{Kml2eh} * (\text{CBlcy} + \text{Vmaxl1} * 1E3 * \text{VI} * \text{CI} / \text{Qendo} * (\text{PI} * \text{Kml1} + \text{CI}))))^{0.5}$$

{GSH}

$$\text{init GSHluc} = \text{fs} * \text{GSHlu0}$$

$$\text{init GSHlua} = (1 - \text{fs}) * \text{GSHlu0}$$

$$\text{init GSHI} = \text{GSHI0}$$

$$\text{CGSHluc} = \text{GSHluc} * \text{fs} / \text{Vluc}$$

$$\text{CGSHlua} = \text{GSHlua} * (1 - \text{fs}) / \text{Vlua}$$

$$\text{CGSHI} = \text{GSHI} / \text{VI}$$

$$\text{fGSH} = 0.75$$

$$\text{GSHlu0} = 1.95 * \text{Vlu}$$

$$\text{GSHI0} = 5.9 * \text{VI}$$

{Biochemical parameters, mmol/hr/mL, mmol/L; 1 = P450, 2 = EH, 3 = GST}

$$\text{Vmaxl1} = 0.002$$

$$\text{Kml1} = 0.01$$

$$\text{Vmaxl2} = 0.0045$$

$$\text{Kml2eh} = 0.001$$

$$\text{Kml2app} = 0.01$$

$$\text{Vmaxl3} = 0.028$$

$$\text{Kml3G} = 0.1$$

$$\text{Kml3so} = 2.5$$

$$\text{Kdl} = 0.2$$

$$\text{Vmaxlu1} = 2.5E-6$$

$$\text{Kmlu1} = 0.0175$$

$$\text{Vmaxlu2} = 6.73E-4$$

$$\text{Kmlu2} = 0.0156$$

$$\text{Vmaxlu3} = 0.082$$

$$\text{Kmlu3G} = 0.1$$

$$\text{Kmlu3so} = 2.5$$

$$\text{Kdlu} = 2.0$$

{Differential equations for styrene}

$$d/dt(Aluc) = Qalv*(Cair*fs + fs*(1 - fs)*(Clua/Pb) - (fs + fs*(1-fs))*Cluc/Pb) - Vmaxlu1*1E3*Vlu*fs*Cluc/(Kmlu1 + Cluc)$$

$$d/dt(Alua) = Qalv*(Cair*(1-fs) - (1-fs)*Clua/Pb) - Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua) - (Scap*Dst/tcap)*(Clua/Plu - Clubld)$$

$$d/dt(Alubld) = (Scap*Dst/tcap)*(Clua/Plu - Clubld) + Qtot*(Cven - Clubld)$$

$$d/dt(Aart) = Qtot*(Clubld - Cart)$$

$$d/dt(Afat) = Qfat*(Cart - Cfat/Pfat)$$

$$d/dt(Avrg) = Qvrg*(Cart - Cvrg/Pvrg)$$

$$d/dt(Amusc) = Qmusc*(Cart - Cmusc/Pmusc)$$

$$d/dt(AI) = QI*(Cart - CI/PI) - VmaxI1*1E3*VI*CI/(PI*Kml1 + CI)$$

$$d/dt(Aven) = (Qfat*Cfat/Pfat + Qvrg*Cvrg/Pvrg + QI*CI/PI + Qmusc*Cmusc/Pmusc) - Qtot*Cven$$

$$d/dt(Amet1luc) = Vmaxlu1*1E3*Vlu*fs*Cluc/(Kmlu1 + Cluc)$$

$$d/dt(Amet1lua) = Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua)$$

$$d/dt(Amet1lu) = Vmaxlu1*1E3*Vlu*fs*Cluc/(Kmlu1 + Cluc) + Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua)$$

$$d/dt(Amet1I) = VmaxI1*1E3*VI*CI/(PI*Kml1 + CI)$$

{Differential equations for styrene oxide, B}

$$d/dt(ABluc) = Vmaxlu1*1E3*Vlu*(1-fs)*Cluc/(Kmlu1 + Cluc) - Vmaxlu2*1E3*Vlu*fs*CBluc/(Kmlu2 + CBluc) - Vmaxlu3*1E3*Vlu*fs*CBluc*CGSHluc/(Kmlu3so*CGSHluc + Kmlu3G*CBluc + CBluc*CGSHluc)$$

$$d/dt(ABlua) = Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua) - Vmaxlu2*1E3*Vlu*(1-fs)*CBlua/(Kmlu2 + CBlua) - Vmaxlu3*1E3*Vlu*(1-fs)*CBlua*CGSHlua/(Kmlu3so*CGSHlua + Kmlu3G*CBlua + CBlua*CGSHlua) - (Scap*Dso/tcap)*(CBlua/PBlu - CBlubld)$$

$$d/dt(ABlubld) = (Scap*Dso/tcap)*(CBlua/PBlu - CBlubld) + Qtot*(CBven - CBlubld)$$

$$d/dt(ABart) = Qtot*(CBlubld - CBart)$$

$$d/dt(ABfat) = Qfat*(CBart - CBfat/PBfat)$$

$$d/dt(ABvrg) = Qvrg*(CBart - CBvrg/PBvrg)$$

$$d/dt(ABmusc) = Qmusc*(CBart - CBmusc/PBmusc)$$

$$d/dt(ABlcy) = QI*(CBart - CBvlcy) + Qendo*(CBendo - CBlcy) - VmaxI3*1E3*VI*CBlcy*CGSHI/(Kml3so*CGSHI + Kml3G*CBlcy + CBlcy*CGSHI)$$

$$d/dt(ABler) = VmaxI1*1E3*VI*CI/(PI*Kml1 + CI) - Qendo*(CBendo - CBlcy) - VmaxI2*1E3*VI*CBendo/(Kml2eh + CBendo)$$

$$d/dt(ABven) = (Qfat*CBfat/PBfat + Qvrg*CBvrg/PBvrg + QI*CBvlcy/PBI + Qmusc*CBmusc/PBmusc) - Qtot*CBven$$

$$d/dt(ABmet2luc) = Vmaxlu2*1E3*Vlu*fs*CBluc/(Kmlu2 + CBluc)$$

$$d/dt(ABmet2lua) = Vmaxlu2*1E3*Vlu*(1-fs)*CBlua/(Kmlu2 + CBlua)$$

$$d/dt(ABmet2I) = VmaxI2*1E3*VI*CBendo/(Kml2eh + CBendo)$$

$$d/dt(ABmet3luc) = Vmaxlu3*1E3*Vlu*fs*CBluc*CGSHluc/(Kmlu3so*CGSHluc + Kmlu3G*CBluc + CBluc*CGSHluc)$$

$$d/dt(ABmet3lua) = Vmaxlu3*1E3*Vlu*(1-fs)*CBlua*CGSHlua/(Kmlu3so*CGSHlua + Kmlu3G*CBlua + CBlua*CGSHlua)$$

$$d/dt(ABmet3I) = VmaxI3*1E3*VI*CBlcy*CGSHI/(Kml3so*CGSHI + Kml3G*CBlcy + CBlcy*CGSHI)$$

$$d/dt(AUCBluc) = CBluc$$

$$d/dt(AUCBlua) = CBlua$$

$$d/dt(AUCBI) = CBlcy$$

{differential equations GSH, no circadian term included}

$$\begin{aligned} d/dt(\text{GSHluc}) &= fs * Kdlu * Vluc * (fGSH * 1.95 - \text{CGSHluc}) - \\ &Vmaxlu3 * 1E3 * Vlu * fs * CBluc * \text{CGSHluc} / (Kmlu3so * \text{CGSHluc} + Kmlu3G * CBluc + CBluc * \text{CGSHluc}) \\ d/dt(\text{GSHlua}) &= (1 - fs) * Kdlu * Vlua * (fGSH * 1.95 - \text{CGSHlua}) - Vmaxlu3 * 1E3 * Vlu * (1 - \\ &fs) * CBlua * \text{CGSHlua} / (Kmlu3so * \text{CGSHlua} + Kmlu3G * CBlua + CBlua * \text{CGSHlua}) \\ d/dt(\text{GSHI}) &= Kdl * VI * (fGSH * 5.9 - \text{CGSHI}) - VmaxI3 * 1E3 * VI * CBicy * \text{CGSHI} / (Kml3so * \text{CGSHI} + \\ &Kml3G * CBicy + CBicy * \text{CGSHI}) \end{aligned}$$

