Meeting Materials
For a Peer Consultation on a Draft Framework To Evaluate Whether the Default Uncertainty Factor for Human Kinetic Variability is Adequate for Protecting Children

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1.0 INTRODUCTION

This report describes a framework (presented in Section 6 below and depicted in Figure 11a for inhalation of particles and Figure 11b for inhalation of gases and vapors) for evaluating the adequacy of the human kinetic variability subfactor for protecting children in the development of risk values. While the ideal approach for addressing this issue is using a physiologically-based pharmacokinetic (PBPK) model, when data or resources are not available to build such a model, a framework such as this may help identify cases where there is concern that the default is inadequate or where there is substantial uncertainty about the magnitude of kinetic differences between adults and children. Although the framework presented in this report is primarily for the inhalation route, application to the oral route is also discussed. The framework categorizes the chemical endpoint based on particle versus gas, and based on the target area (region of the respiratory tract or extrarespiratory).

Sections 3 and 4 below present methods and results of analyses of relative dosimetry, based on the U.S. Environmental Protection Agency (U.S. EPA) Reference Concentration (RfC) dosimetry and other steady-state approaches for extrarespiratory effects. These analyses were used in the draft framework to divide exposures into three groups based on chemical characteristics (e.g., blood:air partition coefficient) or exposure conditions (e.g., duration of exposure): (1) the default uncertainty factor is unlikely to be sufficiently protective, (2) the default uncertainty factor appears to be protective, and (3) the default uncertainty factor may be protective, but more information is needed to adequately evaluate the kinetic differences. Limitations and potential expansions to the framework are also discussed.

2.0 BACKGROUND

A number of scientific and policy initiatives beginning in the mid to late 1990s have resulted in increased interest in 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 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 (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]

[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. 2004). Toxicokinetic differences may result from numerous age-related differences in absorption, distribution, metabolism, and excretion, and their resulting effect on tissue dose of the active form of the chemical. These differences have been catalogued in numerous papers, as described below. This report focuses on the impact of toxicokinetic differences between adults and children.

These differences have led to the question of whether the standard approach for developing risk values adequately protects children. Expressed in terms of the methods for developing chronic risk values, this raises the issue of whether the uncertainty factor for human variability (UF_H) adequately addresses the full range of human variability, including differences between adults and children. A recent international effort, led by the International Programme on Chemical Safety (IPCS), has developed a framework for using chemical- or category-specific data to develop Chemical-Specific Adjustment Factors (CSAFs) (IPCS 2001). The CSAF methodology breaks the uncertainty factors for interspecies extrapolation (UF_A) and human variability (UF_H) into kinetic and dynamic components[2]. Using the CSAF paradigm, the work in this report is designed to evaluate the adequacy of the kinetic component of UF_H for protecting children. The default factor for this component, also referred to as HK_{AF}, is 3.2 (rounded to 3 by some organizations). The CSAF is calculated as the ratio of a key determinant of tissue dose (e.g., clearance or Area Under the Curve (AUC)) between the mean of the population and a specified percentile of the population (e.g., the 95^{th} or 99^{th} percentile).

Note that neither the CSAF nor the standard UF is intended to cover the entire population variability from the most sensitive to the least sensitive. Thus, it is not appropriate to consider the entire range of human variability (e.g., the 5^{th} percentile to the 95^{th} percentile) in considering the adequacy of uncertainty factors. Even using the ratio of the mean to the 95^{th} percentile is a health-protective approach, since in practice the extrapolation from effect levels in an animal study is from a low response rate - not the mean response. As described by Dourson et al. (2002), use of the interspecies uncertainty factor, UF_A, to extrapolate from a No-Observed-Adverse-Effect-Level (NOAEL) or benchmark dose (BMD) obtained from a study in laboratory animals results in a dose that is at the low end of the human dose-response curve (shown in Figure 1a based on cumulative response and in Figure 1b based on response at the dose). The Reference Dose (RfD) is then obtained by using the human variability uncertainty factor, UF_H, to extrapolate from the general population to a dose that would not be expected to cause effects in sensitive populations. This analysis means that defining the CSAF based on the ratio from the

[2] The CSAF guidance tends to define metabolic changes to a chemical in the target tissue as part of toxicodynamics, but notes that there is overlap between kinetics and dynamics, since PBPK models can address metabolic transformation occurring in the target tissue. Since much of this document focuses on portal-of-entry effects, the distinction of target tissue vs. systemic dose is less useful, and kinetics is considered to include all aspects of the body's processing of the chemical, while dynamics is used to refer to the toxic effects of the chemical for a given tissue dose.

mean to the specified percentile (as opposed to the ratio from, e.g., the 95th percentile to the 99.999 percentile) is a health protective approach that is expected to adequately cover the entire population, and has fewer uncertainties than estimating percentiles farther into the tail of the distribution.

Figure 1a. Cumulative Response as a function of Dose for Humans and Rats. Data are hypothetical, but approximate real situations.

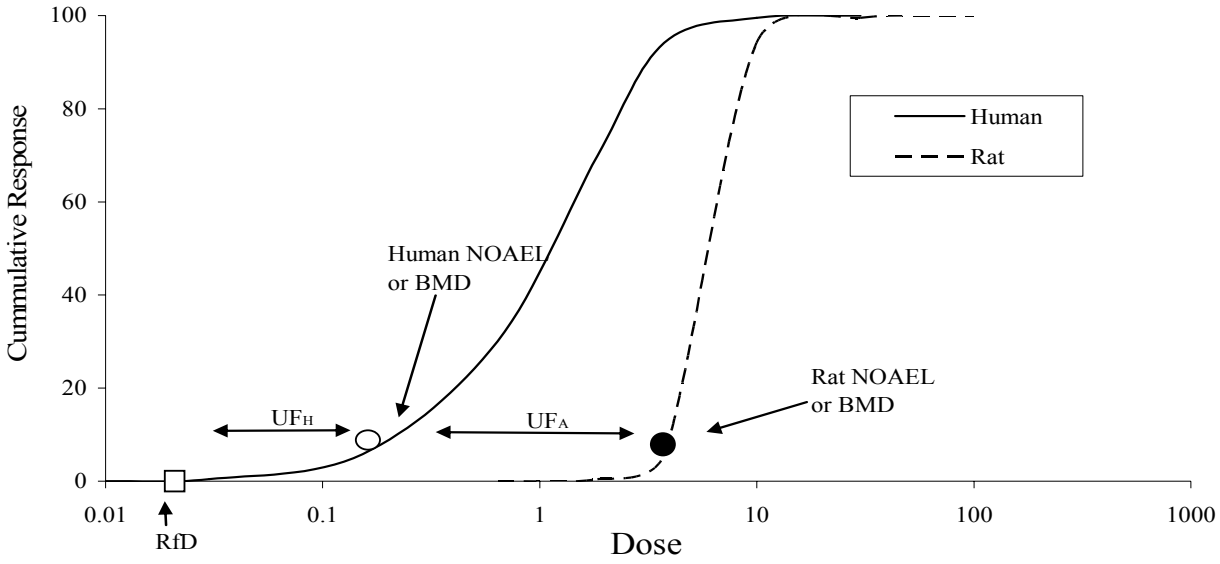


Figure 1b. Response as a function of Dose for Humans and Rats. Hypothetical data are the same as in Figure 5a.

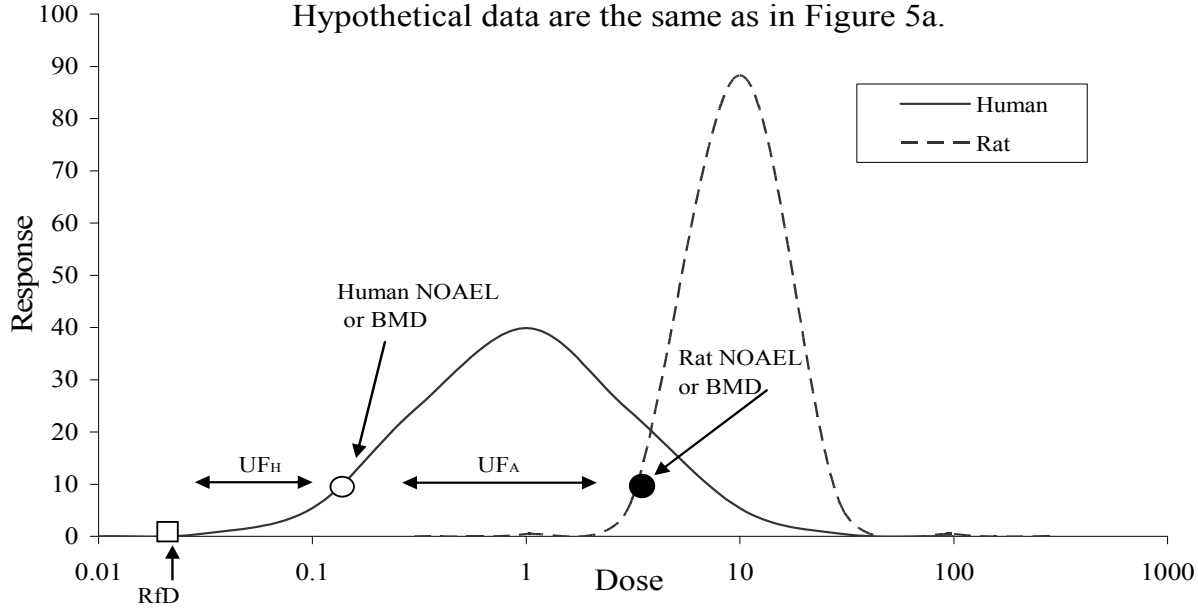


Figure 1a and 1b from Dourson et al. 2002.

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). Determining the impact of these differences on tissue 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 tissue dose (Renwick 1998; Renwick et al. 2000; Ginsberg et al. 2002; Hattis et al. 2003; Ginsberg et al. 2004b). These latter studies have concluded that the major differences are in the first six months of life, primarily in the first two months. In a broad review of kinetic and physiological differences between adults and children, including clinical differences observed for specific drugs, Renwick et al. (1998) concluded that the default uncertainty factor is sufficient for protecting children, except for preterm neonates in the first weeks of life. They also suggested that, because of enhanced metabolism by children after the neonatal period, particular attention should be paid to chemicals that undergo metabolic activation.

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; Ginsberg et al. 2004b). 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-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.

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. (2004c) 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 using semi-quantitative methods and illustrative quantitative analyses to begin to identify cases where the default uncertainty factor of 3.2 for human kinetic variability appears unlikely to be sufficiently protective of children, cases where the default is clearly protective, and cases where more information is needed to adequately evaluate the issue. This report also begins to identify key considerations that can be used to extend this work to additional cases, and key uncertainties.

In light of the complexity of the problem being considered, the material presented in this report addresses a limited set of cases, using a number of simplifying approaches. First, this report focuses on inter-individual variability for endpoints other than reproductive or developmental toxicity. When risk values are developed based on reproductive or overt developmental endpoints, one typically already has data indicating the susceptible age range, and that sensitive subgroup is used as the basis for the risk value. Fetal exposure is not addressed in

this analysis, since the outcomes of such exposure would result in developmental effects that might serve as the basis of risk values. In addition, this report excludes variability in exposure, except as it relates to variability in tissue dose at a given concentration in air, due to varying minute volumes. Instead, the framework is most relevant for considering whether children have windows of increased susceptibility (due to kinetic differences) to endpoints identified in studies conducted in young adult animals of effects on organ or system structure or function. For example, if the critical effect is on the liver, lung, or immune system observed in a standard toxicity study, this report addresses whether the default approach adequately addresses *kinetic* differences (but not dynamic) between adults and children. Conversely, this report does not address whether kinetic variability is adequately addressed when the critical effect is a teratogenic or neurodevelopmental endpoint, or an effect on spermatogenesis, since extrapolation from adults to children would not be involved for these endpoints, and the critical age range has been identified. Second, most of the current analysis is for the inhalation route, since dosimetry is further developed for this route, but the oral route is also discussed qualitatively.

A primary goal of this report is to identify the situations of highest concern, where children are expected to be, or may be, more sensitive than adults, in order to 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. While there are clearly a number of caveats in the approaches presented, and numerous refinements that would enhance them, we hope that this report and framework will serve as a starting point for future analyses and recommendations regarding the impact of age-related toxicokinetics.

3.0 METHODS FOR ANALYSES OF RELATIVE DOSIMETRY

This section describes the quantitative analyses used to evaluate the tissue dose in children and adults. For effects in the respiratory tract, analyses were done primarily using the U.S. EPA RfC dosimetry methods (EPA 1994). As described below, the methods differentiate between particles (including aerosols) and gases, and the gases are differentiated based on reactivity and water solubility. The analyses for extrarespiratory effects evaluated tissue dose

using steady-state assumptions, based on bounding estimates and age-specific data on maturation of enzyme capacity.

