Discussion of the Adequacy of Current Regulatory Risk Assessment Approaches for Protection of Children's Health and the Health of Other "Sensitive" Human Subpopulations

Testimony of

Laura M. Plunkett, Ph.D, DABT
Integrative Biostrategies, LLC
Houston, Texas

April 29, 2008

Before the
Senate Environment and Public Works Committee

My name is Dr. Laura Plunkett. The following is my testimony regarding the adequacy of current risk assessment methods used by EPA to evaluate chemicals for identifying risks to sensitive human subpopulations such as the developing fetus, infants and children. This testimony reflects my own views as a pharmacologist, toxicologist and risk assessor. The views presented are my independent perspectives as a scientist and are not the views of my clients.

A. Qualifications

1. I am a pharmacologist, toxicologist, human health risk assessor, registered patent agent, and principal of a consulting company known as Integrative Biostrategies, LLC. Integrative Biostrategies is a consulting firm that works at the interface of the biological sciences, regulatory affairs, and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Prior to becoming a partner in Integrative Biostrategies, I was head of Plunkett & Associates, a health and environmental sciences consulting firm based in Houston, Texas. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research and have taught pharmacology and toxicology at the undergraduate and postgraduate levels. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations, and have authored or co-authored numerous scientific publications.

2. I received my B.S. degree in 1980 from the University of Georgia, and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy, in 1984. My doctoral research was focused in the area of cardiovascular pharmacology and

specifically dealt with delineating mechanisms responsible for the cardiac toxicity of digitalis glycosides. My doctoral training, however, covered all aspects of pharmacology and toxicology, including reproductive and developmental effects of drugs and chemicals. From June of 1984 through August of 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health. From September 1986 to June 1989 I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences.

3. From December of 1989 to August 1997 I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. At ENVIRON, I worked specifically within the health sciences group and most of my projects dealt with issues surrounding the effects of chemicals on human health. During my consulting career at ENVIRON, while with Plunkett & Associates, and now at Integrative Biostrategies, I have worked on a variety of projects dealing with the regulation of products by the U.S. Environmental Protection Agency (EPA) including pesticides and industrial chemicals, as well as working on projects dealing with assessing risks to human health due to exposure to chemicals through the environment (*i.e.*, air, water, soil, food). Many of the projects I worked on while at ENVIRON, while at Plunkett & Associates, and now at Integrative Biostrategies have involved evaluation of

the reproductive and developmental effects of drugs and environmental chemicals, with a focus on the protection of children's health. A true and correct copy of my current curriculum vitae is attached hereto as Appendix A.

B. Introduction

4. I have been asked to provide a risk assessor's perspective on issues related to the adequacy of current regulatory risk assessment approaches for protection of children's health. I have worked in the area of risk assessment and children's health for over 15 years, with some of my first work related to preparation of a chapter for the proceedings of a 1990 conference organized by the International Life Sciences Institute (ILSI) entitled *Similarities and Differences Between Children and Adults: Implications for Risk Assessment* (held November 5-7, 1990, Hunt Valley, MD). The chapter I authored discussed issues related to exposure differences between children and adults (Plunkett, et al. 1992). Since that time, I have worked actively to study and analyze data defining the biological basis for age-related differences in chemical toxicity as well as the methods used to assess risks to humans at all stages of development (from development *in utero*, infancy, childhood, adulthood and with aging).

5. Review of the extensive published literature relating to human sensitivity due to age and stage of development and the methods used to assess risks due to chemical exposures reveals several key principles and findings including:

- Children are not "little" adults. Age and stage of development are important factors in assessing risks due to chemical exposures.