E.5.15 Model Code for Carbon tetrachloride 0-6 yr Child

METHOD Stiff

STARTTIME = 0

STOPTIME=48

DT = 0.001

{CCl4 moles}

init Af = 0

init AI = 0

init Am = 0

init Avrg = 0

init Abr = 0

init Apu = 0

{moles CCl4 metabolized}

init AmetI = 0

init AUCvtot = 0

init AUCvl = 0

{tissue flows L/hr}

Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414

Qalv = 0.82*Qtot

Qf = 0.053*Qtot

QI = 0.0795*Qtot

Qm = 0.03*Qtot

Qvrg = Qtot -(Qf + QI + Qm)

Qpu = 0.93*Qtot

Qbr = 0.07*Qtot

{tissue volumes L}

Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000

VI = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000

Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000

Vvrg = BW - (Vf + VI + Vm + Vlu)

Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000

Vpu = 0.9*Vlu

Vbr = 0.1*Vlu

BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000

{blood/air and tissue/blood partition coefficients, CCl4}

$$Pb = 4.52$$

$$PI = 3.14$$

$$Pf = 79.4$$

$$Pm = 1.00$$

$$Pvrg = 1.00$$

$$Ppu = 1.00$$

$$Pbr = 1.00$$

{CCl4 oxidation metabolic parameters, mol/hr/mg protein, mol/L, mol/hr}

$$Vmax = 1.35E-7*(70/BW)^{0.25}$$

$$VmaxI = Vmax*VI*23.0*1E3$$

$$Km = 5.68E-5$$

{exposure in ppm converted to moles/L}

$$Cair = IF TIME \leq 24 THEN 1*(1E-6/25.45) ELSE 0$$

$$Age = 5$$

{calculated concentrations of CCl4}

$$Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot$$

$$Cvf = Af/(Vf*Pf)$$

$$Cvl = AI/(VI*PI)$$

$$Cvm = Am/(Vm*Pm)$$

$$Cvrg = Avrg/(Vvrg*Pvrg)$$

$$Cvpu = Apu/(Vpu*Ppu)$$

$$Cvbr = Abr/(Vbr*Pbr)$$

$$Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvrg)/Qpu$$

$$Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)$$

$$Cexh = Cvipu/Pb$$

{differential equations for CCl4 uptake and metabolism}

$$d/dt(Apu) = Qpu*(Cvipu - Cvpu)$$

$$d/dt(Abr) = Qbr*(Cart - Cvbr)$$

$$d/dt(AI) = QI*(Cart - Cvl) - VmaxI*Cvl/(Km + Cvl)$$

$$d/dt(Af) = Qf*(Cart - Cvf)$$

$$d/dt(Am) = Qm*(Cart - Cvm)$$

$$d/dt(Avrg) = Qvrg*(Cart - Cvrg)$$

{amount of CCl4 metabolized in liver}

$$d/dt(AmetI) = VmaxI*Cvl/(Km + Cvl)$$

$$d/dt(AUCvtot) = Cvtot$$

$$d/dt(AUCvl) = Cvl$$

*E.5.16 Model Code for Toluene 0-6 yr Child***METHOD Stiff****STARTTIME = 0****STOPTIME=48****DT = 0.001**

{Toluene moles}

init Af = 0**init AI = 0****init Am = 0****init Avrg = 0****init Abr = 0****init Apu = 0**

{moles toluene metabolized}

init Ametl = 0**init AUCvtot = 0****init AUCvl = 0**

{tissue flows, L/hr}

Qtot = 0.012*Age³ - 1.2144*Age² + 40.324*Age + 44.414**Qalv = 0.82*Qtot****Qf = 0.053*Qtot****Ql = 0.0795*Qtot****Qm = 0.03*Qtot****Qvrg = Qtot -(Qf + Ql + Qm)****Qpu = 0.93*Qtot****Qbr = 0.07*Qtot**

{tissue volumes, L}

Vf = (0.0165*Age⁵ - 1.9784*Age⁴ + 51.963*Age³ - 459.38*Age² + 1566.8*Age + 1004.2)/1000**VI = (0.0072*Age⁵ - 0.3975*Age⁴ + 7.9052*Age³ - 65.624*Age² + 262.02*Age + 157.52)/1000****Vm = (-0.0623*Age⁵ + 2.3433*Age⁴ - 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2)/1000****Vvrg = BW - (Vf + VI + Vm + Vlu)****Vlu = (-0.0346*Age⁴ + 1.5069*Age³ - 20.31*Age² + 123.99*Age + 59.213)/1000****Vpu = 0.9*Vlu****Vbr = 0.1*Vlu****BW = (-1.9*Age⁴ + 72.8*Age³ - 813.1*Age² + 5535.6*Age + 4453.7)/1000**

{blood/air and tissue/blood partition coefficients, toluene}

Pb = 15.6**PI = 2.98****Pf = 65.8****Pm = 1.37****Pvrg = 2.66****Ppu = 2.66****Pbr = 2.66**

{toluene oxidation metabolic parameters, mol/hr, mol/L}

$$V_{maxI} = 5.2E-5 * BW * (70/BW)^{0.25}$$

$$K_m = 5.97E-6$$

{exposure in ppm converted to moles/L}

$$C_{air} = \text{IF TIME} \leq 24 \text{ THEN } 1 * (1E-6/25.45) \text{ ELSE } 0$$

$$\text{Age} = 5$$

{calculated concentrations of toluene}

$$C_{art} = (Q_{pu} * C_{vpu} + Q_{br} * C_{vbr}) / Q_{tot}$$

$$C_{vf} = A_f / (V_f * P_f)$$

$$C_{vl} = A_l / (V_l * P_l)$$

$$C_{vm} = A_m / (V_m * P_m)$$

$$C_{vrg} = A_{vrg} / (V_{vrg} * P_{vrg})$$

$$C_{vpu} = A_{pu} / (V_{pu} * P_{pu})$$

$$C_{vbr} = A_{br} / (V_{br} * P_{br})$$

$$C_{vtot} = (Q_l * C_{vl} + Q_f * C_{vf} + Q_m * C_{vm} + Q_{vrg} * C_{vrg}) / Q_{pu}$$

$$C_{vipu} = (Q_{alv} * C_{air} + Q_{pu} * C_{vtot}) / ((Q_{alv} / P_b) + Q_{pu})$$

$$C_{exh} = C_{vipu} / P_b$$

{differential equations for toluene uptake and metabolism}

$$d/dt(A_{pu}) = Q_{pu} * (C_{vipu} - C_{vpu})$$

$$d/dt(A_{br}) = Q_{br} * (C_{art} - C_{vbr})$$

$$d/dt(A_l) = Q_l * (C_{art} - C_{vl}) - V_{maxI} * C_{vl} / (K_m + C_{vl})$$

$$d/dt(A_f) = Q_f * (C_{art} - C_{vf})$$

$$d/dt(A_m) = Q_m * (C_{art} - C_{vm})$$

$$d/dt(A_{vrg}) = Q_{vrg} * (C_{art} - C_{vrg})$$

{amount of toluene metabolized in liver and AUCs in blood and liver}

$$d/dt(A_{metl}) = V_{maxI} * C_{vl} / (K_m + C_{vl})$$

$$d/dt(AUC_{vtot}) = C_{vtot}$$

$$d/dt(AUC_{vl}) = C_{vl}$$

E.5.17 Model Code for Xylene 0-6 Yr Child

METHOD Stiff

$$\text{STARTTIME} = 0$$

$$\text{STOPTIME} = 48$$

$$\text{DT} = 0.001$$

{Xylene moles}

$$\text{init } A_f = 0$$

$$\text{init } A_l = 0$$

$$\text{init } A_m = 0$$

$$\text{init } A_{vrg} = 0$$

$$\text{init } A_{br} = 0$$

init Apu = 0

{moles xylene metabolized}

init Ametl = 0

init AUCvtot = 0

init AUCvl = 0

{tissue flows, L/hr}

Qtot = 0.012*Age³ - 1.2144*Age² + 40.324*Age + 44.414

Qalv = 0.82*Qtot

Qf = 0.053*Qtot

Ql = 0.0795*Qtot

Qm = 0.03*Qtot

Qvrg = Qtot -(Qf + Ql + Qm)

