Journal of Environmental and Occupational Science
www.jenvos.com
DOI: 10.5455/jeos.20150202022401

Review Article

ScopeMed

Factors modifying children's inhalational risk assessment

Rami Saadeh, James Klaunig

Department of Environmental Health, School of Public Health, Indiana University at Bloomington, Bloomington, Indiana, USA

Address for correspondence: Rami Saadeh, Department of Environmental Health, School of Public Health, Indiana University at Bloomington, Bloomington, Indiana, USA. E-mail: rsaadeh@indiana.edu

Received: December 20, 2014
Accepted: February 02, 2015
Published: February 18, 2015

ABSTRACT

Context: This study reviews factors in children, which alter their risk to inhalational exposures, and modify the inhalational risk assessment process. Factors identified in the literature distinguish children from adults when assessing risk of inhalational exposures. Such factors are determined based on children's unique physiological, anatomical, and biochemical characteristics, which extend to include a unique inhalational dosimetry. Numerous methods have been developed to account for such factors in children. However, some factors are more inclusive than others are, and a comprehensive assessment of these factors is important to enhance risk analysis in children. **Objective:** The aim was to identify factors in children that modify the four steps of risk assessment and assess the magnitude of uncertainty associated with these factors. **Methods:** Authors did not follow a specific system for selecting articles from the literature. However, original and review articles were chosen based on their relevancy to the objectives of this paper. Five EPA documents and one WHO document were used to identify factors shown in Figure 1. EPA guidelines for inter and intra species differences and for inhalational dosimetry were used in calculating uncertainty associated with the identified factors. **Results:** Figure 1 illustrates factors identified as influential in children's inhalational risk assessment, with the elucidation of possible correlations that exist among these factors. Table 1 ranks factors in order of their importance and determination in two selected steps of risk assessment. Figure 2 evaluates uncertainty related to factors shown in Figure 1 based on criteria described in Methodology. Figure 3 demonstrates the inclusiveness of each of the methods used to assess risk in children. **Conclusion:** Children's risk assessment demands special considerations and the inclusion of factors specific to them because of their continuous developmental changes, which differentiate them from adults.

KEY WORDS: Inhalational risk assessment, pharmacokinetics, pharmacodynamics, physiologically based pharmacokinetic models, uncertainty factors

INTRODUCTION

A great deal of effort has been dedicated to enhancing children's risk assessment; and improving procedures involved in determining their health needs. Advancements in understanding children's distinctive characteristics in the last few years have helped in the development of concepts used specifically for children's health assessment [1]. Children's unique body system and their continuous body development requires the establishment of a special framework regarding risk assessment [1-3], which explains their unique physiological, anatomical, and biochemical characteristics. Furthermore, this uniqueness includes their respiratory system development, which provides a specific inhalational dosimetry that is different from adults' inhalational dosimetry, and as a result, requires additional considerations for inhalational risk assessment in children [4-6]. A perfect framework for children would include all variables and parameters, which distinguish their responses from adults' responses, as well as distinguish the responses of children of different ages [7]. However, not all factors specific to children have been previously included in a single model, nor have they been completely identified or verified. Quantitatively measuring all factors and placing them within clear and predetermined mathematical equations is a tedious undertaking. A major reason for this is the great variability among individuals and the high degree of uncertainty in most of these factors.

The identification of factors related to children should be considered within the framework of risk assessment, which is composed of four main steps, known as hazard identification, exposure assessment, dose-response assessment, and risk characterization. Mathematical equations and calculations in each step are modified by certain factors [2,8,9]. Some of these are factors are related to their physiological, anatomical, and biochemical development [10], and others to previous exposures, physical activity, or race [11]. Therefore, in order to achieve highly adequate and accurate risk estimate, it is extremely important to include all factors specific to children [9,12]. The present study, therefore, aims to identify factors modifying the four steps of risk assessment in order to accommodate children's needs, evaluate uncertainty associated with the identified factors, rank factors based on

their importance and influence at each step, and review the best available methods to include such factors.

