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# CHILDREN'S ENVIRONMENTAL HEALTH: WHAT ROLE FOR THE FEDERAL GOVERNMENT?

**PAPERS SUBMITTED AT A SEMINAR SPONSORED BY THE CONGRESSIONAL RESEARCH SERVICE**

TO REVIEW FEDERAL POLICIES WITH RESPECT TO THE RISKS OF ENVIRONMENTAL HAZARDS ON CHILDREN AND YOUTH

NOVEMBER 30, 2001

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## FOREWORD

This publication is the culmination of proceedings and papers delivered at a day-long seminar held by the Congressional Research Service: "Children's Environmental Health: What Role for the Federal Government?" Senators John H. Chafee of Rhode Island and Max Baucus of Montana, then the chairman and ranking member of the Committee on Environment and Public Works, asked the Library of Congress to provide a scientific forum on this issue.

The Committee on Environment and Public Works is the panel of the Senate that oversees the environmental laws of the United States, including the effects of environmental hazards on human health. Federal rules regulating exposure levels to ecological hazards have been developed in law and regulation over the last 30 years by the Environmental Protection Agency. Federal policy makers have relied on the a wide variety of scientific evaluations of the risks posed by environmental causes. Guidelines for setting protective levels against hazardous exposure are designed for application to large population groups.

Senator Chafee and Baucus asked the Congressional Research Service to evaluate the impact of Federal regulation of environmental hazards on children and youth. As more research of impacts of environmental hazards on human populations was published, evidence increasingly indicated that children respond differently to environmental hazards than the general population. The request to CRS to sponsor a gathering of experts provided a starting place for review of this issue with the purpose of learning whether refinements were needed in the regulatory process.

Since 1996 Senator Boxer has sponsored bills to provide for protection of children against environmental hazards. In the 107th Congress, she introduced S. 855, "A bill to protect children and other vulnerable subpopulations from exposure to environmental pollutants, to protect children from exposure to pesticides in schools, and to provide parents with information concerning toxic chemicals that pose risks to children, and for other purposes."

The committee wishes to commend the staff of the Congressional Research Service for their diligence in fulfilling the task given to them by the committee. The national debate on children's health issues has been advanced by the scholarship and high quality of the debate among the participants.

*Remembering Senator John H. Chafee*

On behalf of the committee members, I also would like to take this opportunity to recognize the leadership and achievements of Senator John H. Chafee as a vanguard in protecting the nation's children. As a Senator, he was an early advocate for children's rights and health safeguards. He was a leader in the health care

and Social Security Act debates of the 1990's. He was one of the anchor members of the "Centrist Group" of moderate Senators, of which I was a member. He was a key reformer of the long process to overhaul the nation's health care system. He was instrumental in pointing out the impacts of environmental hazards, such as second-hand tobacco smoke, on children and elderly populations.

John sponsored legislation to protect children in foster-care housing, and to prevent the sale of tobacco to minors. He supported the requirements to adjust air bags regulations in automobiles to accommodate children's physical needs, and to require safer safety practices for transporting children on the nation's roads. Senator Baucus said of his work as a Senator who fought for powerless people: "John spoke for those people in the shadows—the poor, the elderly, and children. Especially children with special needs, whether it was Medicaid or welfare reform, John was a very strong advocate. In fact, he was a stronger advocate by far than most Members of the Senate."

During the special order of the Senate held after his death on October 24, 1999, at which all the Members of the Senate offered their thoughts on his passing, the comments were universal about John's style of leadership. Senator Bob Graham said, "John Chafee was a very humble, unassuming giant in the Senate. He had a broad, inclusive vision. He was a principled and thoughtful person. He was kind and generous. He asked and gave the best of himself in everything he did. He never sought recognition. He rolled up his sleeves and went to work."

Senator Jim Inhofe remarked that in the years that he and Senator Chafee had been members of the Republican Conference, they sometimes disagreed on the issues. By experience, however, Jim had come to appreciate the style of advocacy shown by his friend, "I would stop and think it over: This is John, so maybe I need to be listening a little bit more. I think he had a greater impact on people who disagreed with him than he did on people who agreed with him."

Senator Bob Smith, who assumed the chairmanship of the committee for the remainder of the 106th Congress after Senator Chafee's death, remembered Chairman Chafee as a peacemaker and advocate for strongly held views. "If there was anyone who ever lived who perfected the art of disagreeing without being disagreeable, it was John Chafee. Many times I marveled at his ability to participate in a heated debate, in close quarters, without losing his composure and his good humor."

John Warner and John Chafee had worked side by side since they were assigned to the Department of the Navy in the Nixon Administration. Reflecting upon John's death, Senator Warner said, "We have to remember every day in this great institution that, yes, we have our debates, we have our differences, but the man or the woman to your left or right in this magnificent institution could be gone the next day by the will of God. I always think of that. We have to treasure and value every moment we have with each other in this great institution because it brings us together."

Senator Harry Reid summarized the views of the committee members and the Senate as a whole when he stated, "Some of the giants of the Senate in the 20th century are people who have

served as chairmen of the Environment and Public Works Committee, men such as Robert Stafford of Vermont, Jennings Randolph of West Virginia, and Daniel Patrick Moynihan, of New York. John Chafee clearly deserves to be mentioned in the same breath as all of them. He truly was a great Senator. In fact, it is fair to say when we list the great Senators of the 20th century, it would not be complete without the name of John Chafee."

As a former member of the committee and now returning to it as its chairman in the 107th Congress, I think back to the example of leadership and open hand of friendship that John showed me as a newly elected backbencher from Vermont. The towering legacy left behind by my predecessor in the Senate, Chairman Bob Stafford of Vermont, was a formidable challenge when I first joined the committee. John Chafee was one of the first Senators to seek me out as a friend and colleague. Over the years, our friendship grew and we came to find ourselves increasingly on the same side of issues facing our nation. I always relied on his good judgment, good humor, and good sense.

It is with great appreciation that the members of the Committee on Environment and Public Works remember the leadership of Senator John H. Chafee, a patriot, Secretary of the Navy, Governor, and Senator. He continues to inspire us who follow him in this institution with his passion for public service, his consummate skills as a legislator, and his generosity of spirit.

JAMES M. JEFFORDS, *Vermont.*

# Children's Environmental Health: What Role for the Federal Government?

**November 30, 2001**

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# Executive Summary

During the late 1990s, perceived threats to children from pollutants in the ambient environment moved the U.S. Congress to pass legislation, President Clinton to issue an Executive Order, and the U.S. Environmental Protection Agency (EPA) to establish a new office aimed at enhancing children's environmental protections. The 107th Congress is considering additional proposals.

Because the scientific and policy issues involving children's environmental health risks are complex, the Senate Committee on Environment and Public Works asked CRS to commission pediatricians and research scientists to prepare authoritative papers discussing the scientific evidence regarding children's health risks from chemicals in the ambient environment, and policy experts to identify possible policy options for the federal government. CRS convened an all-day seminar on May 22, 2000 for Members and congressional staff on children's environmental health issues. At the seminar, *Children's Environmental Health: What Role for the Federal Government?*, authors presented draft papers, and experts representing a wide range of viewpoints critiqued them, addressing scientific papers in the morning and policy papers in the afternoon. The seminar and the commissioned papers were supported, in part, by a grant from the Robert Wood Johnson Foundation. Based on these papers and discussions, CRS constructed consensus statements. Authors revised their papers in response to comments and reviews by CRS. This report contains the final papers, summaries of critiques and discussions of earlier drafts, and introductory and explanatory material prepared by CRS. Appendix A contains the seminar program. Appendix B is a compilation of biographical information provided by authors and peer reviewers. Authors of the major papers retain responsibility for the accuracy and balance of their work. CRS assumes responsibility for the balance of the overall report.

The aim of the scientific papers is to review relevant, scientific publications, draw on the authors' expertise, evaluate the weight of scientific evidence, and draw conclusions about the state of scientific knowledge related to environmental health risks to children. The scientific papers and discussions address four general topics:

- How do children's environmental health risks differ from those of adults? Are children more sensitive, vulnerable, or exposed than adults? What scientific evidence exists to support these claims/conclusions? How do environmental health risks compare to other health risks for children?
- Which environmental pollutants may pose a special health risk to children and what level of evidence exists?
- Do environmental exposures to pollutants increase the rates of adverse health outcomes among children or adversely affect children's health in a manner or degree that is different from that of adults?
- Based on available scientific evidence about environmental health risks to children, what can we conclude? To what extent do we have consensus? To resolve the areas of disagreement, what types of research would be most helpful?

The first scientific paper was authored by Ruth A. Etzel, M.D., Ph.D., a pediatrician and epidemiologist, who is a Captain in the U.S. Public Health Service in Washington, D.C. She

is the immediate past chairperson of the American Academy of Pediatrics (AAP) Committee on Environmental Health and the editor of the AAP Handbook of Pediatric Environmental Health. Dr. Etzel began by explaining how and why children's environmental health risks are different from those of adults. She noted that –

- Children may be exposed differently to pollutants;
- Children may absorb pollutants differently;
- Children have a higher rate of metabolism; and
- Children have "windows of vulnerability" while they are growing and developing, when their target organs for various exposures may be more susceptible than the target organs of adults.

A table in Dr. Etzel's paper summarizes developmental stages and illustrative environmental health risks that occur during each stage.[1]

To address the question of how environmental health risks compare to other health risks for children, Dr. Etzel discussed the five leading causes of death among infants less than one year, children between 1 and 4 years, children between 5 and 9 years, children between 10 and 14 years, and children 15 to 19 years. Changes over time in these risks also were discussed. She concluded that with respect to childhood mortality, environmental health risks are greatest during gestation and during the first year of life. Estimates of the proportion of infant deaths that might be due to environmental causes, Dr. Etzel noted, vary widely–between 5% and 40%. If one assumes that the lower estimate is accurate, then 1,424 infant deaths (5% of 28,488 infant deaths) would be attributed to environmental causes, she explained. However, she emphasized that mortality is a poor indicator to use when assessing how environmental risks compare to other health risks for children. Most environmental health risks do not result in deaths among children, but in illnesses and disabilities, which are not routinely tracked.