- Although children are not "little" adults, their sensitivity to chemical exposure is highly dependent on the nature of the chemical. In some cases children are more sensitive, in some cases there is no difference in sensitivity, and in some cases they are less sensitive.
- Age is not the only factor related to human variability in chemical toxicity responses. Other factors include gender, genetics, and health status. In some cases, age is less important than other human factors such as genetics.
- Apart from differences in sensitivity to toxic responses, exposure is a critical consideration when age is of concern. In fact, available data indicate that exposure differences between infants, children and adults is often more important when assessing risks in order to ensure that all human populations are protected.
- It is a general consensus of scientists in the published literature that the use of uncertainty factors[1] allows risk assessors to develop health risk values that are protective of all potentially sensitive human populations, including children.
- Analysis of studies in the published, peer-reviewed literature reveals that currently available risk assessment methods, methods used by EPA, have provisions in place that allow the risk assessor to ensure that the developing fetus, infants and children are protected. These provisions include accounting for differential sensitivity in toxic responses as well as differences in exposure.
- Finally, current risk assessment methods for chemicals that employ tiered-testing strategies allow resources to be focused on the evaluation of the most sensitive adverse effects of chemical exposures of greatest concern but are also adequate to

[1] The term "uncertainty factor" is defined and discussed in detail later in section D.

assess potential risks to sensitive human populations such as the developing fetus, infants, and children.

6. Based on consideration of all of the available data relevant to assessing the adequacy of current risk assessment methods to protect human health, I believe that there are sound, scientific data that demonstrate the adequacy of current risk assessment methods to protect human health, including sensitive subpopulations such as children. This fact, combined with the knowledge that hazard alone is not sufficient to characterize actual risk, would argue against a need to develop alternative regulatory approaches for chemicals when the concern is protecting children's health.

C. Overview of the Risk Assessment Process

7. "Risk assessment" is a tool used by scientists and regulators to help decide what restrictions to place on the uses of chemicals and to determine the risks to humans posed by exposure to chemicals in the environment. "Risk" is defined as the probability that injury, disease or death may result from a chemical exposure under certain specific circumstances. All human activities are associated with some degree of risk to health and well-being, activities such as driving a car, climbing a ladder, crossing a street, or even taking a bath or shower. In the context of chemical risk assessment, the term "safe" does not mean without risk. Instead, a "safe" level of chemical exposure is a level with which there is "practical certainty" that no harm will result in exposed individuals.

8. In 1983, the National Academy of Sciences outlined the steps that should be included in any scientifically sound risk assessment process (NAS 1983). They

defined risk assessment as the characterization of the probability of potentially adverse health effects from human exposures to environmental hazards (*e.g.,* chemicals). The NAS included four basic steps in every complete risk assessment: hazard identification; dose-response assessment; exposure assessment; and risk characterization. Each of these four steps is critical to assuring that scientifically sound decisions can be made by regulators when those decisions are being made about the impact of chemical exposures on human health.

Step 1: Hazard identification This step involves gathering and evaluating toxicity data on the effects of chemical on body systems and the exposure conditions necessary to produce those effects. Risk is not assessed at this stage but instead the scientist or regulator focuses on whether the effects seen in toxicity studies are relevant and useful for assessing risk, and which effects should be the focus of the risk assessment. It is important to note that in the case of most chemicals, hazard information will be in the form of laboratory animal toxicity studies, not studies in humans. Although laboratory animals are not "small humans", it is a general principle of both pharmacology and toxicology that the types of effects (qualitative) seen with chemical exposure in mammalian species are predictive of the types of effects to be expected in humans. This general principle has been validated over a century of chemical testing in animals.

Step 2: Dose-response assessment Dose-response assessment is a critical step and a critical concept. It involves quantifying the relationship between exposure to a chemical and the extent of injury or disease produced. It is a basic principle of toxicology that "the dose makes the poison", or in other words

that all chemicals can produce adverse effects at some dose. This is a guiding principle for development of human drugs where physicians need to know at what dose the drug/chemical produces beneficial effects as well as the dose of the drug/chemical that is associated with adverse effects. It is important to note that the dose that produces a particular effect in an animal will not always be the dose that will have that same effect in humans. Animals are assumed to be less sensitive to the effects of chemical exposures than humans and as a result, studies performed in animals are routinely performed at doses that greatly exceed any anticipated or measured level of human exposure.

Step 3: Exposure assessment This step is an important consideration in the risk assessment process and involves describing the nature and size of various populations exposed to a chemical as well as the magnitude and duration of exposure. Many human health risk assessments look at past, present, as well as future or expected exposures. It is another general principle of toxicology that exposure is a necessary action for toxicity to occur. In other words, unless a human is exposed to the chemical, the chemical does not pose a risk to health. EPA currently has in place methods for considering infants and children as separate exposed populations apart from adults, allowing a risk assessment to consider and account for differences in exposure patterns.