Qpu = 0.93*Qtot

Qbr = 0.07*Qtot

{tissue volumes, L}

Vf = (0.0165*Age⁵ - 1.9784*Age⁴ + 51.963*Age³ - 459.38*Age² + 1566.8*Age + 1004.2)/1000

VI = (0.0072*Age⁵ - 0.3975*Age⁴ + 7.9052*Age³ - 65.624*Age² + 262.02*Age + 157.52)/1000

Vm = (-0.0623*Age⁵ + 2.3433*Age⁴ - 26.559*Age³ + 144.75*Age² + 339.84*Age + 1648.2)/1000

Vvrg = BW - (Vf + VI + Vm + Vlu)

Vlu = (-0.0346*Age⁴ + 1.5069*Age³ - 20.31*Age² + 123.99*Age + 59.213)/1000

Vpu = 0.9*Vlu

Vbr = 0.1*Vlu

BW = (-1.9*Age⁴ + 72.8*Age³ - 813.1*Age² + 5535.6*Age + 4453.7)/1000

{blood/air and tissue/blood partition coefficients, xylene}

Pb = 26.4

PI = 3.02

Pf = 77.8

Pm = 3.00

Pvrg = 4.42

Ppu = 4.42

Pbr = 4.42

{Xylene oxidation metabolic parameters, mol/hr, mol/L}

Vmaxl = 7.9E-5*BW*(70/BW)^{0.25}

Km = 1.88E-6

{exposure in ppm converted to moles/L}

Cair = IF TIME <= 24 THEN 1*(1E-6/25.45) ELSE 0

Age = 5

{calculated concentrations of xylene}

Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot

Cvf = Af/(Vf*Pf)

Cvl = Al/(VI*PI)

Cvm = Am/(Vm*Pm)

Cvrg = Avrg/(Vvrg*Pvrg)

Cvpu = Apu/(Vpu*Ppu)

$$Cvbr = Abr/(Vbr*Pbr)$$

$$Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qpu$$

$$Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)$$

$$Cexh = Cvipu/Pb$$

{differential equations for xylene uptake and metabolism}

$$d/dt(Apu) = Qpu*(Cvipu - Cvp_u)$$

$$d/dt(Abr) = Qbr*(Cart - Cvbr)$$

$$d/dt(AI) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km + Cvl)$$

$$d/dt(Af) = Qf*(Cart - Cvf)$$

$$d/dt(Am) = Qm*(Cart - Cvm)$$

$$d/dt(Avrg) = Qvrg*(Cart - Cvvrg)$$

{amount of xylene metabolized in liver and AUCs in blood and liver}

$$d/dt(Ametl) = Vmaxl*Cvl/(Km + Cvl)$$

$$d/dt(AUCvtot) = Cvtot$$

$$d/dt(AUCvl) = Cvl$$

E.5.18 Model Code for Toluene-Xylene Mixed Exposure 0-6 Yr Child

METHOD Stiff

STARTTIME = 0

STOPTIME=48

DT = 0.001

{Toluene moles}

init Af = 0

Limit Af >= 0

init AI = 0

Limit AI >= 0

init Am = 0

Limit Am >= 0

init Avrg = 0

Limit Avrg >= 0

init Abr = 0

Limit Abr >= 0

init Apu = 0

Limit Apu >= 0

{Xylene moles}

init ABf = 0

Limit ABf >= 0

init ABI = 0

Limit ABI >= 0

init ABm = 0

Limit ABm >= 0
init ABvrg = 0
Limit ABvrg >= 0
init ABbr = 0
Limit ABbr >= 0
init ABpu = 0
Limit ABpu >= 0
 {moles toluene metabolized}
init Ametl = 0
init AUCvtot = 0
init AUCvl = 0
 {moles xylene metabolized}
init ABmetl = 0
init AUCBvtot = 0
init AUCBvl = 0
 {tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = Qtot
Qf = 0.053*Qtot
Ql = 0.0795*Qtot
Qm = 0.03*Qtot
Qvrg = Qtot - (Qf + Ql + Qm)
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
 {tissue volumes L}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
VI = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + VI + Vm + Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
 {blood/air and tissue/blood partition coefficients, toluene}
Pb = 15.6
PI = 2.98
Pf = 65.8
Pm = 1.37
Pvrg = 2.66
Ppu = 2.66
Pbr = 2.66
 {blood/air and tissue/blood partition coefficients, xylene}
PBb = 26.4
PBI = 3.02

$$PBf = 77.8$$

$$PBm = 3.00$$

$$PBvrg = 4.42$$

$$PBpu = 4.42$$

$$PBbr = 4.42$$

{toluene oxidation metabolic parameters, mol/hr, mol/L}

$$Vmax1 = 5.2E-5 * BW * (70/BW)^{0.25}$$

$$Km = 5.97E-6$$

$$Ki = 3.8E-6$$

{xylene oxidation metabolic parameters, mol/hr, mol/L}

$$Vmax12 = 7.9E-5 * BW * (70/BW)^{0.25}$$

$$Km2 = 1.88E-6$$

$$K2i = 5.6E-6$$

{toluene exposure in ppm converted to moles/L}

$$Cair = \text{IF TIME} \leq 8 \text{ THEN } 10 * (1E-6/25.45) \text{ ELSE } 0$$

{xylene exposure in ppm converted to moles/L}

$$CBair = \text{IF TIME} \leq 8 \text{ THEN } 1 * (1E-6/25.45) \text{ ELSE } 0$$

$$\text{Age} = 5$$

{calculated concentrations of toluene}

$$Cart = (Qpu * Cvpu + Qbr * Cvbr) / Qtot$$

$$Cvf = Af / (Vf * Pf)$$

$$Cvl = Al / (Vl * Pl)$$

$$Cvm = Am / (Vm * Pm)$$

$$Cvrg = Avrg / (Vrg * Prg)$$

$$Cvpu = Apu / (Vpu * Ppu)$$

$$Cvbr = Abr / (Vbr * Pbr)$$

$$Cvtot = (Ql * Cvl + Qf * Cvf + Qm * Cvm + Qvrg * Cvrg) / Qpu$$

$$Cvipu = (Qalv * Cair + Qpu * Cvtot) / ((Qalv / Pb) + Qpu)$$

$$Cexh = Cvipu / Pb$$

{calculated concentrations of xylene}

$$CBart = (Qpu * CBvpu + Qbr * CBvbr) / Qtot$$

$$CBvf = ABf / (Vf * PBf)$$

$$CBvl = ABl / (Vl * PBl)$$

$$CBvm = ABm / (Vm * PBm)$$

$$CBvrg = ABvrg / (Vrg * PBvrg)$$

$$CBvpu = ABpu / (Vpu * PBpu)$$

$$CBvbr = ABbr / (Vbr * PBbr)$$

$$CBvtot = (Ql * CBvl + Qf * CBvf + Qm * CBvm + Qvrg * CBvrg) / Qpu$$

$$CBvipu = (Qalv * CBair + Qpu * CBvtot) / ((Qalv / PBb) + Qpu)$$

$$CBexh = CBvipu / PBb$$

{differential equations for toluene uptake and metabolism}

$$d/dt(Apu) = Qpu * (Cvipu - Cvpu)$$

$$d/dt(Abr) = Qbr * (Cart - Cvbr)$$

$$d/dt(Al) = Ql * (Cart - Cvl) - Vmax1 * Cvl / (Km * (1 + CBvl / K2i) + Cvl)$$

$$\mathbf{d/dt(Af) = Qf*(Cart - Cvf)}$$

$$\mathbf{d/dt(Am) = Qm*(Cart - Cvm)}$$

$$\mathbf{d/dt(Avrg) = Qvrg*(Cart - Cvrg)}$$

{differential equations for xylene uptake and metabolism}

$$\mathbf{d/dt(ABpu) = Qpu*(CBvipu - CBvpu)}$$

$$\mathbf{d/dt(ABbr) = Qbr*(CBart - CBvbr)}$$

$$\mathbf{d/dt(ABl) = Ql*(CBart - CBvl) - Vmaxl2*CBvl/(Km2*(1 + Cvl/Ki) + CBvl)}$$

$$\mathbf{d/dt(ABf) = Qf*(CBart - CBvf)}$$

$$\mathbf{d/dt(ABm) = Qm*(CBart - CBvm)}$$

$$\mathbf{d/dt(ABvrg) = Qvrg*(CBart - CBvrg)}$$

{amount of toluene metabolized in liver, AUCs in blood and liver}

$$\mathbf{d/dt(Ametl) = Vmaxl*Cvl/(Km*(1 + CBvl/K2i) + Cvl)}$$

$$\mathbf{d/dt(AUCVtot) = Cvtot}$$

$$\mathbf{d/dt(AUCvl) = Cvl}$$

{amount of xylene metabolized in liver, AUCs in blood and liver}

$$\mathbf{d/dt(ABmetl) = Vmaxl2*CBvl/(Km2*(1 + Cvl/Ki) + CBvl)}$$

$$\mathbf{d/dt(AUCBVtot) = CBvtot}$$

$$\mathbf{d/dt(AUCBvl) = CBvl}$$

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Appendix F: Estimating Human Equivalent Concentrations Using the U.S. EPA Default Approach