3.1 Physiological Parameters for the Respiratory Tract

Age-specific physiological parameters for determining respiratory tract dosimetry were based on the values calculated by Stanek and colleagues (2004) from physiological data developed by the International Commission on Radiological Protection **(**ICRP) (Valentin 2002)**.** These data are summarized in Table 1. While Stanek and colleagues presented separate physiological parameters for males and females in the 15- and 30-year old age groups, the calculations presented here are based on the average of male and female data for these age groups, in order to simplify the calculations.

Table 1. Physiological Parameters for Respiratory Tract in Humans of Different Age Groups, and Derived Ratios.

Age	BW (kg)	Ve (L/min)	SA-ET (cm^2)	Ve/SA-ET	SA-TB (cm^2)	Ve/SA-TB	SA-PU (cm^2)	Ve/SA-PU
3 month	6	2	66	0.03	710	2.8E-03	1.1E+05	1.8E-05
1 yr	10	3.6	97	0.037	860	4.2E-03	1.8E+05	2.0E-05
5 yr	20	6.1	200	0.031	1300	4.6E-03	3.7E+05	1.6E-05
10 yr	33	11	290	0.036	1800	5.8E-03	6.2E+05	1.7E-05
15 yr	55	12	420	0.03	2400	5.5E-03	1.1E+06	1.3E-05
30 yr	67	14	440	0.032	2600	4.8E-03	1.0E+06	1.1E-05

Ve = Minute volume

SA-ET = surface area of extrathoracic region

SA-TB = surface area of tracheobronchial region

SA-Pu = surface area of pulmonary region

Physiological parameters and ratios between surface areas and minute volume are from Stanek et al. (2004).

3.2 Particles

The primary approach used to estimate particle deposition in the respiratory tract was using the RDDR (Regional Deposited Dose Ratio) software developed by the U.S. EPA and provided as part of the RfC guidelines (EPA 1994). This is an empirical model that calculates deposition based on particle characteristics (e.g., particle size and its distribution) and physiological parameters (e.g., minute volume and surface area in the airway region).

In this document, this empirical human model (EPA 1994) was used to estimate the age-related differences in regional dose deposition. The approach used is briefly summarized below.

As defined by EPA (1994),

$$RDDr = 10^{-6} \times Ci \times V_E \times Fr$$

where:

RDDr = dose deposited in region r, mg/min,
Ci = concentration (this will be canceled out in the calculation of regional target dose ratios between different age groups),
V_E = minute volume, mL/min, obtained from Stanek et al. (2004)
Fr = fractional deposition in region r.

To estimate relative particle deposition dose in children and adults, regional target dose ratios (RTDR) were calculated relative to the adult dose (30-year old) as shown in the following equation; regional surface area was used as the normalizing factor. The term RTDR is introduced here to avoid confusion with the term RDDR, which generally refers to the interspecies deposition ratio. In addition, while the RDDR is expressed with the reference data (the animal data) in the numerator of the ratio, the RTDR is expressed with the reference data (adult) in the denominator. This is so that the ratio can more easily be used directly to evaluate age-dependent kinetic differences. A RTDR larger than one indicates that child receives a higher target dose than the adult.

RTDRr = RDDr child /RDDr adult

= $[(SAr)a/(SAr)c] \times [(V_E)c/(V_E)a] \times [(Fr)c/(Fr)a]$

where:

RTDRr = regional target dose ratio of particles for respiratory tract region (r)

a = adult

c = child

Sar = surface area in respiratory region (r) for the particular age group obtained from Stanek et al. (2004)

The calculations shown in the equation above evaluated deposition only for mono-dispersed particle distributions (sigma g $\leq$ 1.3). A similar calculation of RTDR can also be conducted for polydisperse particles (sigma g>1.3) by using the RDDR software provided with EPA's RfC guidelines (EPA 1994). Additional details regarding the calculation of RTDR are presented in the appendix.

As an initial step in evaluating the impact of age-specific differences in RTDR on the effects of longer-term exposure, an age-weighted RTDR was calculated for the first 10 years of life.

Weighting was done based on the time interval between the data points available. For children ages ranging from 3 months to 10 years, the age weighted RTDR for each region was calculated as follows:

Age weighted RTDR = [(average of RTDRs (3-month and 1-year)/0.75 year)

+ (average of RTDRs (1-year and 5-year)/4 year)

+ (average of RTDRs (5-year and 10-year)/5 year]/9.75 years

3.3 Category 1 Gases

Category 1 gases are defined in EPA's RfC methods as gases that are highly water-soluble and/or rapidly irreversibly reactive in the respiratory tract. Age-specific differences in regional respiratory tract deposition for category I gases, were estimated using the approach described in the U.S. EPA RfC methods (EPA 1994) for calculating Regional Gas Dose (RGDr). The RTDR between adults and children was calculated using the equations derived in the RfC methods, and presented below. The use of the term RTDR is similar to that described for particles, but in this case, the RTDR is analogous to the Regional Gas Dose Ratio (RGDR).

Extrathoracic Effects. For extrathoracic effects of category 1 gases, the following equation was used to calculate the $RTDR_{ET}$:

$$RTDR_{ET} = (RGD_{ET})_c/(RGD_{ET})_a$$
$$= [(V_E/SA_{ET})]_c / [(V_E/SA_{ET})]_a$$

Tracheobronchial Effects: For tracheobronchial effects of category 1 gases, the scrubbing in the upper airways of the chemical is taken into account empirically, and the concentration of the air exiting the ET region is used in the derivation of dose to the TB region.

$$RTDR_{TB} = (RGD_{TB})_c/(RGD_{TB})_a$$
$$= \{[(V_E/SA_{TB})]_c / [(V_E/SA_{TB})]_a\} \times \{[e^{-(SA_{ET}/V_E)}]_c/[e^{-(SA_{ET}/V_E)}]_a\}$$

Pulmonary Effects: The gas concentration that reaches the PU region is affected by the amount of uptake in both the ET and TB regions, so that the derivation for the PU gas dose ratio ($RTDR_{PU}$) incorporates the penetration fraction both for the ET and TB regions, respectively.

$$RTDR_{PU} = (RGD_{TB})_c/(RGD_{TB})_a$$
$$= \{[(V_E/SA_{PU})]_c / [(V_E/SA_{PU})]_a\} \times \{[e^{-(SA_{ET}/V_E)}]_c/[e^{-(SA_{ET}/V_E)}]_a\}$$
$$\times \{[e^{-(SA_{TB}/V_E)}]_c/[e^{-(SA_{TB}/V_E)}]_a\}$$

Age-specific physiological parameters were obtained from Stanek (Stanek et al. 2004), as presented in the previous section.

3.4 Category 2 Gases

Category 2 gases are defined in the RfC methods as moderately water soluble, and rapidly reversibly reactive or moderately to slowly irreversibly metabolized in respiratory tract tissue. Due to some inconsistencies in the calculations for Category 2 gases in the RfC methods (EPA 1994), Category 2 gases are treated in practice as either Category 1 gases or Category 3 gases, depending on the target (Jarabek, personal communication). Thus, respiratory effects of Category 2 gases are evaluated using the Category 1 approach, while extrarespiratory effects are evaluated using the Category 3 approach. These approaches can be considered reasonable approximations while the Category 2 approach is being further refined. Since there is currently no publicly available Category 2 approach, no separate calculations were conducted to evaluate age-specific differences in dosimetry for Category 2 gases.

3.5 Category 3 Gases

Category 3 gases are defined in the RfC methods as relatively water insoluble and not reactive in the airways of the lung, and these gases are absorbed into the systemic circulation (EPA 1994). Age-specific differences in steady-state concentration in blood (a surrogate for tissue dose) were calculated using several approaches.

The first approach was analogous to the RfC methods, which extrapolate from animals to humans based on blood:air partition coefficients (EPA 1994). Age-dependent blood:air partition coefficients were computed using the physiologically-based prediction algorithm of Poulin and Krishnan (1996b),

$$Pb{:}a = (Po{:}a * Fl) + (Pw{:}a * Fw),$$

where Pb:a is the blood:air partition coefficient, Po:a is the octanol:air partition coefficient, Pw:a is the water:air partition coefficient, Fl is the lipid content of blood, and Fw is the water content

of blood. While this algorithm tends to under predict apparent partitioning into blood based on solubility alone, perhaps due to plasma-protein binding (Poulin and Krishnan 1996a; Fouchecourt et al. 2001; Sterner et al. 2004), it is physiologically-based, allowing age-dependent changes in blood to be examined. The available data indicate that plasma proteins are less abundant in children, and possible structural differences may exist for some proteins. Miller et al. suggested that reduced plasma protein binding in newborns is due to reduced affinity of albumin for acidic drugs and lower levels of globulins and lipoproteins in the plasma of newborns, although protein levels reach adult values by 1 year of age (Miller et al. 2002). Lerman et al. (1984) measured slightly less albumin and globulin in the serum of newborns and 5-year-old children compared to adults. However, age-related differences in blood protein content are relatively small, and thus are expected to have a small impact on the predicted ratios of blood:air partition coefficients. The water content of blood was computed using age-dependent hematocrit data and the empirical relationship of Herscovitch and Raichle (1985):

$$C = 0.95 \text{ g/ml} - (0.22 \text{ g/ml})*H,$$

where C is the water content of whole blood and H is the hematocrit. The age-related lipid content of blood needed for the calculations was measured by Berensen et al. (1982). Gargas et al. (1989) reported the octanol:air and saline:air (used for water:air) values for several chemicals (see Table 3). The blood:air partition coefficients were computed for several age groups, including newborns, ages 6 months to 2 years, 2 to 6 years, 6 to 12 years, 12 to 18 years, and over 18 years.

A bounding estimate of the pharmacokinetic differences between children and adults was computed using the steady-state equations for the concentration of volatile chemicals in blood (Pelekis et al. 1997; Sarangapani et al. 2003; Clewell et al. 2004)

$$CA = CI / (1/Pb{:}a + QLC*E),$$

where CA is the steady-state concentration in arterial blood, CI is the inhaled concentration, Pb:a is the blood:air partition coefficient, QLC is the fractional blood flow to the liver, and E is the hepatic extraction ratio. The age-specific fractional blood flow to the liver computed by Clewell

et al. (2004) was used for the calculations. To obtain an upper bound on the differences in steady-state concentrations due to an immature metabolic system, the adult hepatic extraction ratio was assumed to be 1, while an extraction ratio of 0 was assumed for young children. Under these conditions, the chemical-specific blood:air partition coefficient was varied to obtain a range of steady-state chemical concentration ratios between children and adults. The concentration in blood was computed for ages 3 months, 1 year, 5 years, 10 years, 15 years, and 25 years.

4.0 RESULTS OF ANALYSES OF RELATIVE DOSIMETRY

The general approach used for this preliminary evaluation of relative dose in children and adults following inhalation exposure was based on the dosimetry developed by the U.S. EPA for development of RfCs (EPA 1994). This approach has the advantage of ease of use for a broad range of chemicals and a relatively long history of use. However, there are also a number of well-recognized limitations to the RfC dosimetry, including aspects of kinetics that are not addressed. Some of these considerations were addressed by additional work or additional models, as described below. Other limitations and possible approaches to address these limitations are noted as potential future enhancements to the proposed framework, but were not included in the current evaluation.

The RfC methods describe approaches for calculating the tissue dose in animals and humans resulting from inhalation exposure. The major focus of the RfC dosimetry is on developing factors that can be applied to exposure concentrations used in animal studies to determine the exposure concentration in humans that would result in the same tissue dose, the Human Equivalent Concentration (HEC). For this work, the focus is on comparing the tissue dose in adults and children, in order to evaluate whether the default factor of 3.2 for human kinetic variability is sufficient to protect children. To facilitate a more direct comparison with the uncertainty factor, the term Regional Target Dose Ratio (RTDR) is introduced here. The RTDR is conceptually the inverse of the RDDR or RGDR presented in the RfC methods, with the reference value (i.e., the adult data) in the numerator. Thus, a ratio larger than 1 means that children receive a higher dose, and a ratio greater than 1 means that the average child is predicted

to receive a higher dose than the average adult. The implications of the derived ratios for the adequacy of the default uncertainty factor are addressed in the Discussion.

4.1 Particles

Particle RTDRs were calculated by respiratory tract region using the methods described in the RfC guidelines (EPA 1994), and using the age-specific surface areas and minute volumes developed by Stanek et al. (2004) from the ICRP (Valentin 2002) data. All ratios are calculated as the deposition in child relative to the deposition in a 30-year-old adult. For the purpose of illustration, calculations were conducted for selected particle diameters in the range of 0.5 μm to 10 μm. The estimated results for the extrathoracic region, tracheobronchial region, pulmonary region, total respiratory tract, and extrarespiratory effects are summarized in Figures 2-7. Note that these analyses were all conducted using deposited dose and either regional surface area (for the ET, TB, PU and total respiratory tract [RT]) or body weight (for extrarespiratory effects) as the normalizing factor; the implications of clearance and considerations of retained dose are addressed in the Discussion.