METHODOLOGY

A literature review was conducted to identify factors that have a significant impact on children's inhalational risk assessment. All available literature, including review articles, original articles, in addition to documents published by the US Environmental Protection Agency (USEPA), World Health Organization (WHO), and International Commission on Radiological Protection (ICRP), were used in this evaluation. This is a narrative review, and authors did not follow a specific system to select articles from the literature; however, selected review and original articles were chosen based on relevancy to the objectives of this paper. Calculations of uncertainty factors (UF) in this article and identification of factors shown in Figure 1 are mainly derived from EPA and WHO documents. EPA documents reviewed for this study, and used in our calculations, specifically for inhalational dosimetry are "Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (2009)" and "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (1994)." Other EPA documents used to provide a guidance on inter and intra species difference are "Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (2005)," "A framework for assessing health risks of environmental exposures to children (2006)," and "Child-Specific Exposure Factors Handbook." The WHO document used in this study provided an insight on the application of computational modeling in risk assessment, specifically the physiologically based pharmacokinetic models, in a document named "Characterization and Application of Physiologically Based Pharmacokinetic Model in Risk Assessment."

Our search also included the evaluation of UF associated with the assessment of these factors. The methodology used for these calculations is shown below. In addition, methods currently available for children's inhalational risk assessment have been determined with illustration of their abilities to include the factors identified in this study [Figure 2]. More details about usefulness and limitations of such methods are provided in the Discussion.

Calculation of Uncertainty Associated with Identified Factors

When considering each of these factors in estimating risks in communities, there has to be a certain amount of uncertainty within our estimations. Such uncertainty result from measurements' difficulties, variability among individuals, or other factors, as explained within each of the calculations listed below. However, our calculations are based on two conditions. First, the default UF used to extrapolate from animals to humans, is equal to 10. Second, the UF suggested for variability among individuals in their pharmacokinetics