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Appendix F. Estimating Human Equivalent Concentrations Using the U.S. EPA Default Approach

F.1 Estimating Human Equivalent Concentrations Using the U.S. EPA Default Approach

The United States Environmental Protection Agency (U.S. EPA) Human Equivalent Concentration (HEC) approach (U.S.EPA, 1994a) is designed to adjust the dose in an animal inhalation experiment to the dose that a human would receive at the same air concentration. The adjustment is based on some of the physiological differences between humans and animals. The Office of Environmental Health Hazard Assessment has recommended the necessary physiological parameters for children from the literature needed to adjust the dose in an animal inhalation experiment to the dose that children would receive at the same air concentration.

The U.S. EPA HEC approach was initially adopted by OEHHA for derivation of chronic inhalation Reference Exposure Levels (RELs). The 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). For both the U.S. EPA Reference Exposure Concentrations (RfCs) and earlier OEHHA chronic RELs, the U.S. EPA default HEC approach was used when more data-intensive methods and specific parameters were unavailable.

The U.S. EPA HEC methods are presented in detail in U.S. EPA (1994a) and will be briefly reviewed here (Section F.1). Modifications to the U.S. EPA method developed by OEHHA to incorporate child-specific parameters are also described (Section F.2).

The U.S. EPA HEC method assumed that interspecies toxicokinetic differences were adequately accounted for by the method and thus the value of the interspecies uncertainty factor (UF_A) was reduced from 10 to $\sqrt{10}$. However, the U.S. EPA HEC procedure deals only with deposition of the original material. It does not consider interspecies differences in distribution of the parent compound after absorption into the respiratory system, in metabolism, or in the distribution of metabolites. The present guidance therefore regards this procedure as providing only a partial estimate of toxicokinetic differences, and an additional uncertainty factor of at least 2 is recommended (*i.e.* the full value of UF_A would be 6 if, as is most often the case, there is no reduction of the toxicodynamic component of interspecies uncertainty). A larger uncertainty factor to account for remaining toxicokinetic differences may be warranted in special cases where evidence indicates a larger interspecies toxicokinetic difference (with humans being the more sensitive species).

F.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:

$$RGDR = (MV_a/MV_h) / (SA_a/SA_h)$$

Default lung surface area estimates presented by U.S. EPA (1994a) are used (Table F.1.1).

TABLE F.1.1. DEFAULT LUNG SURFACE AREA ESTIMATES

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

U.S. EPA, 1994a

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 (1994a). Intercept (b_0) and slope (b_1) values are presented in Table F.1.2.

TABLE F.1.2. 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

F.1.2 Gases with Systemic Effects

Gases leading to systemic health effects were calculated using the default assumptions used by the 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:

$$\text{RGDR} = (H_{b/g})_A / (H_{b/g})_H$$

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

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 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 $\text{RGDR} = 1$ 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.

F.1.3 Particulates with Respiratory Effects

The U.S. EPA HEC method for particulates (U.S.EPA, 1994a) estimates fractional deposition in different lung regions for both animal species and humans, and calculates the regional deposited dose ratio (RDDR) as the ratio of animal fractional deposition to human fractional deposition. Fractional deposition is assumed to be dependent on minute volume, mass median aerodynamic diameter (MMAD), geometric standard deviation (σ_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 σ_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 F.1.3):

$$\text{Flow rate (Q)} \approx \text{MV} / 30$$

$$x = \text{MMAD}^2 \times Q$$

$$\text{DE} = 1 / (1 + e^{\alpha + \beta \log_{10} x})$$

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

U.S. EPA RDDR software (U.S. EPA, 1994a) has been used to calculate RDDR and HEC for OEHHA RELs for particulates with respiratory effects. Parameters used include experimentally-determined values for the particle distribution, characterized by the mass median aerodynamic diameter (MMAD) and σ_g , the experimental species, and experimentally-determined or

estimated body weights. Minute volumes are estimated from body weights and default estimates of lung surface areas were used. Deposition and RDDRs are estimated for different lung regions.

TABLE F.1.3. 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

F.2 Human Equivalent Concentration Calculation for Children

OEHHA examined differences related to postnatal development of the lung, including such factors as differences in respiratory frequency, minute volume, lung surface area, lung deposition, and lung compliance. We also noted other factors such as mouth vs. nasal breathing habits and differences in physical activity. Different scenarios can lead to somewhat different results, but, in general, most differences between children and adults are no greater than several-fold in magnitude. The patterns of postnatal development indicate that susceptibility may change throughout childhood, and exposure during the first year of life may be of special concern.

OEHHA compares the human adult physiological and anatomical parameters used by U.S. EPA with the same parameters for children. We then examine the difference that the use of these child specific parameters would make in the HEC calculations. We thus determine if the HEC adjustment to a NOAEL derived from an animal study is protective of children.

F.2.1 Respiratory Differences between Children and Adults

Various factors can affect particle deposition. The respiratory tract is often considered to consist of three anatomically and functionally distinct units: (a) the extra-thoracic (ET - from the mouth and nose to the larynx); (b) the tracheo-bronchial (TB - from the larynx through the conducting airways; and (c) the alveolar (AL - the gas exchange zone). In general, more serious pollution-related health outcomes are related to effects in the TB and AL regions. The patterns of particle deposition in the respiratory tract do not, however, correspond well to the categories used to classify particles (PM₁₀, fine (PM_{2.5}) and coarse (PM₁₀ - PM_{2.5}) fractions). Generally, larger particles demonstrate a greater fractional deposition in the ET and upper TB areas, while smaller particles show greater deposition in the deep lung (lower TB and AL). These regional patterns reflect principally the mechanisms of deposition that differentially influence particles by size.

Mechanisms of nonfibrous particle deposition include: (i) gravitational settling, for particles more dense than air; (ii) impaction on the wall of a bronchus or bronchiole, due to inertia maintained when the airstream changes direction at an anatomical bend or bifurcation; (iii) diffusion related to Brownian motion; and (iv) electrostatic attraction, which is generally considered of lesser importance than the other three. Settling and diffusion are more important for particles less than about 3 μm , while inertial impaction generally affects larger particles, particularly in the ET and upper TB area (Foster, 1999). For ultrafine particles (with diameters $<0.1 \mu\text{m}$ in diameter), diffusion represents the dominant mode of deposition.

The ET region and especially the nose effectively filter out a large fraction of inhaled particles, mainly those above 1 μm in diameter, and also ultrafine particles. In general, inertial impaction predominates in the ET region, so increasing particle size and increasing flow rates will tend to increase particle deposition. However, fractional deposition of ultrafine particles (inhaled at flow rates between 5.9 and 22 liters/min) in the nose has also been reported to be very high (in excess of 93%) (Swift and Strong, 1996).

In the TB and AL areas, increased depth of breathing tends to enhance the deposition of fine particles, while an increased respiratory rate has the opposite effect (Foster, 1999). Exercise and increased respiratory rates also tend to result in greater deposition in larger, central airways, and less in the AL region (Foster, 1999). Using inert particles 1, 3, and 5 μm in diameter, Kim et al. (1996) showed that, even in healthy adults, there is striking heterogeneity of deposition patterns, with airway surface doses 2 to 16.6 times greater in large airways and up to 4.5 times greater in small airways than in the alveolar region for larger (3 and 5 μm) particles. A similar, but less pronounced, pattern was also observed for particles of 1 μm diameter.