Step 4: Risk characterization This is the final step in the risk assessment process where the results of the first three steps are integrated and analyzed. In this step the likelihood that the human population of interest would experience any toxic effects from chemical exposure is determined.

9. Because it is highly unlikely that the scientist or regulator will have complete information on any chemical for each of the first three steps in the risk assessment process (hazard identification, dose-response assessment, exposure assessment), regulatory risk assessments have developed a process for quantifying "uncertainty" in the assessment, where "uncertainty" is a measure of the level of confidence the risk assessor has in the data that is used. "Uncertainty" is also a measure of the level of variability that is always seen within a population, in terms of variability in response as well as variability in exposure. The most common approach to quantifying uncertainty has been to apply "safety factors" or "uncertainty factors" during the risk assessment. The use of such uncertainty or safety factors is an important concept in the discussion of protection of children's health.

D. What Are Safety Factors or Uncertainty Factors?

10. "Safety factors" were first introduced in the 1950's by scientists at the U.S. Food and Drug Administration (FDA) as part of the process for assuring the safety of humans exposed to food additives and food residues of pesticides. These factors were used to account for the variability in biological responses between animals and humans (interspecies variability) and between individuals in the human population (intraspecies variability). These scientists had recognized that variability in biological responses between animals and humans was generally within a range of two to three-fold while the variability among individuals of both sexes, all ages, and of different states of health generally fell within a range of a factor of 10. As a result, when the FDA was determining what a safe level of exposure to a food additive might be for humans in the

general population, they applied a factor of 100 to the level they determined in an animal study to be without any adverse effect on health. This 100-fold factor was applied to the endpoint in an animal study that was the most sensitive endpoint (lowest effect dose) from the most sensitive species.

11. In the context of risk assessments at the EPA, the agency which is responsible for assessing risks to humans posed by chemicals in the environment (air, water, and soil), and often termed unintentional exposures[2], agency scientists have employed a similar approach to assessing risk by using "uncertainty factors". "Uncertainty factors" are again those factors used to account for variability in biological response and population exposure. However, the factors have a more complex application and are defined even more specifically in terms of the exact type of variability that is being measured and corrected for during the risk assessment.

12. There are currently at least six different uncertainty factors (UFs) that are employed as part of a chemical risk assessment: interspecies UF; intraspecies UF; subchronic to chronic UF; LOAEL to NOAEL UF[3]; incomplete data base UF; and modifying UF. Each of these UFs is typically a factor of 10, although the value of any one UF can be reduced from 10 to either 3 or 1 when available data support such a reduction. These factors are used by risk assessors to ensure that the risk values quantified are protective of human health, including the health of sensitive human subpopulations. The interspecies and intraspecies UFs are routinely applied in chemical

[2] In the context of this discussion, an unintentional exposure is an exposure that occurs due to breathing air, drinking water, contacting soil or other types of particulate matter on surfaces, and eating food (exceptions would be intentional food additives).

[3] LOAEL is an acronym for the "lowest observed adverse effect level", which is typically the lowest dose in an animal study at which some type of adverse effect is seen. NOAEL is an acronym for the "no-observed adverse effect level", which is typically the dose in an animal study at which no adverse or toxic effects are seen. Another acronym related to NOAEL is NOEL or "no observed effect level" , which is the dose in an animal study at which absolutely no effect of any kind (adverse of not) is observed.

risk assessment and are considered part of standard risk assessment practice. The other four UFs are applied only when appropriate, mainly in cases where the quality or quantity of the available toxicology data is lacking. The typical UFs used in chemical risk assessment can be described as follows:

Intraspecies UF Used in most chemical risk assessments to account for variation in sensitivity to toxic responses among humans. The major characteristics that are believed to contribute to variation in sensitivity include gender, age, genetics, and disease state. Note that age in this case would include the differences between adults and developing fetuses, infants and/or children. Studies have indicated that an intraspecies UF = 10 is more than adequate to assure protection of all sensitive human subpopulations (to be discussed in more detail below in section E).

Interspecies UF Used in most chemical risk assessments to account for variation in sensitivity to toxic responses between animals and humans. Studies have indicated that an interspecies UF = 10 is adequate to account for differences between species in almost all cases examined.