Dr. Etzel and other scientists who participated in the discussion of Dr. Etzel's paper at the CRS seminar generally agreed on the following points –

- As a group, children's environmental health risks differ from those of adults. The differences may be large and may go in either direction.
- Differences in exposure and vulnerability to health effects among individual children may be less than, equal to, or greater than differences between children as a group and adults. Differences among individual children also may be less than, equal to, or greater than differences among groups of children at different stages of development – prenatal, perinatal, infant, toddler, pre-teen, and adolescent.
- As a group, children differ from adults in exposure to potentially toxic chemicals in the environment; their absorption and metabolism of such chemicals; and their susceptibility to harmful effects. Some of these differences arise from differences in behavior (for example, drooling and mouthing objects, or crawling), physical size, maturity of organs or

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[1]The word "developmental" is used throughout this document. It is defined in Dr. Mattison's paper as related to "the process of growth and maturation from an immature to a more mature stage."

physiological processes, or presence in different environments (e.g., *in utero*, occupational, recreational, or educational).
- Socio-economic conditions, health and nutritional status, genes, and access to medical care mediate environmental health effects.
- Children's biological exposure from chemical contaminants in the air, some foods, and water may be greater than that of adults in the same environment, because children breathe more, eat more, and drink more, relative to their size, and the skin of a newborn child may absorb more, pound for pound.
- Children experience periods of special vulnerability to some toxic effects of some chemicals as their organs develop. Some of these vulnerable periods are quite extended.
- Although U.S. death rates due to childhood exposure to environmental contamination are not known, they should be viewed in the context of known causes of death, which vary depending on age.
- U.S. death rates might not be the best basis for comparing health risks to children; some measure of illness or disability would be useful, if data were available.

Lynn Goldman, M.D., a professor at Johns Hopkins School of Hygiene and Public Health, prepared the second paper. As a former Assistant Administrator of the Office of Prevention, Pesticides and Toxic Substances at the Environmental Protection Agency, she has broad knowledge of the range of chemicals regulated by the federal government. Dr. Goldman gave an overview of the chemicals and pesticides on the market today and the available information about them to assess risks to children. Her points were illustrated by case studies of lead, mercury, and polychlorinated biphenyls (PCBs). She concluded that children may be more susceptible than adults to chemicals in the environment, and that scientists now recognize a need to gather child-specific data.

In general, Dr. Goldman and the other scientists who participated in the discussion of Dr. Goldman's paper at the CRS seminar agreed on the following points –

- Information about the potential toxicity to children of chemicals in U.S. commerce is very limited and usually based on indirect measures. There are few experimental data related to developmental neurotoxicity.[2]
- Data on children's exposure to chemicals, including prescription drugs, remain sparse.
- Data on childhood exposure to lead in the United States provide a sound basis for risk assessments. Lead exposure in children can lead to IQ deficits, impaired school performance, distractability, short attention spans, and impulsive behavior.
- Even when data clearly establish the toxicity of a chemical to children, such as the toxicity of methyl mercury to developing brains, exposure data for U.S. children are lacking. Epidemiological studies suggest that a small proportion of U.S. infants, whose mothers consume large amounts of fish

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[2]Developmental neurotoxicity is the capability of producing an alteration in an embryo, fetus, or child up to the time of sexual maturation that adversely affects growth, structure, or function of the nervous system.

and seafood during pregnancy, may be at risk due to prenatal exposure to methyl mercury.

- New data are being collected by industry and government to improve estimates of exposure and toxicity to U.S. children of pesticides, some pediatric drugs, and methyl mercury.
- Chemicals like lead and methyl mercury, that are toxic to nervous system tissue in similar ways in children and adults, are more likely to harm young children, whose brains are still developing, than adults, given comparable levels of exposure.
- Where data exist on other chemicals, they are not always well utilized. For example, data gathered by the Food and Drug Administration (FDA) and EPA as part of a product registration application have not been used extensively to develop models for predicting toxicity of unstudied chemicals, often because access to such data is restricted in order to protect confidential business information (CBI, also known as trade secret claims).

Donald Mattison, M.D., M.Sc., is the Medical Director of the March of Dimes. In the third scientific paper, he summarized the state of knowledge about birth defects and other adverse effects on growth and development to illustrate his answer to the question "Do environmental exposures to pollutants increase the rates of adverse health outcomes?" Birth defects are the leading cause of death among infants and the second leading cause of death among children generally (after motor vehicle accidents). About 150,000 babies are born each year with birth defects (at a rate of 35,714 per million births, about 1 in 28). Yet, the causes of many birth defects are poorly understood, according to Dr. Mattison. He described major difficulties encountered by scientists studying birth defects and discussed the strengths and weaknesses of various kinds of data.

Dr. Mattison and other scientists who participated in the discussion of Dr. Mattison's paper at the CRS seminar generally agreed on the following points –

- Exposure during development to certain chemicals at toxic levels may cause death, structural abnormality, altered growth, or functional deficits. Some effects may take years to be evident, while others may be immediate, short-lived, and reversible. Increased probability of premature birth also might be an effect of toxic exposure.
- For most chemicals, it is not known whether adverse health effects might result from prenatal, infant, or childhood exposure to low levels in the environment.
- The causes of most significant health problems in infants and children (for example, some birth defects and asthma) are only partially understood.
- The overall infant mortality rate and the rate of infant deaths due to birth defects have fallen significantly in recent years. Nevertheless, the United States has a higher rate of infant mortality than 25 other nations.
- Birth defects are the leading cause of infant mortality in the United States. Birth defects most commonly affect the cardiovascular system, respiratory system, chromosomes, and nervous system, in that order.
- Premature birth is the second most common cause of infant mortality, and the number of pre-term births has increased slightly in recent years.

- Estimates of the percentage of all birth defects that may be caused, at least in part, by environmental factors (including smoking and alcohol use) vary widely from about 3% to as much as 75%. More recent estimates are on the higher end of this range. Individual susceptibility to environmental pollutants may often be determined genetically.
- All known human developmental toxicants cause developmental disease in at least one species of experimental animals. Animal tests for effects on development often are accurate predictors of human developmental toxicity.
- There is no indication that background ambient levels of teratogens in the air, water, or soil have caused human birth defects in the United States.[3]
- There is limited evidence that birth defects have increased in the vicinity of some contaminated industrial sites.
- Asthma rates have been rising in the general U.S. population for 30 years, but scientists do not know why.
- Public health surveillance of asthma morbidity and other disorders in children is needed.
- It is not clear whether the observed increase between 1973 and 1994 in rates of some types of childhood brain tumors indicates a real increase in cases or improved medical technologies.
- Generally, it is not clear whether cancer rates in children are rising.

Andrew Olshan, Ph.D., is a professor in the Department of Epidemiology, School of Public Health at the University of North Carolina. His paper examining the state of research on children's environmental health is the fourth and final paper in the scientific portion of this report. Dr. Olshan used his own research on the relationship between brain cancer in children and pesticide exposure to portray the more general issues in children's environmental health research.

Dr. Olshan and other scientists who participated in the discussion of Dr. Olshan's paper at the CRS seminar generally agreed on the following points –

- The environmental factors that might increase childhood cancer rates generally are not known, with a few exceptions, most notably ionizing radiation.
- A large increase is needed in chemical testing to support risk assessments for potential health effects in children due to environmental exposure to chemicals.
- Better chemical exposure data are needed for parents and children. Currently, most studies estimate pesticide exposure levels for all pesticides as a group, rather than for particular products, and estimates almost always are based on indirect measures of uncertain validity.
- Although data on pesticide exposure are limited, it is likely that home, lawn, and garden uses of pesticides may be larger sources of pesticide exposure to most parents and children than agriculture.

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[3]According to Dr. Mattison's paper, a teratogen is any chemical, physical or biological agent capable of producing a preventible developmental disease in an embryo or fetus who otherwise might have been normal at birth.

- The biological mechanisms by which pesticide exposure might lead to cancer in children remain speculative and should be investigated.
- The totality of epidemiologic evidence is not sufficient to conclude causal association of pesticide exposure and brain cancers, though the data are suggestive.
- There is a need for much more screening of chemicals for environmental risks to children's health. New research methods, including toxicogenomics and bioinformatics, should be developed to screen chemicals.[4]
- Research should take into account the effects of age at exposure, timing, and duration of chemical exposure. There is a need for better experimental data on the health effects of pesticides on offspring of laboratory animals.
- New methods are needed for toxicological testing, and for evaluating existing databases, especially for factors that determine toxicity, allergenicity, and for non-cancer endpoints like developmental immunology. Structure-activity relationships (SAR) among chemicals might be used to evaluate absorption, distribution, metabolism, and interaction with cells, but a need remains for new animal strains suitable for testing.

Policy experts were asked to advocate a particular policy approach in response to the question "What, if any, is the appropriate role of the federal government (as opposed to state or local government) in managing children's environmental health risks?" Four individuals who had publicly expressed diverse views on this subject were asked to prepare scholarly papers describing the approach they favored and discussing its strengths and weaknesses.

Convergence of opinion was evident among the authors and discussants of policy papers: authors seemed unanimously to favor governmental action in the form of research. They indicated agreement on a number of possible areasa for federal activities. The following statements of consensus were approved by participants in the May 22, 2000, seminar.

