Workshop to Develop a Framework for Assessing Risks to Children from Exposure to Environmental Agents

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Characterization of children's health risks from environmental exposures requires special consideration of life-stage–specific periods of unique susceptibility in relation to childhood activities, behaviors, and intakes. At a workshop in Stowe, Vermont, in mid-summer 2001, 54 experts developed a systematic conceptual framework for assessing the impact of these factors on children's risks. This meeting report provides a brief overview of the workshop. ***Key words:*** **Children's health, life stage, risk assessment, toxicodynamics, toxicokinetics.** ***Environ Health Perspect*** **111:1524–1526 (2003). doi:10.1289/ehp.6183 available via *http://dx.doi.org/* [Online 13 August 2003]**

"Children are not simply small adults but rather are a unique population for health risk assessment." So begins the summary of the International Life Sciences Institute (ILSI) Risk Science Institute's conference on Similarities and Differences Between Children and Adults: Implications for Risk Assessment, convened in Hunt Valley, Maryland, in November 1990 (Guzelian et al. 1992). That conference summary also recognized the need for further work on the "specific application of the information presented at this conference to risk assessment methodologies," thus setting the stage for the workshop that is the subject of this meeting report.

Nearly 11 years after the Similarities and Differences conference, the ILSI Risk Science Institute (RSI) held a workshop in Stowe, Vermont, 30 July–2 August 2001, to develop a framework for assessing risks to children from exposure to environmental agents. The 54 invited experts, working in three breakout groups (on toxicokinetics, toxicodynamics, and risk characterization), drafted a structured approach to identifying and assessing potential risks from exposures occurring during development. This meeting report briefly describes the workshop and summarizes the workshop conclusions.

The workshop was organized by a 16-member planning committee that drafted an outline for the framework, prepared and reviewed several background papers for the workshop, and nominated experts in the key scientific disciplines as potential workshop participants. Among the areas of expertise represented in the workshop were developmental biology and toxicology (neurologic, reproductive/developmental, immunologic, pulmonary, general), pediatrics, genetics, epidemiology, pharmacokinetics, modeling, exposure assessment, and risk assessment. Workshop participants were drawn from government, academia, industry, and the public health community. Most of the time was devoted to the work of the breakout groups.

The breakout group chairs (Ginsberg, Faustman, and Daston) and their rapporteurs were the keys to the success of the workshop, as they moved their respective groups through their tasks. With their leadership and the active participation of the breakout group members, the framework outline drafted by the planning committee was discussed, further developed and modified, and adopted by the workshop participants; focus questions were addressed; concepts, insights, conclusions, and recommendations developed in breakout groups were presented and discussed in plenary sessions and revised, as appropriate, by the breakout groups; and critical data needs for improving the assessment of children's risks were identified.

Following the workshop, the chairs and rapporteurs, in collaboration with their respective breakout groups, prepared the breakout group reports. These reports were compiled and synthesized into a workshop report by the overall workshop chair. This report was then circulated to all workshop participants and observers for comment, and a final workshop report was prepared.

The conceptual framework created by the workshop (Figure 1) is based on the

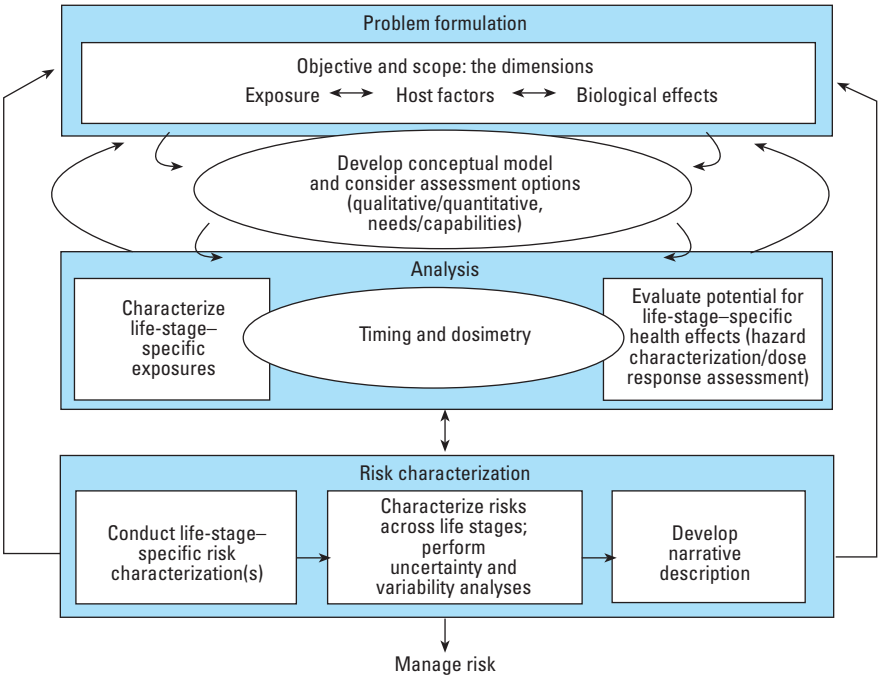

Figure 1. Proposed framework for assessing risks to children from exposure to environmental agents.