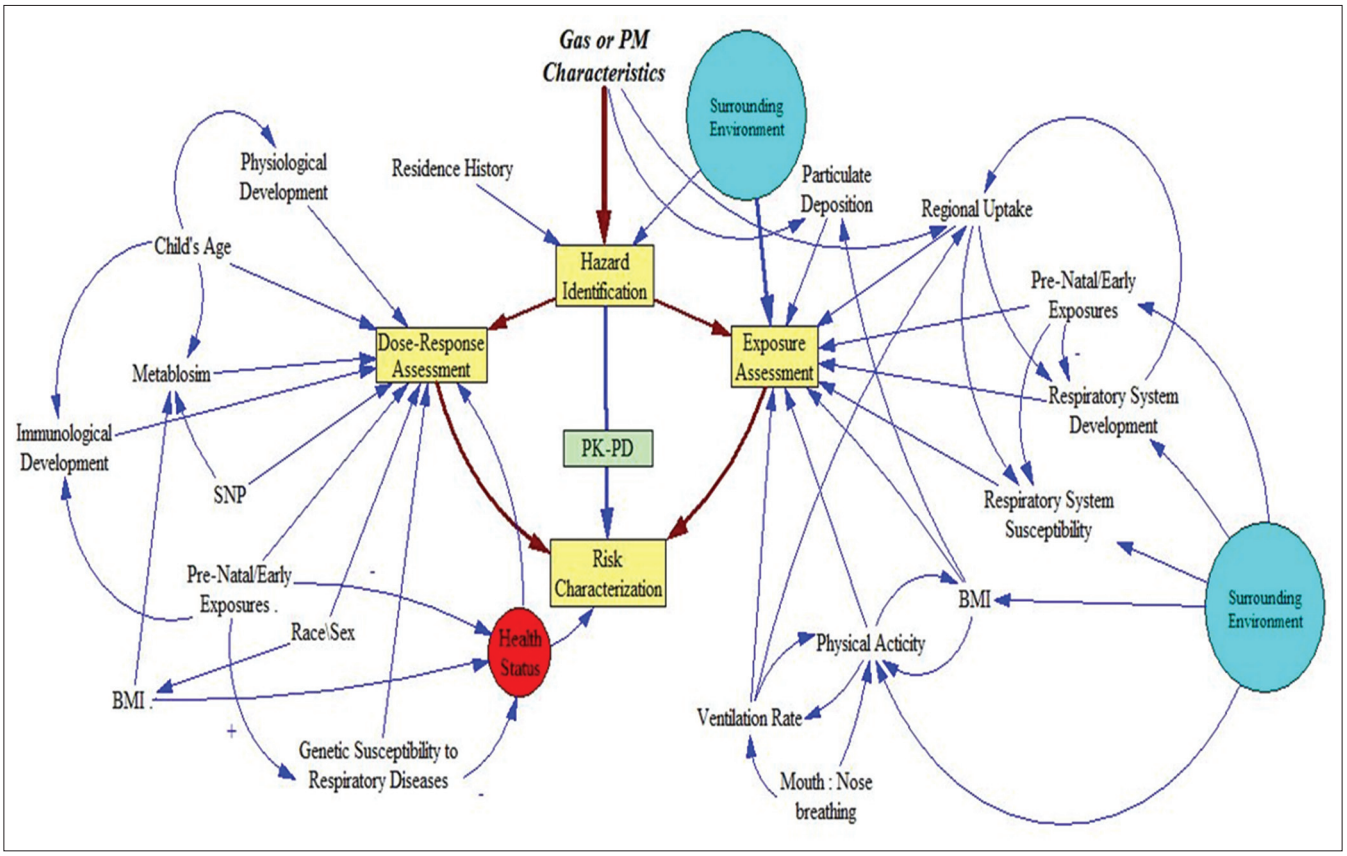

Figure 1: Factors related to each step of inhalational risk assessment in a comprehensive framework

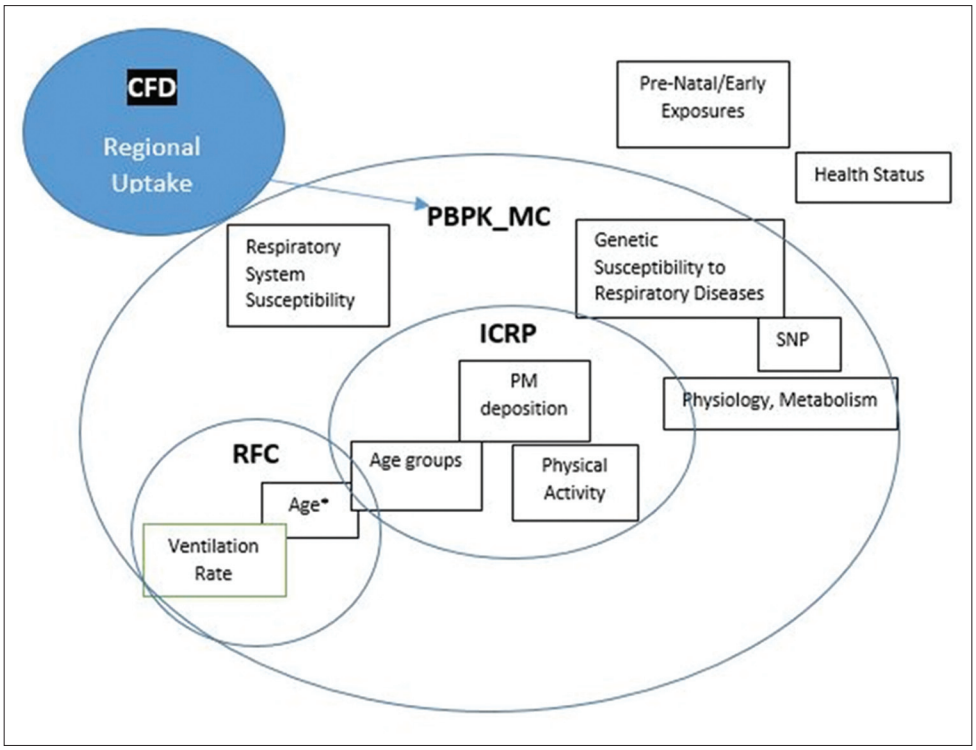

Figure 2: Current risk assessment methods available to be used in children's inhalational risk assessment

(PK) or pharmacodynamics (PD) is equal to 3.16 or 3 (8). This number is supposed to cover racial, gender, age, genetic, and health condition differences among individuals [13].

The intra-species UF, which is human adults to children extrapolation, is recommended to be 10 by the EPA [1]. However, this is not relevant to our calculations because the uncertainty estimated in this study are for each of the factors identified in the assessment, and are not meant to account for all differences between adults and children. Furthermore, it is assumed that variation among individuals exists in each of the factors; therefore, a UF of 3 is used for inter-individual variability in all of our calculations.

The first value in our calculations represents animal to human extrapolation in case human data is not available. The second value is intra-human variability, which is a human adult to children extrapolation, and the third value is the inter-individual variability among children.

Ventilation rate: $0 \times 1 \times 3 = 0$ (lowest estimate value)

There is no animal to human extrapolation because children's ventilation rate can be measured directly. Therefore, Intra-human variability is 1 or 0 because extrapolation from adults to children is not needed.

OR: $1 \times 1 \times 3 = 3$ (highest estimate value)

If not every individual's ventilation rate is tested, a variability of 1 or more might exist. Adults to children extrapolation or intra-human variability are 1 because children data is available for ventilation rates. Inter-individual ventilation rate variation is assumed to have a value of 3.

