# Meeting Materials
# For a Peer Consultation on a Draft Framework To Evaluate Child-Adult Differences in Inhalation Dosimetry of Gases: Application to Selected Systemically-Acting Volatile Organic Chemicals

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# 1.0 BACKGROUND

A number of scientific and policy initiatives beginning in the mid to late 1990s have resulted in increased attention to considerations of the risk to fetuses, infants, and children and consideration of how such risks should be evaluated. The U.S. EPA is explicitly mandated to consider fetuses, infants and children as potentially sensitive subpopulations. In 1995, EPA established an agency-wide policy that calls for consistent and explicit consideration of the risk to infants and children in all risk assessments and characterizations, as well as in environmental and public health standards (Memorandum from the Office of the Administrator, October 20, 1995). The Food Quality Protection Act (FQPA) of 1996 mandated that, in setting pesticide tolerances, an additional ten-fold margin of safety be applied to infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children, but noted that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." The Safe Drinking Water Act amendments of 1996 also stipulated that in establishing Maximum Contaminant Levels (MCLs) the Agency shall consider "the effect of such contaminants upon subgroups that comprise a meaningful portion of the general population (such as infants, children, pregnant women, the elderly, individuals with a history of serious illness or other subpopulations) that are identifiable as being at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population." On April 21, 1997, President Clinton signed an Executive Order (13045) that federal health and safety standards must include an evaluation of the potential risks to children in planned regulations.

Similar policies have been initiated in Europe and Canada to evaluate more fully the potential differences in risk from chemical exposure to children. For example, a recent report by the European Environment Agency (EEA) and the World Health Organization (WHO) identified policy priorities for protecting children's health from environmental hazards (EEA and WHO 2002). The European Union also recently announced a new initiative, **S**cience, **C**hildren, **A**wareness, EU **L**egislation and Continuous **E**valuation (SCALE), focusing on children. In

addition, Canada's Pesticide Management Regulatory Agency has developed a policy notice regarding children (Health Canada 2002), and the National Institute of Public Health and the Environment (RIVM) in the Netherlands has conducted research on pharmacokinetics of xenobiotics in children (de Zwart et al. 2002).[1]

These differences have led to research by a number of investigators comparing kinetic parameters in adults and children, and, where possible, comparing internal dose in adults and children. A number of studies have reviewed physiological and metabolic differences between adults and children (e.g., Renwick 1998; Ginsberg et al. 2002; Scheuplein et al. 2002; Wolterink et al. 2002; de Zwart et al. 2004; IPCS 2007). Determining the impact of these differences on internal dose is challenging. However, data on pharmaceuticals have been used to evaluate age-related differences in such parameters as clearance, half-life, area under the blood concentration-time curve (AUC) and blood concentration, and the resulting impact on internal dose (Renwick 1998; Renwick et al. 2000; Ginsberg et al. 2002, 2004; Hattis et al. 2003). These latter studies have concluded that the major differences are in the first six months of life, primarily in the first two months.

Hattis, Ginsberg, and colleagues have developed a substantial database of kinetic parameters for 44 chemicals (primarily pharmaceuticals), available at http://www2.clarku.edu/faculty/dhattis. This database has been used for a number of analyses describing variability of half-life with age and by metabolic enzyme class (e.g., CYP3A substrates, CYP1A2 substrates, etc.) (Ginsberg et al. 2002, 2004). These studies found that the average ratio of child:adult half-life for all substrates, and for most individual classes, was greater than 3 for premature neonates. The average ratio was also elevated for full-term neonates through about two months, depending on the substrate. The child half-life tended to be less than adult half-life in the six-month to two-

[1] The risk to adults and children could differ due to differences in exposure, toxicodynamics, or toxicokinetics. (Unless otherwise specified, the term *child* is used in this report to refer to the entire period between birth and attainment of physical and sexual maturity.) For example, differences in intake parameters or activity patterns (e.g., hand-to-mouth behavior in infants, children playing in dirt) can affect exposure. Toxicodynamic differences may result from windows of increased susceptibility in developing tissues. In addition, damage to developing tissue may manifest at a later stage in growth (de Zwart et al. 2002). Toxicokinetic differences may result from numerous age-related differences in absorption, distribution, metabolism, and excretion, and their resulting effect on internal dose of the active form of the chemical. These differences have been catalogued in numerous papers. This report focuses on the impact of toxicokinetic differences between adults and children.

year age range, with lower half-lives sometimes extending through 12 years, depending on the substrate.

These analyses, based primarily on pharmaceutical data, provide much useful information regarding the impact of age-related kinetic differences. However, there are a number of issues that need to be considered in extrapolating such data to environmental chemicals. Many of these issues have been described by Clewell et al. (2004). They include: (1) pharmaceuticals are usually water-soluble, while environmental chemicals are often lipophilic; (2) different metabolic systems may apply; (3) the parent is usually (though not always) the active agent for pharmaceuticals, while competing activation and detoxification reactions may be important for environmental chemicals; (4) pharmaceutical data are primarily for administration via the oral route; and (5) exposure to pharmaceuticals is usually at doses designed to cause an effect, meaning that it is at the upper end of the dose-response curve for therapeutic effectiveness, while exposure to environmental chemicals is typically at the low end of the dose-response curve. An additional factor is that much of the data collected on pharmaceuticals are based on half-life, and differences in half-life do not necessarily translate directly into differences in clearance (which is inversely related to AUC). Half-life needs to be corrected for volume of distribution to be related to clearance. While Ginsberg et al. (2002) concluded that differences in volume of distribution did not affect the elimination half-life for the drugs they studied, differences in volume of distribution may be more important for chemicals that are lipophilic, concentrate in other tissues, or bind significantly to plasma proteins.

To address these considerations, a number of analyses have been conducted with a focus on environmental chemicals. Age-specific metabolic and physiological data have been collected and collated in several studies (Renwick 1998; Hattis et al. 2003). PBPK models and other kinetic analyses (Haddad et al. 1999; Pelekis et al. 2001; Sarangapani et al. 2003; Ginsberg et al. 2004a; Clewell et al. 2004; Ginsberg et al. 2005; Price et al. 2003; Nong et al. 2006) and particle dosimetry models (Martonen et al. 2000; Ginsberg et al. 2005; Jarabek et al. 2005) have been used by several authors to evaluate age-related differences in kinetics. Consistent with results reported for pharmaceuticals (Renwick et al. 2000; Hattis et al. 2003), these authors found that the largest differences were in the first year of life. The largest differences were observed at the

earliest time point (1 month of age), and differences were generally in the range of two-fold or less by 1 year. This is consistent with the early immaturity and development of enzyme systems.

As part of a project of the International Life Science Institute (ILSI) on evaluating children's risk from exposure to environmental chemicals, Daston et al. (2004) developed a framework for assessing children's risk, ranging from problem formulation through analysis and risk characterization, and Ginsberg et al. (2004) presented a framework for considering toxicokinetic issues related to children's risk, highlighting a number of questions and issues that need to be considered.

The purpose of this current report is to build on the frameworks developed as part of the ILSI process. The framework presented here (Figure 1) presents an analytical approach for evaluating the relative tissue dosimetry in adults and children for inhaled gases. Case studies were conducted for systemic effects of gases under various metabolic scenarios to provide some perspective on the potential range of internal dose in children and adults for various combinations of physicochemical characteristics and mode of action. Illustrative analyses are also presented on relative dosimetry for chemicals that show significant age-related variability in enzyme capacity. To illustrate the application of the framework and demonstrate consistency with more data-intensive approaches, the results of these analyses were compared with the results obtained using PBPK modeling for chemicals with similar metabolic characteristics.

The framework presented here reflects the input from a peer consultation with an expert panel. The initial peer consultation on an early draft provided substantial input on the structure of the framework. Based on this input, additional analyses were conducted, and a second peer consultation is being held to consider the revised framework, including the bounding analyses and case studies conducted as part of verification of the framework.

The framework focuses on the dosimetric comparison, i.e., a comparison of the mean internal dose in adults and children. This information is useful both for analyses of individual chemicals, and to aid risk assessors in identifying the parameters and chemical characteristics that result in children receiving a higher (or lower) internal dose than adults. Such information can provide

useful perspective to individual chemical assessments, and can focus efforts for obtaining additional data and for more refined analyses to those cases and categories of chemicals where there is the greatest potential or likelihood of children being at greater risk. Although the focus is on mean dose, risk assessors and risk managers can use the dosimetry data, combined with information on variability, to evaluate the adequacy of default uncertainty factors for protecting children, or to determine if chemical-specific modifications to uncertainty factors are needed to adequately protect children. While there are a number of areas in which this initial framework can be enhanced and expanded, the intent is to provide a structure that highlights key issues and identifies some standard approaches. It is hoped that this report and framework will serve as a starting point for more in-depth analyses, and to focus generic and chemical-specific research on the key issues for addressing children's risk due to kinetic differences.

# 2.0 FRAMEWORK

## 2.1 Overview

Figure 1 presents the draft framework for evaluating age-related differences in inhalation dosimetry and the resulting impact on internal dose. This framework, as well as the associated analyses presented below, is designed to help the risk assessor choose the appropriate tools and approaches to be applied for evaluating dosimetry differences between adults and children, as well as to identify chemical characteristics leading to markedly higher or lower internal dose for children compared to adults.

The first step in this process is to consider the duration of exposure, the nature of the critical effect and the mode of action for that effect. The initial decision point in this framework relates to the duration of exposure for which child-adult comparisons of dosimetry are intended. Chronic exposures will generally follow the right-hand side of the framework. The exception is if there is a window of vulnerability (based on toxicodynamic considerations). Such a critical window would mean that the effects and dosimetry associated with a shorter-term exposure would drive the assessment, and therefore the exposure would be considered using the same approach as used for acute exposures. Therefore, the left-side arm of the diagram will be described as "acute" for the rest of this discussion. The next consideration, applicable to both

arms of the diagram, is whether the critical effect is systemic (i.e., remote effects) or local (i.e., portal of entry effects)[2] in nature. For gases and vapors that cause local effects (e.g., highly reactive or water soluble gases), the child-adult comparison is based on dose to the specific regions of the respiratory tract (section 2.2). However, for systemically-acting gases and vapors, child-adult comparisons would be based on active form (parent chemical or metabolite), its level (concentration or amount), and intensity (peak, average or integral), calculated using pharmacokinetic models and equations that reflect the attainment or not of steady-state during the specified exposure condition (section 2.3).

## 2.2 Evaluating child-adult differences in dosimetry of gases and vapors causing portal of entry effects (Category 1 and 2 gases under the U.S. EPA RfC scheme):

For chemicals that are highly reactive or highly water soluble, effects are often local in nature and as such estimates of the delivery of chemical to the various regions of the respiratory tract should be obtained. Typically the Category 1 gases and vapors do not accumulate significantly in blood, and as such systemic distribution and the extent of extrapulmonary effects is minimal or negligible (e.g., formaldehyde, hydrogen fluoride, chlorine, volatile organic esters). Category 2 gases (e.g., ozone, sulfur dioxide, xylenes, propanol) are moderately water soluble and rapidly reversibly reactive or slowly irreversibly metabolized in the respiratory tract. This lower reactivity means that they can both cause respiratory tract effects and accumulate in the blood, causing systemic effects.

For the respiratory tract effects of Category 1 and 2 gases, the airway regions such as larynx, trachea, bronchi and bronchioles cannot be considered as inert tubes carrying the chemical to the alveolar region. For these chemicals, several modeling approaches are useful, including the more sophisticated CFD (computational fluid dynamics) descriptions, that take into account the regional mass transfer coefficients, as well as surface area and ventilation rates (US EPA 1994; Kimbell et al. 1993; Asgharian et al. 1995; Hanna et al. 2001; Bogdanffy and Sarangapani 2003). Data on ventilation rates and pulmonary surface area for children of various age groups as well

[2]Respiratory effects occasionally occur as the result of systemic exposure from the endothelial side of the cell layer, or as a combination of both direct contact effect and systemic exposure. Such effects would be addressed using both the methods for systemic and portal of entry dosimetry.

as adults are available in the literature (Clewell et al. 2002; Snodgrass 1992; Plunkett et al. 1992; U.S. EPA 1997). Hofmann (1982) published empirical equations to determine the length and diameter of the trachea, bronchial airways, and alveoli diameter in children as a function of age. These data, integrated within full-blown regional dosimetry models or steady-state solutions for these models, as appropriate, can be used to compute the child-adult differences in regional dosimetry (Hoffman 1982; Overton and Graham 1989; Martonen et al. 1989). In these approaches, the mass transported per surface area per unit time is calculated as follows:

$$\text{Flux} = V_E/SA\ (C_i - C_x) \qquad \text{Equation 1}$$

where $V_E$ is the ventilation rate, SA is the surface area of the region of interest, and $C_i$ and $C_x$ are the inlet and outlet concentrations, respectively (Hanna et al. 2001).

Depending upon the mode of action, the flux or another measure of dose metric (e.g., peak tissue concentration (Cmax), area under the tissue concentration vs time curve (AUC)) may be computed for evaluating child-adult differences in regional dosimetry gases and vapors causing direct respiratory tract effects. If the parent chemical is the toxic moiety implicated in the portal of entry effects, then the appropriate dose metric is likely to be Cmax for acute effects and AUC for chronic effects. When additional data on the nature and extent of toxic moiety-tissue interaction exist, they may permit the use of other mechanistically relevant dose metrics (e.g., pH alteration resulting from exposure to vinyl acetate, [Bogdanffy et al. 2001]).