- The federal government should identify research priorities and conduct and sponsor basic medical, biological, environmental, and public health research to improve scientific understanding of children's health and development.
- The federal government should organize, fund, and evaluate monitoring programs to collect data on chemicals in the environment, children's health trends, and children's exposure to chemicals.
- The federal government should help shape, manage, and support a public health infrastructure capable of preventing and responding to significant children's environmental health risks, with special attention to children with limited access to medical care.
- Federal policies should recognize that economic status, environment, and health interact, and that diseases usually are caused by a confluence of genetic and environmental factors.

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[4]Toxicogenomics is an emerging scientific discipline that combines genomics (the study of genes and their function) and bioinformatics (the management and analysis of biologic research data using advanced computing techniques) to identify and describe the ways that chemical molecules affect and are affected by human bodies.

- Federal policies for research and risk management related to children's health should recognize the significance of morbidity, although no satisfactory unit of measurement is available for quantitative comparisons.[5]

Differences of opinion lie in more detailed prescriptions for public policy. Major points of each presentation are summarized below.

Kenneth Chilton, Ph.D., presented the first policy paper in the afternoon session of the CRS seminar on May 22, 2000. Dr. Chilton, a Distinguished Senior Fellow and Manager of Environmental Research at the Center for the Study of American Business at Washington University in St. Louis, Missouri, argued that environmental risks to children's health are not large relative to other risks, and were exaggerated by the Clinton Administration. He expressed concern that this exaggeration might distort priorities in public health programs, diverting public resources away from programs targeting greater risks. He urged restraint in public resource allocations and in public communication about children's environmental health risks, tempering pronouncements about risks with acknowledgments of associated benefits that may justify risks.

Dr. Chilton described current federal research efforts as "considerable" and "adequate." He said he would broaden or rescind President Clinton's Executive Order 13045, which mandates development of child-centered programs. Environmental protection legislation, Dr. Chilton stated, should be written to include consideration of costs, benefits, and other risks when regulating environmental contaminants. Finally, Dr. Chilton recommended that a broadly focused public health agency, rather than EPA, should lead any federal children's environmental health initiative. This arrangement would be more likely to preserve an appropriate balance among programs devoted to various risks, he argued.

Rabbi Daniel Swartz, Executive Director of the Children's Environmental Health Network (CEHN), emphasized the importance of social, ethical, and political values, in addition to biological and economic factors, in determining what federal policies should be with respect to children's environmental health, particularly in light of the uncertainty of scientific estimates of risk. He argued that equity, liberty, and justice were values Americans hold in common. He expressed a preference for policies aimed at prevention, as opposed to treatment after exposure. Reductions in poverty should be pursued along with reduced environmental hazards, according to the Rabbi. He admired the example set by the Food Quality Protection Act standard for protecting children, in which pesticides are not assumed to be completely safe for children, but are not assumed to be dangerous at all levels in all circumstances, either: data drive the decision whether to provide an extra margin of precaution in standard setting.

Rabbi Swartz provided several suggestions for federal action to protect children's environmental health, including more protective standard setting, consideration of cumulative and aggregate risks to children in risk assessments and rule development, development of national monitoring and research strategies, establishment of a broad

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[5]Participants discussed the advantages and disadvantages of various health benefit measures in use today, such as lives saved, life-years saved, quality-adjusted life-years (QALYs) saved, and disability-adjusted life-years (DALYs) saved, but disagreed about their utility.

parental right to know about potential risks to their children, better intragovernmental and intergovernmental coordination of relevant programs, support for a moral code that protects children, and responsible behavior with respect to children. Finally, Rabbi Swartz warned of the limitations of economic analyses and advised the federal government to revise economic assumptions that he alleged are incompatible with protection of children's environmental health. Rabbi Swartz said he would recommend retaining and supporting Executive Order 13045 on Children's Environmental Health, establishing a White House Council on Children's Environmental Health and Safety, and employing whatever means are appropriate at the federal level to achieve protection of children's health, including regulation, voluntary programs, grants, demonstration programs, outreach and education, and legislation.

Kimberly Thompson, Sc.D., Assistant Professor of Risk Analysis and Decision Science at Harvard University's School of Public Health, presented the third policy paper. Dr. Thompson provided an overview of the recent history of federal agency involvement in children's health issues. She argued that the focus of recent initiatives on children's environmental health, with a heavy focus on chemicals, failed to recognize or address the most significant risks to children's health, such as poverty, accidents, and violence. However, she noted the lack of data that would permit relative risk assessment. She summarized research needs identified by various workgroups in recent years.

The federal government should evaluate and address environmental risks, she urged, in light of more certain risks of equal or greater magnitude, such as children's risk of dying as a result of automobile accidents, gun violence, and child abuse. She argued that both exposure to, and toxicity of, chemicals in the environment must be assessed chemical-by-chemical, because the quality and quantity of health effects are variable. Dr. Thompson concluded that sparse data do not provide a solid scientific basis for rulemaking. She urged policy makers and researchers to clearly define terms, identify inequities, and target policies to relatively high risks.

The role of the federal government should be to coordinate programs concerned with child welfare, address children's health issues of national or international scope, support medical and public health research, regulate multinational industries, provide resources to meet children's needs, and monitor children's health, according to Dr. Thompson. She questioned the national commitment to improving children's health, however, and expressed special concern about the health of uninsured children and the congressional failure to ratify the International Convention on the Rights of the Child. Dr. Thompson stated that federal support and oversight is needed for traditional local public health programs, such as immunization and food stamp programs.

Dr. Thompson argued that a more analytic approach is needed to ensure accountability and efficient use of federal resources available for children's health programs. A prerequisite to analysis, she claimed, is more transparency in how resources are allocated to research and risk management programs. Dr. Thompson criticized policy decisions that fail to consider tradeoffs among risks and benefits, and she concluded that future research should collect data on costs and benefits of alternative risk management policies, as well as information needed to put environmental risks in perspective.

Richard Jackson, M.D., M.P.H., Director of the National Center for Environmental Health at the Centers for Disease Control and Prevention (CDC), contributed the final major policy paper, in which he argued that federal responses to chemical risks historically have been delayed pending data collection and analysis, resulting in unnecessary suffering and permanent disabilities. He urged vigorous enforcement of existing regulations and aggressive promulgation of "child-centered, science-based, prevention-oriented environmental health and safety policies that protect children now and in the future." The special role of the federal government should include public health surveillance, data collection and analysis, and development of national goals for children's health, he stated.

Much more funding for research is needed, Dr. Jackson argued, in order to fully understand the health effects resulting from exposures to environmental toxicants, particularly when those health effects appear only many years after exposure. Dr. Jackson praised the Food Quality Protection Act provision mandating addition of up to a 10-fold safety factor to federal standards limiting pesticide residue levels on food eaten by children. He argued that the FQPA forces manufacturers of pesticide products to prove their safety, an approach which he favored. Swift implementation of the FQPA provisions is needed, he said. He also urged continued and increased funding for the existing interagency task force on children's environmental health.

Discussants raised a number of significant policy-related issues. For example, Dr. Trudy Cameron, a professor of economics at the University of California at Los Angeles, noted that the policy papers all seemed to recommend selection of measurable public health goals prior to decisions about how to allocate federal resources. She advised selection of rather broad measures so that goal attainment would not be impeded. In addition, Dr. Cameron argued that the federal government should intervene to manage the availability of public goods like health protection, because preventive measures in particular are unlikely to attract much private investment.

Many speakers expressed concern about the focus on mortality, when illnesses are so much more prevalent in children. It was noted that defining children's risk in terms of deaths during childhood would miss any increase in death rates during the adult years due to childhood exposure to environmental contaminants.

Dr. James Wilson, Senior Fellow at Resources for the Future, stated that most federal laws governing chemicals and the environment protect women of child-bearing age and children, making additional chemical regulations unnecessary. The key lesson of the seminar, he asserted, should be that the effect of poverty on the health of children is a more significant problem than environmental pollution.

Ms. Karen Florini, a Senior Attorney with Environmental Defense, argued that the United States is rich enough to be both safe and healthy, that is, to address injuries as well as environmental risks to children. What she termed a "lack of political will" to address poverty, guns, and smoking does not excuse delays in addressing environmental health hazards for which political will does exist, she said. In addition, Ms. Florini claimed that at least some progress in reducing environmental risks to children may be relatively inexpensive or even profitable for the regulated industries.

Ms. Florini added that data are too sparse to rule out exposures in childhood to environmental chemicals as causes of chronic diseases in adulthood. Until data can be collected, she urged use of conservative, protective assumptions to fill in any scientific gaps.

Ms. Sandra Tirey, an Assistant Vice President of the Chemical Manufacturers' Association (now the American Chemistry Council), suggested that a key role for the federal government should be in communicating accurate children's health risk information to the general public. She also favored federal incentives for collaboration "among government, academic, industry, and other stakeholder interests."

The ultimate purpose of research sponsored by the federal government seemed to be at issue, according to Mr. Jim O'Hara, formerly with the Food and Drug Administration and now directing Health-Track (a project supported by The Pew Charitable Trusts through a grant to Georgetown University). He noted that some policy advocates want research to inform regulations while others seem to see research only as a tool to inform the public. He urged integration of public health and environmental protection approaches in federal policies.

In conclusion, it appears that concerns about children's exposure to chemicals in the environment are based, at least in part, on scientific observation of past experiences with toxic chemicals and adverse effects of exposure to them in the environment. However, data on children specifically are very limited and do not permit generalizations about the universe of chemical contaminants. Scientists generally agree that children's environmental health risks from chemicals differ from those of adults; depending on the chemical, children's risks may be much greater or much smaller than those of adults. A greater health risk to children has been found for environmental exposure to lead, and research demonstrates a potentially greater toxicity to children (because they are continuing to develop), if they are exposed to high enough levels of other pollutants like PCBs and mercury. Thus, the science indicates that there might be increased environmental health risks to children from chemical contaminants, but the extent and significance of the risks currently are unknown and remain debatable.