Regional uptake/PM deposition: $1 \times 1 \times 3 = 3$ (lowest estimate value)

No animal to human extrapolation is required if a gas regional uptake or particulate matter deposition areas are identified in humans' studies, and modeled accurately. Intra-human variability for uptake is 1 because uptake or deposition area in humans is very similar for many gases and PM. However, Inter-individual variability value of 3 is used because the amount absorbed or deposited varies between individuals.

OR: $5 \times 2 \times 3 = 15$ (highest estimate value)

If only animal studies are available, then a value 5 is used instead of 10 because uptake or deposition can be predicted in humans based on similar gases or particulate matter size, especially if computational fluid dynamics (CFD) models have been previously developed and used. A value of 2 for intra-human variability is suggested, because some variation might exist within the region of uptake between children and adults. Inter-individual variability value is 3.

Respiratory system susceptibility: $1 \times 2 \times 3 = 6$ (lowest estimate value)

If human data are available for a certain gas, and this gas is known for having very minimal harmful effects on the respiratory system of humans, then a value of 1 is used. Intra-human variability is 2, because as many studies show, children are 2-4 times

more susceptible to gases/PM than adults [4]. Inter-individual variability value of 3 is suggested because there is a variation in susceptibility to gases or PMs that exist among children.

OR: $10 \times 4 \times 3 = 120$ (highest estimate value)

If human data is not available for certain gases, and only animal data is available and in the time informative, then a value of 10 is used for animal to human extrapolation. A value of 4 is used for intra-human variability because the difference between adults and children can reach up to 4-folds, and a value of 3 is used for inter-individual variability.

Pre-natal/Early Exposures

Estimation of pre-natal and early exposures is a tedious task. Uncertainty value can vary a lot. For instance, UF can be low if a mother and perhaps the father are part of a study monitoring and evaluating all pre-gestational exposures. On the other hand, it can be very high if no knowledge about early exposures is available.

Genetic Susceptibility to Respiratory diseases and Single Nucleotide Polymorphisms (SNPs)

Which varies among communities, ethnicities, and individuals. Although there are many SNPs and genetic variations that are known and been identified, a link to respiratory diseases is not definitely clear, based on an altered metabolism. However, when risk assessment is done at a population level, a certain percentage of the community is hypothesized to hold such variations, and risk is adjusted based on that.

RESULTS

Figure 1 serves as a comprehensive framework to assess risks from inhalational exposures in children. Factors that have a link to any of the four main steps of risk assessment are shown in Figure 1, a link is represented by an arrow. In addition, some factors influence other factors and therefore, are also linked by arrows. Most arrows does not have a sign, either positive or negative, because an influence represented by an arrow can be either way based on the condition of the factor. For example: Children with higher body mass index (BMI), have a lower physical activity, and they tend to have a higher deposition rate of particles [14]. In contrast, the opposite is true for children with lower BMI. However, some factors can relate only in one-way, thus, an arrow representing such relation, can only have one sign, negative or positive.

Figure 3 evaluate uncertainty related to factors shown in Figure 1. However, not all factors are included. Coordinates are scaled 0 through 120. Uncertainty of 0 indicates complete certainty, and 120 indicates high uncertainty. Estimates of uncertainty are based on estimates published in the literature.

Table 1 contains factors with their corresponding risk assessment step. Factors are ranked in order of their importance and determination in the particular step. This means that factors with a higher rank have the priority to be included in the risk estimates. Moreover, uncertainty and data gaps related to these high-priority factors should be under a higher consideration in order get a better risk estimates.

Table 1: Factors ranked in order of their influence and importance in two major steps of risk assessment

Exposure assessment	Dose-response relationship
Pre-natal/early exposures	Genetic susceptibility to respiratory diseases
Respiratory system susceptibility	Polymorphism (SNP)
Regional uptake/PM deposition	Pre-natal/early exposures
Ventilation rate	Health status
BMI	Body growth and development
Physical activity	Race/sex