### 2.3 Evaluating child-adult differences in dosimetry of gases and vapors causing systemic effects (Category 2 and 3 gases under the U.S. EPA RfC scheme):

Category 3 gases are relatively water-insoluble, with little reactivity in the respiratory tract and perfusion-limited uptake in the pulmonary region, uptake in the blood, and toxic effects usually occurring remotely. The approaches described in this section also apply to systemic effects of Category 2 gases. However, because Category 2 gases also react in the respiratory tract, the steady state equations described in this section may be less accurate for those gases. Differences between respiratory tract dose in adults and children (and therefore differences in the amount of chemical available for uptake to the blood) are not fully captured by the steady state equations

353 presented here, but both the general approach of the framework and the general trends illustrated
354 in the case studies in Section 3.3 would also apply to Category 2 gases.
355
356 For systemically-acting gases and vapors, the inhalation dosimetric adjustment between animals
357 and humans has been conducted on the basis of the ratio of blood:air partition coefficients (U.S.
358 EPA 1994). This approach, applied in the absence of PBPK models, is most appropriate when
359 (i) the parent chemical is the toxic moiety, (ii) hepatic and extrahepatic metabolism processes are
360 not significant, and (iii) the arterial blood concentration attains steady-state during the relevant
361 duration of exposures. Accordingly, for evaluating the child-adult differences in the dosimetry of
362 Category 3 chemicals, the differences in blood:air partition coefficients may be evaluated.
363 However, due to existing evidence on the child-adult differences in metabolic clearance, the
364 direct application of the RfC default approach to evaluate age-related dosimetry differences for
365 Category 3 gases and vapors may not be adequate. As indicated in Figure 1, the evaluation of
366 child-adult differences in dosimetry for these chemicals may be conducted on the basis of
367 whether the endpoint of interest is caused by the parent or a metabolite. For many chronic toxic
368 effects, the concentration of the toxic form of chemical in target tissue integrated over time has
369 been considered to be a reasonable dose metric (U.S. EPA 2006). Accordingly, the child-adult
370 comparisons of internal dose of Category 3 chemicals may be conducted using the AUC or daily
371 average of the dose metric. When the parent chemical is the toxic form, the average
372 concentration in arterial blood (proportional to the AUC) during chronic exposures can be
373 computed as: dose rate/clearance. Whereas the dose rate is determined by the inhaled
374 concentration and alveolar ventilation rate, the clearance is the net result of the pulmonary,
375 metabolic (hepatic and extrahepatic) as well as renal elimination processes, all of which are to
376 known vary as a function of age (Clewell et al. 2002).
377
378 The next consideration is whether the toxic effect is due to the parent, a stable metabolite, or a
379 reactive metabolite. IPCS (2005) discusses considerations and data that can be used to make this
380 determination.
381

The child-adult differences in dosimetry of Category 3 gases and vapors, for which parent chemical is the toxic moiety, can be evaluated using a steady-state algorithm of the following form:

$$CA_{ss} = \frac{QP * CI}{QP/PB + QL*E} \qquad \text{Equation 2}$$

where CAss is the arterial blood concentration; QP is the alveolar ventilation rate, CI is the chemical concentration in inhaled air, QL is liver blood flow, E is hepatic extraction ratio; and PB is the blood:air partition coefficient.

Using the age-specific values for each of the above parameters, CAss can be computed and compared among the different age groups. There is no need to perform calculations of steady-state concentrations of chemicals in target tissues (as opposed to arterial blood concentration) because: (i) target tissue concentrations are proportional to CAss as defined by the partition coefficients (Lam et al. 1982; Krishnan 2007; Pelekis et al. 1997), and (ii) there is no evidence to date that indicates the tissue water and lipid contents would be significantly different, particularly for children aged >3 months in comparison with adults (Price et al. 2003; White et al. 1991; Woodward and White 1986).

For Category 3 gases which exert their toxicity via the formation of reactive metabolites, the child-adult dosimetry comparison can be conducted on the basis of the rate of metabolism in the tissue (i.e., amount per L tissue per unit time). The steady-state rate of metabolism (i.e., average during chronic exposures) may be calculated on the basis of the steady-state arterial blood concentration (Equation 3). In this case then,

$$AMT = (CA_{ss} \times QL \times E)/VL \qquad \text{Equation 3}$$

where AMT = amount of metabolite formed per unit time per unit volume of tissue, $CA_{ss}$ = arterial blood concentration of the parent chemical, QL = hepatic blood flow rate, E = hepatic extraction ratio and VL = liver volume.

For Category 3 chemicals producing stable or circulating metabolites, the rate of clearance of the metabolite in both adults and children should be additionally taken into account for calculating the dosimetry differences (Figure 1). In the case of metabolites, the clearance via kidney is likely to become more important (compared to parent form of Category 3 gases) such that child-adult differences in glomerular filtration rate (Clewell et al. 2002) might play an important role in determining the magnitude of the dose differences between various age groups. The steady-state equation in such cases would be of the following form:

$$Cmet = \frac{CA_{ss} \times QL \times E}{CL_{metabolite}} \qquad \text{Equation 4}$$

Steady-state is achieved rapidly for gases and vapors that have a low volume of distribution and those that are cleared effectively by the biochemical processes. Category 3 gases generally have low blood:air partition coefficients but variable fat:blood partition coefficients (Table 1). U.S. EPA (1994), based on PBPK modeling in rats, indicated that steady-state is attained during subchronic or chronic inhalation exposures to gases with a blood:air partition coefficient < 100 and fat:blood partition coefficient < 100. In effect, almost all of the known Category 3 gases and vapors are expected to attain steady-state during continuous inhalation exposures in humans, even though only the proof of concept is available (Pelekis et al. 1997). In such cases, the use of a steady-state algorithm is likely to be sufficient for evaluating child-adult differences in dosimetry. The same approach is applicable to "acute" scenario, if the parent compound is the toxic agent and steady state is reached. However if the steady state is not reached in the "acute" scenario, regardless of whether toxic moiety is the parent chemical or metabolite (reactive or stable), the child-adult difference in systemic uptake and internal dose may be computed using full-blown physiologically-based pharmacokinetic (PBPK) models.

It is recognized that for several chemicals, based on the current state of knowledge of the mode of action, greater or less information may be available. For example, information on the extent of receptor occupancy, DNA adducts in target site, depletion of glutathione in target tissues, etc. can be used for estimating the child-adult differences in internal dose; however, such data are often not available. In fact, for many chemicals, the appropriate dose metric is not known. In

such cases, it is reasonable to use the AUC of the parent chemical as the dose surrogate (U.S. EPA 2000, 2006; Clewell et al. 2002) and evaluate the child-adult differences in dosimetry. This is consistent with the approach for calculating Human Equivalent Concentrations (HECs) under the U.S. EPA's RfC guidance (U.S. EPA 1994). However, in such cases, the assessor should note the uncertainty introduced by this assumption, and include appropriate caveats.

For some chemicals, limited information may be available for the estimation of chemical-specific kinetic parameters needed for the application of the proposed framework. In those cases, information from a surrogate compound with similar chemical properties or structure activity relationships may be useful in evaluating potential child-adult differences. For example, Beliveau et al. (2003, 2005) used quantitative structure-property relationships to estimate partition coefficients and hepatic clearance for a number of volatile organic compounds. Again, the risk assessors would need to consider any uncertainty introduced by the reliance upon information for a surrogate.

# 3.0 ANALYSES: APPLICATION OF THE CHILD-ADULT FRAMEWORK TO CHEMICALS WITH SYSTEMIC EFFECTS (CATEGORY 2 AND CATEGORY 3 GASES)

## 3.1 Introduction

The magnitude of child-adult differences in internal dose of Category 3 gases and vapors has been evaluated using age-specific physiological data as well as chemical-specific partitioning and clearance data in PBPK models or steady-state algorithms (Price et al. 2003; Pelekis et al. 2003; Clewell et al. 2004; Ginsberg et al. 2002; Hattis et al. 2003; Sarangapani et al. 2003). As outlined in Section 2, steady-state algorithms are adequate for estimating the magnitude of child-adult difference in the dosimetry of Category 3 gases when the toxic moiety is the parent chemical or a metabolite. The steady-state approach requires the knowledge of certain parameters that are known to vary as a function of age: alveolar ventilation rate, hepatic blood flow, liver volume and clearance (renal, hepatic and/or pulmonary). Most of the previous analyses estimated the child-adult magnitude in internal dose of Category 3 gases and vapors, using physiological parameters for children (particularly neonates) derived from adult values on

the basis of an allometric or regression relationships (Clewell et al. 2004; Ginsberg et al. 2002; Sarangapani et al. 2003). In order to facilitate a broader understanding of the extent of child-adult differences in dosimetry for Category 3 gases as well as to identify situations and parameters leading to maximal magnitude of child-adult differences in the dosimetry for these gases, the present study conducted a number of bounding analyses and case studies in various age groups: (neonates (3 months), toddlers (1 year), preschooler (5 years), middle schooler (10 years)). Accordingly, calculations of internal dose (i.e., steady-state concentration of parent chemical in blood, steady-state concentration of reactive metabolite in liver, and steady-state concentration of circulating metabolite in the body) in adults and children of various age groups were performed by setting hepatic clearance in children equal to (1) zero, (2) blood flow rate to the organ, or (3) a fraction of metabolic capacity of adults based on information on delayed enzyme ontogeny.

## 3.2 Approach

### 3.2.1 Child-adult differences in dosimetry for Category 3 gases for which parent chemical is the toxic moiety

The steady-state blood concentration of Category 3 gases that are metabolized primarily in liver and eliminated by clearance processes in both liver and lung can be calculated with the knowledge of age-specific blood:air partition coefficient (Pb), alveolar ventilation rate (QP), hepatic blood flow rate (QL) and intrinsic clearance (CLint) (Andersen 1981; Pelekis et al. 1997; Csanady and Filser 2001; Clewell et al. 2004). Available information suggest that neither the blood:air partition coefficient nor the composition of blood (lipid and water content) vary markedly as a function of age (Table 2) (Berenson et al. 1982; Lerman et al. 1984; White et al. 1991; Family Practice Notebook 2005). Therefore, the evaluation of child-adult differences in parent chemical concentrations can be performed with the knowledge of QP, QL and CLint for the various age groups, as well as using the Pb value for one of the age groups (usually adults).

The computation of steady-state blood concentration of Category 3 gases was performed on the basis of Eqn. 2 of the framework:

$$CA_{ss} = \frac{QP * CI}{CLp + CLh}$$

where CAss = steady-state arterial blood concentration (µg/L), QP = alveolar ventilation rate (L/h), CI = inhaled concentraton (µg/L), CLp = pulmonary clearance (= QP divided by blood:air partition coefficient (PB)) and CLh = hepatic clearance (= CLint x QL/ (CLint + QL) where CLint = intrinsic clearance (= maximal velocity divided by Michaelis constant) and QL = hepatic blood flow rate (L/h).

The upper-bound of the magnitude of child-adult difference in CAss was calculated, initially, by assuming minimal metabolism in children (i.e., CLh = 0) and maximal metabolism in adults (i.e., CLh = hepatic blood flow rate) such that the hepatic extraction ratio equals 1. The calculations conducted under this scenario focused on identifying the maximal child-adult factor that is likely to be associated with Category 3 gases and vapors for which the parent form represents the toxic moiety. A second bounding analysis was conducted using Eqn. 2 for highly metabolized chemicals, for which hepatic clearance is blood-flow limited in both adults and children. The resulting child-adult ratios of CAss from this scenario would essentially reflect the lower-bound of the child-adult differences in internal dose. A third scenario involved the use of age-specific data on metabolizing enzyme capacity in Eqn. 2. Enzyme ontogeny data were used to estimate CLint in children on the basis of adult values as follows (Clewell et al. 2004; Nong et al. 2006):

$$CLint_{Child} = CLint_{Adult} * F * VL_{Child}/VL_{Adult},$$

where VL is the volume of liver and F is the enzyme activity as a fraction of the adult value. This particular approach was applied to hepatic CYP2E1 and alcohol dehydrogenase (ADH) using data summarized by Clewell et al. (2004).

### 3.2.2 Child-adult differences in dosimetry for Category 3 gases for which reactive metabolite is the toxic moiety

For Category 3 gases exerting toxicity via reactive metabolites, the child-adult dosimetry comparisons of internal dose (i.e., amount per L tissue per unit time) was computed on the basis of Eqn. 3 of the framework:

$$AMT_{Reactive\ metabolite} = (CA_{ss} \times CLh)/VL$$

The magnitude of child-adult differences in internal dose was calculated for the three scenarios described in section 3.1. Accordingly, the CLh value was first set to 0 in children and to QL in adults, as a bounding case. Then, the CLh was set equal to hepatic blood flow in both children and adults, to compute an upper bound of the child-adult difference in internal dose of reactive metabolites. Finally, the age-specific CLh was computed according to the information on the relative content of metabolizing enzyme (CYP2E1, ADH) in children relative to adults.