Policy analysts representing a broad spectrum of political philosophies support additional federal funding for toxicological and risk assessment research and for monitoring of environmental contamination and human exposure, in order to improve assessments of children's environmental health risks. But, beyond research, policy preferences diverge, despite shared knowledge of available scientific evidence. Some would enhance protection of children by attempting to minimize chemical exposure through federal pollution prevention incentives or regulations. Others would avoid actions with impacts on the private sector until additional data had been gathered and competing priorities had been analyzed, allowing resources to be targeted to where they would have the best chance of saving lives or improving quality of life.

The policy debate is driven largely by differences in how people weigh quantitative risk estimates against personal and societal values in determining when or whether federal action is justified. Policy analysts' diverse definitions of "environment" and "risk," and varied preferences for local, state, or federal governmental action further complicated discussion. However, the policy experts appear to share the goal of enhanced health for children, which may lead to opportunities for eventual agreement on appropriate federal action.

# Introduction

## Background

The middle to late 1990s saw a flurry of federal activity concerned with environmental risks to children's health. EPA Administrator Carol Browner launched EPA's Children's Environmental Health Initiative in October 1995, when she announced a policy to "consistently and explicitly evaluate environmental health risks of infants and children" in all of EPA's risk assessments and risk characterizations and in setting environmental and public health standards. The following year, EPA issued a report, *Environmental Health Threats to Children*, identifying environmental hazards of concern and a strategy for addressing them.

Among the many environmental hazards, EPA highlighted:

- lead poisoning,
- pesticide exposures,
- asthma,
- drinking water contaminants (especially microbiological),
- polluted surface waters,
- toxic waste dumps,
- PCBs (due to their persistence and developmental effects),
- environmental tobacco smoke, and
- overexposure to ultraviolet light.

In addition, EPA planned research to learn more about the potential health effects of chemical exposures on hormone-regulated processes (i.e., the endocrine system) and the potential respiratory effects of particulate matter air pollution.

In 1996, the U.S. Congress enacted the Food Quality Protection Act (FQPA) to better protect children from pesticides. The legislation incorporated provisions recommended in a 1993 report to Congress by the National Research Council, *Pesticides in the Diets of Infants and Children*. To ensure the safety of children, the FQPA requires EPA review of all pesticide registrations for food uses and standards for pesticide residue levels on food (tolerances) before August 2006. EPA is required to consider all routes of exposure to pesticides (food, air, and water) and cumulative risks from pesticides that have similar toxic effects on human health. Where there is reason to believe that children might be at greater risk, and there are insufficient data to assess risk, FQPA directs EPA to set standards that are up to 10 times safer than would be required to ensure adult safety. Amendments to the Safe Drinking Water Act in 1996 (Public Law 104-182) also mandated additional protection of children.

On February 27, 1997, Administrator Browner announced creation of the new Office of Children's Health Protection (within the Office of the Administrator), which was given responsibility for implementing the strategy. A few months later, President Clinton issued Executive Order 13045, *Protection of Children from Environmental Health Risks and Safety Risks* (April 21,1997). It extended the EPA initiative on children's environmental health

protection to all federal agencies by directing agencies to "make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children" and to ensure that "policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks."

A task force, co-chaired by the Secretary of the Department of Health and Human Services (DHHS) and the Administrator of the EPA (or their designated representatives), was established to recommend federal environmental health and safety policies, priorities, and activities to protect children. In April 1998, the President's Children's Environmental Health and Safety Task Force identified four priority areas for immediate attention:

- childhood asthma,
- unintentional injuries,
- developmental disorders (including such problems as autism and attention deficit disorder), and
- childhood cancer.

In April 1998, Vice President Gore announced a related federal initiative to expand communities' right to know about toxic chemicals with special impacts on children. The Vice President proposed considering the need for additional toxicological testing by chemical manufacturers of such chemicals to determine the potential effects of exposure on children's health. EPA plans on collecting information for this initiative, in part, through voluntary agreements with industries. EPA will issue a test rule under the Toxic Substances Control Act to collect any information still needed after receiving the results of the voluntary testing.

In August 1998, the Vice President announced the establishment of eight federal research centers devoted to the study of children's environmental health and to working directly with communities to reduce environmental health threats. The research centers were designated and are funded jointly by EPA and the Department of Health and Human Services (DHHS). Five centers are dedicated to reducing asthma, two to the effects of pesticide exposure, and one to developmental effects due to household chemical exposures. The eight centers are at the University of Southern California, Los Angeles; University of Iowa, Iowa City; University of Michigan, Ann Arbor; Johns Hopkins University, Baltimore; University of California, Berkeley; University of Washington, Seattle; Mount Sinai School of Medicine, New York; and Columbia University, New York.

Also in 1998, the 105th Congress enacted the Birth Defects Prevention Act (Public Law 105-168), which authorized the Centers for Disease Control and Prevention (CDC) to collect, analyze, and make available data on birth defects.

A Children's Health Protection Advisory Committee was formed by EPA to recommend rules that, if reviewed, might lead to better protection for children. EPA announced January 29, 1999, that in response to Advisory Committee recommendations and public comments, it would increase efforts in ongoing activities in the following areas:

- guidance, research, and outreach programs relating to indoor and ambient air quality with respect to asthma;
- National Emission Standard for mercury emissions from chloralkali plants;
- rules to protect agricultural workers from pesticide risks;

- the maximum contaminant level (drinking water standard) and pesticide residue tolerance for atrazine on food; and
- the pesticide residue tolerances on food for dimethoate, chlorpyrifos, and methyl parathion (all organophosphate insecticides).

The Children's Health Act of 2000, enacted October 17, 2000, established a National Center on Birth Defects and Developmental Disabilities (NCBDDD) at the Centers for Disease Control and Prevention (Public Law 106-310). It also authorized research and outreach on asthma, cancer, lead poisoning, and autism. Title X of the Act lays the groundwork for a major national study, originally suggested by a work group of the President's Task Force, of the impact of the environment on child health. The National Institute of Child Health and Human Development (NIH), EPA, and the National Center for Environmental Health are planning and implementing the "longitudinal cohort" study, which will attempt to identify and quantify environmental risks to children. The study will be of sufficient size and design to identify subtle, but important, effects of low level environmental exposures.

EPA issued a second report, *America's Children and the Environment: A First View of Available Measures,* in December 2000. The report proposed additional monitoring of pollution and children's exposure and tracking of children's health.

Faced with all this activity, some policymakers are asking, "Do U.S. children need more federal protection from environmental risks?" "Do our environmental laws need to be more protective of children?" Although few doubt that children are more vulnerable to certain environmental hazards, such as lead poisoning, some question the need for increased federal efforts to protect children from other environmental risks, sometimes because the risks appear small and uncertain, relative to other health risks in childhood (such as risks of poisoning or falling), or perhaps because the homes, playgrounds, and other places where children are most likely to be exposed to chemicals traditionally have been regulated at the local or state level. Others question the statutory authority or competence of EPA for addressing hazards that might be handled better by public health practitioners or housing specialists, rather than by environmental protection specialists. On the other hand, advocates for stronger environmental laws have argued that environmental regulations should provide greater child protection in all program areas, not just for pesticides and drinking water.

## Seminar and CRS-Contracted Papers

Both the scientific and policy issues involving children's environmental health are complex and broad in scope. Therefore, the Senate Committee on Environment and Public Works asked the Congressional Research Service (CRS) to commission outside experts in fields related to children's environmental health to review recent research, evaluate the weight of scientific evidence, and explore policy opportunities for the federal government.

Because congressional interest centered on perceived threats to children's health from pollutants in the ambient environment – air, soil, water, and food – and on the role of EPA in managing them, CRS attempted to define the project to exclude consideration of potential hazards over which EPA has little authority, because they are not in outdoor air, water, or soil. However, concerns about particular health trends among children, for example in cancer and asthma incidences, prompted broadening the definition of "environmental

hazards" to include indoor air pollutants (e.g., environmental tobacco smoke, particulate matter from use of a gas stove, or pesticides used in indoor air pollutants). Nevertheless, the project definition of "environmental" generally is narrower than the traditional public health definition. Public health professionals generally use "environmental hazard" to refer to any factor that is not genetic (i.e., inherited), including infection by pathogens, accidents of all kinds, and so-called "lifestyle" factors like diet, exercise, violence, smoking, and drug use, as well as, exposure to pollution indoors and out. The pediatricians and other public health professionals who participated in the CRS project occasionally blurred the boundary between the broader public health and narrower project definitions.

CRS asked knowledgeable scientists to prepare scholarly papers exploring the scientific research basis for assessing potential environmental health threats to children. Policy experts were asked to write scholarly papers evaluating federal policy opportunities with respect to such risks. CRS convened an all-day seminar on May 22, 2000 for Members and congressional staff on children's environmental health issues. At the seminar, *Children's Environmental Health: What Role for the Federal Government?*, authors presented draft papers, and experts representing a wide range of viewpoints critiqued them, addressing scientific papers in the morning and policy papers in the afternoon. Informal discussion among authors, reviewers, and the audience followed the presentation of critiques for each scientific paper and the policy papers. The seminar and the commissioned papers were supported, in part, by a grant from the Robert Wood Johnson Foundation. The seminar program is provided in Appendix A. Authors of papers and peer reviewers have provided biographic information, which is included in Appendix B.