Subchronic to Chronic UF This UF is applied when the animal studies to be used in the risk assessment involved shorter durations of exposure than the expected human exposure. For example, if the animal study to be used involved only dosing for one month but humans could be exposed throughout their lifetime, than an additional UF = 10 would be applied to account for the potential effect of duration of exposure on level of response.

LOAEL to NOAEL UF This UF is applied when the animal study to be used in the risk assessment did not identify a NOAEL, or a level where there were no adverse effects following chemical exposure. Instead, the study identified a LOAEL. In this case, an additional UF = 10 would be applied.

Incomplete data base UF This is an important UF for many chemical risk assessments and allows the risk assessor to account for a lack of certain types of studies on any one chemical. For example, in the case of concern for children's health, if the toxicity study data base for a chemical lacked testing in pregnant animals or in developing animals, then an additional UF = 10 might be applied in the risk assessment. In this way, the use of the additional UF allows the risk assessor to account for the inability of any single study to adequately address all possible adverse outcomes.

Modifying Factor Although this factor is not routinely applied in risk assessments, it is another way that the risk assessor can correct for perceived deficiencies in the studies being used. For example, if an animal study was deficient in some design characteristic such as the number of animals being tested or lack of testing in both sexes, then a modifying factor from some value > 1 to 10 could be applied in the risk assessment.

13. Published literature and regulatory guidance documents have weighed in on the appropriate uses and magnitude of UFs for datasets with a variety of deficiencies or limitations, as well as for datasets that are believed to lack certain types of toxicity studies (*e.g.,* Dourson et al. 1996; Dourson et al. 2002; see also various risk assessment

guidance documents available on the EPA and FDA websites). As discussed in some of these references, composite UFs of 100 are routinely applied (interspecies and intraspecies UFs) but that composite UFs of as high as 3,000 or 10,000 are also possible depending on the quantity of quality of the data used in the risk assessment. Most risk assessors believe, however, that if a composite UF of greater than 10,000 is deemed necessary, then a quantitative risk assessment should not be performed until more reliable and relevant data are available. In the case of EPA, the agency would seek submission of additional data by companies. It is a general consensus of scientists in the published literature that the use of UFs allows risk assessors to develop health risk values that are protective of all potentially sensitive human populations, including the developing fetus, infants, and children.

E. Do Currently Available Risk Assessment Methods Protect the Developing Fetus, Infants, and Children?

14. As discussed in the introduction to this testimony, the critical question to be addressed is whether current risk assessment methods are adequate to ensure protection of human health for individuals of all ages, including the developing fetus. In order to best answer this question, I reviewed the published literature to identify studies that have attempted to answer this question with actual analysis of data rather than simply opinion based on common practice.

15. The focus of many of the available studies is whether the difference in sensitivity among human populations is adequately accounted for by an intraspecies UF of 10. In Table 1 below, I have listed the studies that focus on comparisons of adults with

either children or infants. There is also a body of studies that focus on adults and the variation due not to age but instead other factors such as genetics, sex and disease state (*e.g.*, Dourson and Stara 1983; Brown 2001; Hattis et al. 1999a, 1999b; Brock 1991; Hattis 1987; Calabrese 1985; Renwick and Lazarus 1998; Renwick et al. 2001; Silverman et al. 1999; Nong and Krishnan 2007). Regardless of the comparison group examined (studies focusing on age; studies focusing on issues other than age), the results were the same. The data consistently showed that the level of variability in response among the human population is adequately accounted for by a UF of 10 for intraspecies variability, or by a UF of 3.16 if only the toxicokinetic component of the intraspecies UF is being considered[4].