### 3.2.3 Child-adult differences in dosimetry for Category 3 gases for which circulating metabolite is the toxic moiety

As noted above, for calculating the internal dose of stable or circulating metabolites, the clearance of metabolites subsequent to their formation should be taken into account (Krishnan and Andersen 1991; Sarangapani et al. 2003; Gentry et al. 2002). Because kidney clearance is likely to play an important role for such metabolites, child-adult differences in glomerular filtration rate need to be taken into account in determining the magnitude of the dose differences between various age groups. The steady-state equation for computing the internal concentration[3] of circulating metabolites (as shown in section 2.3) is:

$$C_{Stable\ metabolite} = \frac{CA_{ss} \times QL \times E}{CL_{metabolite}}$$

The magnitude of child-adult differences in internal dose was initially calculated for the three scenarios described in section 3.2.1. (i.e., bounding case, flow-limited clearance, delayed ontogeny of metabolizing enzymes). For all three scenarios, $CL_{metabolite}$ was assumed to be adequately represented by renal clearance which was set equal to the age-specific value of glomerular filtration rate (GFR). Additionally, calculation of $C_{Stable\ metabolite}$ was done for a situation in which $CL_{metabolite}$ is determined by both renal and metabolic clearance processes, subsequent to flow-limited metabolism of parent chemical in adults and children. This particular scenario facilitates the evaluation of an extreme case of child-adult difference in internal dose, in which the capacity-limited difference in clearance of metabolite and flow-limited clearance of

[3] Because the dose metric of interest is the concentration of the chemical, comparison of concentrations can be considered a comparison of internal dose.

parent chemicals might both apply and result in higher child-adult dose ratio (Clewell et al. 2004; Sarangapani et al. 2003; Ginsberg et al. 2005).

### 3.2.4 Parameter and data sources

For the analyses presented here, the value of CI for all age groups was set to 1 μg/L in air. The physiological parameters (QP, QL and VL) for the children of various age groups were obtained from Price et al. (2003), whereas those for adults were obtained from Arms and Travis (1988). The delayed development of renal function (GFR) and liver metabolism (CYP2E1, ADH) in children was expressed as a fraction of the adult value based on data summarized by Clewell et al. (2004) and Sarangapani et al. (2003). For the various calculations, CLint was varied from 0.1 L/hr (capacity-limited metabolism) to 1000 L/hr (flow-limited metabolism), and the PB was varied between 0.1 and 50 (which generally reflects the values for commonly known Category 3 gases and vapors (Table 1)). The internal dose at steady-state was calculated using Microsoft EXCEL® for each age group using Eqns. 2 – 4, and then the child-adult factors were derived for each of the three scenarios as ratios of internal doses.

## 3.3 Results

### 3.3.1 Child-adult differences in dosimetry for Category 3 gases for which parent chemical is the toxic moiety

Figures 2-3 summarize the results of child/adult steady-state concentration ratios for the first two scenarios of bounding cases, (1) upper bound based on zero metabolism in children of all age groups and maximal metabolism (i.e., equal to hepatic blood flow) in adults (scenario 1), and (2) lower bound based on flow-limited clearance in both adults and children (scenario 2). Figure 2 shows that the child:adult ratio of CAss would increase with increasing PB for scenario 1 when $E_{child} = 0$ and $E_{adult} = 1$. For this worst-case scenario, hepatic clearance was set to zero for all four ages of children, and so only one curve is shown. The increase of the child:adult ratio of CAss is a direct result of the fact the CAss in children in this scenario is determined only by pulmonary clearance, whereas in adults it is determined additionally by CLh. For chemicals with very low CLint values (e.g., 0.01 L/hr), hepatic clearance (CLh) is negligible compared to

pulmonary clearance (CLp) such that the child/adult ratio of CAss approximates the ratio of PB in child and adult, which essentially is 1. For increasing CLint values, however, the child/adult ratio exceeds 1, with the actual magnitude being determined by the relative contributions of pulmonary clearance and hepatic clearance to total clearance in adults as well as the extent of the deviation of total clearance in adults from the pulmonary clearance in children. If $CLh_{adults}$ is near full capacity and $CLh_{child}$ is near zero (worst case scenario), then the child/adult ratio of CAss will continue to increase as a function of PB (Figure 2). At any given PB value, the lower bound of child/adult ratio for parent chemical dose can be simulated by assuming blood flow-limited metabolism in both adults and children (scenario 2; Figure 3). In this case, the maximal value of child/adult ratio of CAss (2.1) is associated with the age group of 3 month-old and gases with high PB values (e.g., 50) (Figure 3). When age group-specific metabolic capacity is known, a better estimate of the magnitude of child/adult ratio of CAss can be obtained, which should be between the upper and lower bound estimates presented above, as shown in scenario 3 with ADH and CYP2E1 as examples.

The results of the steady-state analysis for CAss based on age-dependent CYP2E1 and ADH activity are shown in Figures 4a and 4b, respectively (scenario 3)[4]. In both cases, the 3 month old, the youngest group evaluated, has the greatest difference in parent concentration relative to the adults. This is not surprising since the ADH and CYP2E1 are at the lowest levels at birth, and gradually increase to adult levels. Similar to the results obtained for scenarios 1 and 2, the highest child/adult ratio for CAss (approximately 2.3 for ADH) (Figure 4b) was associated with high CLint values (i.e., 1000 L/hr) reflective of flow-limited metabolism in adults but not necessarily in all other age groups. For gases with very low CLint values, however, the metabolism rate is unlikely to be a sensitive parameter in estimating CAss and thus the child/adult ratio is close to unity (not shown).

[4] Note: Ratio 3/A = 3 months:adult; 1/A = 1 year:adult; 5/A = 5 years:adult; 10/A = 10 years:adult

### 3.3.2 Child-adult differences in dosimetry for Category 3 gases for which reactive metabolite is the toxic moiety

Figure 5 depicts the child-to-adult ratio of the internal dose of reactive metabolite resulting from continuous exposure to Category 3 gases with PB values up to 50. Here, the upper bound of the child/adult ratios (shown in Figure 5) results when metabolism is flow-limited in both adults and children whereas the lower bound (i.e., zero) is associated with scenario 1 (i.e., when $CLh_{child}$ is zero and $CLh_{adults}$ is near full capacity). The highest value of the upper-bound of child-to-adult ratios of internal dose of reactive metabolites (1.45) was obtained for 10-year-old children. Under flow-limited conditions, the internal dose of reactive metabolites is determined by QL/VL which is about 33 in younger age groups (3 months to 5 years) and 47 in 10-year-old children, compared to 53 in adults (Price et al. 2003). The relative difference in these determinants between children and adults, coupled with the difference in CAss (section 3.3.1) would explain the magnitude of child-adult ratios in the liver concentration of reactive metabolites computed in this study (Figure 5).

Using information on delayed ontogeny of metabolizing enzymes (ADH and CYP2E1), it would appear that the internal dose of reactive metabolites for poorly metabolized Category 3 gases (assuming an intrinsic clearance of 0.1 L/hour) would be lower in children of all age groups compared to adults (Figures 6 for ADH and Figure 7 for CYP2E1). In case of highly metabolized gases (e.g., CLint = 1000 L/hour), however, the formation of reactive metabolites in older children (5 year old and 10 year old) and in the 3-month-old (but not in the 1-year-old) might slightly exceed the levels formed in adults (Figure 8). The quantitative behavior depicted in Figure 8 applies to both ADH and CYP2E1 (not shown).

### 3.3.3 Child-adult differences in dosimetry for Category 3 gases for which circulating metabolite is the toxic moiety

The child/adult ratios of the steady-state concentration of stable (circulating) metabolite were initially calculated on the basis of the rate of formation (i.e., hepatic metabolism of parent chemical) and rate of elimination (i.e., renal clearance of metabolite) for the three scenarios described in section 3.1. In this case, the upper bound of the child-adult ratios resulting from

flow-limited metabolism in both adults and children combined with renal excretion as described by the developmental data, range between 0.9 – 1.3 (Figure 9). The lower bound of the child/adult ratio of the stable metabolite is essentially zero, which is associated with scenario 1 described in section 3.1. (i.e., when $CLh_{child}$ is zero and $CLh_{adults}$ is near full capacity). Calculations based on the delayed ontogeny of ADH and CYP2E1 enzymes involved in the formation of stable metabolites yield child/adult factors that are essentially in this range both for highly metabolized vapors and gases (Figures 10a for ADH and 10b for CYP2E1) and poorly metabolized ones (Figures 11a for ADH and 11b for CYP2E1).

The rate of formation of stable metabolite is determined by QL, E and CAss. Therefore, for flow-limited metabolism in both children and adults (i.e., when E=1), the values of QL and CAss would determine the magnitude of child/adult ratio of the amount of stable metabolites formed at steady-state. Given that child/adult ratio of CAss for Category 3 gases is within a factor of 2, and that the QL is about 14 times lower in neonates compared to adults, the overall amount formed would be several times (up to 7-fold) lower in young children. However, since the GFR is also lower in neonates compared to adults (by a factor of about 7), the net effect is that the resulting child/adult ratio of steady-state concentration of circulating metabolite is about 1. The relative dose in children could be substantially higher if there is significant child-adult difference in metabolic clearance (e.g., when $CLh_{child}$ is zero and $CLh_{adults}$ is near maximum capacity). Figures 12-13 depict the adult/child factors for highly metabolized (Figure 12) and poorly metabolized (Figure 13) Category 3 gases and vapors, for which the toxic moiety is a stable metabolite cleared efficiently in adults (i.e., flow limited process) but not at all in children (i.e., hepatic extraction ratio = 0). The upper bound value for this child-adult difference would be approximately 17 (Figure 12); however, if the CLh of metabolites in children varies as a function of metabolic capacity of the enzymes involved (e.g., ADH or CYP2E1), then the child/adult factors are likely to be lower than these upper bound values.

# 4.0 DISCUSSION

This document presents a framework for evaluating relative dosimetry in children and adults for inhaled gases. For effects at the portal of entry, a range of potential approaches are noted;

however, the focus of this analysis was for those gases or vapors expected to have an impact systemically, with the appropriate choice of approach depending on the chemical's mode of action. The framework presents specific considerations for systemic effects, with certain modes of action and exposure scenarios leading to recommended analytical approaches. Case studies were conducted to demonstrate the potential quantitative differences between children and adults for chemicals for which the parent, reactive metabolite, or stable metabolite is the toxic moiety of concern.

The differences in internal dose to adults and children evaluated by the framework have the largest impact under two scenarios. The first is when there is a window of increased susceptibility. If the window of susceptibility falls during childhood, the internal dose during that period of time is a key determinant of response, and it is important to consider the relative internal dose to children and adults for a given air concentration, regardless of the total exposure duration. The second situation when differences in the child and adult dose would be of particular interest is when the exposure duration is generally comparable to or shorter than the duration of the age range of interest. Although the approach used in the framework can be used to evaluate the relative dose to children and adults in scenarios involving longer durations of exposure, the impact on response would be much smaller when the response is related to lifetime exposure (e.g., when the appropriate metric is Lifetime Average Daily Dose, or LADD). This is because estimates of cumulative dose over a lifetime resulting from exposure to low concentrations of environmental chemicals are fairly insensitive to age-related kinetic differences, because the greatest differences persist for only a short time (Pelekis et al. 1997; Clewell et al. 2004). Thus, if toxicity for the relevant endpoint is related to cumulative dose, these increases in internal dose would not have a significant effect on risk, unless a window of susceptibility coincided with the period of increased dose.

It should also be noted that analyses presented here are a simplified approach and are not intended to be used quantitatively in risk assessment, in the absence of chemical-specific data. Instead, the intent is to identify situations in which dose metrics in the child may be substantially different from those in the adult. The proposed framework would provide a potential screen to

720 determine if the default toxicokinetic component is adequate when considering exposure to
721 children, noting the additional need to consider variability.
722
723 **4.1 Comparison with results in the literature**
724
725 The analyses presented along with the framework were conducted to provide some initial
726 direction regarding conditions under which there are significant dosimetric differences between
727 adults and children. The results of these analyses are consistent with individual chemical-
728 specific analyses in the literature. They suggest that the child/adult difference in steady state
729 arterial concentration (CAss) of the parent chemical is likely to be within a factor of 2.1 for
730 highly metabolized Category 3 gases and vapors. This observation is consistent with the
731 conclusions of the detailed inhalation PBPK modeling studies conducted with selected Category
732 3 chemicals (furan: 1.5 (Price et al. 2003); styrene 1.8 and vinyl chloride 1.13 (Sarangapani et al.
733 2003). This is also consistent with the results of Ginsberg et al. (2005), who reported that the
734 maximal child/adult factor for steady-state arterial blood concentration of parent chemicals
735 belonging to Category 3 was 1.75, particularly for flow-limited metabolism in both adults and
736 neonates. In the case of poorly metabolized gases and vapors, the child/adult ratio is likely to be
737 about 1, since child-adult differences in metabolic clearance barely have an influence on the
738 kinetics and internal dose, as shown in this study. This observation is consistent with that of
739 Sarangapani et al. (2003) for perchlorethylene (child/adult ratio = 1.02), a poorly metabolized
740 Category 3 vapor. Larger child/adult ratios would result in the hypothetical case where there is
741 no hepatic clearance in the child and high hepatic clearance in the adult, but such extreme cases
742 were not located in the chemical literature.
743
744 Regarding Category 3 gases forming reactive metabolites, the analyses conducted here indicate
745 that the child-adult difference would be maximal when metabolism is flow-limited in adults and
746 children. The maximal value of child-to-adult ratios of internal dose of reactive metabolites
747 found in the present study (1.45) is comparable to those reported for vinyl chloride (1.34) and
748 styrene (1.83) by Sarangapani et al. (2003). The small difference between the present study and
749 the previous studies might be due to the derivation of liver blood flow values by the previous
750 studies on the basis of difference in liver volume between children and adults. The present

study, however, used liver blood flow values determined in children following radioactive gold administration (Szantay et al. 1974). The child/adult ratio of the internal dose of reactive metabolite approaches zero as the intrinsic clearance (Clint) becomes smaller (Figures 6 and 7). This is also in agreement with the results of the PBPK modeling study by Sarangapani et al. (2003) in which the child/adult ratio for a poorly metabolized Category 3 chemical (perchloroethylene) was reported to be 0.27.