In addition to providing an opportunity for an informed dialogue among key experts to aid congressional debate, the seminar ensured adequate topical coverage, verbal clarity, and factual accuracy in the papers individually, and overall balance in viewpoints as expressed in the papers as a group. Proceedings of the seminar were taped and transcribed. Transcripts were corrected for accuracy by CRS in consultation with seminar participants. Because the transcripts included a considerable amount of specialized language and discussion informed by technical expertise, summaries of substantive discussions of the draft papers (rather than complete transcripts) were prepared by a rapporteur, Dr. David Butler, a senior program officer in the division of Health Promotion and Disease Prevention of the Institute of Medicine, National Academy of Sciences. Participants reviewed and approved the summaries of discussions. Following the seminar, authors revised their papers to address comments by peer reviewers.

This report contains the final papers, along with summaries of critiques and discussions of the drafts presented at the seminar. Discussion summaries immediately follow the scientific papers to which they refer. The policy discussion addressed all four policy papers, so the summary of the policy discussion follows the fourth policy paper. It should be kept in mind that these discussion summaries refer to the first drafts, rather than to the final papers as they are printed here; the final papers were revised in response to seminar comments and again were distributed to reviewers and other authors, to encourage full discussion of how papers might be improved. Summaries of comments on early drafts nevertheless are included here to illustrate the extent to which opinions converged or diverged among experts on various points of substance, as well as to make the basis for the conclusions reached by the authors more transparent. Authors of the major papers retain responsibility for the

accuracy and balance of their work. CRS assumes responsibility for the balance of the overall report.

## Acknowledgments

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In addition, CRS thanks the authors of major papers. Those who were employees of the federal government received no compensation from CRS for their efforts. The United States is fortunate to have such dedicated public servants.

## State of the Science

Scientists were asked to address four general topics in their papers and during the morning session of the CRS seminar:

- How do children's environmental health risks differ from those of adults? Are children always more sensitive, vulnerable, or exposed than adults? What scientific evidence exists to support these claims/conclusions? How do environmental health risks compare to other health risks for children?
- Which environmental pollutants may pose a special health risk to children and what level of evidence exists?
- Do environmental exposures to pollutants increase the rates of adverse health outcomes among children or adversely affect children's health in a manner or degree that is different from that of adults?
- Based on available scientific evidence about environmental health risks to children, what can we conclude? To what extent do we have consensus? To resolve the areas of disagreement, what types of research would be most helpful?

The aim of these papers and discussions was to review relevant scientific publications, evaluate the weight of scientific evidence, draw conclusions about the state of scientific knowledge related to environmental health risks to children, and summarize these deliberations and conclusions in a way that would be useful for policy makers. CRS asked each author to reference statements of fact to published, peer-reviewed research or to an independent authority. Matters of personal opinion were to be identified as such, according to CRS policy. We also asked scientific authors to refrain from discussing matters of public policy. Authors retain responsibility for the accuracy and balance of their final papers. CRS assumes responsibility for the balance of the overall report.

The first scientific paper was authored by Ruth A. Etzel, M.D., Ph.D., a pediatrician and epidemiologist who is a Captain in the U.S. Public Health Service in Washington, D.C. She is the immediate past chair of the American Academy of Pediatric's (AAP) Committee on Environmental Health and the editor of the AAP Handbook of Pediatric Environmental Health. Dr. Etzel began by explaining how and why children's environmental health risks are different from those of adults. She noted that –

- Children may be exposed differently to pollutants;
- Children may absorb pollutants differently;
- Children have a higher rate of metabolism; and
- Children have "windows of vulnerability" while they are growing and developing, when their target organs may be more susceptible than the target organs of adults.

She summarized in a table the developmental stages and illustrative environmental health risks that occur during each stage.

To address the question of how environmental health risks compare to other health risks for children, Dr. Etzel discussed the five leading causes of death among infants less than one

year, children between 1 and 4 years, children between 5 and 9 years, children between 10 and 14 years, and children 15 to 19 years. Changes over time in these risks also were discussed. She concluded that with respect to childhood mortality, environmental health risks are greatest during gestation and during the first year of life. Estimates of the proportion of infant deaths that might be due to environmental causes vary widely between 5% and 40%. If one assumes that the lower estimate is accurate, then 1,424 infant deaths (5% of 28,488 infant deaths) would be attributed to environmental causes. However, she emphasized that mortality is a poor indicator to use when assessing how environmental risks compare to other health risks to children. Fortunately, most environmental health risks do not result in deaths among children, but in illnesses and disabilities which are not routinely tracked.

Discussants at the CRS seminar agreed on the following points –

- As a group, children's environmental health risks differ from those of adults. The differences may be large and may go in either direction.
- Differences in exposure and vulnerability to health effects among individual children may be less than, equal to, or greater than differences between children as a group and adults. Differences among individual children also may be less than, equal to, or greater than differences among groups of children at different stages of development – prenatal, perinatal, infant, toddler, pre-teen, and adolescent.
- As a group, children differ from adults in exposure to potentially toxic chemicals in the environment; their absorption and metabolism of such chemicals; and their susceptibility to harmful effects. Some of these differences arise from differences in behavior (for example, drooling and mouthing objects or crawling), physical size, maturity of organs or physiological processes, or presence in different environments (e.g., *in utero*, occupational, recreational, or educational).
- Socio-economic conditions, health and nutritional status, genes, and access to medical care mediate environmental health effects.
- Children's biological exposure from chemical contaminants in the air, some foods, and water may be greater than that of adults in the same environment, because children breathe more, eat more, and drink more, relative to their size, and the skin of a newborn child may absorb more, pound for pound.
- Children experience periods of special vulnerability to some toxic effects of some chemicals as their organs develop. Some of these vulnerable periods are quite extended.
- Although U.S. death rates due to childhood exposure to environmental contamination are not known, they should be viewed in the context of known causes of death, which vary depending on age.
- U.S. death rates might not be the best basis for comparing health risks to children; some measure of illness or disability would be useful, if data were available.

# Men Are from Mars, Women Are from Venus, and Children Are from Pluto: Pediatric Environmental Health

Ruth A. Etzel, M.D., Ph.D.

The environment in which we live has a profound effect on our health and well-being. Humans thrive in environments in which they breathe clean air, drink clean water, and eat healthy foods. Filthy air, dirty water, and contaminated foods present risks to our health and to our children's health. Environmental hazards may pose different risks for children than for adults.[6] This is because children are not simply miniature adults, a fact of which pediatricians are especially aware, as they tailor treatments and doses to the unique, complex and changing needs of each developing child.

The purpose of this paper is to (1) provide information about why children's risks are different, illustrated with some very specific examples, (2) present data about the five leading causes of death in different age groups of children, and (3) present the changing threats to health over the last several millennia.

## Why Children's Environmental Health Risks Differ

Table 1 shows six stages of child development and gives examples of some stage-specific environmental health risks to the child. Not only are risks different at each stage of development, but risks for children are different than for adults. There are a number of reasons why the risks from living in a polluted environment are not the same for children as for adults:

- Children may be exposed differently to pollutants;
- Children may absorb pollutants differently;
- Children have a higher rate of metabolism; and
- Children have "windows of vulnerability" while they are growing and developing when their target organs may be more susceptible than the target organs of adults.

**Exposure.** An important reason why children's exposures are different from those of adults is their level of behavioral development. Children behave differently from adults, and their behaviors change as they develop. Most children actively explore their environments, and young children exhibit frequent hand-to-mouth and object-to-mouth

[6]Throughout this document, "children" are defined as youngsters from birth to age 19, as suggested by Behrman, R.E., R.M. Kliegman, and H.B. Jenson on page 3 of the 16th edition of the *Nelson Textbook of Pediatrics* (2000, WB Saunders Co., Philadelphia). "Environmental risks" refer to exposures to chemical, biological, and physical hazards in the air, water, soil, and food, at home, at school, and in the community. Some of these hazards are manmade such as environmental tobacco smoke and polychlorinated biphenyls (PCBs), others are natural, such as radon and mycotoxins.

**Table 1. Developmental stages and special environmental health risks during each stage**

| Developmental stage | Time period | Developmental milestones | Special environmental health risks |
|---|---|---|---|
| Embryonic | 8 days to 9 weeks of pregnancy | Organogenesis at approx. days 20 to 60 of gestation | Thalidomide exposure at 34-50 days *in utero* linked to phocomelia (limb reductions) |
| Fetal | 9 weeks of pregnancy to birth | Control of autonomic nervous system at approx. 24 weeks | Radiation exposure at 8-15 weeks *in utero* linked to microcephaly (small head circumference) and mental retardation |
| Infancy | Birth to 12 months | Rolling over at 2-3 months; sitting at 3 months; standing with support at 6 months; walking begins at 10-12 months | Mercury vapor exposure linked to acrodynia ("pink disease" characterized by hypertension, tachycardia, profuse sweating, muscle weakness anorexia, and insomnia)<br>Nitrate exposure linked to methemoglobinemia<br>Sensitivity to carbon monoxide exposure<br>Environmental tobacco smoke exposure linked to lung diseases<br>Toxigenic mold exposure linked to pulmonary hemorrhage |
| Young toddler<br>Older toddler<br>Preschooler | 1 to 2 years<br>2 to 3 years<br>3 to 5 years | Self feeding at about 1 year<br>Toilet trained at about 2 years<br>Motor skills well developed at about 5 years | Radiation exposure linked to thyroid cancer — e.g., at Chernobyl<br>Selenium deficiency linked to coxsackie B virus — Keshan disease (cardiomyopathy) |
| School-aged | 5 to 12 years | Specific synapse formation in brain | Soot exposure and cancer of scrotum |
| Adolescent | 12 to 19 years | Maturation of organs | Soot exposure linked to cancer of scrotum |

behavior.[7] Until they are able to walk, children cannot avoid hazardous environments. Until they have grown intellectually, children may not be able to recognize potential hazards. As

[7]Bearer, C.F. (1995) How are children different from adults? *Environmental Health Perspectives*, v. 103, Supplement, p. 7-12.

they grow older, they begin to explore outdoor environments – old tires, empty lots, used drums, and rivers and streams.