Figure 2. Particle Deposition Ratio in the Extrathoracic Region

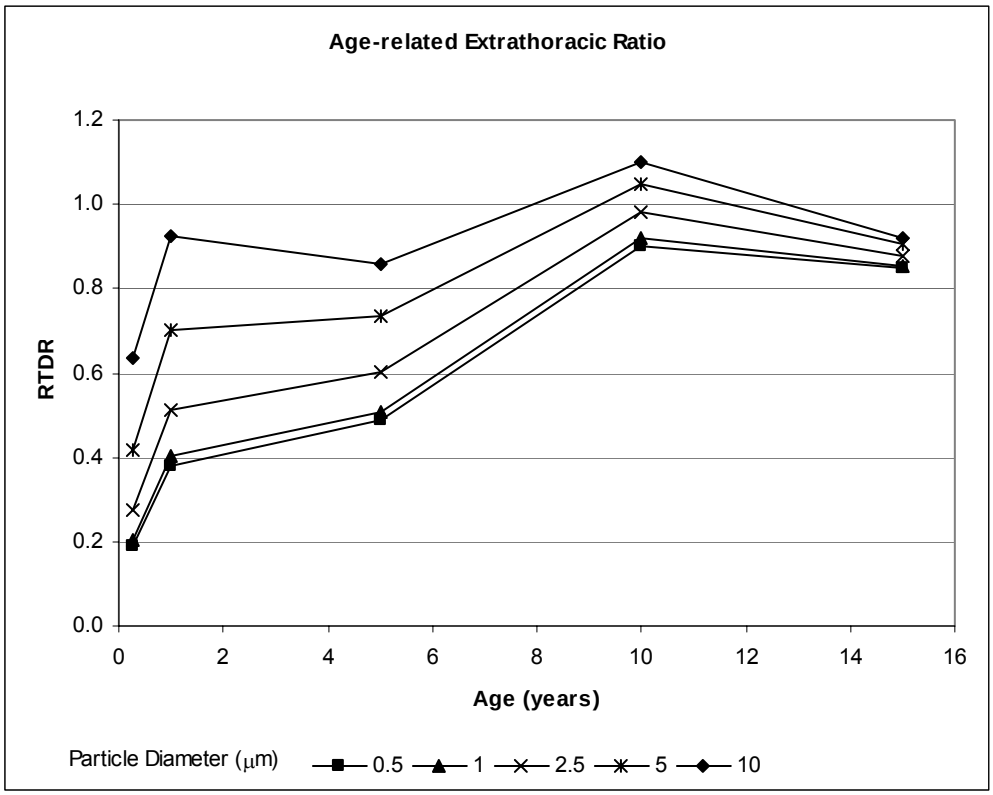


Figure 2 shows the age-related RTDR in the extrathoracic (ET) region. As shown in Figure 2, no age group has an RTDR greater than 1.1. This means that the particle deposition in the extrathoracic region of children is calculated to be less than or comparable to that of adults. For all of the particle sizes evaluated (0.5 to 10 μm), the amount of particle deposition in the ET region is less for younger children than for adults. These results are consistent with the biology and physics of particle deposition in the extrathoracic region of the airway. In this region, airflow speed is high and inertial impaction is the main mechanism of particle deposition. Impaction describes the tendency of the particle to deposit at the airway bifurcation due to inertial impaction and is positively related to the particle size and flow rate. The larger the particle size, the more deposition that occurs due to impaction. Since the Ve/SA ratio for the extrathoracic region is comparable among various age groups (see Table 1), the particle deposition in this region also depends on the airflow rate which is estimated by Ve/30 (rather than on the Ve/SA ratio). Younger children have a much lower air flow rate (e.g., Ve=2 L/min

in 3-month old children) than adults (e.g., Ve=14 L/min); therefore, younger children have less particle deposition in this region than adults. As shown in the Figure, the effect becomes more dramatic for smaller particles, where the significantly higher air flow rate in adults can cause impaction of a greater portion of smaller particles than can be impacted at the low flow rate in children. In addition, the overall mass of particle deposition was also higher for larger particle sizes than for smaller particles for both adults and children (data not shown). This reflects the fact that impaction is significantly influenced by the particle size, and so a significant percentage of large size particles (e.g., 10 μm) will deposit in this region, whereas only a negligible percentage of the small size particles (e.g., 0.5 μm) will deposit in this region.

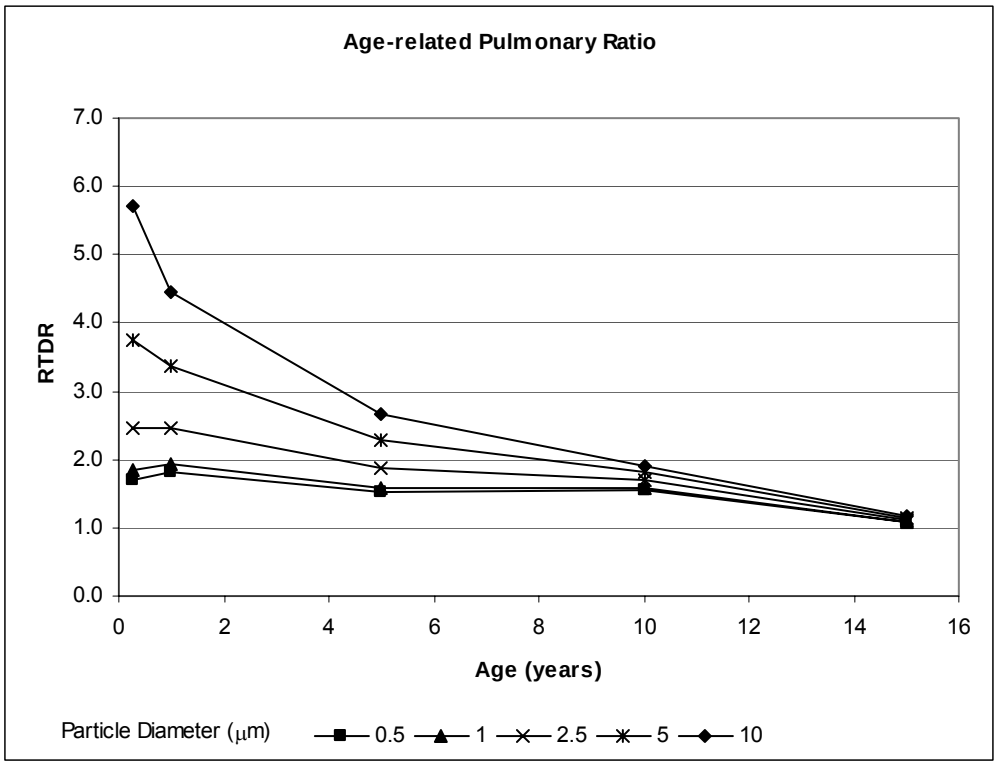
Figure 3. Particle Deposition Ratio in the Tracheobronchial Region

As shown in Figure 3, the dose deposited in the tracheobronchial region of young children (3 months and 1 year) is about 1.5- to 2.0-fold higher than the dose deposited in adults for particle sizes ≥ 5 μm. Regardless of the age, the RTDR is higher for the larger particles than

the small ones. Because the main mechanism of particle deposition in this region is sedimentation (as compared with impaction being the primary mechanism in the ET region), the higher deposited dose in young children for large particle sizes appears to be due to a combination of two factors. The first factor is the amount of material that passes through the ET region and is available for deposition in the TB region. As described above, a higher percentage of particles is deposited in the ET region of adults than children. Although the RTDR for the ET region for smaller particles is less than that for the large particles, the absolute amount of deposition of the small particles in the ET region (i.e., not relative to adult) is insignificant. This means that the effect of the filtering in the ET region is much more important for the larger particles than for the smaller ones, and is insignificant for the 0.5 μm particles. The lower ET deposition in children means that more particles are available for deposition in the tracheobronchial region in young children than in adults. The second factor is the Ve/SA ratio in the TB region among the different age groups. For example, the Ve/SA ratio in 3-month-old children (2.8) is about half that of 30-year-old adults (5.3), leading to less impaction at airway bifurcations, and tending to reduce deposition in the TB region. Together, these two opposing factors result in RTDR values between 0.5 and 1.9 for 3-month-old children, depending on the particle size. Similar considerations apply for children of other ages.

508 Figure 4. Particle Deposition Ratio in the Pulmonary Region

509



510

511

512 Figure 4 shows the age-related RTDR in pulmonary region. As shown in this figure,
513 particle deposition doses depend on the age and particle size. The youngest children receive the
514 highest deposited dose. The largest estimated ratio is a 5.7-fold higher dose in 3-month-old
515 children exposed to a particle size of 10 μm, compared to adults. Ratios greater than 3 were
516 estimated for children up to about 4 years exposed to 10 μm particles, and children up to about 3
517 years exposed to 5 μm particles. This observation may be due to a high Ve/SA ratio in young
518 children in this region. For example, the Ve/SA ratios are roughly 2-fold higher in 3-month and
519 1-year old children (0.02) than in adults (0.01) (see Table 1). As for the extrathoracic and
520 tracheobronchial regions, the RTDR increases with particle size. This reflects the size-related
521 differences in the implications of impaction in the ET region. Regardless of the age, the RTDR
522 is higher for the larger particles than the small ones. This reflects the effect of removal in the ET
523 region by impaction (as described for the TB region), plus the higher Ve/SA ratio in young
524 children. Unlike the TB region where these two factors acted in opposite directions, the two

factors act in the same direction in the PU region, leading to larger values for the RTDR for large particles at young ages.

Figure 5. Particle Deposition Ratio in the Entire Respiratory Tract

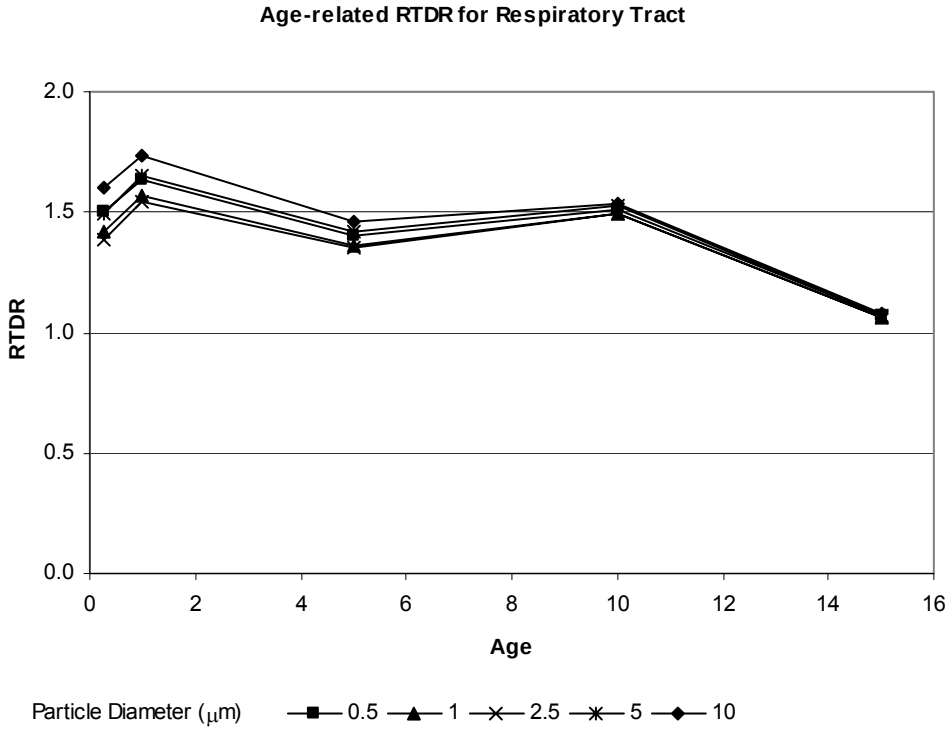
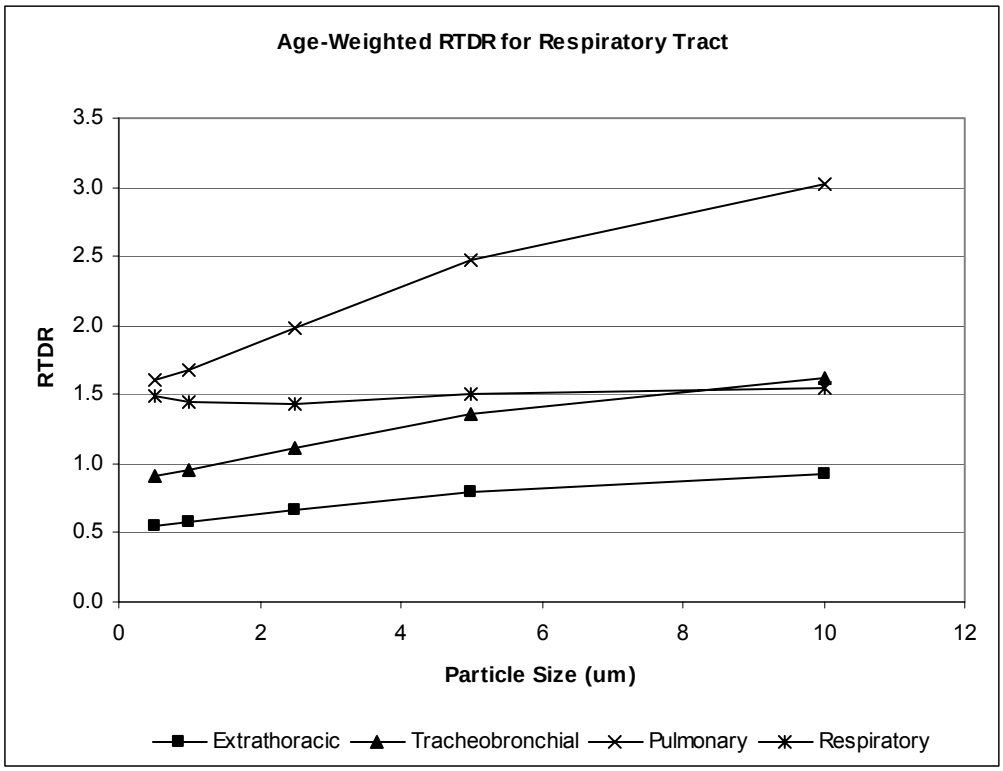