For Category 3 gases forming stable metabolites, the analyses were based on the assumption that renal clearance would be the sole mechanism of elimination, or it considered both the renal and hepatic routes of clearance to be relevant. In the first case, the calculated ratios ranged from 0.9 to 1.3. However, the child/adult ratio increased if there was a significant child-adult difference in metabolic clearance of the metabolite. In the case of Category 3 gases and vapors for which the stable metabolite (toxic moiety) is cleared efficiently in adults (i.e., flow limited process) but not at all in children (i.e., hepatic extraction ratio = 0), the child/adult ratio can be as high as 18. This is in accord with the observations of a PBPK modeling study of the formation and clearance of a stable metabolite (acetone from isopropanol), which reported a neonate/adult factor ranging from approximately 7 to 9 (Saragapani et al. 2003). Note also that isopropanol is a Category 2 gas, illustrating that the simplified steady state approaches described here give reasonable estimates of the relative systemic dose for children and adults, even for a moderately water soluble chemical. Further studies are required to systematically evaluate the relative contribution of renal, hepatic and pulmonary clearance processes to the total clearance of circulating metabolites formed from similar gases, as well as their overall contribution to the relative dose in children and adults, so as to be able to pinpoint characteristics of gases and vapors that might lead to situations where the dose to children is much higher than that to adults.

Quantitative differences between the examples presented here and previous published analyses were generally due to differences in the age-specific parameters. For example, in addition to the differences noted above regarding age-specific liver blood flow, there were differences in the alveolar ventilation rate (QP). Sarangapani et al. (2003) and Clewell et al. (2004) estimated the age-dependent alveolar ventilation as 66% of the pulmonary ventilation data compiled by U.S. EPA (1997). Because the alveolar dead space may vary with age, the current analysis focused on

actual measured values when possible, using the approach of Price et al. (2003). Specifically, the QP for the 3-month old used measured data from Lees et al. (1967), and Price et al. (2003) developed a regression equation to calculate the QP values for ages 1, 5 and 10 years. Inputs to the development of the regression equation were age-specific data on respiratory frequency and tidal volume, and an equation relating physiological dead space to body weight

The results presented here are also consistent with those of Ginsberg et al. (2005), who identified several conditions under which greater metabolite levels may occur in the infant liver than the adult liver. These conditions include: (1) highly metabolized gases; (2) Category 3 gases at 1 year of age for metabolism pathways that have reached full maturity by this age; and (3) cases where the metabolite formation rate is considerably greater than the metabolite removal rate and the metabolite removal rate involves a cytochrome P450 (CYP) or other pathway that is immature early in life. Except for the third group, these conditions do not consider removal of the metabolite. As another example of identification of the rate-limiting step, if a chemical is cleared primarily by glucuronidation, the low activity at early ages suggests that particular attention should be paid to urinary metabolites to determine whether adequate clearance occurs via alternative conjugation pathway (e.g., sulfation).

### 4.2 Potential enhancements to the framework and data needs

The framework presented here focuses on dosimetry comparisons between adults and children for inhaled gases and vapors. It could be further enhanced to consider variability, as part of evaluation of the appropriate intraspecies uncertainty factor. Only limited investigations were identified that evaluated variability within the child population. Pelekis et al. (2003) conducted PBPK modeling for methylene chloride using ranges for estimates of age-related physiological and biochemical parameters to develop annual average concentrations as population distributions. This approach could be used to evaluate total population variability. Consideration of first principles would suggest that children would vary less than adults in many physiological parameters. While some physiological parameters (e.g., body fat) tend to exhibit greater variability at later ages, child variability in dose appears to be comparable to or greater than in adults. Renwick et al. (2000) reported that the magnitude of inter-individual variability

in drug clearance (expressed as a percentage) is not influenced by age. However, Hattis et al. (2003) found that the neonates had greater variability for some, but not all drugs and metabolic pathways. Common pathogenic processes, such as asthma, may also alter the respiratory tract dimensions, and thus the dosimetry, in ways not accounted for in the current analysis (Ginsberg et al. 2005).

The framework focused on inhaled gases, and did not address inhaled particles or exposure via other routes. Extensive analyses of particle dosimetry have been conducted by Jarabek et al. (2005) and Ginsberg et al. (2005). Jarabek et al. (2005) used the Multiple Path Particle Dosimetry Model (MPPD)[5] to calculate the ratio of the human equivalent concentration (HEC) to laboratory animal exposure concentration for people ranging from 3 months to adulthood for poorly soluble nonfibrous particles (PSP) with mass median aerodynamic diameters (MMAD) ranging from 0.3 to 6 μm. The authors used a dose metric of retained mass in the tracheobronchial region normalized to surface area, taking into account deposition and clearance (but not age-specific clearance). Ginsberg et al. (2005) used the ICRP (Smith 1994) model to model deposited dose per unit surface area for 3-month-old infants and adults as a function of particle size. Martonen et al. (2000) developed a particle deposition model that takes into account structural elements of the lungs and used the model to calculate deposited dose per unit surface area as a function of particle size for four age groups. These sorts of analyses, along with analyses built on more recent data, such as the deposition calculations of Oldham and Robinson (2006), based on asymmetrical growth geometries of the tracheobronchial region, can be used to develop a framework for exposure to particles and aerosols. Similarly, frameworks for the oral and dermal routes of exposure would be useful. For example, the oral route would need to consider the implications of first-pass metabolism. Interagency efforts (Jarabek 2000; Rigas et al. 2000) to develop dosimetric approach for the oral route (in addition to dermal dosimetry and improved inhalation dosimetry) are likely to provide additional guidance for this route.

The intent of the proposed framework is to provide a structure for consideration of the implications of age-related kinetic differences for internal dose and to focus future research in this area. The results of the initial application of this framework suggests a selected number of

[5]Version 1.0, © CIIT and RIVM, 2002. Obtained from B. Asgharian, CIIT.

data gaps, where additional research may help to refine analyses of age-related differences in dosimetry. These areas include: (1) age-dependence of blood:air partition coefficients; (2) liver blood flow for children less than 4 years of age; (3) enhanced understanding of age-dependent changes in enzyme activities; and (4) characterization of extrahepatic metabolism.

Table 1. Compilation of Partition Coefficients for Some Category 3 Gases

| Chemical | Blood:Air Partition Coefficient[1] | Fat:Blood Partition Coefficient[2] |
|---|---|---|
| Methyl chloride | 2.5 | 5.4 |
| Dichloromethane | 8.9 | 13 |
| Chloroform | 6.9 | 29 |
| Carbon tetrachloride | 2.7 | 133 |
| Chlorodibromomethane | 53 | 36 |
| Chloroethane | 2.7 | 14 |
| Vinyl Chloride | 1.2 | 17 |
| 1,1-Dichloroethane | 4.9 | 33 |
| 1,1,2-Trichloroethane | 36 | 40 |
| Benzene | 8.2 | 24 |
| Chlorobenzene | 30 | 43 |
| o-Xylene | 35 | 43 |
| m-Xylene | 33 | 56 |
| p-Xylene | 45 | 39 |
| Styrene | 48[3] | 72[4] |

[1]Gargas et al. (1989)

[2]Estimated based on rat Fat:Air partition coefficients and human Blood:Air partition coefficients reported by Gargas et al. (1989).

[3]Csanady et al. (1994)

[4]Estimated based on rat Fat:Air partition coefficient reported by Gargas et al. (1989) and human Blood:Air partition coefficient reported by Csanady et al. (1994).

Table 2. Age-dependent Lipid and Water Content of Whole Blood

| Age (yr) | % Lipid[1] | % Water[2] |
|---|---|---|
| 0 | 0.11 | 84 |
| 1/2 to 2 | 0.22 | 87 |
| 2 to 6 | 0.21 | 87 |
| 6 to 12 | 0.22 | 86 |
| 12 to 18 | 0.21 | 86 |
| Over 18 | 0.22 | 85 |

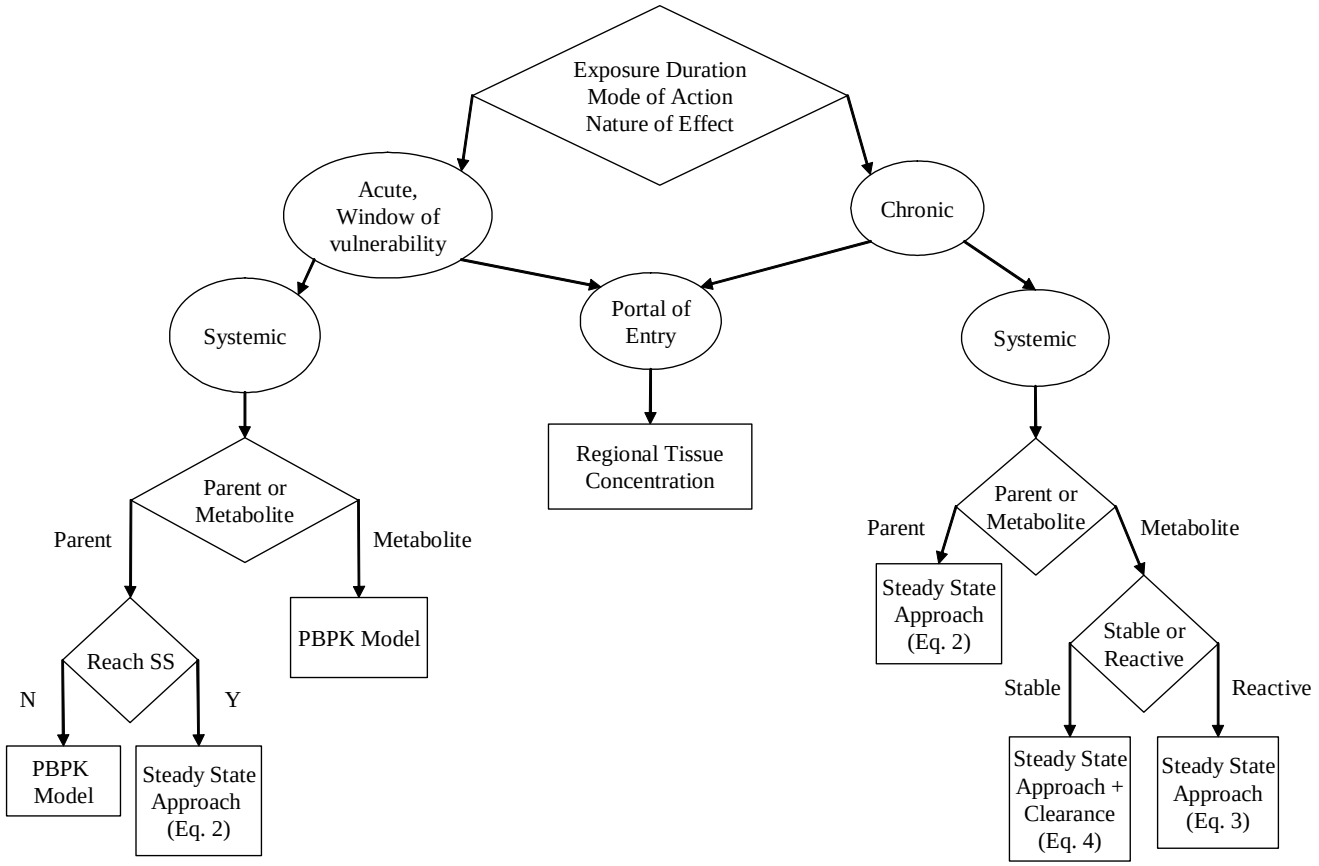
[1](Berenson et al. 1982)

[2](Family Practice Notebook, 2005)

868

869 Figure 1. Revised framework for evaluating the relative tissue dosimetry in adults and children
870 for inhaled gases.