Children spend their time in different physical locations than adults. Infants and young children spend lots of time on the floor. Because of their height, children inhale in a different breathing zone than adults. Young children breathe close to the floor, while the adult of average height is breathing five to six feet above the floor.[8] In addition, children are exposed to pre-school or school classroom environments and playgrounds, rather than to work and commuter environments. Schools may be built on relatively undesirable lands or may be old, poorly maintained, and poorly ventilated facilities.

Even when adults and children are present in the same location and occupied in similar activities, children may be exposed internally to different concentrations of pollutants. Infants' respiratory rate for their body weight is much greater, perhaps twice as great as for adults.[9] Children's exposures also differ in the quantity and the type of food they consume.[10] Because they are growing, children eat more food and drink much more water per pound of body weight than do adults.[11] For example, if an adult male consumed as much fluid as a young child does, it would be equivalent to drinking 35 cans of soda per day. Furthermore, children's diets are different than those of adults. They contain more milk, more fruits, and often more vegetables. Moreover, infants and young children generally eat a much less varied diet, a difference that can lead to even larger differences in exposure.

How does this exposure difference lead to different health effects in children? One example is adverse health effects due to different levels of exposure to mercury vapor, which is heavier than air.[12] Because of that, the highest concentrations of mercury vapor occur near the floor. Before 1991, many different brands of interior latex paint contained mercury, primarily for its preservative effects. Paint stores sold mercury paint additives that were used for control of mildew. During the first several months after paint was applied to a wall, mercury vapor was emitted into the indoor air, sometimes exposing children to high levels of mercury vapor and resulting in acrodynia, or mercury poisoning.[13] In one case, a four-year-old boy became poisoned after the entire interior of his fire-damaged home had been painted with 17 gallons of paint containing mercury.[14] Remarkably, four other family

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[8]Johnson, T.R., W.M. Moore, and J.E. Jeffries (eds.). (1978) *Children Are Different: Developmental Physiology*, 2nd edition. Columbus, Ohio: Ross Labs, p. 128-129.

[9]Committee on Environmental Health, American Academy of Pediatrics. (1999) *Handbook of Pediatric Environmental Health.* Elk Grove Village, IL: American Academy of Pediatrics. 420 p.

[10]National Research Council. (1993) *Pesticides in the Diets of Infants and Children*. Washington, DC: National Academy Press. p. 196.

[11]Guzelian, P.S., C.J. Henry, and S.S. Olin (eds.). (1992) *Similarities and Differences Between Children and Adults: Implications for Risk Assessment.* Washington, DC: ILSI Press. 285 p.

[12]Foote, R.S. (1972) "Mercury vapor concentrations inside buildings." *Science*, v. 177, p. 513-514.

[13]Hirschmann, S.Z., M. Feingold, and G. Boylen. (1963) "Mercury in house paint as a cause of acrodynia: Effect of therapy with N-acetyl-D,L-penicillamine." *New England Journal of Medicine*, v. 269, p. 889-893.

[14]Agocs, M.M., R.A. Etzel, R.G. Parrish, et al. (1990) "Mercury exposure from interior latex paint."

(continued...)

members living in the same house under the same conditions remained unaffected, although urine tests documented that they were excreting elevated levels of mercury.[15]

Scrotal cancer in chimney sweeps provides another example. In 1775, Percival Pott described an elevated incidence of cancer of the scrotum among boys who had assisted chimney sweeps by climbing into chimney flues in Victorian England.[16] Chimney sweeping led to heavy soot exposure. Boys were selected for this work because it was easier for them to get into the chimneys than it was for most full-sized adults. Scrotal tumors occurred in these boys and young men who had worked as sweeps, but were not common in adults with other occupations.

**Absorption.** A second way that children differ from adults is in their absorption of chemicals from the environment. A major chemical exposure route during gestation is through the placenta, especially for compounds of low molecular weight that cross readily through the placenta.[17] The newborn's skin is also more absorptive than an adult's skin.[18] The skin surface area in infants and young children is much greater in relation to body mass than in adults.

The gastrointestinal tract of a child is less acidic than that of an adult.[19] How could this affect infant health? One example is methemoglobinemia. This occurs among infants living in places where well water is contaminated by runoff from fertilizer and animal operations. Infants younger than 4 months are susceptible, because the gastric pH of infants is higher than that in older children and adults, and infants lack or have minimally functional enzymes that might prevent the illness.[20] The enhanced susceptibility to methemoglobinemia is of concern for infants fed formula prepared with contaminated well water. When the infant consumes nitrates, the less acidic environment of the stomach allows proliferation of normally present intestinal bacteria that reduce nitrates to nitrites.[21] An excess of nitrites results, which is absorbed; the nitrites then bind with hemoglobin, the oxygen-carrying molecule in red blood cells. This forms methemoglobin, a form of hemoglobin with reduced oxygen-carrying capacity. Because the infants have less functional enzymes generally, and specifically less functional methemoglobin reductase, they are not

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[14](...continued)
*New England Journal of Medicine*, v. 323, p. 1096-1101.

[15]Ibid.

[16]Pott, P. (1775) Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, and different kinds of ruptures, and mortification of the toes and feet. London, Hawes, Clark, Collins, page 63.

[17]Behrman, R.E., R.M. Kliegman, and H.B. Jenson. (2000) *Nelson Textbook of Pediatrics*, 16th Edition. Philadelphia: WB Saunders Co.

[18]Ibid.

[19]Johnson, T.R., W.M. Moore, and J.E. Jeffries (eds.). (1978) *Children Are Different: Developmental Physiology*, 2nd edition. Columbus, Ohio: Ross Labs, p. 150.

[20]Dagan, R., E. Zaltzstein, and R. Gorodischer. (1988) "Methemoglobinemia in young infants with diarrhea." *European Journal of Pediatrics*, v. 147, p.87-89.

[21]Committee on Environmental Health, ibid.

able to convert methemoglobin back to hemoglobin, as would adults and older children.[22] The presence of methemoglobin and reduction in oxygen makes blood appear blue.

**Metabolism.** Newborns and young infants have immature metabolic systems that break down certain chemicals with difficulty, if at all. This can mean that they have trouble eliminating and excreting a number of a toxic chemicals. There are many examples well known to pediatricians, one being the antibiotic chloramphenicol, which when administered to a newborn, causes an overdosage called "gray baby syndrome."[23] Or , it may mean that a child will not produce a more toxic breakdown product of a relatively innocuous chemical. This sometimes can be protective for infants. For example, if a pregnant woman takes an overdose of acetaminophen (e.g., Tylenol®), she will likely have severe liver damage. However, the same overdose will probably not damage the liver of the infant, because the infant is unable to metabolize it, and the toxic metabolite does not cross the placenta.[24]

Children's metabolism, on the other hand, is faster than that of adults. This can be protective in some instances, but in other cases it increases their susceptibility. An example is the occurrence of carbon monoxide poisoning in young children. Children are more susceptible, because organ systems with high metabolic rates and high oxygen demand are most severely affected by oxygen deprivation, the mechanism by which carbon monoxide affects health.[25] There have been winter time cases when a snowbound automobile was found with adults in the front seat, unconscious, but children in the back seat dead.[26] A fetus is also more vulnerable than an adult to carbon monoxide poisoning. Fetal blood has a higher affinity for carbon monoxide than has adult blood, and the fetus eliminates carboxyhemoglobin more slowly than does the adult. Thus, when women are exposed to carbon monoxide during pregnancy, less oxygen is available to the fetus. This is why it is especially important to avoid exposure to carbon monoxide during pregnancy.[27]

**Windows of Vulnerability.** The fourth reason that children can be more susceptible is that they have windows of vulnerability while their organs are growing and developing when their organs are immature and may be more fragile than the organs of adults. For most chemicals, exposure at a young age appears to be more harmful to the developing organs than exposure at an older age. In fact, the younger the infant, the more likely the window of vulnerability for organ damage will be open. Exposure to environmental chemicals during the first trimester of pregnancy may be the most harmful to

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[22]Ibid.

[23]Behrman et al. ibid.

[24]Byer, A., T.R. Traylor, and J.R. Semmer. (1982) "Acetaminophen overdose in the third trimester of pregnancy." *Journal of the American Medical Association*, v. 247, p. 3114-3115.

[25]Committee on Environmental Health, ibid.

[26]Centers for Disease Control and Prevention. (1991) "Fatal carbon monoxide poisoning in a camper-truck – Georgia," *Morbidity and Mortality Weekly Report*, v. 40, p. 154-155.

[27]Longo, L.D., and E.P. Hill. (1977) "Carbon monoxide uptake and elimination in fetal and maternal sheep." *Am J Physiol*, v. 232, p. H324-H330.
Longo, L.D. (1970) "Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta." *Annals of the New York Academy of Science*, v. 174, p. 312-314.

the developing organs, because this is when organogenesis occurs.[28] (See Table 1.) The most famous example of this period of vulnerability is thalidomide, a drug used for morning sickness in the 1950s and early 1960s. Thalidomide became well-known when its use during pregnancy was associated with birth defects in infants (limb reductions, or phocomelia). This drug was never licensed for use in the United States, but over 10,000 children were born in other countries with deformed arms and legs; 8,000 children in Germany alone. The exact gestational age at which thalidomide was most harmful was on days 34 to 50 of pregnancy.[29] It is thought that thalidomide acts by interfering with angiogenesis (the development of the blood vessels), and especially with angiogenesis to the limb buds during this window of vulnerability. This interferes with normal development, which results in truncation of the limb. Because of this "window of vulnerability" during the first trimester, physicians do not prescribe thalidomide during pregnancy.