Figure 5 shows the overall particle deposition in the respiratory tract (including the extrarespiratory, tracheobronchial, and pulmonary regions). Total respiratory tract deposition in children was about 1.5- to 1.7-fold higher in children than in adults. This observation is consistent with the observation of relatively high Ve/SA in the overall respiratory region in young children relative to adults and the previous suggestion that on a body-weight basis, the volume of air passing through the lungs of a resting infant is twice that of a resting adult under the same conditions and, therefore, twice as much of any chemical in the atmosphere could reach the lungs of an infant (EPA 2002).

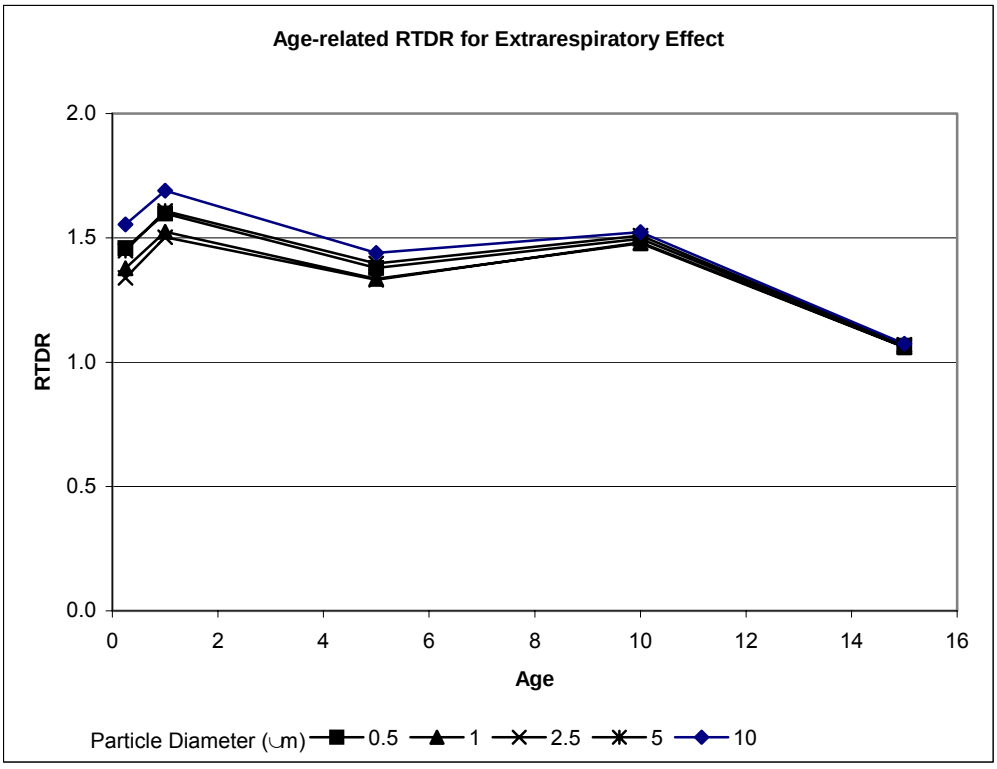
Figure 6. Time-Weighted (10-year) Average Particle Deposition Ratio in the Respiratory Tract



As an initial step in evaluating the impact of age-specific differences in RTDR on the effects of longer-term exposure, an age-weighted RTDR for the various regions of the respiratory tract was calculated for the first 10 years of life. The results plotted against particle size are shown in Figure 6. As indicated in Figure 6, the dose deposited in each respiratory tract region is related to particle size. Even after calculating the age-weighted average, the deposited dose in the pulmonary region of children is twice the adult value for particles of 2.5 μm and higher, and reaches a ratio of 3 times the adult value for the largest particle size evaluated (10 μm). The over all particle deposition in the respiratory tract is about 1.5-fold the adult value. In the TB region, the age-weighted average deposition ranged from comparable to that in adults for smaller particles, to approximately1.5-fold the adult value for larger particles. In the ET region, the age-weighted average deposition in children is comparable to or lower than the adult value. These ratios provide insight into the relative amount of deposition when longer time frames are taken into account. Note, however, that retained dose is generally a more appropriate dose metric than

deposited dose for these longer-term exposures, and clearance mechanisms become important in determining the retained dose. Implications of clearance are addressed in the Discussion.

Figure 7. Extrarespiratory Dose Metric Ratio for Particle Inhalation



According to the RfC guidelines (EPA 1994), the default normalizing factor for extrarespiratory (ER) effects is body weight, and dosimetric adjustments across species are based on the mass of particles per unit body weight. As noted in the guidelines, this approach assumes that all of the material deposited in the respiratory tract is available for uptake and systemic circulation. Thus, age-related differences in respiratory tract clearance or in dissolution of the material and absorption from the respiratory tract are not included. This approach also does not take into account the effect of age-related differences in the kinetics of clearance from the body. However, analysis of the RTDRs calculated using body weight as a normalizing factor are presented in Figure 7 as a first step in considering age-related differences in tissue dose for extrarespiratory effects of inhaled particles. As shown, all estimated RTDRs were ≤ 1.7, and the differences with particle size were lower than seen for the various regions of the respiratory tract.

This result is reasonable, since minute volume is positively related to body weight, and minute volume and body weight enter the calculation of ER dose as inverses of each other. In addition, the ratios shown here are very similar to those for the entire respiratory tract (RT, Figure 5). This is because the calculations for the RT and extrarespiratory differ only in that the weighting factor for the RT is surface area, while the weighting factor for ER effects is body weight. Since these two weighting factors are positively related, the resulting RTDRs are very similar. The analysis for ER effects could be enhanced by taking into account absorption of the chemical, as well as the types of considerations addressed in the context of Category 3 gases and oral dosing.

4.2 Gases - Introduction

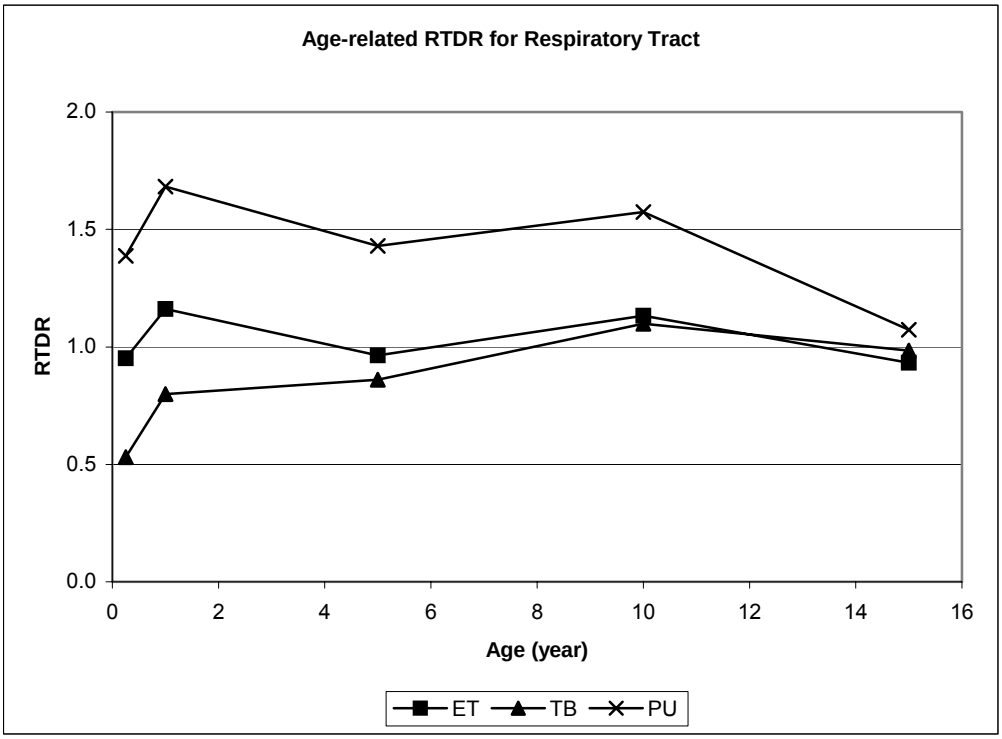
The general approach used to evaluate vapors and gases used the gas categorization approach in EPA's RfC methods (EPA 1994). In those methods, Category 1 gases are defined as gases that are highly water-soluble and/or rapidly irreversibly reactive in the respiratory tract. Category 2 gases are defined in the RfC methods as moderately water soluble and rapidly reversibly reactive or moderately to slowly irreversibly metabolized in respiratory tract tissue. Category 3 gases are defined in the RfC methods as relatively water insoluble and not reactive in the airways of the lung, and these gases are absorbed into the systemic circulation. Due to some inconsistencies in the calculations for Category 2 gases in the RfC methods, Category 2 gases are currently treated in practice as either Category 1 gases or Category 3 gases, depending on the target (Jarabek, personal communication). Therefore, this document presents methods for (1) respiratory effects, using the Regional Gas Dose (RGDr), and for (2) extrarespiratory effects. Several different methods were used to evaluate age-specific differences in tissue dose for extrarespiratory effects.

4.3 Category 1 Gases

To estimate age-related differences in regional respiratory tract dose following the inhalation of Category I vapors, RTDRs were calculated for the three regions of the respiratory tract, using the age-related physiological parameters developed by Stanek et al. (2004). As shown in Figure 3**,** the results indicate that the dose to the tracheobronchial region in children is

lower than or comparable to the dose in adults. In contrast, children up to 10 years of age receive a slightly higher dose (<2-fold) in the pulmonary region. There is no substantial difference in the regional dose received in the extrathoracic region among various age groups. This pattern of regional gas dose is consistent with the ratios of minute volume to regional surface area (Ve/SA) in the corresponding age groups.

Figure 8. Category I Vapor Dosimetry



4.4 Category 3 Gases

Category III vapors are relatively water insoluble and not reactive in the airways of the lung, and these gases are absorbed into the systemic circulation (EPA 1994). This systemic absorption and availability of the chemical clearly adds several complicating aspects. Since the chemical exerts its toxic action at a site remote from the respiratory tract, absorption, distribution, metabolism, and excretion can all possibly play a major role.