871

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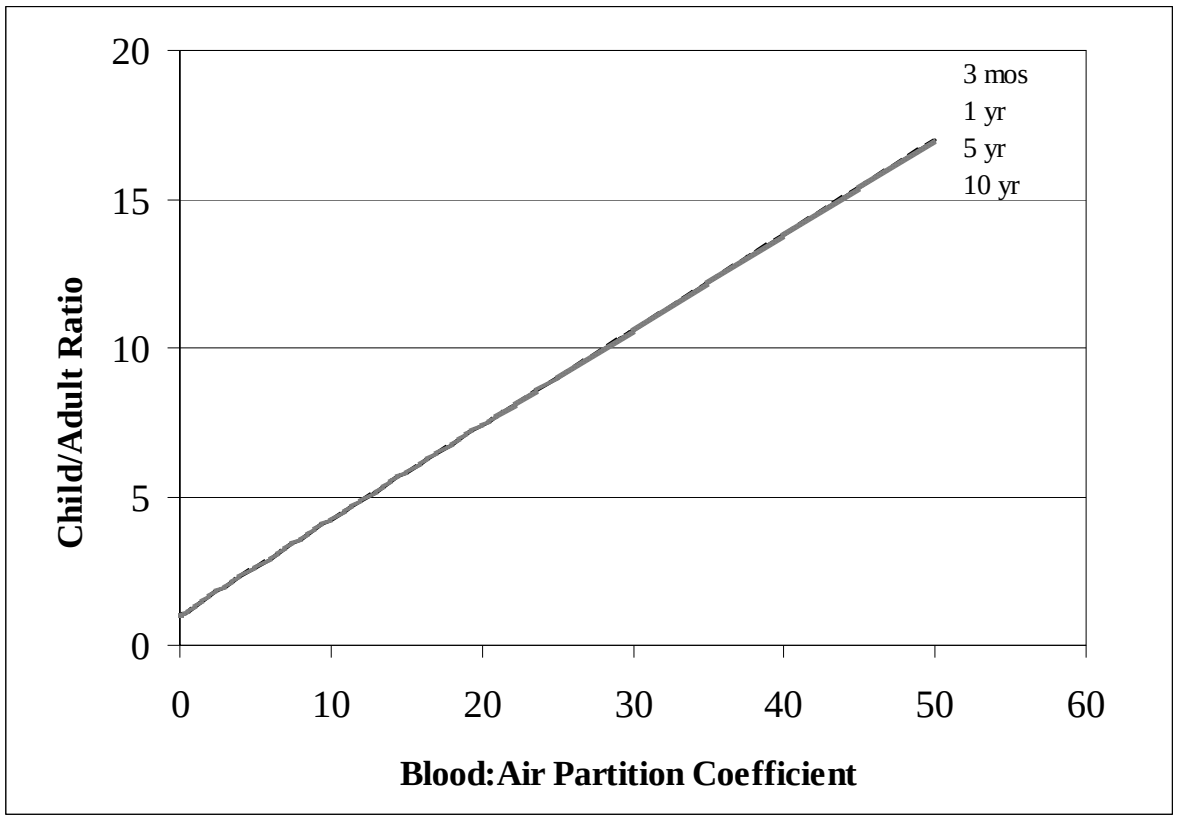
873

Figure 2. Child/adult ratio of the steady-state concentration of inhaled parent chemical: A bounding case study. The hepatic clearance in children of all ages is set to zero, whereas that in adults is assumed to equal the maximal level (i.e., hepatic blood flow rate).



884

885 Figure 3. Child/adult ratio of the parent chemical concentration at steady-state when metabolism
886 is flow-limited in both adults and children.

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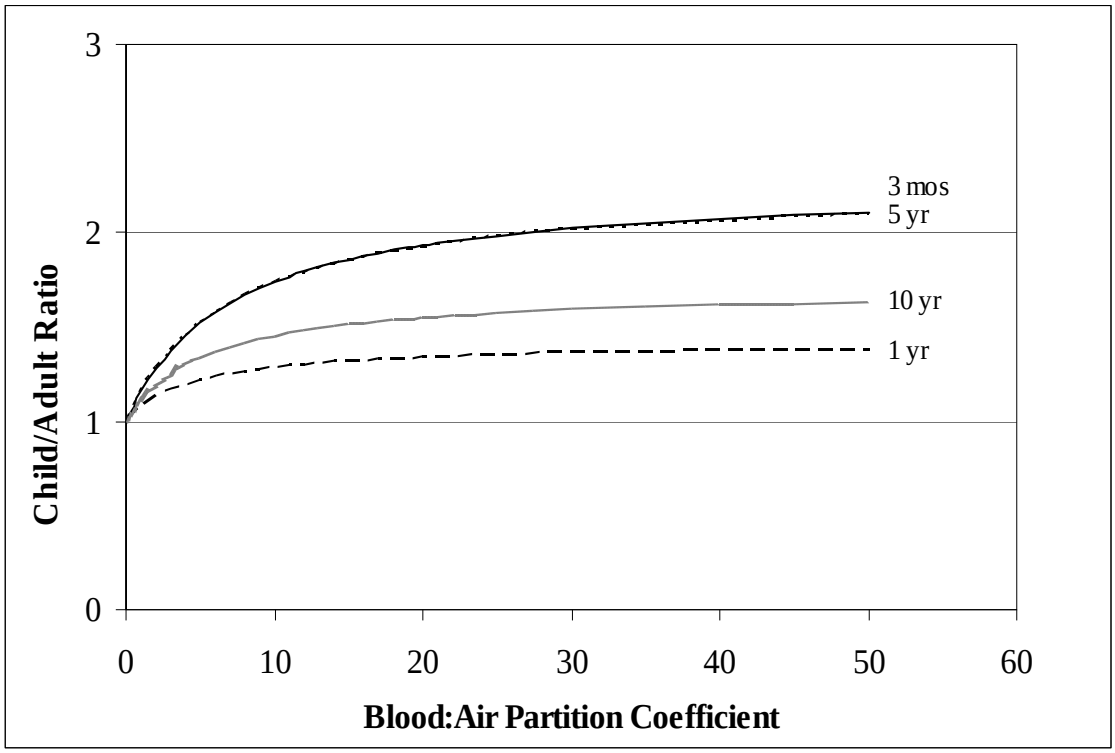


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Figure 4a. Child/adult ratio of the steady-state concentration of parent chemical for which the formation rate is proportional to the CYP2E1 content (intrinsic clearance is 1000/hr).

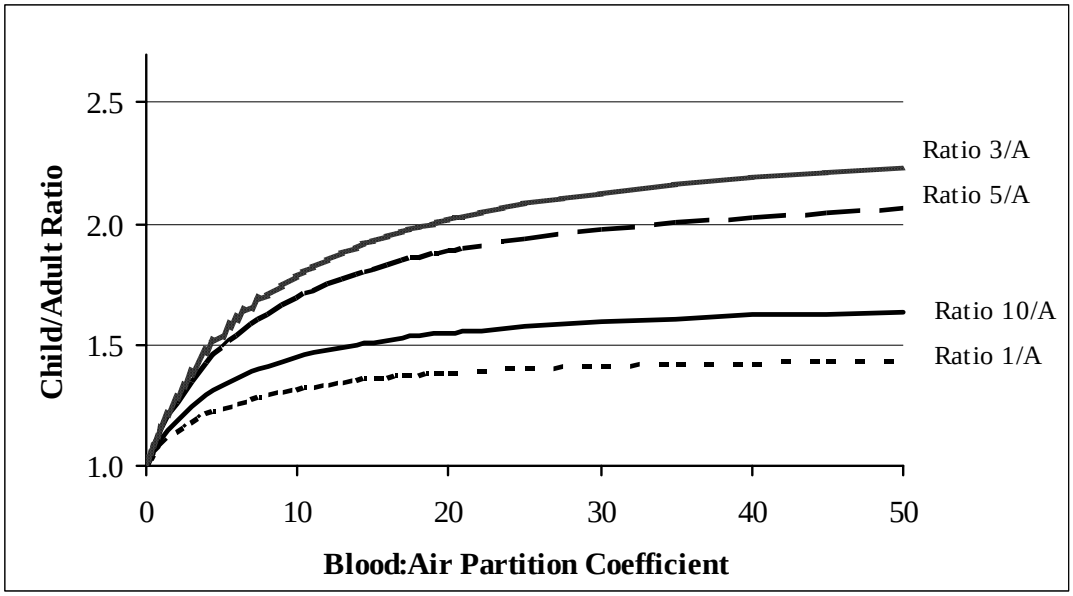
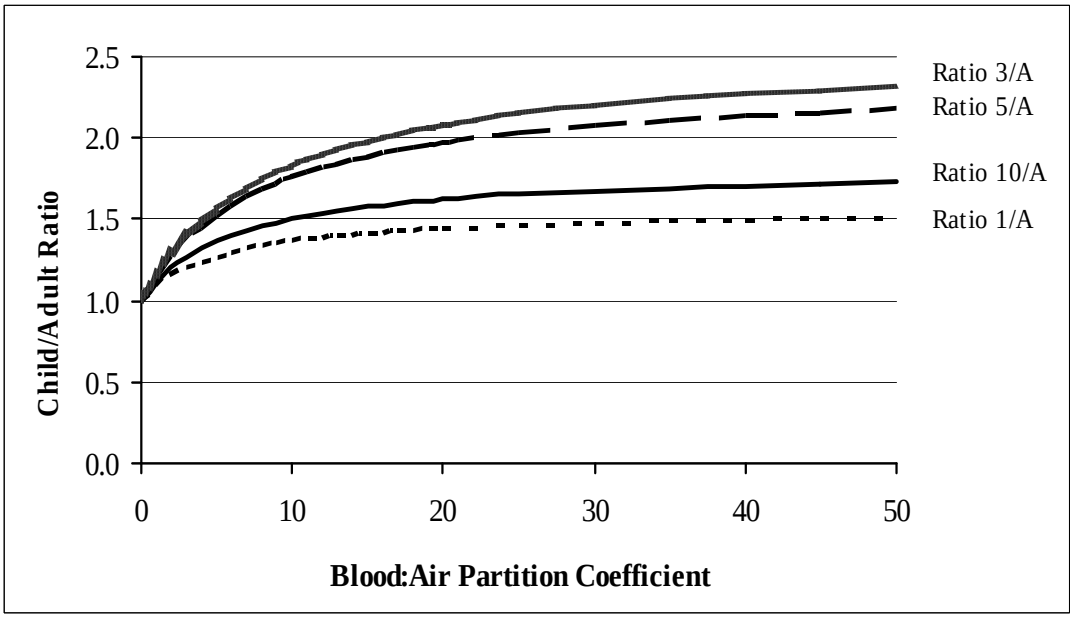



Figure 4b. Child/adult ratio of the steady-state concentration of parent chemical for which the formation rate is proportional to the ADH content (CLint is 1000/hr).




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

Figure 5. Child/adult ratio of the concentration of reactive metabolite at steady-state when metabolism is flow-limited in both adults and children.