SNP: Single nucleotide polymorphisms, BMI: Body mass index

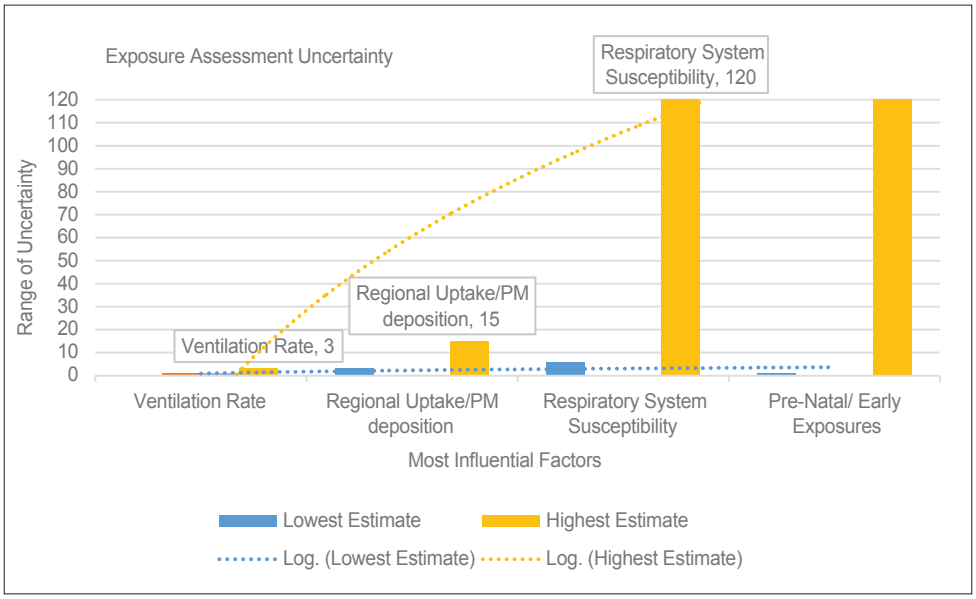

Figure 3: Assessment of lowest and highest possible uncertainty values for some factors

Figure 2 shows current risk assessment methods available to use in children's inhalational risk assessment, with the illustration of factors valid for use in each method, based on the capabilities of each method. Comparisons between methods, and explanations of their capabilities are discussed more in the Discussion.

DISCUSSION

It is obvious that children are different from adults by a many means. Children are not little adults, but rather, a different target population with different variables and parameters, which have to be considered during risk assessment. As mentioned previously, children differs in their physiology, anatomy, and biochemistry, which alter their PK and PD continuously as long as their bodies are growing [1,13]. They have their own structural and functional respiratory characteristics that alter their inhalational dosimetry [6,7,12]. Further, their continuous cell division, differentiation, and maturation make them more susceptible to environmental stressors than adults are [7,10,15].

The continuous growth and development of children rise a concern on how to modify our risk assessment methods to fit them. Growth of the lung is not what only matters, but all developmental changes in a child's body possess important considerations. Such changes make it necessary to have all the appropriate equations involved in the risk assessment process for children. The assessment process should be modified to correspond with developmental characteristics of children of different ages [10].

Although such differences significantly emphasize the importance of risk assessment frameworks developed specifically for children, the lack of required data hinders the formation of a complete risk assessment framework. A perfect framework for children would include all variables and parameters, which make them different from adults, as well as differentiate them at different ages, as just previously stated [Figure 1]. Therefore, models that been developed to the moment tried to include as much variables as possible [Figure 2], but nothing has been comprehensive yet. However, each of the models has its own limitations, but each of them is useful. For instance, the Inhalation Reference Concentrations (RFC) methodology, is an approach developed by the EPA (1994) to assess inter-species extrapolation for inhalational chemicals or gases, use an UF as an attempt to cover intra-human variability in PK and PD, but it doesn't not cover exposure variability nor does it consider age group differences [6,16]. The International Commission on Radiological Protection ICRP is a useful bio-kinetic model first developed by the international commission on radiological protection to estimate radionuclides in workers [9,17]. In a later publication of ICRP, a model more refined than RFC, was developed to estimate deposition of particles of different sizes in a wide range of children ages starting as early as 3-month-old [18]. However, RFC and ICRP have many limitations, and they only estimate exposure levels and not exposure doses [4,9]. To have better estimation, models that are more recently used in risk assessment, have shown the ability to estimate internal tissue doses from external exposures, and by that, represent a more powerful tool for risk assessment purposes. The best commonly known used models are physiologically based pharmacokinetic models (PBPK). PBPK models are flexible and have the ability to include many parameters, easily updated if new information is available, and has the ability to accept a variety of modifications. Their flexibility extends to model any environmental chemical administered through any route of exposure, in spite of the nature of species, population, or subpopulation [8,19,20]. Applying PBPK for children's inhalational risk assessment is very promising, especially when it's enhanced by other methods such as Monte Carlo (MC) simulation or Bayesian analysis [21]. MC simulations supports PBPK models to predict variability among children population, and Bayesian analysis is used to refine uncertainty related to variability among individuals and characterize this uncertainty. Such models have the ability to differentiate risk effects in children and adults if required data is available. CFD is a great tool to determine areas of deposition and absorption along the respiratory tract from the nose to lungs' alveoli [16]. Such advanced application can serve as an input for PBPK models. Yet, all new methods using computational application needs validation with experimental data to verify the use of the model in risk assessment and other applications.