Because of the potential for competing roles of metabolism and excretion, a PBPK model is desirable to quantitatively address adult:child toxicokinetic differences. However, additional

625 approaches may be needed when there are insufficient resources to develop or adequately
626 parameterize a model for adults and children, or to run such a model. In such cases, one can
627 make additional comparisons based on steady state tissue levels. The EPA RfC methods use a
628 similar approach in evaluating kinetic differences between animals and humans, requiring that
629 "periodicity" be reached in animal studies for most (i.e., at least 90%) of the study duration (EPA
630 1994). (Periodicity means that the concentration vs. time profile is the same each week.) Using
631 the EPA methods, the ratio of blood:air partition coefficients in animals to that in humans is used
632 as a surrogate for target tissue dose. As an initial approach for evaluating age-dependent kinetic
633 differences, partition coefficients were calculated based on the physiology of different age
634 groups, and the ratio of the blood:air partition coefficients in adults and children was used to
635 predict differences in steady-state kinetics. Further steady-state analysis of physiologically-
636 based pharmacokinetic model equations was also conducted to assess the impact of age-
637 dependent metabolism parameters.
638 The following assumptions were made to apply steady-state approaches. First, it was
639 assumed that the chemicals of interest reach a steady-state level in the blood rapidly. That is, the
640 time to steady-state is short relative to the age range of interest or developmental window of
641 susceptibility. For example, if the developmental period of concern is 3 months in length, and
642 we want to be at steady-state for 90% of the interval, then the concentration in blood must reach
643 steady-state by 9 days. This condition must be met for the chemical to be at steady state long
644 enough to be able to apply steady state approaches. Second, it was assumed that the steady-state
645 arterial blood concentration of the parent chemical is an appropriate dose metric for toxicity.
646 This means that the parent chemical, not a metabolite, is the toxic form, and that alternative
647 metrics such as peak concentration in the blood are not appropriate dose metrics. If an
648 alternative dose metric applies, or the metabolite is the toxic form, calculations based on the
649 parent may be erroneous. These first two assumptions are analogous to those described in the
650 RfC methods for Category 3 gases. Finally, it was assumed that the exposure period of interest
651 is comparable to or shorter than the duration of the age range of interest, or the critical effect
652 related to the window of susceptibility. The last assumption is specific to the current analysis
653 and is related to the relevance of short-term peaks in the concentration-time profile to chronic
654 toxicity and average lifetime or cumulative exposure. This issue is addressed in greater detail in
655 the Discussion.

As described in the Methods section, age-dependent blood:air partition coefficients were computed using the physiologically-based prediction algorithm of Poulin and Krishnan (1996b). The lipid and water content for each age group is shown in Table 2. Table 3 shows age-dependent blood:air partition coefficients calculated using the algorithm of Poulin and Krishnan, chemical-specific octanol:air, water:air, and blood:air partition coefficients experimentally measured by Gargas et al. (1989). As shown, the estimated partition coefficients are very similar across age groups. Analogously to the approach described for Category 1 gases, the ratio of the partition coefficient in children to the partition coefficient in adults is an estimate of the difference in sensitivity, with numbers larger than 1 indicating that children are more sensitive. Note that this approach is the inverse of the factor used to calculate an HEC. Using this approach, the differences in blood concentration between children and adults were minimal. In addition, where there are larger differences, such as between adults and newborns for m-xylene, the partition coefficient for the adult is larger than for the child, indicating a lower tissue dose (based on this metric) for young children. The minimal difference calculated using this approach is primarily a result of similar lipid content of the blood across the age groups, particularly beginning at six months of age. Given the small amount of variability in lipid content among the different ages, the variability in lipid content due to other factors will likely dominate differences in partitioning across the population. Blood lipid values can be affected by obesity, and short-term levels can be elevated by consumption of a high-fat meal (Lin et al. 2002).

Comparison of the partition coefficients estimated for adults using this method with those measured in adult blood by Gargas et al. (1989) indicates that the Poulin and Krishnan algorithm systematically underpredicts the partition coefficients. This underprediction ranges from 20 to 60% of the measured value. This difference between predicted and measured partition coefficients is likely to be due to the effect of binding to plasma proteins, as described by various investigators (Lerman et al. 1984; Poulin and Krishnan 1996a; Fouchecourt et al. 2001). Lerman et al. (1984) studied the partitioning of anesthetics in the blood of newborns, children (3-7 years old), and adults. Partitioning was found to be directly correlated with albumin and globulin levels in blood, with greater blood:air partitioning in adults compared to children. Poulin and Krishnan (1996a) attributed the underprediction of partition coefficients for lipophilic VOCs to reversible binding to hemoglobin. Fouchecourt et al. (2001) indicated that rat blood:air partition coefficients of low molecular weight VOCs may be underpredicted by a factor of four when

687 protein binding is ignored. However, binding to plasma proteins is unlikely to increase the *ratio*
688 of child to adult partition coefficients because adults have slightly higher serum concentrations
689 of albumin and globulin (Lerman et al. 1984), and slightly lower concentrations of total protein
690 in whole blood (White et al. 1991). Higher protein content would increase the partition
691 coefficient, but the small difference in protein content is unlikely to affect the partition
692 coefficient (relative to adults) by more than a few percent. Overall, this initial analysis based on
693 partition coefficients alone indicates that the default factor of 3.2 is sufficient to address
694 differences in tissue dose. While this initial analysis is somewhat simplistic, an important
695 conclusion is that age-related differences in partition coefficients are unlikely to be a significant
696 determinant of tissue dose.
697 A more flexible steady-state approach (Pelekis et al. 1997; Sarangapani et al. 2003;
698 Clewell et al. 2004) was used to evaluate the steady-state concentration of volatile chemicals in
699 blood. Because this approach requires chemical-specific data (both the blood:air partition
700 coefficient and the hepatic extraction ratio [the fraction of chemical delivered to the liver that is
701 metabolized]), a bounding analysis was used to estimate the relative steady-state arterial blood
702 chemical concentrations in adults and children. The steady-state equation provided in the
703 Methods section was evaluated using adult parameter values for the liver blood flow and a
704 hepatic extraction ratio of 1, and then using child-specific values for liver blood flow and a
705 hepatic extraction ratio of 0, representing the maximum possible difference resulting from
706 metabolic differences between the child and adult. The assumptions implicitly required to use
707 these values with the steady-state equation are that 100% of the chemical that reaches the liver of
708 the adult is metabolized, while the child liver is unable to metabolize the chemical, and that
709 clearance in the child results solely from exhalation, while other elimination routes (e.g., extra-
710 hepatic metabolism or renal excretion) are ignored. Based on the analysis of age-specific
711 blood:air partition coefficients presented above, our worst-case steady-state analysis assumed
712 that partition coefficients were constant with respect to age. The blood:air partition coefficient
713 was then varied to examine the relationship between blood:air partitioning and the child-to-adult
714 ratio of steady-state blood chemical concentration.
715 The results of this approach, shown in Figure 9, indicate that for chemicals with a
716 blood:air partition coefficient less than 11, the child-to-adult difference in parent chemical
717 concentration will be less than a factor of 3.2 regardless of the degree of metabolic immaturity in

718 the child. For chemicals with higher partition coefficients, chemical-specific (or perhaps
719 enzyme-specific) data must be obtained to estimate age-specific differences in metabolism, since
720 these differences may be important. No systematic review of partition coefficients was located.
721 However, in one significant compilation (Gargas et al. 1989), 14/36 (39%) volatile organic
722 chemicals had human blood:air partition coefficients greater than 11. This list was not, however,
723 random, and included several closely-related compounds, so it is unlikely that this high
724 percentage is representative of the universe of volatile organic compounds. Some examples of
725 chemicals with blood:air partition coefficients greater than 11 include xylenes; 1- and 2-
726 nitropropane; 1,1,2,2-tetrachloroethane; and chlorodibromomethane.
727 In addition to the assumptions noted above, note that this steady-state worst-case estimate
728 does not take age-related differences in clearance into account. Because this worst-case scenario
729 assumed 100% hepatic extraction in the adult, any capacity for excretion of the parent compound
730 in the adult would not further decrease the steady-state blood concentration. In contrast, since it
731 was assumed that no hepatic metabolism occurs in the child, the parent compound may be
732 excreted unchanged in the child, reducing the steady-state blood concentration. Thus, any
733 potential for excretion in the child would decrease the age-related difference in steady state blood
734 concentration. This would mean that the minimum blood:air partition coefficient resulting in a
735 ratio of 3.2 or greater would be higher, and fewer chemicals would be of concern.
736 Age-dependent enzyme data can be easily incorporated using the steady-state approach
737 for chemicals that are predominantly metabolized by a single isoform of the enzyme if the parent
738 is the toxic form. The age-dependent enzyme data can be used to adjust the maximum rate of
739 metabolism following Clewell et al. (2004):
740
741 $$VMax_{Child} = VMax_{Adult}*F*VL_{Child}/VL_{Adult},$$
742
743 where VMax is the maximum metabolism velocity, VL is the volume of the liver, and F is the
744 enzyme activity as a fraction of the adult value. This approach was applied to the alcohol
745 dehydrogenase (ADH) activity data reported by Clewell et al. (2004) and the results are shown in
746 Figure 10. For this hypothetical case, changes in the blood:air partition coefficient and intrinsic
747 clearance (CL = VMax/KM) were examined based on analysis of bounding conditions.
748 According to the steady-state equation, if the clearance is much larger than the blood flow to the

liver, then the metabolism is flow-limited and the concentration is approximately independent of clearance:

$$CA = CI/(1/Pb{:}a + QLC)$$

where CA is an approximation of the arterial blood concentration and CI is the inhalation concentration.

If the clearance is much smaller than the blood flow to the liver, then the arterial blood concentration does depend on clearance:

$$CA = CI/(1/Pb{:}a + CL/QC)$$

where QC is the total cardiac output (L/min).

If the chemical is very poorly metabolized and the clearance is much less than 1, then the concentration is again independent of clearance:

$$CA = CI*Pb{:}a,$$

although other routes of elimination (e.g., renal excretion) would have to be considered if the chemical were not metabolized.

The results of the steady-state analysis using age-dependent ADH activity are shown in Figure 10. The 3 month old, the youngest group evaluated, has the greatest difference from the adult blood steady-state concentration. This is not surprising since the ADH enzyme is at the lowest levels at birth, and gradually increases to adult levels. The simulation indicates that, for chemicals metabolized by this enzyme with a partition coefficient greater than approximately 20, the steady-state concentration in the child may be more than 3 times greater than in the adult.

The child:adult steady-state concentration ratio profiles shown in Figure 10 will be steeper or shallower depending on the hepatic clearance in the adult. Note also that, as shown above, there is a range for CL, above or below which the steady-state concentration is not

dependent on CL. In fact, for a given blood:air partition coefficient, there is a value for the intrinsic clearance that will maximize the difference in steady-state blood levels between adults and children. For figure 10, a clearance value of approximately 125 L/hour is used. This value gives the greatest difference between the concentration in blood of a 3-month-old and an adult for a chemical with a blood:air partition coefficient of 100. A clearance value of 250 L/hour is the maximum if the blood:air partition coefficient is 20.

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)

794 Table 3. Calculated Age-dependent Blood:Air Partition Coefficients

795

			Ages (years)						Measured	Greatest Positive
	Octanol:Air[1]	**Water:Air[1]**	**0**	**0.5-2**	**2-6**	**6-12**	**12-18**	**>18**	**Blood:Air[1]**	**Relative Difference[2]**
Methyl chloride	8.57	0.88	0.75	0.78	0.78	0.78	0.77	0.77	2.5	1.02
Dichloromethane	131	5.96	5.2	5.5	5.5	5.4	5.4	5.3	8.9	1.02
Chloroform	402	3.38	3.3	3.8	3.8	3.8	3.8	3.7	6.9	1.03
Carbon tetrachloride	374	0.35	0.7	1.1	1.1	1.1	1.1	1.1	2.7	1.03
Chlorodibromomethane	2683	7.34	9.1	12	12	12	12	12	53	1.03
Chloroethane	38.9	1.09	1.0	1.0	1.0	1.0	1.0	1.0	2.7	1.02
1,1-Dichloroethane	186	2.45	2.3	2.5	2.5	2.5	2.5	2.5	4.9	1.02
1,1,2-Trichloroethane	1776	13.3	13	16	15	15	15	15	36	1.03
Benzene	465	2.75	2.8	3.4	3.4	3.4	3.3	3.3	8.2	1.03
Chlorobenzene	2188	2.81	4.8	7.3	7.1	7.1	7.0	7.1	30	1.03
o-Xylene	3534	2.65	6.1	10	10	10	10	10	35	1.03
m-Xylene	3245	1.92	5.2	8.9	8.6	8.7	8.5	8.6	33	1.03
p-Xylene	3319	1.77	5.1	8.9	8.6	8.7	8.5	8.7	45	1.03

796

797 [1]Gargas et al. (1989)

798 [2]The *positive* difference is highlighted in this table since an increase in blood:air partition
799 coefficient would increase the steady-state blood concentration, while a smaller blood:air
800 partition coefficient would lead to a smaller steady-state concentration.