Among healthy adults, airway caliber (measured by specific airway resistance) appears to be an important determinant of particle deposition, with a generally inverse relationship between airway diameter and deposition efficiency (Bennett et al., 1996). This may result from the decreased cross-sectional distance that particles have to traverse (by inertial velocity, gravitational settling, or diffusion) before depositing. Women tended to display a greater deposition fraction than men of 3-5 μm particles (perhaps because of a smaller respiratory tract anatomy overall), particularly in the ET and TB regions (Kim and Hu, 1998).

Individuals with asthma and chronic obstructive lung disease experience greater fractional deposition of fine particles (1 μm in diameter) than individuals with healthy, normal lungs, with the degree of particle retention roughly proportionate to the severity of airway obstruction (Kim and Kang, 1997). Anderson et al. (1990) showed a similar increase in deposition efficiency of fine and ultrafine particles, defined here as those with 0.02 – 0.24 μm in diameter, in several individuals with asthma and COPD relative to healthy subjects.

In such individuals, one can observe focal hyperdeposition of particles, often in sites of airflow limitation in central airways, even when nominal ambient particle concentrations are relatively low (Foster, 1999). Airway hyperresponsiveness, which is one of the hallmarks of asthma, is likewise associated with enhanced regionalization of deposition to the central airways (Foster, 1999). The work of Kim and Kang (1997) indicates that such dose amplification can occur because individuals with obstructive lung disease: (1) ventilate only a portion of their lungs, (2) experience increased deposition compared with healthy individuals, and (3) if symptomatic, tend

to have increased minute ventilation. Assessing these factors together, Kim and Kang (1997) estimate that such individuals may have more than three-fold greater total lung deposition than healthy subjects, with this enhanced deposition concentrated in small areas of the lung.

One group of investigators modeled short-term particle deposition in various regions of the respiratory tract using a dosimetry model developed by the International Committee on Radiological Protection (Snipes et al., 1997). They identified large differences in deposition between the ET, TB and AL regions. Daily deposition of all particle sizes was estimated to be greater (by one to three orders of magnitude) in the TB compared with the AL region.

Results of the deposition modeling forming the basis for the report by Snipes et al. (1997) are presented in slightly different form in the 1996 U.S. EPA Criteria Document for particulate matter (U.S. EPA, 1996; vol II, chapter 10). For normal adult males in the general population exposed to a Phoenix-like aerosol (tending to coarse mode), the model predicted daily deposition of 2 and 6 $\mu\text{g}/\text{day}$ of fine and coarse mode particles, respectively, in the bronchi, 3 (fine) and 4 (coarse) $\mu\text{g}/\text{day}$ in the bronchioles, and 17 (fine) and 12 (coarse) in the alveolar region. Particle doses were estimated to increase substantially in all zones of the lower respiratory tract among “mouth breathers (U.S. EPA, 1996). Higher doses were also predicted to occur as a result of light or heavy work (involving increased breathing rates). Somewhat lower doses were estimated to result from exposure to a Philadelphia-like aerosol, which is characterized by a particle distribution favoring smaller particles. The model employed in these deposition exercises is based on average doses and does not take into account the potential impacts of age, gender, disease states or inter-individual variations in anatomy, ventilation patterns, short-term peak exposures, and so forth.

The human respiratory system undergoes developmental changes throughout childhood. Full lung maturity may not occur until the age of 20 or 25 (Yu and Xu, 1987).

The structural development of the respiratory system varies markedly among species (Mauderly, 2000). Humans as well as rabbits and dogs have developed alveoli at birth, but these structures have not yet developed their mature form, and undergo septal wall thinning and capillary fusion postnatally. Humans form 80% of alveoli postnatally (Plopper and Fanucchi, 2004). Human alveolar multiplication can continue until about 8 years of age (Boyden, 1971). Development of intra-acinar vessels also occurs postnatally (Boyden, 1971). Guinea pigs and sheep have morphologically mature alveoli at birth that only increase in number and size after birth. At birth rats, mice, and hamsters have immature lungs that lack developed alveoli. Thus different species are at markedly different stages of development and may differ in susceptibility to toxicants during the early postnatal period.

There are significant anatomic and physiological differences between the developing lungs of children and those of mature adults (Snodgrass, 1992). These include differences in the size and shape of the conducting airways, the number and orientation of physiologically active gas exchange regions, and ventilation rates. Though the basic structure of the airways is established *in utero*, most of the alveoli ($\approx 85\%$) develop in infancy and early childhood. Alveolar multiplication coincides with incorporation of elastin and collagen in the lung, which are responsible for the mature lung's mechanical properties (Lipsett, 1995). With growth and development other patterns of anatomical differences emerge. For instance, TB airways increase

in diameter and length until adulthood. Lung volume expands disproportionately in relation to the increasing number of alveoli during somatic growth, indicating enlargement of individual alveoli (Murray, 1986).

Because of differences in anatomy, activity, and ventilation patterns, children are likely to inhale and retain larger quantities of pollutants per unit body surface area than adults (Adams, 1993). Phalen et al. (1985) developed a model incorporating airway dimensions measured in lung casts of people (aged 11 days to 21 years) and predicted that particle deposition efficiency would be inversely related to body size, which would tend to accentuate differences in exposure related to activity and ventilation patterns. Phalen et al. (1985) estimated that 5 micron diameter particles will deposit in a 6-fold higher dose per kilogram body weight in the tracheobronchial region in a resting newborn compared to a resting adult. Corroborative evidence for this was provided by Oldham et al. (1997), who found that in models of the proximal TB airways (i.e., the trachea and the first two bronchial bifurcations) of 4- and 7-year-old children and an adult, deposition efficiencies for radiolabelled particles 1.2, 4.5, 9.7 and 15.4 μm in median aerodynamic diameter were greater in the child models in almost all cases. As expected, particle deposition efficiency increased markedly with increasing particle size in this model system. For instance, in the model of the four-year-old child, the deposition efficiency increased from 0.3% to 10.7% when the smallest and largest particle sizes were used, respectively.

Inhalation experiments comparing particle deposition patterns in children and adults have produced somewhat inconsistent results. Schiller-Scotland et al. (1994) reported greater fractional deposition in healthy children, aged 3 – 14 years, compared with adults, when breathing 1, 2 or 3 μm particles spontaneously through a mouthpiece. The differences were greater with the larger particles. However, as noted by the authors, these children were breathing more deeply than expected, which is a common tendency when breathing through a mouthpiece. This propensity may result in greater time-dependent deposition of fine particles (by sedimentation and diffusion). Schiller-Scotland et al. (1994) also noted that, among the older children (mean age = 10.9 years) who were capable of controlled breathing in time with a metronome, particle deposition was inversely related to body height, so that the shorter children demonstrated greater fractional deposition (for 1 and 2 μm particles, the only categories analyzed in this manner). In contrast, Bennett and Zeman (1998) found no significant differences between children (7 – 14 yr), adolescents (14 to 18 yr), and young adults (19 – 35 yr) in deposition (measured as deposition fraction or rate) of 2 μm particles during spontaneous breathing at rest. Unlike the study by Schiller-Scotland et al. (1994), this investigation tailored the participants' mouthpiece breathing patterns to those measured during unencumbered breathing, in order to control for the tendency to breathe more deeply through a mouthpiece. Another difference between the study by Bennett and Zeman (1998) and that by Schiller-Scotland et al. (1994) is that the former did not include very young children, who would have had difficulty in mimicking their normal breathing patterns while using a mouthpiece. However, Schiller-Scotland et al. (1994) found that older children (mean age = 10.9 years) as well as the younger ones (mean age = 5.3 years) also showed increased fractional particle deposition relative to adults.

Children demonstrate lower absolute minute ventilation at rest than adults, despite having higher breathing rates. Relative to lung volume, however, children demonstrate a higher minute ventilation than adults. Thus, Bennett and Zeman (1998) noted that children tended to have a somewhat greater normalized deposition rate (by about 35%) than the combined group of

adolescents and adults, suggesting that children at rest would receive higher doses of particles per unit of lung surface area than adults. This tendency might be additionally enhanced by activity patterns, as children spend more time than adults in activities requiring elevated ventilation rates. However, it is unknown whether flow-dependent deposition mechanisms operative at higher ventilation rates in children would offset the decreases that would occur in time-dependent mechanisms (sedimentation and diffusion). If this offset does occur, then particle deposition would likely be shifted more towards the larger, more central airways, which would tend to increase the dose per surface area in children versus adults (Bennett and Zeman, 1998).