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Problem Formulation → Analysis → Risk Characterization paradigm that has been incorporated in many risk assessment frameworks over the past decade, and applies that paradigm to early life-stage exposures. The framework recognizes the potential significance of the timing of exposures in relation to the susceptibility of the developing human, from the perspective of both toxicokinetics and toxicodynamics. It offers a systematic approach to the consideration of factors that may influence risk during development, from conception through organ maturation (in adolescence). And it acknowledges that the complexity and unique insights of a risk assessment focusing on early life stages will depend critically on the data available and the scope of the assessment.

Among the conclusions from the workshop were the following:

- There are distinct life stages during development with both known and hypothesized "windows of susceptibility" in humans and in experimental animal models. These developmental life stages are defined by differences in relevant kinetic and dynamic processes occurring at the molecular, cellular, organ, and physiologic levels. Interspecies comparisons must consider differences in life stages and kinetic and dynamic processes, including timing and dosimetry.
- In addition to considerations of intrinsic sensitivity of the developing human, life-stage–specific behaviors, activity patterns, functions, and intakes often can lead to dramatic differences in exposures. Life-stage–linked exposure assessment is a critical component of any children's environmental health risk assessment.
- In Problem Formulation, in the context of the proposed framework (Figure 1), defining the overall scope and objectives of the risk assessment is important for the initial assessment of life stages, exposure scenarios, and toxic effects to be considered.
- Problem Formulation produces a conceptual model of the likely key relationships between exposures and the effects of the environmental agent(s) on host (exposed) populations, informed by the initial identification of exposure scenarios, exposed life stages, and the known or anticipated biologic effects of the environmental agent(s). The conceptual model for the risk assessment arises from and guides the collection of data in preparation for the Analysis phase.
- Toxicokinetic considerations in Analysis include agent/chemical-specific factors and life-stage/age-specific factors, both of which can include effects on absorption, distribution, metabolism, and excretion. Examination of these factors may reveal one or more age groups of particular toxicokinetic concern.
- Toxicodynamic considerations in Analysis include the identification of uniquely susceptible dynamic processes of concern and the functional consequences of altering these processes, and consideration of available data that may indicate differential toxicity from exposures during susceptible periods.
- Analysis of the timing of development and exposures and of the dosimetrics of the agent (including both kinetic and dynamic factors) links the characterization of life-stage–specific exposures with life-stage–specific effects.
- Risk Characterization for early life-stage exposures may be qualitative (e.g., when quantitative data are lacking or a quantitative analysis is unnecessary) or quantitative (e.g., incorporating a life-stage–specific physiologically