CONCLUSION

Assessing inhalational risk in children is different from adults, because of their continuous developmental changes. Such differences demand the incorporation of such differences into risk assessment by modifying each of the four risk assessment steps in a way to adapt children's characteristics.

REFERENCES

1. USEPA (EPA). A Framework for Assessing Health Risks of Environmental Exposures to Children. EPA/600/R-05/093F. Washington, DC: National Center for Environmental Assessment; 2006.
2. Daston G, Faustman E, Ginsberg G, Fenner-Crisp P, Olin S, Sonawane B, *et al.* A framework for assessing risks to children from exposure to environmental agents. Environ Health Perspect 2004;112:238-56.
3. Ginsberg G, Slikker W Jr, Bruckner J, Sonawane B. Incorporating children's toxicokinetics into a risk framework. Environ Health Perspect 2004;112:272-83.
4. Ginsberg GL, Foos BP, Firestone MP. Review and analysis of inhalation dosimetry methods for application to children's risk assessment. J Toxicol Environ Health A 2005;68:573-615.
5. Foos B, Marty M, Schwartz J, Bennett W, Moya J, Jarabek AM, *et al.* Focusing on children's inhalation dosimetry and health effects for risk assessment: an introduction. J Toxicol Environ Health A 2008;71:149-65.
6. USEPA (EPA). Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA 600/8-90/066F. Washington, DC: National Center for Environmental Assessment; 1994.
7. USEPA (EPA). Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. EPA/630/P-03/003F. Washington, DC: National Center for Environmental Assessment; 2005.
8. WHO. Characterization and Application of Physiologically Based Pharmacokinetic Model in Risk Assessment. IPCS Harmonization Project Document; No. 9. 2010.
9. USEPA (EPA). Risk Assessment Guidance for Superfund. Human

Health Evaluation Manual (Part F, Supplemental Guidance for Inhalation Risk Assessment). EPA-540-R-070-002. Vol. I. Washington, DC: USEPA; 2009.
10. USEPA (EPA). Child-Specific Exposure Factors Handbook. EPA/600/R-06/096F. Washington, DC: USEPA; 2008.
11. Bennett WD, Zeman KL, Jarabek AM. Nasal contribution to breathing with exercise: effect of race and gender. J Appl Physiol (1985) 2003;95:497-503.
12. Ginsberg GL, Asgharian B, Kimbell JS, Ultman JS, Jarabek AM. Modeling approaches for estimating the dosimetry of inhaled toxicants in children. J Toxicol Environ Health A 2008;71:166-95.
13. Ginsberg G, Hattis D, Sonawane B, Russ A, Banati P, Kozlak M, *et al.* Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 2002;66:185-200.
14. Bennett WD, Zeman KL. Effect of body size on breathing pattern and fine-particle deposition in children. J Appl Physiol (1985) 2004;97:821-6.
15. Anderson BJ, Holford NH. Understanding dosing: children are small adults, neonates are immature children. Arch Dis Child 2013;98:737-44.
16. Ginsberg G, Foos B, Dzubow RB, Firestone M. Options for incorporating children's inhaled dose into human health risk assessment. Inhal Toxicol 2010;22:627-47.
17. ICoRP (ICRP). Limits for Intakes of Radionuclides by Workers. New York: Pergamon Press; 1982.
18. ICoRP (ICRP). Human Respiratory Tract Model for Radiological Protection. Oxford, UK: Pergamon Press; 1994.
19. Barrett JS, Della Casa Alberighi O, Läer S, Meibohm B. Physiologically based pharmacokinetic (PBPK) modeling in children. Clin Pharmacol Ther 2012;92:40-9.
20. Björkman S. Prediction of drug disposition in infants and children by means of physiologically based pharmacokinetic (PBPK) modelling: theophylline and midazolam as model drugs. Br J Clin Pharmacol 2005;59:691-704.
21. Clewell RA, Clewell HJ 3rd. Development and specification of physiologically based pharmacokinetic models for use in risk assessment. Regul Toxicol Pharmacol 2008;50:129-43.

Source of Support: Nil, Conflict of Interest: None declared.