801

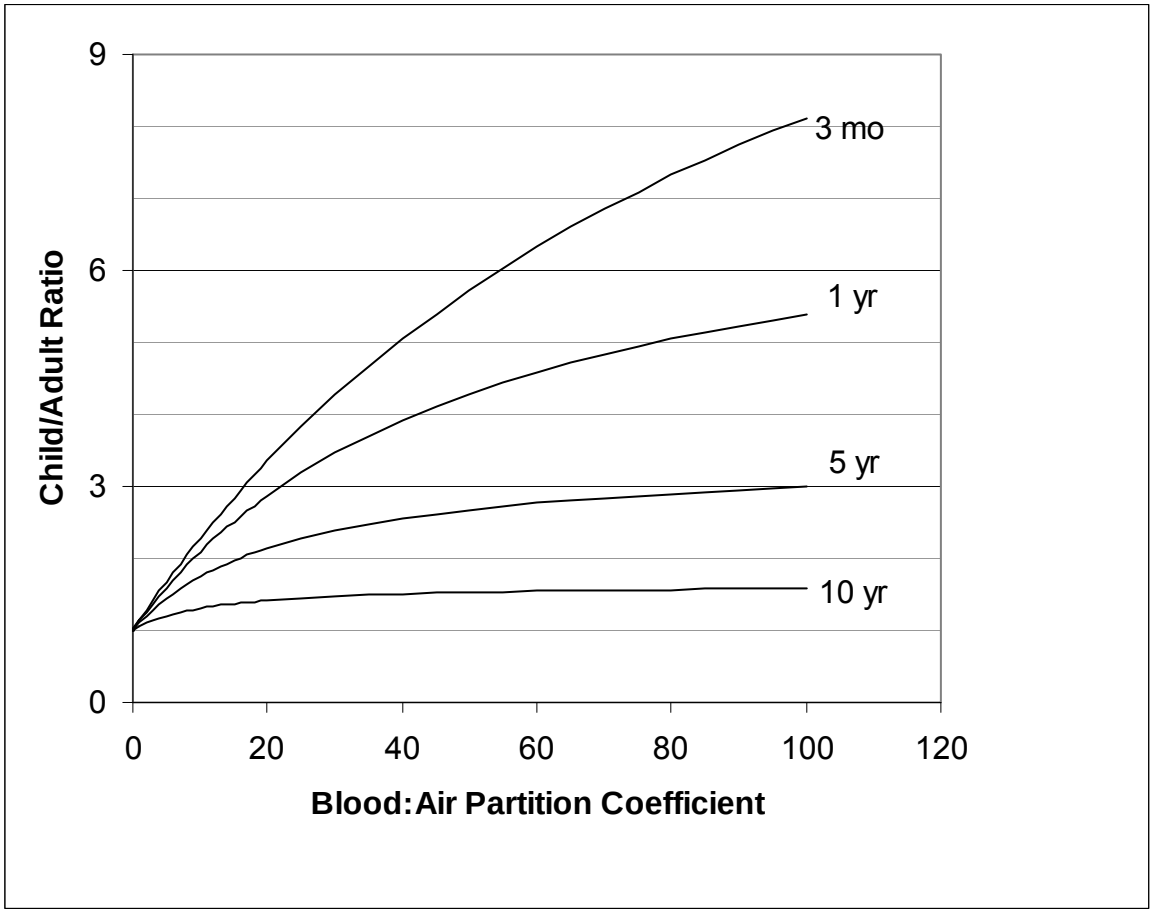
802

803

804

Figure 9. Bounding Estimate of Ratio Between Steady State Arterial Blood Concentration in Child and Adult Hepatic Extraction 100% in Adult and 0% in Child

Figure 10. Ratio of Steady-State Concentration in Blood of Children to Adults Child Hepatic Clearance Scaled by % of Adult ADH Activity



4.5 Oral Route

In light of the absence of a developed dosimetric approach for the oral route, the report has not attempted to conduct detailed analyses for oral exposures. However, consideration of the key determinant of tissue dose can assist in such analyses. For example, for chemicals that are very highly absorbed, widely and evenly distributed throughout the body, very poorly metabolized, and completely excreted in urine, the renal clearance will drive the steady state concentration in the blood. In general, hydrophilic chemicals are excreted in urine, while lipophilic chemicals are not. Urinary excretion is driven by three processes, glomerular filtration, tubular secretion, and tubular resorption. Filtered chemicals are low molecular weight, small diameter, neutral, lack significant protein binding, and are not affected by tubular secretion or tubular resorption. Tubular secretion and resorption are important for many organic chemicals and for electrolytes, but glomerular filtration is the key determinant for many inorganics, such as boron (Zhao et al. 1999).

Sarangapani et al. (2003) tabulated age-dependent GFR values that may be used to predict the kinetic differences between children and adults for chemicals excreted via glomerular filtration. Under the conditions listed above, these ratios may be used as a surrogate for the steady-state concentration ratios between children and adults. That is, the ratio is approximated by the adult GFR divided by the child GFR. Using this approximation and the data in Table 4, the difference in steady-state concentration in the blood of children under 5 years old and adults is more than 3-fold, and children aged 5 years or more are within a factor of 3 compared to adults.

Table 4. Age-specific GFR (fraction of adult value)

	GFR	
Age	**Male**	**Female**
1 mo	0.126	0.134
3 mo	0.145	0.152
6 mo	0.171	0.178
1 yr	0.209	0.218
5 yr	0.336	0.364
10 yr	0.556	0.619
15 yr	0.841	0.907
25 yr	1	1

For chemicals that may be excreted via tubular secretion or reabsorbed in the tubules, little can be done to predict differences in renal clearance between adults and children without urinalysis. If there is no tubular resorption, the renal clearance can range from the GFR to the renal blood flow, depending on the extent of secretion. If resorption occurs as well, then the clearance can range from 0 to the renal blood flow. These bounds are too wide to be useful for predicting age-specific differences.

The analysis of age-specific GFR to predict kinetic differences ignores the differences in plasma protein binding between adults and children. Only unbound chemical can be removed by glomerular filtration, and the renal clearance is modified by multiplying the GFR by the fraction of chemical that is not bound to plasma proteins. Miller et al. suggest that reduced plasma protein binding in newborns is due to reduced affinity of albumin for acidic drugs and lower levels of globulins and lipoproteins in the plasma of newborns, though protein levels reach adult values by 1 year of age (Miller et al. 2002). White et al. (1991) found slightly higher total protein content in the blood of newborns compared to adults, but measured whole blood rather than plasma. Lerman et al. (1984) measured slightly less albumin and globulin in the serum of newborns and 5-year-old children. The reduced binding in newborns would offset the effect of reduced GFR in the first years of life, so using GFR without considering the fraction bound is a reasonable approach.

5. DISCUSSION

Age-related differences in tissue dose from inhalation exposure to chemicals have been evaluated here using the RfC dosimetry for respiratory tract effects, and using the steady-state assumption for systemic effects. These results can be used to identify (1) conditions (e.g., chemicals, particle sizes, exposure durations, ages) where the default uncertainty factor for human kinetics is sufficient to protect children, (2) conditions where the default factor does not appear to be sufficient, and (3) conditions where further analysis is needed.

The child:adult ratios developed in the Results section can be used for comparisons with the default uncertainty factor. However, one first needs to consider the scenarios for which the analyses apply. First, the ratios derived here are most relevant for exposures that are generally comparable to or shorter than the duration of the age range of interest. This is because cumulative doses due to lifetime exposure to low doses 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). For example, calculation of time-weighted average dose shows that a tripling of the tissue dose (for a given intake) for the first 6 months of life relative to adults would increase the cumulative (lifetime) dose by less than 2%, while a tripling of the dose for 2 years would increase the cumulative dose by only 6%. Thus, if toxicity for the relevant endpoint is related to cumulative dose, these increases in tissue dose would not have a significant effect on risk, unless a window of susceptibility coincided with the period of increased dose. Therefore, the ratios and framework developed here are primarily relevant to shorter-term exposure values, including acute inhalation values such as Acute Exposure Guidance Limits (AEGLs), Acute Respiratory Exposures (AREs) and California's Acute Reference Exposure Levels (RELs); Drinking Water Health Advisories; and ATSDR Minimum Risk Levels (MRLs) for acute and intermediate exposure.

The second type of situation where the analyses developed here are relevant is when there is a window of increased susceptibility. While differences in response to a given tissue dose are accounted for in the toxicodynamic component of the intraspecies uncertainty factor, differences in tissue dose for a given intake also need to be accounted for in order to ensure that children are protected.

5.1 Implications and Issues for Particles

The results of the analyses in Section 4 can be used to evaluate the adequacy of the default human kinetic uncertainty factor for protecting children, but there are several considerations in doing so. The age-weighted RTDR data shown in Figure 6 are relevant for longer-term exposures, suggesting that particular attention should be paid to effects in the pulmonary region for large (e.g., 10 μm and larger) particles. A more definitive result for longer-term exposure would require taking clearance into account. The analysis in this report was based solely on deposition, and did not take into account clearance from the respiratory tract, and the resulting impact on retained dose. While deposition may be a key determinant of toxicity following acute exposure, chronic pathogenic processes are more likely to be a function of the dose retained in the respiratory tract. For insoluble particles, particle clearance occurs via the mucociliary escalator, and mucous velocity is a key determinant. Soluble and partially-soluble materials present an additional complication for calculating tissue dose, since dissolution processes will also contribute to clearance from the respiratory tract and systemic exposure. While it is reasonable to expect comparable dissolution rates across ages, other aspects of clearance from the lung (e.g., via alveolar macrophages) and the local or systemic kinetics (e.g., metabolism) of the material may exhibit age-related differences. These issues were not further explored in this project, but are considered as part of the overall framework discussed below.

Dosimetry calculations for this project were also conducted using the Multiple Path Model of Particle Dosimetry (MPPD).[3] MPPD is a sophisticated dosimetry model that has advantages over the RDDR program. However, we found uncertainties associated with MPPD. Initial calculations of age-specific deposition fractions for different size particles in the three respiratory tract regions revealed a consistent trend with age for deposition in the extrarespiratory region up through 14 years of age, but a large jump between the deposition fraction for the 14-year-old and the 21-year-old adult. For example, for 0.5 μm particles, the fractional deposition in children at ages 3 months to 14 years ranges from 0.12 to 0.11, while the value for the 21-year old adult is 0.048. For 10 μm particles, the fractional deposition in children ranges from 0.22 to 0.32, compared with 0.875 in the adults. This difference was traced to the

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

fact that the model was developed based on different data sets for calculating ET deposition in children and adults, and there appear to be some systematic differences in the data sets (Asgharian et al. 2004). Because the RTDR values are relative to adult deposition, an inconsistency with the adult value precludes the calculation of reliable ratios. Similarly, because the TB and Pu deposition fractions depend on how much material passes through the ET region without being deposited, we also considered the calculations for the TB and Pu regions to be insufficiently reliable. Therefore, while the MPPD model is mechanistic, and thus has strong advantages over the empirically-derived RDDR program used for the current analyses, the RDDR particle deposition calculations were used in this analysis.

An additional advantage of MPPD is that it also has the potential for calculating clearance, allowing calculation of retained dose. Including information on clearance would be a valuable enhancement of the current work, and would be important for addressing the implications of longer exposure durations. However, calculating retained dose with MPPD 1.0 is limited by two factors. First, clearance calculations in version 1.0 of the MPPD software are based only on measurements of clearance in the TB region (Asgharian, personal communication). More sophisticated approaches, such as that used by Jarabek et al. (2005), are needed to address pulmonary clearance. Second, mucous velocity data are available only for adults. Jarabek et al. (2005) noted that age-related changes in mucous velocity have been observed in Beagle dogs, and that data on mucous velocities in children are needed to evaluate the impact of clearance and mechanistically characterize human variability. As an initial step towards addressing longer-term exposures, it may be useful to further evaluate the limited data available on age-related changes in mucous velocity, and attempt to extrapolate from those data, in order to evaluate the adequacy of the human kinetic variability subfactor based on retained dose.

In the RfC approach used for this analysis, the filtration of particles is estimated using an empirical efficiency function that was calibrated using adult data only. However, Asgharian et al. (2004) used age-specific nasal deposition data to develop age-related efficiency function parameters for ages under 12 years, between 12 and 15 years, and adults. Further analysis using these more appropriate age-specific efficiency parameters could possibly have a substantial impact on the dosimetry for all regions since the ET region effectively acts as a scrubber for the tracheobronchial and pulmonary regions.

All particle dosimetry calculations done for the current analysis were based on monodispersed or near-monodispersed particle distributions. This was done to allow more direct statements regarding comparisons for different particle sizes. In reality, however, exposure is almost always to polydispersed particles. The approach shown here could be expanded to polydispersed particles by taking particle size variability into account in the modeling.