Table 1

Studies Reporting Analysis of Data on Age-Related Variability Within the Human Population that Could Affect Chemical Risk Assessment

Citation	Study Type	Conclusions
Glaubiger et al. 1982	Compared human MTDs[1] of oncology drugs in children vs. adults	No significant difference in toxicity seen between adults and children, indicating an intraspecies UF of 10 is conservative for this class of highly toxic chemicals, where chemicals are given at high doses.
Sheehan and Gaylor 1990	Compared animal LD50[2] ratios of adults vs. young animals.	Among 238 chemicals tested, 86% of the time the UF = 10 would be sufficient to account for variability.
Rane 1992	Compared human newborn vs. adult clearance values	For the majority of the chemicals considered (67%)

[4] In recent years, it has been suggested that the intraspecies UF be split into 2 components (3.16 and 3.16). One component is said to account for variability in pharmacokinetics and the other for variability in pharmacodynamics. Therefore, some of the studies in Table 1 looked at the adequacy of a factor of 3.16 not 10.

	for chemicals (toxicokinetics only considered).	a UF of less than 3.16 would be sufficient to account for variability.
Renwick 1998	Compared clearance and elimination of a variety of drugs in adults vs. infants and children (toxicokinetics only considered).	For 91% of the chemical considered a UF of less than 3.16 would be sufficient to account for variability.
Burin, G.J. and D.R. Saunders. 1999. *Regul. Toxicol. Pharmacol.* 30:209-216	A weight-of-the-evidence assessment of data available at the time that addressed the issue of human variability in risk assessment.	Reported that the use of a intraspecies UF = 10 would be protective of various human subpopulations including infants and children.
Charnley and Putzrath 2001	Comparison of animal cancer testing results across chemicals by age	Results were chemical-specific not age specific. Young animals were less susceptible than adults 47% of the time, equally sensitive 13% of the time, and more sensitive 40% of the time.
Calabrese 2001	Compared animal LD50 ratios of adults vs. young animals.	Among 313 chemicals tested, 86% of the time the UF = 10 would be sufficient to account for variability.
Naumann 2001	Compared kinetic and dynamic endpoints among humans of different ages (adults, elderly, children, and even those with diseases).	Across classes of drugs examined, authors found that the level of variability for toxicokinetics and dynamics separately would be accounted for by currently used UFs (3.3 and 3.3).
Pelekis et al. 2001	Compared pharmacokinetic parameters for volatile organic compounds in children vs. adults.	Currently used UFs for intraspecies variability are adequate without addition of an additional child-specific UF.
Skowranski and Abdel-Rahman 2001	Compared toxicokinetic factors between children, adults and the elderly.	Of the 6 drugs examined, the level of variability always fell within the a UF of 10, considering both kinetics and dynamics.
Ginsberg et al. 2002	Compared pharmacokinetic parameters for 45 different	Results show that the toxicokinetic portion of the

	chemicals (drugs) in adults versus children of various ages (included neonates).	intraspecies UF (3.16) was sufficient to account for the variability seen due to age/development.

1 MTD = maximum tolerated dose; represents a dose in animal studies that can be tolerated for the length of the study without causing either death of significant morbidity
2 LD50 = lethal dose for 50% of the population studied

16. It is clear from examination of Table 1 that the available studies support the adequacy of a 10-fold intraspecies UF to protect children's health. These data are an important part of the reason why current risk assessment approaches, that include use of UFs to determine risk, are stated to be protective of human health for individuals of all ages and stages of development.

17. Another important consideration when assessing the adequacy of current risk assessment methods to protect children's health is that when data on a chemical of concern do not include studies that have examined the potential toxicity in developing fetuses or young animals, standard risk assessment practices would dictate use of additional UFs. In those cases, an additional 10-fold UF could be employed to account for the lack of testing of the population of concern.

18. A question that is often raised in the context of protecting children's health is the question of the adequacy of current toxicology testing methods to assess risks in humans, in particular developing humans. The case study often pointed to is lead exposure. Critics of current methods suggest that without more sophisticated testing of neurological function during development, any risk assessment strategy would result in inadequate protection of children from the hazards of lead exposure. However, in an analysis I performed and published in the peer-reviewed literature in 1999, I showed that

using current methods of testing (guideline FIFRA testing) a safe exposure level in humans would have been set that is below the current regulatory action level for lead, without the use of any additional UF other than the standard intraspecies and interspecies factors (10 x 10 = 100). This is an important finding as it emphasizes that not only are current risk assessment methods protective of children's health but that toxicological testing methods that have been in use for decades are adequate to capture the level of risk posed by one of the most widely cited children's health hazards, lead exposure.