Investigators using models from the ICRP reported that the dosimetry of particles for the 3 month old is different than the adults by region of the respiratory tract (Ginsberg et al., 2005b). The model showed two to fourfold greater deposition of particles in the pulmonary region especially in the submicron size range. In the bronchiolar region, adults had higher deposition rates than the 3 month old lung. Particle deposition was similar for adults and 3 month old children in the extrathoracic and tracheobronchiolar region.

The above studies suggest that children may experience proportionately greater particle deposition than adults. It is also possible that, especially in very young children, immature respiratory defenses may result in lower clearance rates in relation to those observed in adults. For instance, Sherman et al. (1977) reported that alveolar macrophages of neonatal rabbits (1 day old) ingested significantly fewer bacteria than older animals (7 days). To the extent that this phenomenon may also apply across species and to nonbiological particles, the immaturity of the neonatal human lung may result in slower and less complete particle clearance.

In summary, there is substantial evidence to conclude that childhood exposures may differ significantly from those experienced by adults. In some cases doses received by children may be substantially greater than those received by adults. However, the differences may be complex and change somewhat over the period of lung development.

F.2.2 Calculation of Adult and Child HECs

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

Minute volume (volume inhaled per minute) is calculated as the product of tidal volume and respiratory frequency. Using empirical formulas for humans,

$$\text{Tidal volume (cm}^3\text{)} = 21.7 + 35.15t - 0.64 t^2$$

and

$$\text{Respiratory frequency (per minute)} = 15.17 / (0.25t + 0.5) + 11.75,$$

where t is age in years (Hofmann, 1982). Minute volumes (MV) in L/min for five animal species were estimated from body weights (see Section 1.1 and Table 2).

F.2.2.1 Gases with Extrathoracic Effects

Many pollutants fall into the category of gases with extrathoracic effects. These include ammonia, chlorine, formaldehyde, hydrogen chloride, and hydrogen sulfide. Data to estimate child nasopharyngeal surface area are very limited. A simple assumption is that growth of the extrathoracic surface area is proportional to body weight, body surface area, or overall lung surface area.

The approach applied here uses estimates of head volume derived from head growth charts to estimate relative extrathoracic surface area. It assumes that overall extrathoracic surface area is proportional to the surface area of a horizontal plane through the nasopharyngeal region. Based on these assumptions, children are predicted to have lower extrathoracic exposures than adults (Table F.2.1).

TABLE F.2.1. RELATIVE MINUTE VOLUME (MV) TO SURFACE AREA (SA) RATIOS FOR PULMONARY, TRACHEOBRONCHIAL, AND EXTRATHORACIC SPACES IN CHILDREN

A. Chronic Exposure

Age Range (years)	Pulmonary Relative MV/SA	Tracheobronchial Relative MV/SA	Extrathoracic Relative MV/SA
0 to 1	3.0	0.5	0.5
1 to 2	2.0	0.5	0.5
2 to 4	1.5	0.6	0.6
4 to 8	1.5	0.8	0.7
8 to 15	1.3	0.9	0.9
15-25	1.1	1.0	1.0

B. Acute Exposure

Age (years)	Pulmonary Relative MV/SA ¹	Tracheobronchial Relative MV/SA ²	Extrathoracic Relative MV/SA ³
0	3.8	0.5	0.5
1	2.2	0.5	0.5
2	1.8	0.5	0.5
4	1.6	0.7	0.6
8	1.4	0.8	0.8
15	1.2	1.0	0.9

¹Pulmonary calculations based on the lung growth model of Yu and Xu (1987).

²Tracheobronchial calculations based on the data of Phalen *et al.* (1985). Calculations are based on flux per surface area in accordance with the U.S. EPA HEC methodology, and do not take into account increased absorption and greater particle deposition due to much greater relative tracheobronchial surface area in children. For example, Phalen *et al.* (1985) predicted a 6-fold increased tracheobronchial deposition of 5-micron particles in newborns compared with adults.

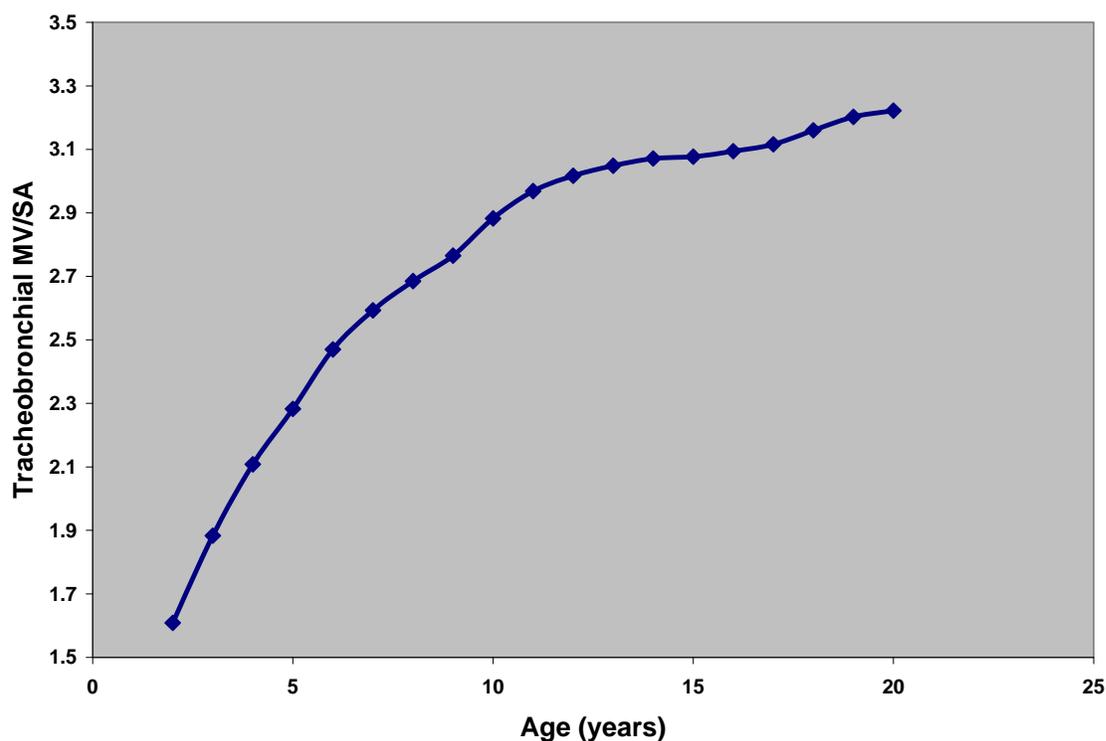
³Extrathoracic calculations based on head growth data of Tanner in Dattani and Preece (1978). The increase in extrathoracic surface area is presumed to be proportional to the increase in head volume.

Using the HEC model, the observed concentration divided by the appropriate relative MV/SA factor may be used as an estimate of equivalent childhood exposure. Thus in terms of relative MV/SA, pulmonary effects are predicted to be greater in children, whereas tracheobronchial and extrathoracic effects are predicted to be less in children. The approach does not take into account other differences between adults and children, such as differences in deposition, mouth breathing, and susceptibility.

F.2.2.2 Gases with Tracheobronchial Effects

Other pollutant gases, such as chlorine dioxide and toluene diisocyanate, have primarily tracheobronchial effects. Good data are available to estimate child tracheobronchial surface areas. Figure F.2-1 below depicts changes in the relative ratio of minute volume to tracheobronchial surface area as children age. This approach results in lower tracheobronchial regional gas doses for children than adults (Table F.2.1).

FIGURE F.2-1. CHANGES IN MINUTE VOLUME/TRACHEOBRONCHIAL SURFACE AREA WITH AGE.



F.2.2.3 Gases with Pulmonary Effects

For gases with pulmonary effects, an opposite result is obtained. There are good data to estimate child pulmonary surface areas. As shown in Figure F.2-2, the number of alveoli increases dramatically from birth to age 8. Figure F.2-3 depicts changes in the relative ratio of minute volume to tracheobronchial surface area as children age. This approach results in higher regional gas doses for children than adults (Table F.2.1). This is most pronounced in newborns and infants.