5.2 Issues Relevant to All Analyses

There are also a number of issues that are relevant to the analyses of both particles and gases. Other issues apply to both inhalation exposures and oral exposures. Age-related changes in respiratory tract geometry were not accounted for in the current analysis of either particles or gases, . The MPPD model, unlike the RfC methods, accounts for age-related differences in respiratory tract geometry. These differences may be particularly important for the ET region, in light of the growth of the nose throughout life.

An additional consideration for all of the calculations presented here is that the ratios calculated are based on the mean child dose relative to the mean adult dose. In contrast, the CSAF is defined as the ratio between the dose for some higher percentile (e.g., 95^{th} or 99^{th} percentile) of the sensitive subpopulation and the mean of the general population. To address this consideration, the framework notes situations where the ratio (e.g., the RTDR) is less than 3.2, but may be sufficiently high that inter-individual variability within an age group could result in some significant percentage of children differing from the adult dose by more than a factor of 3.2.

The framework presents some initial thoughts regarding variability within the child population; additional consideration of this issue is needed. 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).

6.0 FRAMEWORK

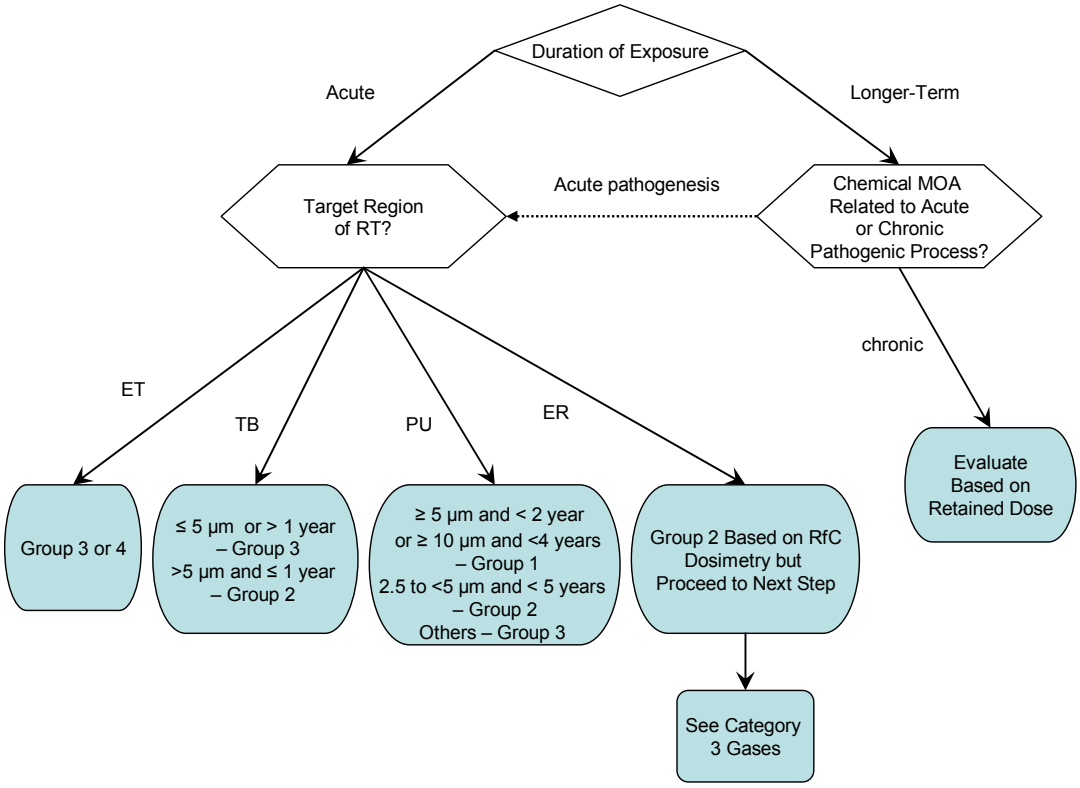
An initial framework for evaluating this issue has been developed based on the results in this report and on the literature describing age-related differences in chemical kinetics and the resulting impact on tissue dose. While there are clearly a number of areas in which this initial framework can be enhanced and expanded, the intent is to provide a structure that highlights key issues and identifies some standard approaches. This framework can then serve as a basis 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.

No attempt has been made at this point to calculate child-informed CSAFs, although doing so is encouraged where adequate chemical-specific data are available. Instead, exposures are grouped based on chemical characteristics (e.g., blood:air partition coefficient) or exposure conditions (e.g., duration of exposure) according to the degree of certainty that the default subfactor for human kinetic variability will be sufficient to protect children. The groups are:

- Group 1 - Of concern. A factor of 3.2 does not appear to be sufficient.
- Group 2 - Interindividual variability needs to be considered. The estimated ratio falls between 2 and 3.2, and sufficient inter-individual variability in children could result in a significant percentage of children differing from the adult dose by more than a factor of 3.2.
- Group 3 - Not of concern. The calculated ratio is between 1 and 2. Inter-individual variability in children is unlikely to result in a significant percentage of children differing from the mean adult dose by more than a factor of 3.2.
- Group 4 - Children are estimated to receive a lower dose than adults.

6.1 Framework for Particles

Figure 11a. Framework for Particles



Group 1 = Of concern. A factor of 3.2 does not appear to be sufficient.
Group 2 = Interindividual variability needs to be considered. The estimated ratio falls between 2 and 3.2
Group 3 = Not of concern. The calculated ratio is between 1 and 2.
Group 4 = Children are estimated to receive a lower dose than adults.

Abbreviations used in Figure 11a:

RT – Respiratory tract

ET – Extrathoracic

TB – Tracheobronchial

PU – Pulmonary

ER – Extrarespiratory

MOA – Mode of action

Figure 11a shows the framework for addressing the sufficiency of the default subfactor for inhaled particulates. As shown, the first consideration is the duration of the exposure of interest. As discussed above, retained dose (which depends on particle clearance) is more likely to be a meaningful dose metric than deposited dose for longer-term exposures. If exposure is longer-term, one asks whether the chemical's mode of action is related to acute or chronic pathogenic processes. If related to acute processes, the acute approach shown in the left side of Figure 11a may still apply. Otherwise, the analysis should be based on retained dose.

If the exposure of interest is acute or short-term (typically 1 day or less, but defined operationally for this document as exposures for which tissue dose is determined primarily by respiratory tract deposition), the next step is to identify the target region of the respiratory tract. As discussed above, all values calculated for RTDR for the ET region were comparable or less than 1 for all particle sizes evaluated (up to 10 μm). Therefore, the human kinetic uncertainty factor is likely to be adequate for protecting children from effects in the respiratory tract. In the tracheobronchial region, there is no concern at any age for exposure to particles of 5 μm or less. For the 10 μm particles, the RTDR is close to 2 for children of 1 year or less, and inter-individual variability needs to be considered to ensure that a factor of 3.2 covers the population. For effects in the pulmonary region, the sufficiency of the default uncertainty factor depends on the particle size and on the age of the child. Based on the deposition ratio alone, the default factor of 3.2 appears unlikely to be sufficiently protective for children of 1 year or less exposed to particles of 5 μm or larger. Based on the graph in Figure 4, this insufficiency may extend up to about age 2 for 5 μm particles, and up to about age 4 for 10 μm particles. For children up to about 5 years exposed to particles in the range of 2.5-5 μm, the considerations regarding inter-individual variability apply.

Although specific particle sizes are listed for the different categories, these particle sizes and ages should be considered as illustrative broad guidance, because they depend on the specific parameters used for the calculations, as well as the model used. For example, we noted that the surface areas used for our calculations differed from those cited by Sarangapani et al. (2003). We did not conduct a full analysis using the surface areas found in the latter paper, but initial calculations indicated that lower RTDR values would have been calculated using those parameters. The minute volumes used and tracheobronchial surface areas also differed from those used by Asgharian et al. (2004) and Jarabek et al. (2005).

Ginsberg et al. (2005) conducted similar analyses for particles, using the ICRP (Smith 1994) model. They noted that the ICRP model estimates deposition by diffusion, as well as impaction and sedimentation, and so is able to simulate models <0.5 μm. Regional surface areas and ventilation rates for 3-month-old children and adult males were collected from a variety of sources, and regional deposition in children and adults were compared for fine (<1 μm) and coarse (>1 μm) particles. They found that, for the particles >1 μm, deposition was comparable for the child and adult in the ET region, child deposition was comparable to or less than adult deposition in the tracheobronchial region (which was subdivided into two subregions), and deposition for children was greater than or equal to adult deposition in the pulmonary region. A primary difference between these results and those presented in the current report appears to be due to the differences in the surface areas and ventilation rates used.

Jarabek et al. (2005) evaluated the human equivalent concentration (HEC, based on relative respiratory dose to humans and animals) 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, taking into account deposition and clearance (but not age-specific clearance). Retained mass in the tracheobronchial region normalized to surface area was used as the dose metric. They found that the HEC was lowest (indicating highest tissue dose for a given air concentration) for the 14-year-old group, and highest for the 3-month-old group, regardless of particle size. The results were not used for detailed comparisons of the age-related differences in retained dose, but the difference between the 14-year-old and the adult appeared to be within a factor of about 3.

Figure 11a also includes dosimetry considerations for extrarespiratory effects of particles. A detailed analysis of age-related kinetics for these effects is not possible at this time, but factors that should be considered include considerations of particle deposition using body weight as the normalizing factor, as well as the factors affecting systemic clearance, as described below for Category 3 gases.

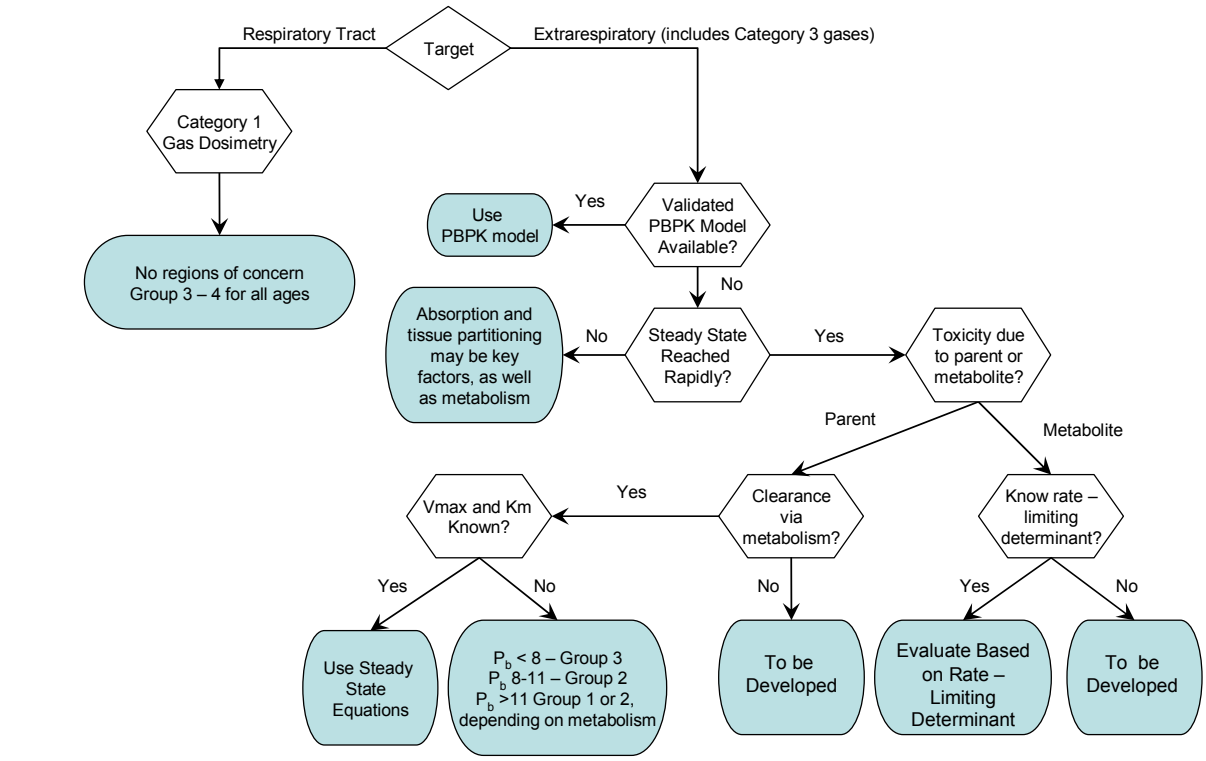
Figure 11b illustrates the framework for addressing the sufficiency of the default subfactor for inhaled gases. The first issue to be considered is whether the effect occurs as a portal-of-entry effect in the respiratory tract, or as a systemic effect.[4] Focusing first on the left-hand side of the figure, the analysis for portal-of-entry effects in the respiratory tract are addressed using the Category 1 gas dosimetry. As shown, the default UF for human kinetic variability is adequate for all regions of the respiratory tract, and for several of the age groups the tracheobronchial dose to children is lower than the dose to adults. This result is comparable to that of Sarangapani et al. (2003), who conducted an analysis using a PBPK model, and found that ozone deposition (% extraction) did not vary significantly with age in any region. Ratios greater than 3 were found at ages up to 6 months in the ET region, and up to 1 year for PU, when expressed in terms of extraction per unit surface area, but Ginsberg et al. (2005) noted that this latter dose metric must be multiplied by the ventilation rate to be converted to the rate of chemical deposition per unit surface area. Our results are also in general agreement with those of Ginsberg et al. (2005), who reported that the child dose is comparable to or smaller than the adult dose for the ET and TB regions, and little material is deposited in the pulmonary region. Ginsberg and colleagues also noted the importance of breathing pattern in determining the dose to different respiratory regions.