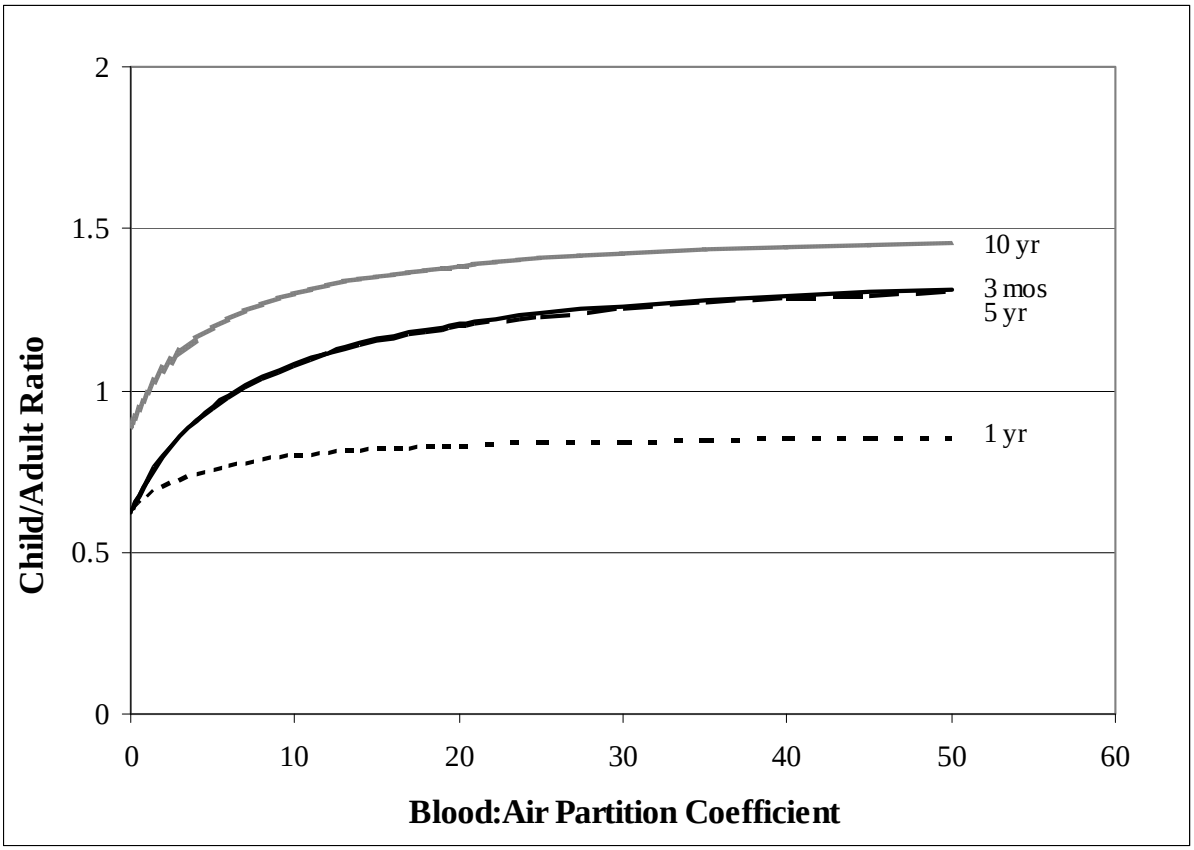
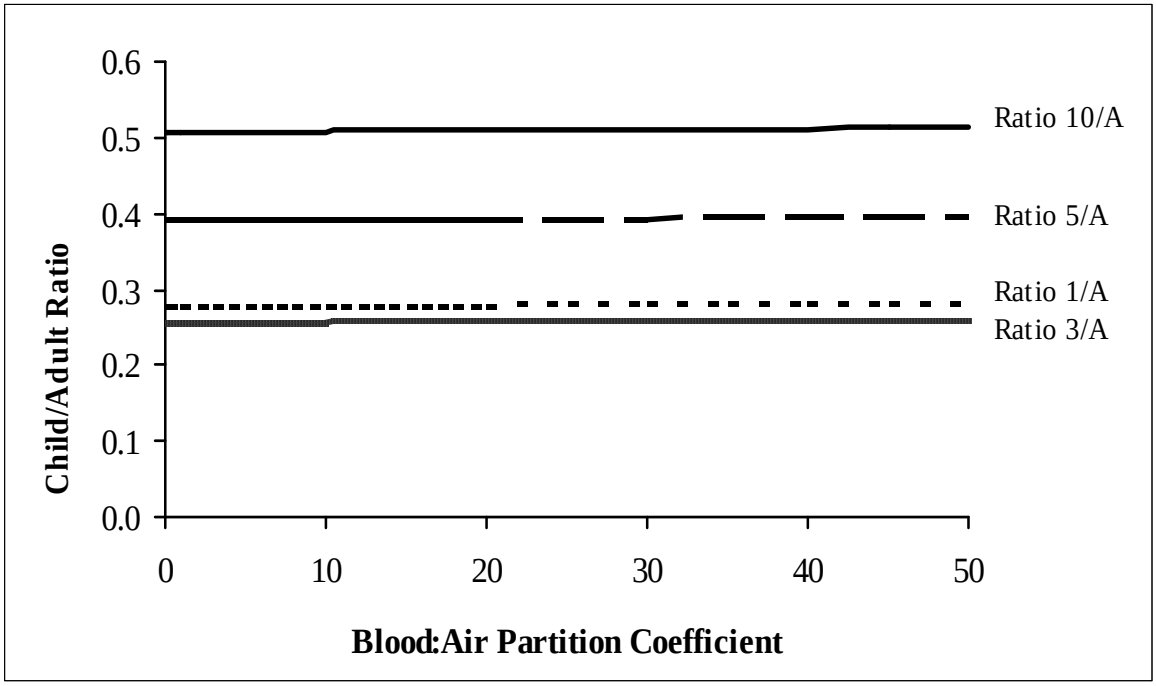
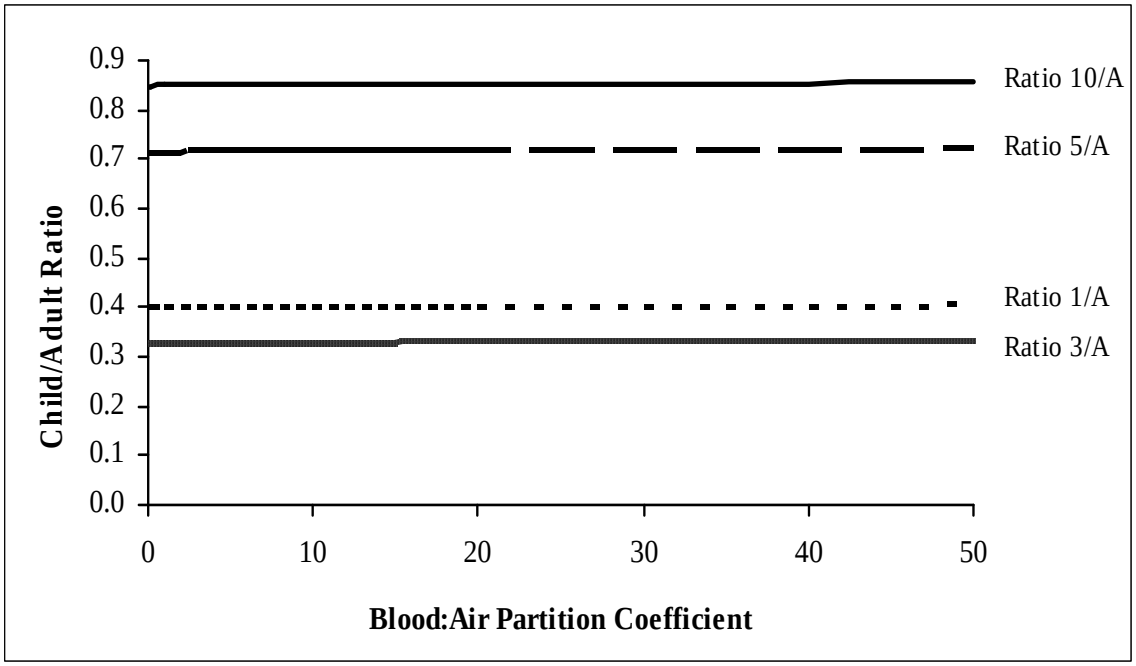


Figure 6. Child/adult ratio of the steady state concentration of reactive metabolite formed from inhaled gases for which the metabolite clearance is proportional to the ADH content (intrinsic clearance is 0.1/hr).



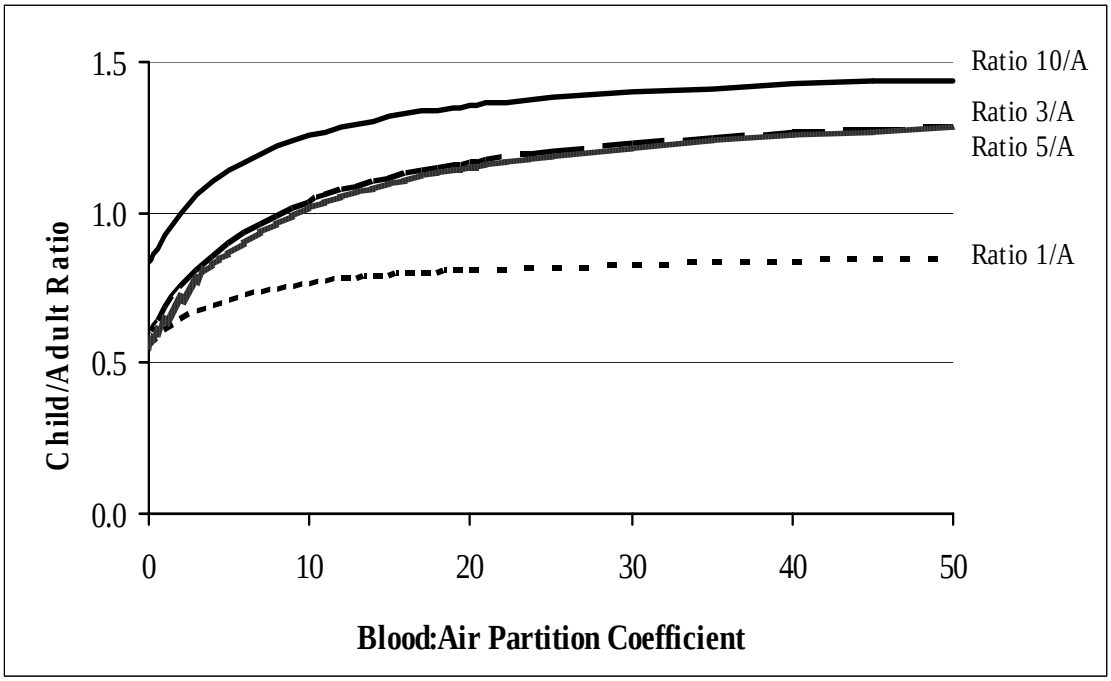

* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

Figure 7. Child/adult ratio of the steady state concentration of reactive metabolite formed from inhaled gases for which the metabolite clearance is proportional to the CYP2E1 content (intrinsic clearance is 0.1/hr).



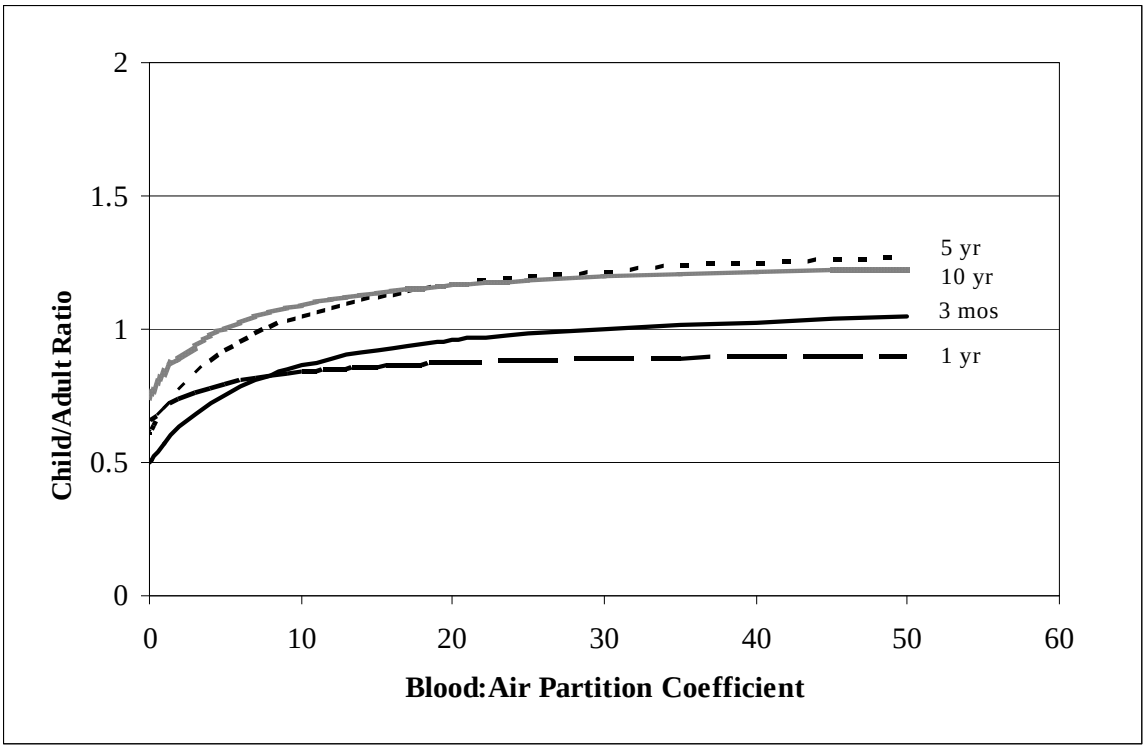

* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

Figure 8. Child/adult ratio of the steady state concentration of reactive metabolite formed from inhaled gases for which the metabolite clearance is proportional to the ADH content (intrinsic clearance is 1000/hr).




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

Figure 9. Child/adult ratio of stable metabolite formed by flow-limited metabolism and cleared by renal excretion.




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

Figure 10a. Child/adult ratio of stable metabolite for which the formation rate is proportional to the ADH content and renal clearance is dependent upon the GFR (intrinsic clearance is 1000/hr).