FIGURE F.2-2. INCREASE IN NUMBER OF ALVEOLI FROM BIRTH TO AGE 8.

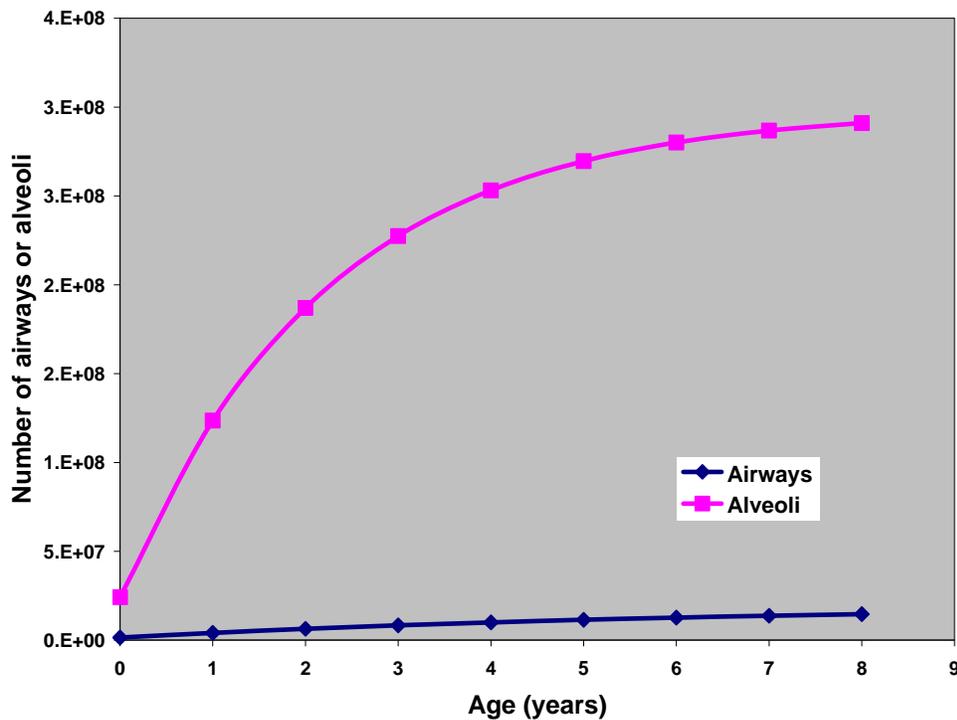
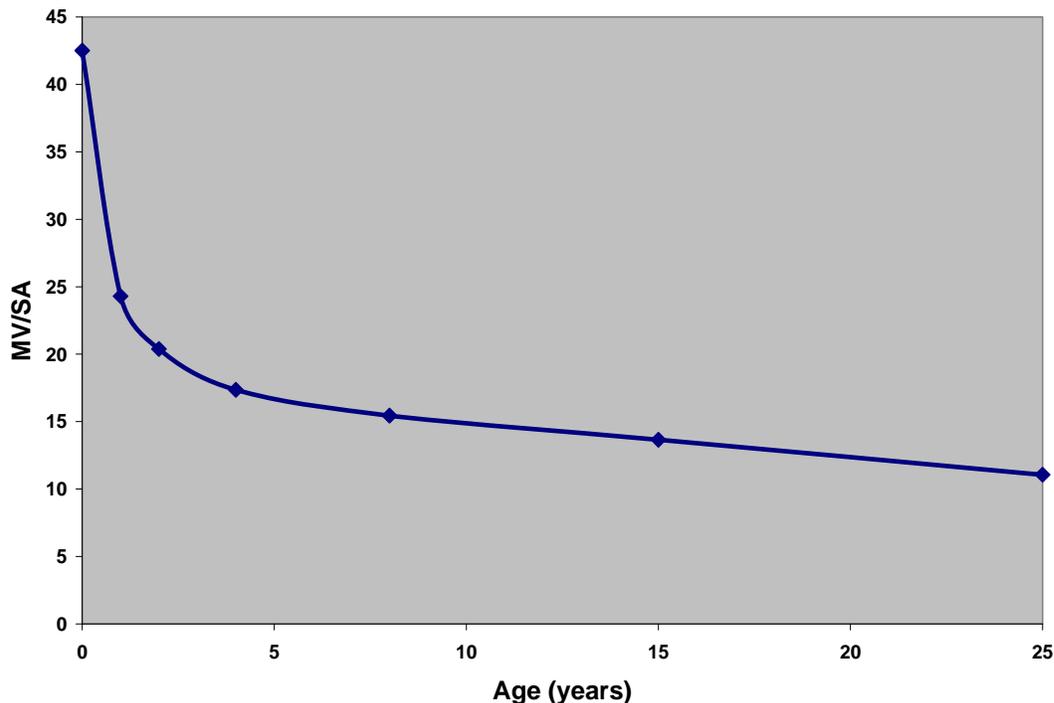


FIGURE F.2-3. DECLINE IN MINUTE VOLUME/TRACHEOBRONCHIAL SURFACE AREA WITH AGE.

F.2.2.4 Vapors with Systemic Effects

The RGDR calculation for systemic effects assumes:

$$\text{RGDR} = \lambda_{\text{animal}} / \lambda_{\text{human}}$$

where λ is the blood to air partition coefficient.

Experimental data for the blood to air partition coefficient were used. A default blood to air partition coefficient value of 1 was used where chemical-specific data were unavailable. Appropriate methods to account for differences between adults and children have not been developed.

F.2.2.5 Particulates/Aerosols/Mists

Deposition efficiency differs as a function of age, as do minute volume, surface area, and body weight. Total deposition fractions tend to be higher in children than adults (Oldham et al., 1997). Deposition fractions of 2 μm particles were 73% in a 7 month old and 38% in an adult (Musante and Martonen, 2000). Children under 8 years of age have the highest deposition fractions. Both tracheobronchial and pulmonary deposition fractions are higher in children. Children may receive a 3-fold higher deposited dose than adults.

Tracheobronchial deposition is inversely proportional to age. Alveolar deposition is maximal at age 4 to 6 as a result of later alveolar development. Aerosol deposition in the nose is also predicted to be greater in children than in adults (Phalen et al., 1989).

As noted earlier, the minute volume to respiratory surface area may be higher or lower for children relative to adults, depending on the region of interest. Thus the net relative RDDR may increase or offset the effect of increased deposition in children, depending on the region of interest.

F.3 Conclusions

Differences between children and adults for relative minute volume to surface area ratios are 4-fold or less. Such differences may be already accounted for in many cases by the 10-fold intraspecies uncertainty factor to protect sensitive subpopulations. There may be cases, however, where other factors lead to greater exposures or susceptibility among children. In these cases, children may be affected at concentrations more than 10-fold lower than concentrations affecting adults. Increased deposition among children can be addressed by child-specific deposition modeling. Known differences in susceptibility should be addressed separately.