Evaluation of the relative tissue dose for systemic effects is much more complex, due to the numerous factors that can influence tissue dose. In light of this complexity, the first choice is to use a validated physiologically based pharmacokinetic (PBPK) model to estimate the tissue dose. This approach has the advantage of having the potential to include numerous age-related differences in physiological and metabolic parameters, but has the disadvantage that information may not be available for key parameters, particularly key metabolic parameters. This approach has been used by a number of authors. Clewell et al. (2004) evaluated the ratio of average daily dose for different ages to average daily dose in an adult, for chemicals with different physicochemical properties (volatile vs. nonvolatile, lipophilic vs. water-soluble) and different active forms (chemical vs. reactive metabolite vs. circulating metabolite), primarily for the oral route, with some analyses for the inhalation route. They found that, for the majority of the model compounds selected, the average daily dose to the child (for a given concentration in

[4]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 Category 2 gas methodology, when that approach is finalized.

6.2 Framework for Gases

Figure 11b. Framework for Gases



Group 1 = Of concern. A factor of 3.2 does not appear to be sufficient.
Group 2 = Interindividual variability needs to be considered. The estimated ratio falls between 2 and 3.2
Group 3 = Not of concern. The calculated ratio is between 1 and 2.
Group 4 = Children are estimated to receive a lower dose than adults.

air, or intake in mg/kg-day) was comparable to or lower than that in adults for all age ranges, and the ratios were less than 2 for almost all chemicals. The exceptions were in the first 6 months of life, for the dose of nicotine (expressed as parent compound following oral exposure) and of the circulating metabolite of isopropanol via inhalation. While the authors noted that their conclusions were limited by the paucity of age-specific information on metabolic clearance, a number of efforts are underway to collect age-specific metabolic and physiological data (Renwick 1998; Hattis et al. 2003; personal communications from H. Clewell and L. Sweeney). In a related study, Sarangapani et al. (2003) evaluated age- and gender-specific differences in tissue dose resulting from inhalation exposure. They evaluated chemicals that were rapidly and irreversibly reactive in the respiratory tract (ozone), relatively water-soluble and nonreactive

(isopropanol), and relatively water-insoluble and nonreactive (styrene, vinyl chloride, and perchloroethylene). Blood concentrations of the *parent* compound exhibited little age-dependency, while *metabolite* concentrations in the blood and the amount metabolized in liver or lung showed stronger age dependence. Consistent with results reported for pharmaceuticals (Renwick et al. 2000; Hattis et al. 2003), the largest differences were in the first year of life. Differences from adult levels greater than 3-fold were observed for several of the chemicals, with the largest differences at the earliest time point evaluated (1 month of age), and differences generally in the range of two-fold or less by 1 year. This is consistent with the early immaturity and development of enzyme systems.

In another example of the use of PBPK models to address this issue, Price et al. (2003) used a PBPK model to evaluate tissue dose resulting from inhalation exposure to furan at ages 6, 10, 14 years, and adult. They found that the maximum ratio of child:adult arterial blood concentration was 1.5. Age-related differences in physiological parameters were collated by the authors, supplemented by regression equations developed by Haddad et al. (2001). PBPK models have also been used by Pelekis et al. (2001), Ginsberg et al.(2004a), and Haddad et al. (1999) to evaluate age-related differences in kinetics.

In many cases, insufficient data or resources are available to develop and parameterize age-specific PBPK models. In that case, the next question is whether steady state is achieved rapidly (relative to the duration of exposure and the size of the age range). This is a key question because several simplifications assume that steady state has been reached, as discussed below. Prior to reaching steady state, factors such as absorption and tissue distribution may play key roles in determining tissue dose (in addition to the metabolic parameters that determine tissue dose after reaching steady state). For example, lipophilic chemicals may not reach steady state over an entire lifetime, and the relative volume of lipid stores may be a key determinant of tissue dose.

The next decision step is whether toxicity is due to parent or metabolite. Increased metabolism of a chemical may decrease toxicity if the parent is the toxic form, but increase toxicity if the metabolite is the toxic form. In addition, when the metabolite is the toxic form, tissue dose is determined by both the rate of production of the metabolite and the rate of its clearance.

When the parent chemical is the toxic agent, the next question is whether the chemical is cleared by metabolism, or by other mechanisms. This determines whether metabolic factors or other factors (e.g., renal clearance) will drive the tissue dose. As an example for the oral exposure route, boron is rapidly and extensively absorbed, widely distributed in body water, not metabolized, and readily excreted in the urine. Therefore, the key determinant of tissue dose is the glomerular filtration rate (GFR), and the RfD for boron used a CSAF for interspecies kinetic extrapolation based on the interspecies ratio of GFR (EPA 2005).

If clearance occurs primarily via metabolism, the next question is whether age-specific data are available for the kinetic parameters (Vmax and Km). If these data are available, the steady state equation can be used to estimate the steady state blood concentration for different age groups. The assumptions described for this method in the Results section apply for such analyses (e.g., metabolism occurs solely in the liver). Age-specific data may be available only for Vmax, but not for Km; in such cases the same Km is often used for all ages. This is a reasonable approach, since the Km is intrinsic to the enzyme, while Vmax (on an organism basis) depends on the *amount* of enzyme in the liver, and it is the enzyme amount that tends to show the largest age-related changes (assuming that the same isoform is produced). When the Vmax and Km for the chemical of interest are not known, information on age-related differences in Vmax for the same enzyme but using a related chemical substrate may provide useful information regarding conditions under which the default factor is not sufficient. However, caution is necessary when extrapolating from other chemicals, because wide differences in intrinsic clearance may occur for the same enzyme with different substrates.

When the Vmax and Km are not known, some additional conclusions about the adequacy of the default uncertainty factor can be drawn based on the worst-case analysis shown in Figure 9 for how the child:adult steady state blood concentrations vary with the blood:air partition coefficient. As shown in the Results section, the default uncertainty factor is sufficient for chemicals with a blood:air partition coefficient less than 8, even making worst-case assumptions regarding the age-related differences in metabolism (100% metabolic clearance in adults, 0% metabolic clearance in children). This conclusion could be enhanced by considering the impact of child variability. In the worst-case scenario, child variability in tissue dose for chemicals with a blood:air partition coefficient of 8-11 may be more important in determining the adequacy of the default uncertainty factor. For chemicals with a blood:air partition coefficient of 11 or

greater, evaluation of the relative amount of metabolic clearance in adults and children becomes key. The default uncertainty factor for such chemicals appears unlikely to be sufficient in the worst-case scenario, but lower metabolic clearance in adults, and/or some metabolic capacity in children will mean that the default uncertainty factor is sufficient for chemicals with higher blood:air partition coefficients. This was highlighted in the example presented on ADH.

Only limited broadly-applicable statements can be made about the adequacy of the default human kinetic uncertainty factor when the metabolite is the toxic agent. For example, for metabolites that are readily excreted, the generally lower metabolic capacity in the first 6 months to a year of life suggest that this age group may not be at greater risk, while the higher metabolic capacity in the 1-2 year range suggest that additional attention may need to be paid to these groups. As described for situations where the parent is the toxic form, additional analyses can be conducted in the specific situations where the rate-limiting determinant of tissue dose has been identified. For example, Ginsberg et al. (2005) identified several conditions under which greater metabolite levels may occur in the infant liver than the adult liver. These conditions are all related to the finding that, for many pathways, there is a period (typically in the range of 2 months to 2 years), when parent chemicals have a shorter half-life compared to adults. 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).

We have not attempted to derive a comparable framework for the oral route. Many of the considerations in the extrarespiratory branch of Figure 11b also would apply to the oral route, but additional complications of first-pass metabolism and absorption need to be considered. Current interagency efforts (Jarabek, personal communication) 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.

7.0 CONCLUSION AND FUTURE STEPS

This report describes a framework for addressing the adequacy of the human kinetic variability subfactor for protecting children. Because short-term differences in kinetics result in small impacts on average lifetime daily dose, the kinetic differences observed in children are of greatest interest for two types of situations. The first is when exposure duration is comparable to or shorter than the duration of the life period of increased susceptibility, such as for acute exposure guidelines. The second situation is when there is a window of increased tissue susceptibility due to age-related toxicodynamic differences, meaning that additional focus on kinetics in the child is appropriate.

A number of enhancements and additional details might be added to the framework. For example, it would be useful to better refine the particle dosimetry calculations by using age-specific efficiency parameters developed by Asgharian et al. (2004), or using a mechanistic model such as MPPD. Better harmonization of age-related parameters for the respiratory tract would also be useful. For the Category 3 gases, further work could be done to bound the range of values for which the intrinsic clearance results in a child:adult ratio >3. The work described for ADH metabolism could be expanded to other enzyme systems. The framework could also be extended to address toxic metabolites, as well as providing additional guidance on how and when to incorporate the available information on age-related differences in excretion. Finally, the development of a dosimetric approach for oral exposure will facilitate more detailed analyses for that route. Despite these opportunities for improvements, it is hoped that this framework will provide a structure for thinking about the implications of age-related kinetic differences for tissue dose and for future research in this area.

8.0 ACKNOWLEDGMENTS

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APPENDIX

To estimate the difference of particle deposited dose among different age groups, a preliminary quantitative estimate was based on U.S. EPA RfC method (EPA 1994) for calculating Regional Deposited Dose (RDDr). The method is briefly summarized below.

$$RDDr = 10^{-6} \times Ci \times V_E \times Fr$$

where:

RDDr = dose deposited in region r, mg/min,
Ci = concentration, mg/m^3 (this will be canceled out in the later age group comparison),
V_E = minute volume, mL/min, obtained from Stanek et al. (2004)
Fr = regional fractional deposition in region r.

The regional fractional deposition, Fr, was calculated using the equation for monodisperse and near monodisperse ($\sigma_g < 1.3$) particles by multiplying the predicted deposition efficiencie factor, E(ηr), and inhalability factor, I.

$$E(\eta r) = 1/(1 + e^{\alpha + \beta \log X})$$

Where E(ηr) was the expected value of deposition efficiency (ηr) for region r, and X was expressed as an impaction parameter, d_{ae}^2Q, for extrathoracic deposition efficiency and as aerodynamic particles size, d_{ae}, for TB and PU deposition efficiencies. The flow rate, Q, in the impaction parameter was approximated by $V_E/30$. The parameters α and β based on nonlinear regression techniques are listed in the Table A1, and they are obtained from the Table G-2 of EPA's RfD guideline (EPA 1994).

Table A1. Regression Coefficients of α and β for Humans in Various Respiratory Regions.

	ET (nasal)	TB	PU
α	7.129	3.298	0.522
β	-1.957	-4.588	-1.389

Inhalability, I, is an adjustment factor for the particles in an ambient exposure concentration that are not inhaled at all. For humans, the equation proposed in the EPA's RfC guideline was used.

$$I = 1 - 1/(1 + e^{10.32 - 7.17 \log dae})$$

The deposition fractions for various regions were estimated after adjusting for inhalability and regional particle deposition efficiencies as well as filtering effect occurred in the airway.

$$F_{ET} = I \times \eta_{ET}$$
$$F_{TB} = I \times (1 - \eta_{ET}) \times \eta_{TB}$$
$$F_{PU} = I \times (1 - \eta_{ET}) \times (1 - \eta_{TB}) \times \eta_{PU}$$
$$F_{RES} = F_{ET} + F_{TB} + F_{PU}$$

Based on calculated RDDr for each age group, ratio differences between each child group and adult (30-year old) can be calculated.

$$RTDRr = \text{RDDr child /RDDr adult}$$
$$= [(SAr)a/(SAr)c] \times [(V_E)c/(V_E)a] \times [(Fr)c/(Fr)a]$$

where:

RTDRr = regional target dose ratio of particles for respiratory tract region (r)
a = adult
c = child

1496	Sar	=	surface area in respiratory region (r) for the particular age group obtained
1497			from Stanek et al. (2004)
1498			