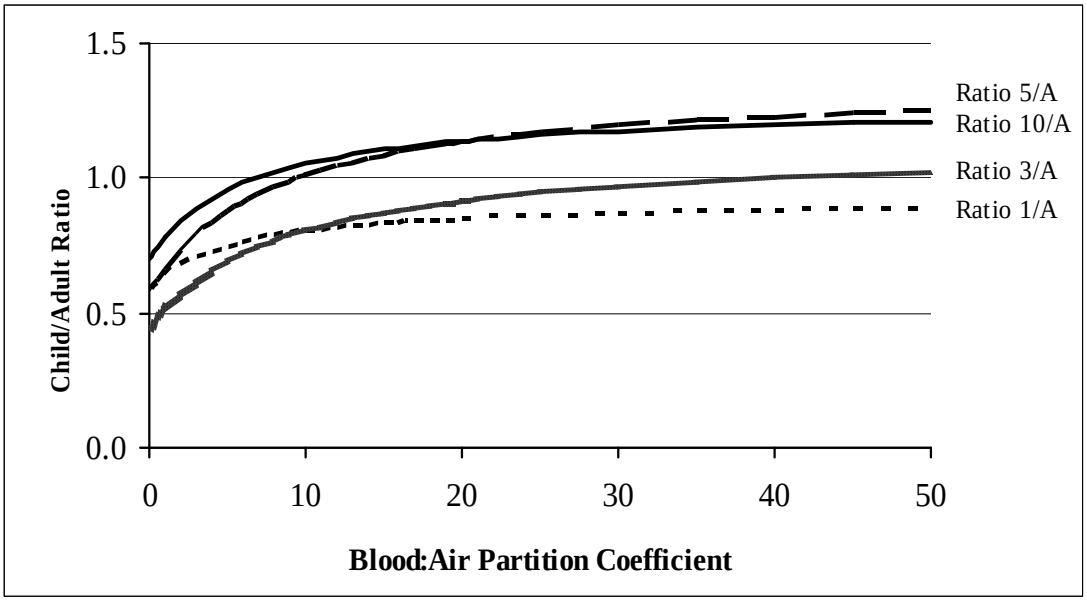
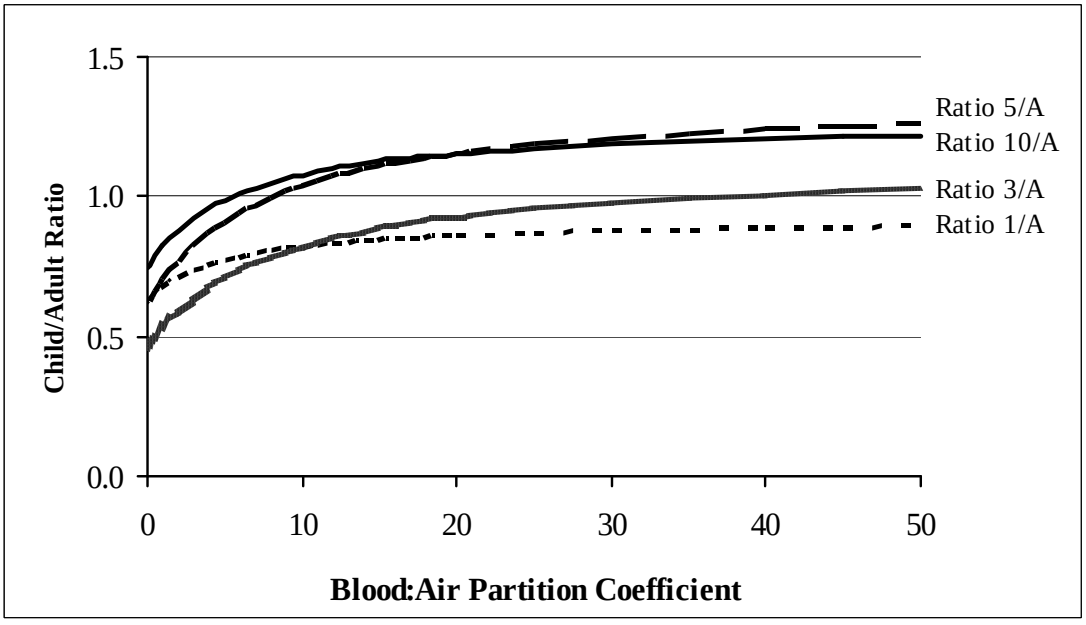



Figure 10b. Child/adult ratio of stable metabolite for which the formation rate is proportional to the CYP2E1 content and renal clearance is dependent upon the GFR (intrinsic clearance is 1000/hr).




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

Figure 11a. Child/adult ratio of stable metabolite for which the formation rate is proportional to the ADH content and renal clearance is dependent upon the GFR (intrinsic clearance is 0.1/hr).

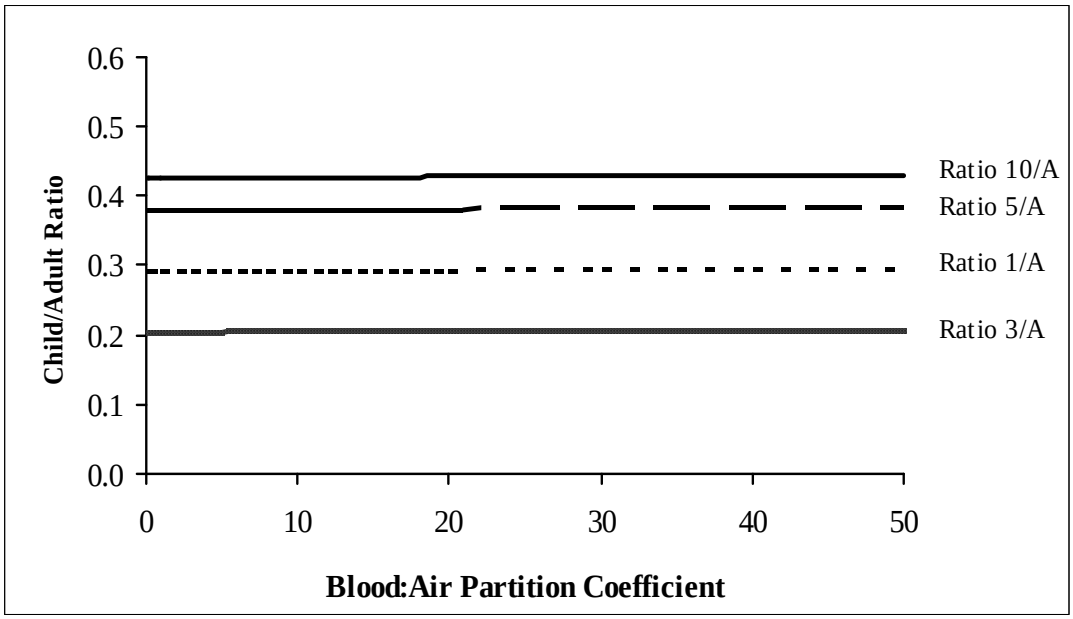
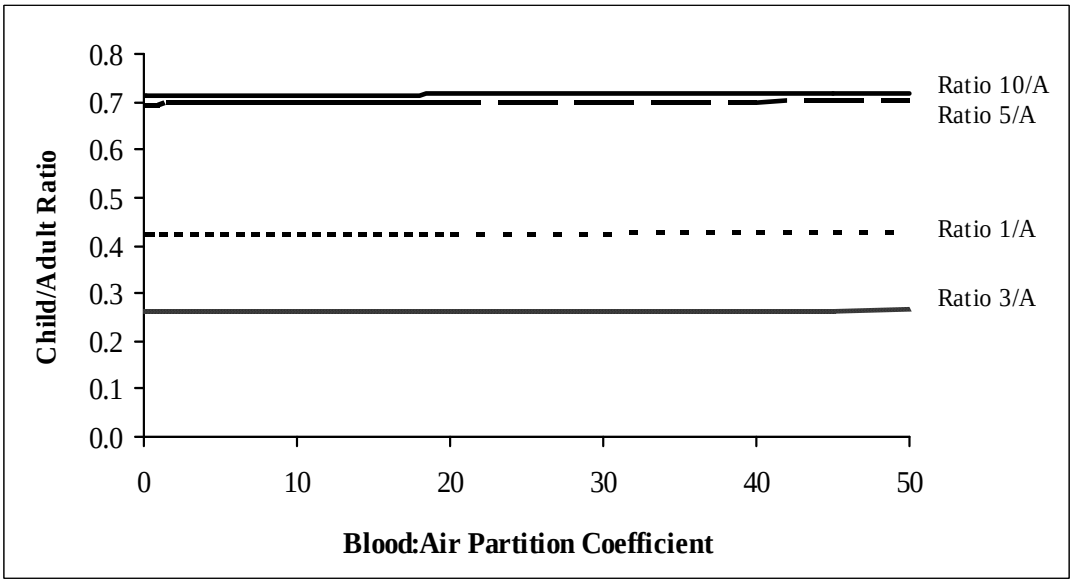
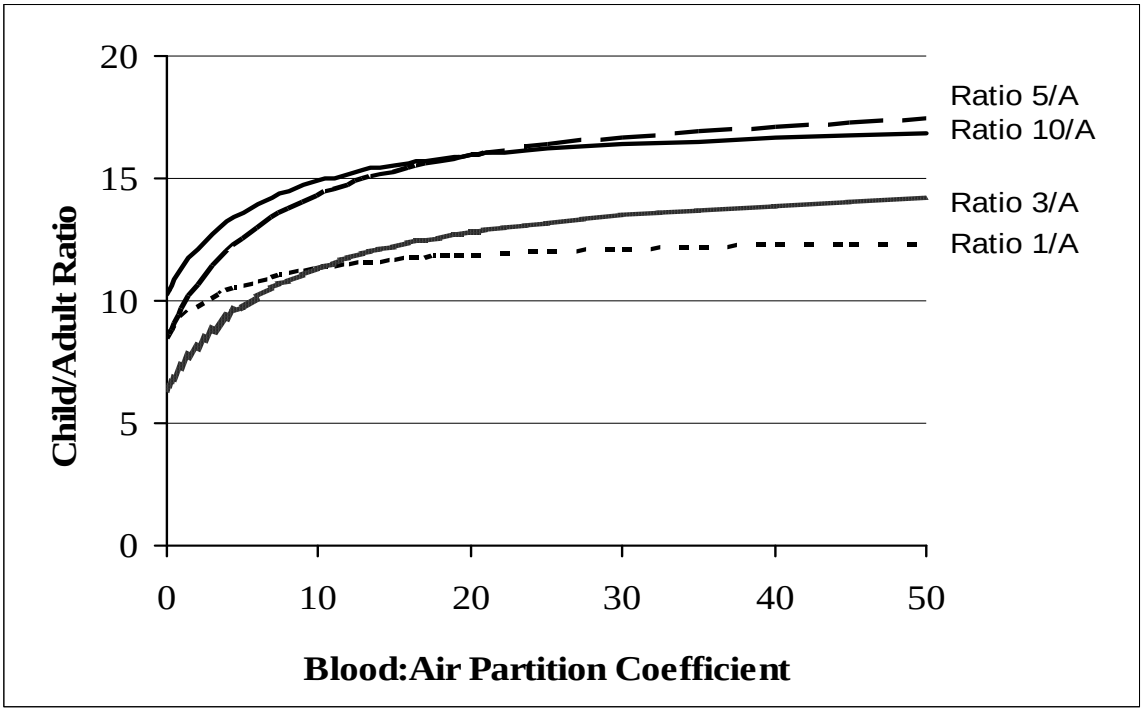



Figure 11b. Child/adult ratio of circulating metabolite for which the formation rate is proportional to the CYP2E1 content and renal clearance is dependent upon the GFR (intrinsic clearance is 0.1/hr).



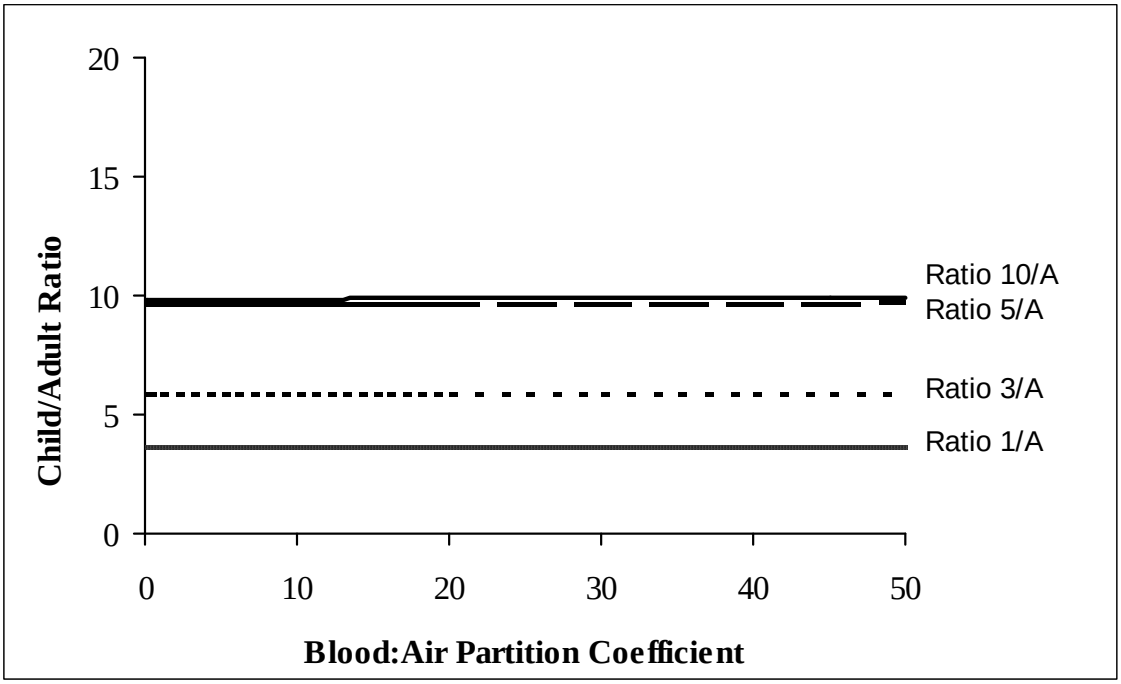

* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

Figure 12. Child/adult ratio of steady state concentration of a stable metabolite with efficient metabolic clearance in adults (i.e., flow limited process) but only renal clearance in children (i.e., hepatic extraction ratio = 0) (intrinsic clearance is 1000/hr).