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Appendix G. Value of the Haber's Law Exponent (n) for various gases and vapors for acute RELs developed using OEHHA (1999) procedures

TABLE G1. VALUE OF THE HABER'S LAW EXPONENT (*n*) FOR VARIOUS GASES AND VAPORS FOR ACUTE RELS¹

Chemical	<i>n</i>	Species/Effect (site of action)	References, Comments
Acrolein	1.2	rat/lethality (local irritant)	U.S. EPA (1992a; U.S.EPA, 1992b) ²
Acrylonitrile	1.1	rat/lethality (systemic)	(Dudley and Neal, 1942; Appel et al., 1981) ³
Allyl chloride	0.5	rat/lethality (local irritant)	Adams <i>et al.</i> (1940) ²
Ammonia	4.6	Human/irritation	Rosenbaum <i>et al.</i> (1993)
	2.02	rat/lethality (local irritant)	Appelman <i>et al.</i> (1982)
Arsine	2.2	rat/lethality (systemic)	IRDC (1985) ² for 0.5 to 1 hr (n dependent on exposure duration)
	1.0	rat/lethality (systemic)	IRDC (1985) ² for 4 hr to 1 hr (n dependent on exposure duration)
	2	mice/lethality (systemic)	Levy (1947)
Benzene	2	not given	AICE (1989)
Bromine	2.2	mice/lethality (local irritant)	Bitron & Aharoson (1978) ³
Carbon monoxide	1	not given	AICE (1989)
Carbon tetrachloride	2.8	rat/lethality (systemic)	Adams <i>et al.</i> (1952) ³
Chlorine	2.8	rat/lethality (local irritant)	Zwart & Woutersen (1988) ² for 0.5 hr to 1 hr (n dependent on exposure duration)
	1.0	rat/lethality (local irritant)	Zwart & Woutersen (1988) ² for 4 hr to 1 hr (n dependent on exposure duration)
	1.3	mouse/lethality (local irritant)	Zwart & Woutersen (1988) ²
	3.5	mouse/lethality (local irritant)	Bitron & Aharoson (1978) ³
Chlorine pentafluoride	2	rat, mouse, dog, monkey/lethality (local irritant)	Darmer <i>et al.</i> (1972) ³
Crotonaldehyde	1.2	rat/lethality (local irritant)	Rinehart (1967) ³
Dibutyl hexamethylene-diamine	1	rat/lethality (local irritant)	Kennedy & Chen (1984) ³
1,2-dichloro-ethylene	2	(not applicable)/lethality (systemic)	U.S.EPA (1996), based on the mid-point range of n values from lethality data of ³
Dimethyldichloro-silane	2	(not applicable)/lethality (local irritant)	U.S.EPA (1996), based on the mid-point range of n values from lethality data of ³
Ethylene dibromide	1.2	rat/lethality (systemic)	(Rowe <i>et al.</i> , 1952b) ³
Ethylene imine	1.1	rat, guinea pig/lethality (local irritant)	(Carpenter <i>et al.</i> , 1948) ³
Fluorine	1.9	rat/lethality (local irritant)	U.S.EPA (1996), derived from LC ₅₀ data of Keplinger & Suissa (1968)
	1.8	mouse/lethality (local irritant)	U.S. EPA (1996), derived from LC ₅₀ data of Keplinger & Suissa (1968)
	1.6	guinea pig/lethality (local irritant)	U.S.EPA (1996), derived from LC ₅₀ data of Keplinger & Suissa 1968)
Formaldehyde	2	not given	AICE (1989)

Chemical	n	Species/Effect (site of action)	References, Comments
Hydrazine	2	(not applicable)/lethality (systemic)	U.S.EPA (1996), based on the mid-point range of n values from lethality data of ³
Hydrogen chloride	1	rat, mouse/lethality (local irritant)	Darmer (1972) ³
	1.5	rat/lethality (local irritant)	Hartzell & Johnson (1985) ²
Hydrogen cyanide	2.7	numerous species/lethality (systemic)	Barcroft (1931) ³
Hydrogen fluoride	2	rabbits, guinea pigs/ lethality (local irritant)	Machle (1934) ³
Hydrogen fluoride (low humidity)	1	rat/lethality (local irritant)	Haskell Lab. (1988) ²
Hydrogen sulfide	2.2	cat, rabbit/lethality (systemic/local irritant)	Lehmann (1892) ³
	8.2	lethality (systemic/local irritant)	Arts (1989)
Methyl bromide	4.0	severe morbidity (systemic/local irritant)	Pharmaco: LSR, (1994) as cited in DPR (2004) ² , DPR (1996)
	1	not given	AICE (1989)
Methylene chlorobromide	1.6	rat/lethality (systemic)	Torkelson (1960) ³
Methyl hydrazine	1.0	squirrel monkey/lethality (systemic and local irritant)	Haun (1970) ²
	1.0	dog/lethality (systemic and local irritant)	Haun (1970) ²
Methyl isocyanate	1.1	human/eye irritation	Mellon Institute (1963) ²
	0.5	rat/lethality (local irritant)	Kimmerle & Eben (1964) ²
	0.7	rat/lethality (local irritant)	DOW Chemical (1990) ²
Methyl mercaptan	2	(Not applicable)/lethality (systemic and local irritant)	U.S.EPA (1996), based on the mid-point range of n values from lethality data of ³
Methyl t-butyl ether	2.0	lethality (systemic)	Snam Progetti (1980) as cited in ten Berge et al., (1986) ³
Nitrogen dioxide	3.5	guinea pig, mouse, dog, rat, rabbit/lethality (local irritant)	Hine <i>et al.</i> , (1970) ³
Nitric acid	3.5	not applicable (local irritant)	U.S.EPA (1996), based on NO ₂ from Hine <i>et al.</i> (1970)
Perfluoroisobutylene	1.2	rat/lethality (local irritant)	Smith <i>et al.</i> (1982) ³
Phosgene	1	lethality (local irritant)	Rinehart & Hatch (1964)
Propylene oxide	2.2	rat/lethality (local irritant)	Rowe <i>et al.</i> (1956) ²
	1.5	guinea pig/lethality (local irritant)	Rowe <i>et al.</i> (1956) ²
Sulfur dioxide	1	not given	AICE (1989)
Tetrachloroethylene	2.0	rat/lethality (systemic)	Rowe <i>et al.</i> (1952a) ³
Toluene	2.5	not given	AICE (1989)
Trichloroethylene	0.8	rat/lethality (systemic)	Adams <i>et al.</i> (1951) ³

¹ developed using procedures specified in OEHHA (1999a). ²derived by OEHHA.³derived by ten Berge (1986).

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Appendix H. Target Organs or Systems used in Acute, 8-Hour and chronic Hazard Index Calculations

The specific examples given below are those used in current REL derivations (as of April 2008). Obviously this list of specific endpoints is not exclusive, and may be augmented or amended as new RELs are developed. In order for the acute and chronic REL HI target organs to be consistent, developmental and reproductive, which were previously combined, have been separated into two categories. New target organ categories may need to be added, based on the toxicological data used to develop additional RELs.

TABLE H1. EXAMPLES OF TARGET ORGANS OR SYSTEMS USED IN ACUTE, 8-HOUR AND CHRONIC HAZARD INDEX CALCULATIONS

Hazard Index target organ categories	Specific health effects currently used in deriving at least one acute REL	Specific health effects currently used in deriving at least one chronic REL
Hematological System	Hemolysis; anemia; platelet abnormalities; adverse effects on hematopoietic stem cells	Lowered red and white blood cell counts
Cardiovascular System	Aggravation of angina	Elevated carboxyhemoglobin levels
Nervous System	Abnormal electroencephalograph (EEG) results; altered performance on neurobehavioral or neuropsychological tests; lightheadedness; clinical neurological exam; headache	Abnormal EEG results; astrogliosis; altered performance on neurobehavioral tests; tremor; lightheadedness; memory disturbances; headache
Eyes	Irritation; histological changes to eye tissue	Irritation of eyes
Alimentary Tract	Hepatotoxicity; nausea; vomiting	Hepatotoxicity; kidney lesions; urinary porphyrins; liver enzymes
Immune System	Abnormal lymphocyte proliferation; impaired host resistance to infection	Macrophage hyperplasia
Reproductive	Anovulation; decreased ovulation, preimplantation loss; altered copulatory behavior; azoospermia; oligospermia; spontaneous abortion	Testicular degeneration

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Hazard Index target organ categories	Specific health effects currently used in deriving at least one acute REL	Specific health effects currently used in deriving at least one chronic REL
Developmental	Fetotoxicity; teratogenicity, intrauterine growth retardation; altered behavior in offspring	Fetotoxicity; teratogenicity; developmental anomalies
Respiratory System	Irritation of nose and throat; increased mucus production; histological changes in nasal epithelium; histological changes in lung tissue; lung function following inhalation challenge	Irritation of nose and throat; hyperplasia of epithelium or nasal mucosa; histological changes in lung tissue; bronchiolar fibrosis; decreased pulmonary function
Skin	Irritation of skin	Potential use in eight-hour and chronic RELs, but no current examples.
Physiological response to odors	Headache; nausea	Potential use in eight-hour and chronic RELs, but no current examples
Endocrine System	Potential use in acute and eight-hour RELs, but no current examples	Thyroid enlargement
General Toxicity (e.g., failure to gain weight; weight loss)	Potential use in acute RELs, but no current examples	Potential use in eight-hour and chronic RELs, but no current examples