19. It is important to realize that the standard toxicological testing paradigm for industrial chemicals has been based on the use of a tiered testing framework. For example, when EPA challenged the chemical industry in 1998 to generate OECD SIDS[5]-level hazard screening data sets for HPV chemicals, under the HPV Challenge Program, companies formally committed to gather and make publicly available existing SIDS-level screening data on HPV chemicals. For each of the HPV chemicals sponsored in the program, industry provided 17 types of information, including summarized results in four categories: physical-chemical properties, environmental fate, and potential to induce toxicity in aquatic organisms and humans. Human toxicity data requested included studies assessing acute toxicity, subchronic toxicity, genotoxicity, and developmental and reproductive toxicity. The information required for human health hazard assessment in the HPV Challenge Program was identical to the internationally-agreed SIDS standards, established by the 30 nations of the OECD. The SIDS and HPV screening level test battery therefore included assessment of toxicity endpoints directly relevant to the

[5] "OECD-SIDS" is the Organization of Economic Cooperation and Development-Screening Information Dataset and refers to a chemical testing battery. The OECD created the Screening Information Data Sets program, commonly known as "SIDS," to secure uniform sets of hazard-screening information on industrial chemicals worldwide. The OECD SIDS standards comprise a series of data sets, tests, testing protocols, and information formats for conducting basic hazard assessments of industrial chemicals.

developing fetus, infants and children (*e.g.*, inclusion of reproductive and developmental toxicity testing with evaluation of sensitive life stages). Further, the standard toxicity testing battery for chemicals includes neurotoxicity assessments since all *in vivo* animal tests include observational endpoints for changes in behavior. In a recent paper (Becker et al. 2007), a tiered toxicity strategy similar to those used as part of the HPV Challenge and OECD-SIDS was proposed and evaluated. In this paper it was shown, using a retrospective validation approach, that the proposed tiered toxicity testing strategy was able to reliably identify chemicals which posed particular hazards to human health, including endpoints relevant to developing organisms. Further support for the use of tiered testing and evaluation for chemical risk assessment is found in the statements of the 2005 report of a committee of the National Academy of Sciences:

> *"Current approaches to toxicity testing include testing batteries, tiered testing, tailored testing, and a combination of the three. The committee finds that there are pros and cons of various approaches but leans toward tiered testing with the goal of focusing resources on the evaluation of the more sensitive adverse effects of exposures of greatest concern rather than full characterization of all adverse effects irrespective of relevance for risk-assessment needs. The committee, however, notes that tiered-testing approaches should be designed to expedite regulatory decisions and to discourage toxicity testing that is not used to address regulatory questions."* (NAS 2005).

20. In conclusion, I believe that there are sound, scientific data that demonstrate the adequacy of current risk assessment methods to protect human health,

including sensitive subpopulations such as the developing fetus, infants, and children. This fact, combined with the knowledge that hazard alone is not sufficient to characterize actual risk, would argue against a need to develop alternative regulatory approaches for chemicals when the concern is protecting children's health.

REFERENCES CITED

Becker, R.A., L.M. Plunkett, J.F. Borzelleca, and A.M. Kaplan. 2007. Tiered toxicity testing: evaluation of toxicity-based decision triggers for human health hazard characterization. *Food Chem. Toxicol*. 45:2454-2469.

Brock, A. 1991. Inter and intraindividual variations in plasma cholinesterase activity and substance concentration in employees of an organophosphorus insecticide factory. *Br. J. Ind. Med*. 48:562-567.

Brown, D.R. 2001. Risk assessment around the country: A forum for risk information and analysis developed to inform regional, state, and local policy decisions. *Hum. Ecolog. Risk Assess.* 7:209-213.

Burin, G.J. and D.R. Saunders. Addressing human variability in risk assessment—The robustness of the intraspecies uncertainty factor. *Regul. Toxicol. Pharmacol*. 30:209-216.

Calabrese, E.J. 1985. Uncertainty factors and interindividual variation. *Regul. Toxicol. Pharmacol.* 5:190-196.

Calabrese, E.J. 2001. Assessing the default assumption that children are always at risk. *Hum. Ecolog. Risk Assess.* 7:37-59.

Charnley, G. and R. Putzrath. 2001. Children's health, susceptibility, and regulatory approaches to reducing risks from chemical carcinogens. *Environ. Health Perspect.* 109:187-192.