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

Figure 13. Child/adult ratio of steady state concentration of a stable metabolite with efficient metabolic clearance in adults (i.e., flow limited process) but only renal clearance in children (i.e., hepatic extraction ratio = 0) (intrinsic clearance is 0.1/hr).




* Ratio 3/A = 3 month:adult; Ratio 1/A = 1 year:adult; Ratio 5/A = 5 years:adult; Ratio 10/A = 10 years:adult

# 5.0 References


Andersen ME. (1981). A physiologically based toxicokinetic description of the metabolism of inhaled gases and vapors: analysis at steady state. Toxicol Appl Pharmacol 60, 509-526.

Arms AD; Travis CC. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. Washington, DC: Office of Health and Environmental Assessment.

Asgharian B; Wood R; Schlesinger RB. (1995). Empirical modeling of particle deposition in the alveolar region of the lungs: a basis for interspecies extrapolation. Fundam Appl Toxicol 27, 232-238.

Beliveau M; Lipscomb J; Tardif R; Krishnan K. (2005). Quantitative structure-property relationships for interspecies extrapolation of the inhalation pharmacokinetics of organic chemicals. Chem Res Toxicol 18, 475-485.

Beliveau M; Tardif R; Krishnan K. (2003). Quantitative structure-property relationships for physiologically based pharmacokinetic modeling of volatile organic chemicals in rats. Toxicol Appl Pharmacol 189, 221-232.

Berenson G; Frank G; Hunter S. (1982). Cardiovascular risk factors in children -- should they concern the pediatrician? Amer. J. Dis. Child. 136, 855-862.

Bogdanffy M; Plowchalk D; Sarangapani R; Starr T; Andersen M. (2001). Mode-of-action-based dosimeters for interspecies extrapolation of vinyl acetate inhalation risk. Inhal Toxicol 13, 377-396.

Bogdanffy MS; Sarangapani R. (2003). Physiologically-based kinetic modeling of vapours toxic to the respiratory tract. Toxicol Lett 138, 103-117.

Clewell HJ; Gentry PR; Covington TR; Sarangapani R; Teeguarden JG. (2004). Evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. Toxicol Sci 79, 381-393.

Clewell HJ; Teeguarden J; McDonald T; Sarangapani R; Lawrence G; Covington T; Gentry R; Shipp A. (2002). Review and Evaluation of the Potential Impact of Age and Gender-Specific Pharmacokinetic Differences on Tissue Dosimetry. Crit Rev Toxicol 32, 329-389.

Csanady GA; Filser JG. (2001). The relevance of physical activity for the kinetics of inhaled gaseous substances. Arch Toxicol 74, 663-672.

Csanady GA; Mendrala AL; Nolan RJ; Filser JG. (1994). A physiologic pharmacokinetic model for styrene and styrene-7,8-oxide in mouse, rat and man. Arch Toxicol 68, 143-157.

Daston G; Faustman E; Ginsberg G; Fenner-Crisp P; Olin S; Sonawane B; Bruckner J; Breslin W; McLaughlin TJ. (2004). A framework for assessing risks to children from exposure to

environmental agents. Environ Health Perspect 112, 238-256.

de Zwart LL; Haenen HE; Versantvoort CH; Sips AJ. (2002). Pharmacokinetics of ingested xenobiotics in children: A comparison with adults. RIVM for Ministry of Health, Welfare and Sports.

de Zwart LL; Haenen HE; Versantvoort CH; Wolterink G; van Engelen JG; Sips AJ. (2004). Role of biokinetics in risk assessment of drugs and chemicals in children. Regul Toxicol Pharmacol 39, 282-309.

EEA (European Environmental Agency); WHO (World Health Organization). (2002). Children's Health and Environment: A Review of Evidence. Copenhagen: Environmental Issue Report. No. 29.

Family Practice Notebook. (2005). A Family Medicine Resource. Hematocrit: Hematocrit Cutoffs for Anemia. vol. 2005.

Gargas M; Burgess R; al. e. (1989). Partition coefficients of Low-Molecular-Weight Volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98, 87-99.

Gargas M; Burgess R; Voisard D; Cason G; Andersen M. (1989). Partition coefficients of Low-Molecular-Weight Volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98, 87-99.

Gentry PR; Covington TR; Andersen ME; Clewell HJ, 3rd. (2002). Application of a physiologically based pharmacokinetic model for isopropanol in the derivation of a reference dose and reference concentration. Regul Toxicol Pharmacol 36, 51-68.

Ginsberg G; Foos B; Firestone M. (2005). Review and analysis of inhalation dosimetry methods for application to children's risk assessment. In press.

Ginsberg G; Hattis D; Miller R; Sonawane B. (2004). Pediatric pharmacokinetic data: Implications for environmental risk assessment for children. Pediatrics 113, 973-983.

Ginsberg G; Hattis D; Russ A; Sonawane B. (2004). Physiologically based pharmacokinetic (PBPK) modeling of caffeine and theophylline in neonates and adults: Implications for assessing children's risks from environmental agents. J Toxicol Environ Health A 67, 297-329.

Ginsberg G; Hattis D; Sonawane B. (2004). Incorporating pharmacokinetic differences between children and adults in assessing children's risks to environmental toxicants. Toxicol Appl Pharmacol 198, 164-183.

Ginsberg G; Hattis D; Sonawane B; Russ A; Banati P; Kozlak M; Smolenski S; Goble R. (2002). Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 66, 185-200.

Ginsberg G; Slikker W, Jr.; Bruckner J; Sonawane B. (2004). Incorporating children's toxicokinetics into a risk framework. Environ Health Perspect 112, 272-283.

Haddad S; Restieri C; Krishnan K. (1999). Physiological modeling to characterize adult-children differences in pharmacokinetics. Toxicologist 48, 657.

Hanna LM; Lou SR; Su S; Jarabek AM. (2001). Mass transport analysis: Inhalation RfC methods framework for interspecies dosimetric adjustment. Inhal Toxicol 13, 437-463.

Hattis D; Ginsberg G; Sonawane B; Smolenski S; Russ A; Kozlak M; Goble R. (2003). Differences in pharmacokinetics between children and adults--II. Children's variability in drug elimination half-lives and in some parameters needed for physiologically-based pharmacokinetic modeling. Risk Anal 23, 117-142.

Health Canada. (2002). Children's Health Priorities within the Pest Management Regulatory Agency. Ottawa, Ontario, Canada: Pesticide Management Regulatory Agency.

Hofmann W. (1982). Mathematical model for the postnatal growth of the human lung. Respir Physiol 49, 115-129.

IPCS. (2006). Environmental Health Criteria 237: Principles for evaluating health risks in children associated with exposure to chemicals. Geneva: World Health Organization.

IPCS (International Programme for Chemical Safety). (2005). Harmonization Project Document No. 2. Chemical-Specific Adjustment Factors For Interspecies Differences And Human Variability: Guidance Document For Use Of Data In Dose/Concentration–Response Assessment. Geneva, Switzerland: World Health Organization.

Jarabek A. (2000). U.S. EPA mode of action: Framework for dosimetry model development. SRA.

Jarabek AM; Asgharian B; Miller FJ. (2005). Dosimetric Adjustments for Interspecies Extrapolation of Inhaled Poorly Soluble Particles (PSP). Inhal Toxicol.

Kimbell JS; Gross EA; Joyner DR; Godo MN; Morgan KT. (1993). Application of computational fluid dynamics to regional dosimetry of inhaled chemicals in the upper respiratory tract of the rat. Toxicol. Appl. Pharmacol. 121, 253-263.

Krishnan K. (2007). Chapter in Principles and Methods of Toxicology. In Hayes W. Boston, MA: CRC, pp. (Release date, September 12, 2007).

Krishnan K; Andersen M. (1991). Physiological Modeling and Cancer Risk Assessment. In Rescignio A; Thakur A, New Trends in Pharmacokinetics. NY: Plenum Press, pp. 335-354.

Lam G; Chen M; al. e. (1982). Determination of tissue to blood partition coefficients in physiologically-based pharmacokinetic studies. J Pharm Sci 71, 454-456.

Lees M; Way R; Ross B. (1967). Ventilation and respiration gas transfer of infants with increased pulmonary blood flow. Pediatrics 40, 262. (as cited by Price et al. 2003).

Lerman J; Gregory GA; Willis MM; Eger EI, 2nd. (1984). Age and solubility of volatile anesthetics in blood. Anesthesiology 61, 139-143.

Martonen TB; Graham RC; Hofmann W. (1989). Human subject age and activity level: factors addressed in a biomathematical deposition program for extrapolation modeling. Health Phys 57 Suppl 1, 49-59.

Martonen TB; Schroeter JD; Hwang D; Fleming JS; Conway JH. (2000). Human lung morphology models for particle deposition studies. Inhal Toxicol 12 Suppl 4, 109-121.

Nong A; McCarver DG; Hines RN; Krishnan K. (2006). Modeling interchild differences in pharmacokinetics on the basis of subject-specific data on physiology and hepatic CYP2E1 levels: a case study with toluene. Toxicol Appl Pharmacol 214, 78-87.

Oldham MJ; Robinson RJ. (2006). Calculated deposition in growing tracheobronchial airways: effect of growth-rate assumptions. Inhal Toxicol 18, 803-808.

Overton JH; Graham RC. (1989). Predictions of ozone absorption in human lungs from newborn to adult. Health Phys 57 Suppl 1, 29-36.

Pelekis M; Gephart LA; Lerman SE. (2001). Physiological-model-based derivation of the adult and child pharmacokinetic intraspecies uncertainty factors for volatile organic compounds. Regul Toxicol Pharmacol 33, 12-20.

Pelekis M; Krewski D; Krishnan K. (1997). Physiologically based algebraic expressions for predicting steady-state toxicokinetics of inhaled vapors. Toxicol Methodol 7, 205-225.

Pelekis M; Nicolich MJ; Gauthier JS. (2003). Probabilistic framework for the estimation of the adult and child toxicokinetic intraspecies uncertainty factors. Risk Anal 23, 1239-1255.

Plunkett LM; Turnbull D; Rodricks JV. (1992). Differences Between Adults and Children Affecting Exposure Assessment. In Guzelian P;Henry C; Olin S, Similarities and Differences Between Children and Adults: Implications for Risk Assessment. Washington, DC: ILSI Press, pp. 79-94.

Price K; Haddad S; Krishnan K. (2003). Physiological modeling of age-specific changes in the pharmacokinetics of organic chemicals in children. J Toxicol Environ Health A 66, 417-433.

Renwick AG. (1998). Toxicokinetics in infants and children in relation to the ADI and TDI. Food Addit Contam 15 Suppl, 17-35.

Renwick AG; Dorne JL; Walton K. (2000). An analysis of the need for an additional uncertainty factor for infants and children. Regul Toxicol Pharmacol 31, 286-296.

Rigas ML; Catlin SN; Ben-Jebria A; Ultman JS. (2000). Ozone uptake in the intact human respiratory tract: relationship between inhaled dose and actual dose. J Appl Physiol 88, 2015-2022.

Sarangapani R; Gentry PR; Covington TR; Teeguarden JG; Clewell HJ, 3rd. (2003). Evaluation of the potential impact of age- and gender-specific lung morphology and ventilation rate on the dosimetry of vapors. Inhal Toxicol 15, 987-1016.

Scheuplein R; Charnley G; Dourson M. (2002). Differential sensitivity of children and adults to chemical toxicity. I. Biological basis. Regul Toxicol Pharmacol 35, 429-447.

Smith H ed. (1994). Human respiratory tract model for radiological protection: A report of a Task Group of the International Commission on Radiological Protection. In: Annals of the ICRP: Published for the International Commission on Radiological Protection by Pergamon Press.

Snodgrass W. (1992). Physiological and Biochemical Differences Between Children and Adults as Determinants of Toxic Response to Environmental Pollutants. In Guzelian P;Henry C; Olin S, Similarities and Differences Between Children and Adults: Implications for Risk Assessment. Washington, DC: ILSI Press, pp. 35-42.

Szantay V; Tamas S; Marian L; Bochis G. (1974). [Changes of hepatic blood flow in children as a function of age]. Rev Roum Med Intern 11, 91-93 (as cited in Price et al. 2003).

US EPA (U.S. Environmental Protection Agency). (1994). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Washington DC: National Center for Environmental Assessment, Office of Research and Development.

US EPA (U.S. Environmental Protection Agency). (1997). Exposure Factors Handbook: Volume I. General Factors. Washington, DC: Office of Research and Development.

US EPA (U.S. Environmental Protection Agency). (2000). Benchmark Dose Technical Guidance Document (external review Draft). Washington, DC: Risk Assessment Forum.

US EPA (U.S. Environmental Protection Agency). (2006). Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment (Final Report). Washington, DC: National Center for Environmental Assessment, Office of Research and Development.

White D; Widdowson E; Woodard H; Dickerson J. (1991). The composition of body tissues (II): Fetus to young adult. Br J Radiol 64, 149-159 (as cited in Price et al 2003).

Wolterink G; Piersma AH; van Engelen JG. (2002). Risk Assessment of Chemicals: What About Children? : RIVM for Ministry of Health, Welfare and Sports.

Woodard HQ; White DR. (1986). The composition of body tissues. Br. J. Radiol 59, 1209-1219 (as cited in Price et al. 2003).