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Toxicokinetics	Toxicodynamics	Risk characterization	Other participants
Chair: Gary Ginsberg[a] Connecticut Department of Public Health	**Chair:** Elaine Faustman[a] University of Washington	**Chair:** George Daston[a] Procter & Gamble	Robert Amler ATSDR
Rapporteur: James Bruckner University of Georgia	**Rapporteur:** William Breslin[a] Eli Lilly & Co.	**Rapporteur:** Penny Fenner-Crisp ILSI Risk Science Institute	Nancy Beck U.S. EPA/ORD/NCEA (AAAS Fellow)
Breakout Group:	**Breakout Group:**	**Breakout Group:**	Richard Becker American Chemistry Council
Hugh Barton U.S. EPA/ORD/NHEERL	Richard Albertini University of Vermont	John Adgate University of Minnesota	Terri Damstra WHO/IPCS
Matthew Bogdanffy DuPont Haskell Laboratory	Adolfo Correa[a] CDC	Sherlita Amler[a] ATSDR	Michael Firestone U.S. EPA/OCHP
Harvey Clewell ICF Kaiser/KS Crump Group	John DeSesso Mitretek Systems	Bob Chapin DuPont Pharmaceutical	Steven Knott U.S. EPA/ORD/NCEA
Karen Davis-Bruno[a] U.S. FDA/CDER	Rodney Dietert Cornell University	Vicki Dellarco U.S. EPA/OPP	Ray McAllister American Crop Protection Association
Dale Hattis Clark University	Joyce Donohue U.S. EPA/OW	Brenda Eskenazi[a] University of California, Berkeley	LaRonda Morford Eli Lilly & Co.
Dan Krewski University of Ottawa	Jean Harry NIEHS	Daniel Goldstein[a] Monsanto	Vanessa Vu U.S. EPA/OPPTS/OSCP
Kannan Krishnan University of Montreal	Robert Kavlock U.S. EPA/ORD/NHEERL	Elaine Cohen Hubal U.S. EPA/ORD/NERL	
Stephen Olin[a] ILSI Risk Science Institute	Gary Kimmel U.S. EPA/ORD/NCEA	Carole Kimmel[a] U.S. EPA/ORD/NCEA	
Wayne Snodgrass University of Texas Medical Center	Bruce Lanphear University of Cincinnati	Philip J. Landrigan[a] Mt. Sinai School of Medicine	
Bob Sonawane[a] U.S. EPA/ORD/NCEA	Merle Paule FDA/NCTR	Melanie Marty CalEPA/OEHHA	
	Kent Pinkerton University of California, Davis	Bette Meek Health Canada	
	Jennifer Seed U.S. EPA/OPPT	Larry Sheets Bayer Corp.	
	Michael Shelby NIEHS	Tracey Zoetis Milestone Biomedical Associates	
	Diana Somers PMRA/Canada		
	Tom Trautman[a] General Mills		
	Isabel Walls ILSI Risk Science Institute		

Abbreviations: AAAS, American Association for the Advancement of Science; ATSDR, Agency for Toxic Substances and Disease Registry; CalEPA, California Environmental Protection Agency; CDC, Centers for Disease Control and Prevention; CDER, Center for Drug Evaluation and Research; FDA, U.S. Food and Drug Administration; NCTR, National Center for Toxicological Research; NERL, National Exposure Research Laboratory; NHEERL, National Health and Environmental Effects Research Laboratory; IPCS, International Programme on Chemical Safety; NIEHS, National Institute of Environmental Health Sciences; OCHP, Office of Children's Health Protection; OEHHA, Office of Environmental Health Hazard Assessment; OPP, Office of Pesticide Programs; OPPT, Office of Pollution, Prevention, and Toxics; OPPTS, Office of Prevention, Pesticides, and Toxic Substances; OSCP, Office of Science Coordination and Policy; OW, Office of Water; PMRA, Pesticide Management Regulatory Agency; WHO, World Health Organization

[a]Planning Committee; William Slikker (FDA/NCTR), Ralph Smialowicz (EPA/NHEERL), and Susan Kess (ATSDR) also participated in the Planning Committee.

based toxicokinetic or biologically based dose–response model) or some other semiquantitative assessment.
- The full spectrum of potential developmental effects cannot be predicted from data on exposed adults. A core data set from studies in developing organisms is essential.

The workshop identified critical research needs for improved assessments. Among the highest research priorities are:
- Improved understanding of critical windows of developmental susceptibility and of comparative developmental schedules of animals and humans
- Characterization of children's habits and practices (e.g., diet, behavior, time-activity patterns) at different stages of development
- Better methodology (e.g., in testing protocols), applied more often, on functional outcomes at relevant life stages in animal models and humans; the methods should be sensitive and specific and should account for variability in responses and norms
- Investigation of the temporal relationships between exposure and outcomes, particularly for delayed outcomes (latent sequelae)
- Understanding of host factors that contribute to susceptibility
- Monitoring of disease trends and exposures.

After the workshop, the ILSI Risk Science Institute formed a Children's Risk Assessment Framework Working Group to coordinate follow-up activities. Initial efforts have focused on developing the workshop observations and recommendations into a concise, pragmatic framework for assessing children's risks and refining, testing, and elaborating the framework by means of case studies. Other Working Group topics include coordinating the creation of a database on physiologic parameters for early life stages and comparing the timing of development of key organ/functional systems in different species.

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Guzelian PS, Henry CJ. 1992. Conference summary. In: Similarities and Differences between Children and Adults: Implications for Risk Assessment (Guzelian PS, Henry CJ, Olin SS, eds). Proceedings of the ILSI Conference on Similarities and Differences Between Children and Adults: Implications for Risk Assessment, 5–7 November 1990, Hunt Valley, Maryland. Washington, DC:ILSI Press, 1–3.