Dourson, M.L., S.P. Felter and D. Robinson. 1996. Evolution of science-based uncertainty factors in noncancer risk assessment. *Regul. Toxicol. Pharmacol.* 24:108-120.

Dourson, M.L. and J.F.Stara. 1983. Regulatory history and experimental support of uncertainty (safety) factors. *Regul. Toxicol. Pharmacol*. 3:224-238.

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

Glaubiger, D.L., D.D. von Hoff, J.S. Holcenberg, B. Kamen, C. Pratt, and R.S. Ungerleider. 1982. The relative tolerance of children and adults to anticancer drugs. *Front. Radiat. Ther. Oncol*. 16:42-49.

Hattis, D., P. Banati, and R. Goble. 1999a. Distributions of individual susceptibility among humans for toxic effects. How much protection does the traditional tenfold factor provide for what fraction of which kinds of chemicals and effects? *Ann. NY Acad. Sci.* 895:286-316.

Hattis, D. P. Banati, R. Goble, and D.E. Burmaster. 1999b. Human interindividual variability in parameters related to health risks. *Risk Anal.* 19:711-726.

Hattis, D. 1987. Human variability in susceptibility to toxic chemicals—A preliminary analysis of pharmacokinetic data from normal volunteers. *Risk Anal.* 7:415-426.

National Academy of Sciences (NAS). 1983. *Risk Assessment in the Federal Government: Managing the Process.* National Academy Press, Washington, D.C.

National Academy of Sciences (NAS). 2005. *Toxicity Testing for Assessment of Environmental Agents, Interim Report.* Committee on Toxicity Testing and

Assessment of Environmental Agents, Board on Environmental Studies and Toxicology. National Research Council of the National Academies, National Academies Press: Washington D.C.

Naumann, B.D. 2001. Studies of categorical data-derived adjustment factors. *Hum. Ecolog. Risk Assess.* 7:61-106.

Nong, A. and K. Krishnan. 2007. Estimation of interindividual variability factor for inhaled volatile organic chemicals using a probability-bounds approach. *Regul. Toxicol. Pharmacol*. 48:93-101.

Pelekis, M., L.A. Gephart, and S.E. Lerman. 2001. Physiological model-based derivation of the adult and child pharmacokinetic intraspecies uncertainty factors for volatile organic compounds. *Regul. Toxicol. Pharmacol*. 33:12-20.

Plunkett, L.M. 1999. Do current FIFRA testing guidelines protect infants and children? Lead as a case study. Regul. Toxicol. Pharmacol. 29:80-87.

Plunkett, L.M., D. Turnbull and J.V. Rodricks. 1992. Differences between adults and children affecting exposure assessment. In: *Similarities and Differences Between Children and Adults: Implications for Risk Assessment*. P.S. Guzelian, C.J. Henry and S.S. Olin (eds.) ILSI Press, Washington D.C., 79-96

Rane, A. 1992. Drug disposition and action in infants and children. In: *Pediatric Pharmacology: Therapeutic Principles and Practice.* S.J. Yaffe and J.V. Aranda (eds.), Saunders: Philadelphia, 10-21.

Renwick, A.G. 1998. Toxicokinetics in infants and children in relation to the ADI and TDI. *Food Addit. Contam*. 15:17-35.

Renwick, A.G. and N.R. Lazarus. 1998. Human variability and noncancer risk assessment—An analysis of the default uncertainty factor. *Regul. Toxicol. Pharmacol.* 27:3-20.

Renwick, A.G., J.L. Dorne and K. Walton. 2000. An analysis of the need for an additional uncertainty factor for infants and children. *Regul. Toxciol. Pharmacol.* 31:286-296.

Sheehan, D.M. and D.W. Gaylor. 1990. Analysis of the adequacy of safety factors. *Teratology* 41:590-591.

Silverman, et al. 1999. Establishing data-derived adjustment factors from published pharmaceutical clinical trial data. *Hum. Ecolog. Risk Assess*. 5:1059-1089.

Skowranski, G.A. and M. Abdel-Rahman. 2001. Relevance of 10X uncertainty factor to the risk assessment of drugs used by children and geriatrics. *Hum. Ecolog. Risk Assess*. 7:139-152.

Appendix A