However, thalidomide has been found to have important therapeutic uses in adults with certain cancers, inflammatory diseases, skin diseases, leprosy, and HIV infection.[30] This demonstrates that just because a substance is determined to be harmful during one period of development does not necessarily mean that it is harmful during subsequent periods. In the case of thalidomide, it is this very same interference with angiogenesis that causes the therapeutic effects in adults.

The developing brain is very vulnerable to injury from radiation during pregnancy. Mental retardation and microcephaly (small head circumference) occurred in children born to women who were pregnant when the atomic bomb was dropped on Hiroshima.[31]

The increased vulnerability of the infant respiratory tract is largely due to the prolonged period of development that occurs for the infant lungs. The lungs are growing rapidly during the first year of life and develop more air sacs up until the fourth year of life.[32] Exposure to environmental tobacco smoke has harmful effects on the developing lungs of fetuses and young infants.[33] Exposure to environmental tobacco smoke also has been

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[28]Selevan, S.G., C.A. Kimmel, and P. Mendola. (2000) "Identifying critical windows of exposure for children's health." *Environmental Health Perspectives,* v. 108, Supplement 3, p 451-455.

[29]Koren, G., A. Pasternak, S. Ito. (1998) "Drugs in pregnancy" *New England Journal of Medicine,* v. 338, p. 1128-37.

[30]Diz Dios, P., P. Sopena, J. Cameselle, M. Butron, M. Crespo, A. Ocampo. (2000) "Thalidomide for the treatment of acquired immunodeficiency syndrome-associated refractory oral ulcers." *Archives of Otolaryngology Head and Neck Surgery*, v. 126, p. 89-92.
Singhal, S., J. Mehta, R. Desikan et al. (1999) "Antitumor activity of thalidomide in refractory multiple myeloma." *New England Journal of Medicine*, v. 341, p. 1565-71.
Raje, N., K. Anderson. (1999) "Thalidomide—a revival story." *New England Journal of Medicine*, v. 341, p. 1606-9.

[31]Mettler, F., and A. Upton. (1995) *Medical Effects of Ionizing Radiation.* Philadelphia: WB Saunders, p. 323.

[32]Cotes, J.E. (ed.) (1993) *Lung Function: Assessment and Application in Medicine.* 5th Edition, Oxford: Blackwell Scientific Publications, p. 448.

[33]Chilmonczyk, B.A., L.M. Salmun, K.N. Megathlin et al. (1993) "Association between exposure to environmental tobacco smoke and exacerbations of asthma in children." *New England Journal*
(continued...)

associated with ear infections in young children.[34] Because the adult lung and respiratory tract is mature, environmental tobacco smoke does not affect them as much. Similarly, outdoor pollutants such as airborne particulates, and nitrogen dioxide have been linked to significant deficits in growth of lung function in fourth graders; less significant lung growth deficits were noted in seventh and tenth graders in the same polluted area.[35]

Acute lung bleeding has occurred among infants exposed to toxigenic molds in the inner city of Cleveland.[36] The infants in these homes in the inner city had very severe, life-threatening, pulmonary hemorrhage, but older children and adults living in the same moldy environments had no visible effects.[37] Although this finding has generated controversy, an independent reanalysis of the data by the CDC, excluding several control infants and using different values for airborne fungal concentrations, yielded an odds ratio that still demonstrated a statistically significant association between moldy homes and pulmonary hemorrhage in infants in Cleveland.[38] Other investigators have reported an association between pulmonary hemorrhage and toxigenic molds in infants and children in Kansas City, Missouri, Houston, Texas, and North Carolina.[39] One hypothesis is that potent toxins present on the surface of certain toxigenic molds are protein synthesis inhibitors, which may cause focal areas of capillary fragility in an infant's lungs and induce bleeding. Additional work is ongoing to further explore this hypothesis.

The vulnerability of some target organs extends into childhood. A good example of an organ with prolonged target organ susceptibility is the thyroid gland. After the nuclear disaster in Chernobyl in 1986, three to four million Ukrainian people were exposed to radiation. About 1.26 million of them were children. Beginning in 1990, there was an

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[33](...continued)
*of Medicine*, v. 328, pp. 1665-1669.
Tager, I.B., S.T. Weiss, A. Munoz, et al. (1983) "Longitudinal study of the effects of maternal smoking on pulmonary function in children." *New England Journal of Medicine*, v. 309, p. 699-703.

[34]Etzel, R.A, E.N. Pattishall, N.J. Haley, et al. (1992) "Passive smoking and middle ear effusion among children in day care." *Pediatrics*, v. 90, p. 228-232.

[35]Gauderman, J., R. McConnell, F. Gilliland, et al. (2000) "Association between air pollution and lung function growth in southern California children." *American Journal of Respiratory and Critical Care Medicine*, v. 162, p. 1383-90.

[36]Etzel, R.A., E. Montana, W.G. Sorenson, et al. (1998) "Acute pulmonary hemorrhage in infants associated with exposure to *Stachybotrys atra* and other fungi." *Archives of Pediatrics and Adolescent Medicine,* v. 152, p. 757-762.

[37]American Academy of Pediatrics, Committee on Environmental Health. (1998) "Toxic effects of indoor molds." *Pediatrics,* v. 101, p. 712-714.

[38]Centers for Disease Control and Prevention. [ http://www.cdc.gov/od/ads/pulhem_inf.htm ] accessed April 2, 2001.

[39]Flappan, S.M., J. Portnoy, P. Jones, et al. (1999) "Infant pulmonary hemorrhage in a suburban home with water damage and mold (*Stachybotrys atra*)." *Environmental Health Perspectives*, v. 107, p. 927-930.
Elidemir, O., G.N. Colasurdo, S.N. Rossmann, et al. (1999) "Isolation of *Stachybotrys* from the lung of a child with pulmonary hemosiderosis." *Pediatrics*, v. 104, p. 964-966.
Novotny, W.E., and A. Dixit. (2000) "Pulmonary hemorrhage in an infant following 2 weeks of fungal exposure." *Archives of Pediatrics and Adolescent Medicine,* v. 154, p. 271-275.

epidemic of thyroid cancer in children, and this is largely because the thyroid glands of children are unusually sensitive to exposure to radioactive iodine. The thyroid in children is approximately 2 to 10 times as radiosensitive to induction of neoplasms as that of the adult.[40]

Not only does too much of a chemical have a harmful effect on developing organs, but too little of certain nutrients may also increase a child's risk of developing certain diseases. One example is a childhood disease known as Keshan's disease.[41] This is a cardiomyopathy (disease of the heart muscle) that was first described among children in Keshan County in China. It occurs in the most selenium-deficient areas of China, and it is linked not only to selenium deficiency, but also to infection with coxsackievirus. In this example, a genetic change in the virus occurs when it passes through a selenium-deficient child, which results in increased virulence of the virus, and the development of a very severe cardiomyopathy that can sometimes lead to death. Adults are not similarly adversely affected. Future research will be needed to determine whether other nutrient changes can change viruses or make them more virulent and, likewise, whether chemicals can change viruses and make them more virulent.

## Environmental Risks Compared to Other Health Risks

How do environmental health risks compare to other health risks for children? First of all, it is important to review some of the causes of children's deaths. Tables 2 through 6 below show preliminary data from 1998 for actual numbers of annual deaths recorded in the United States and for final data from 1979, as well as the percent change in death rates from 1979 to 1998.[42] Table 2 demonstrates that in infants under one year of age, the primary cause of death is birth defects. There has, however, been an almost 40% decrease in mortality from birth defects in the years between 1979 and 1998, almost all of this due to improved medical treatment. The second cause of death in this age group is prematurity. The death rates from prematurity also have gone down, again due to improved medical care, between 1979 and 1998. The third cause is sudden infant death syndrome, or SIDS, which has decreased almost 60% between 1979 and 1998, in part due to the discovery of a number of preventive measures including reducing infant exposure to environmental tobacco smoke and changing infant sleeping position. The fourth cause is respiratory distress syndrome, a complication of prematurity, which has undergone an almost 80% decrease between 1979 and 1998 due to improved treatment. The fifth leading cause of death in infants under one year of age is maternal complications during pregnancy, which has undergone an almost 30% decline in the 20-year period between 1979 and 1998.

It is important to note that today we are seeing more survivors of birth defects, pre-term birth, and pregnancy complications, and that these survivors have high rates of disability

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[40]Mettler, F., and A. Upton. (1995) *Medical Effects of Ionizing Radiation.* Philadelphia: WB Saunders. page 131.

[41]Bowles, N.E., P.J. Richardson, and E.J. Olsen. (1986) "Detection of coxsackie B virus specific sequences in myocardial biopsies from cases of myocarditis and dilated cardiomyopathy." *Lancet,* v. 1, p.1120-1122.

[42]Guyer B., D.L. Hoyert, J.A. Martin, S.J. Ventura, M.F. MacDorman, D.M. Strobino. "Annual summary of vital statistics–1998." *Pediatrics*,1999; v.104:1229-1246

and often require difficult and expensive medical care over a lifetime.[43] There has been little change in the rates of birth defects or premature births during this period.[44]

### Table 2. Five Leading Causes of Death in Children Under 1 Year

| Cause of Death | No. of Deaths 1998 | No. of Deaths 1979 | % Change in Rate |
|---|---|---|---|
| Birth defects | 6,266 | 8,923 | -37.8 |
| Prematurity | 4,011 | 3,495 | 1.7 |
| SIDS | 2,529 | 5,279 | -57.6 |
| Respiratory distress | 1,328 | 5,458 | -78.4 |
| Maternal complication | 1,328 | 1,621 | -27.4 |

Causes of death are different in children who are over one year. Table 3 shows the causes in children between one and four years of age. Table 4 shows the five leading causes of death in children between ages five and nine. In both of these age groups, the major cause of death is unintentional injuries, followed by birth defects, homicide, cancer, and heart disease. And for all of these, we have seen reductions, sometimes as much as 56% in the period between 1979 and 1998. Only homicide had a relatively small reduction during that period. Reductions in mortality from birth defects and cancer were due to improvements in treatment. Injury mortality reductions probably reflect both safety measures (like car seat usage) and improvements in therapy.

### Table 3. Five Leading Causes of Death in Children 1 to 4 Years

| Cause of Death | No. of Deaths 1998 | No. of Deaths 1979 | % Change in Rate |
|---|---|---|---|
| Unintentional injury | 1,881 | 3,349 | -53.2 |
| Birth defects | 531 | 1,021 | -56.8 |
| Homicide | 368 | 314 | -4.0 |
| Cancer | 355 | 578 | -50.0 |
| Heart disease | 198 | 265 | -38.1 |

Table 5 shows the same leading causes of death in children between ages 10 and 14. What is striking here is that suicide is the third leading cause of death in this age group, and birth defects are a lesser contributor. There is a remarkable 100% increase in suicide during this almost 20-year period.

[43]CDC. (1999) "Achievements in public health, 1900-1999: Healthier mothers and babies" *Morbidity and Mortality Weekly Report.* v. 48, p. 849.

[44]CDC (1999) "Temporal trends in the incidence of birth defects" *Morbidity and Mortality Weekly Report.* v. 48, p. 125.

**Table 4. Five Leading Causes of Death in Children 5 to 9 Years**

| Cause of Death | No. of Deaths 1998 | No. of Deaths 1979 | % Change in Rate |
|---|---|---|---|
| Unintentional injury | 1487 | 2707 | -53.1 |
| Cancer | 486 | 791 | -48.9 |
| Birth defects | 199 | 289 | -41.2 |
| Homicide | 153 | 165 | -20.0 |
| Heart disease | 144 | 119 | 0.0 |

**Table 5. Five Leading Causes of Death in Children 10 to 14 Years**

| Cause of Death | No. of Deaths 1998 | No. of Deaths 1979 | % Change in Rate |
|---|---|---|---|
| Unintentional injury | 1,627 | 2,982 | -47.5 |
| Cancer | 539 | 761 | -31.7 |
| Suicide | 311 | 151 | 100.0 |
| Homicide | 270 | 229 | -16.7 |
| Heart disease | 160 | 170 | -11.1 |

Table 6 shows the causes of death in the oldest children. Unintentional injury again is the primary cause of death, followed by homicide, suicide, cancer, and heart disease. Suicide rates did not rise as sharply as for the 10-to-14 year olds, however, homicide rates rose nearly 10%.

In reviewing these data, it appears to me that environmental health risks, at least for mortality, are paramount during gestation and during the first year of life. And this is likely true for illnesses also, although we don't have the kind of data for morbidity that we have for mortality.

**Table 6. Five Leading Causes of Death in Children 15 to 19 Years**

| Cause of Death | No. of Deaths 1998 | No. of Deaths 1979 | % Change in Rate |
|---|---|---|---|
| Unintentional injury | 6327 | 12,689 | -45.5 |
| Homicide | 2216 | 2191 | 9.7 |
| Suicide | 1702 | 1788 | 3.6 |
| Cancer | 701 | 1141 | -32.1 |
| Heart disease | 379 | 395 | 0.0 |

There are many different assumptions about how much of the burden of infant death might be due to environmental causes. Estimates range from 5% to as much as 40%, depending in part on how "environmental" is defined. Let us assume just for a moment that the most conservative estimate, which would be 5%, is the best estimate of the proportion of infant deaths due to environmental causes. If only 5% of 28,488 infant deaths annually

were due to environmental pollution, that means that about 1,424 infant deaths, or about 4 infant funerals every day would be due to environmental causes. Taking the five leading causes of death separately, environmental pollution would account for 313 of the 6,000 deaths due to birth defects, as much as 200 of the 4,000 deaths due to prematurity, 126 of the 2,500 deaths due to SIDS, 66 of the 1,300 deaths due to respiratory distress syndrome, and 66 of the 1,300 deaths due to maternal complications of pregnancy. This would be the most conservative estimate.

Over the last 11 millennia, a number of changes have occurred in the major threats to health. Between 9000 BC and 2000 BC, the major problems were physical deprivation, lack of food, lack of warmth, lack of security. After 2000 BC, we had the major plagues, and the threats seemed to come primarily from the large infectious diseases. From 1900 on, more attention was paid to chronic diseases as we found ways to immunize against the infectious diseases. And, starting in the 1950's, I think we may have entered an era where socio-ecological conditions (including precursors of violence) might be the major threats to health in our society. Trends in children's death rates seem to me to support that theory.

Death and illness rates are the principal measures of health used world-wide, but they are only indirect and very insensitive indicators of a population's health, especially when the 1948 World Health Organization (WHO) definition of health is considered. WHO defines health as a state of complete physical, social, and mental well-being, and not merely the absence of disease or infirmity.[45] If health is the capacity, relative to your potential aspirations, for living fully in a social environment, then I would argue, that requires optimal physical, mental, and social development of children. Environmental risks should not be allowed to impair optimal physical, mental, and social development.

Pediatricians practice prevention. We believe children should not be exposed to poisons, and we try to prevent exposure by working with the parents, for example, to change their purchasing habits, having them purchase less toxic household alternatives or put child locks on the kitchen cabinets. Pediatricians might likewise want to consider that the information they possess about children's environmental risks might usefully inform political and social decisions about the extent to which our children need to be protected from environmental risks.

## Summary

In summary, the environment in which children live has a profound effect on their health and well-being. Children thrive in environments in which they breathe clean air, drink clean water, and eat healthy foods. Filthy air, dirty water, and contaminated foods present unique risks to their health.

Living in a polluted environment is not the same for children as for adults:

- Children may be exposed differently to pollutants;
- Children may absorb pollutants differently;
- Children have a higher rate of metabolism; and

[45]Beaglehole, R., R. Bonita, T. Kjellstrom (eds.) (1993). *Basic Epidemiology*. Geneva: World Health Organization, p. 13.

- Children have "windows of vulnerability" while they are growing and developing when their target organs may be more susceptible than the target organs of adults.

For these reasons, federal rules established to protect public health for adults may or may not be equally protective for children.

## Discussion

**Discussants:**

Philip S. Guzelian, M.D., Professor of Medicine, University of Colorado Health Sciences Center
William H. Farland, Ph.D., Director, National Center for Environmental Assessment, EPA
James Lamb, Ph.D., D.A.B.T., Vice President, Blasland, Bouck & Lee, Inc.
J. Routt Reigart, M.D., Professor of Pediatrics and Director, General Pediatrics, Medical University of South Carolina; Chair, Children's Health Protection Advisory Committee

**Dr. Guzelian** began by citing a book produced for the International Life Sciences Institute and the EPA reporting the results of a conference held on the similarities and differences between children and adults, and the implications of these for risk assessment.[46] The conference was distinctive, he suggested, because it included participants from a profession whose practitioners intentionally administer high doses of chemicals to children: pediatricians. An important result of the conference, he explained, was a recognition that just because children are small in stature and physically vulnerable, does not mean that they are necessarily more susceptible to a particular exposure. He gave the example of the anesthetic Halothane, which can produce severe hepatitis in adults, but no cases resulting from exposure have ever been reported in children. He gave aspirin as a counter example; only children are known to contract Reyes Syndrome. A final example is the therapeutic drug known as AZT (for the control of human immune-deficiency virus) which is about equally toxic in adults and children. The lesson to be drawn from these observations, according to Dr. Guzelian, is that health professionals should consider regulation of chemical exposures on a case-by-case basis, rather than simply assuming that children are intrinsically more vulnerable.

**Dr. Farland** argued that an important message to take from Dr. Etzel's talk was that both data and theory support the hypothesis that children represent a sensitive life stage and may, on an intake per body weight basis, be more highly exposed than adults. He underlined the point that both genetics and environmental factors need to be considered when thinking about how these susceptibilities and exposures determine children's environmental health risks.[47]

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[46] Guzelian, Philip S., Carol J. Henry, and Stephen S. Olin (eds.). *Similarities and Differences between Children and Adults: Implications for Risk Assessment.* Washington, DC: International Life Sciences Institute. (1992) 285 p.

[47]For example, see a recent review of the literature by Suk, W.A., and G.W. Collman, (1998) "Genes and the environment: Their impact on children's health," *Environmental Health Perspectives*, v. 106,

(continued...)

A second message was that biological systems maintain reserve capacity to withstand or repair damage. Therefore, not all damage is irreversible, and not all insults result in adverse health effects. Dr. Farland also offered three observations: 1) Additional hazard potential and exposure data are needed; 2) Researchers should continue working to better understand children's vulnerability and exposure to chemicals in the environment; and 3) Researchers need to recognize the potential for interactions: interactions between genes and environment; viruses and chemicals; and chemicals with one another.

**Dr. Lamb** found Dr. Etzel's presentation excellent. He then observed that children may be more, less, or equally sensitive as adults to environmental risks; risks need to be addressed with specificity. Researchers need to ask what the scientific evidence is to support assumptions that children are more sensitive, vulnerable, or exposed. And, health risks engendered by environmental exposure should be compared to other health risks. He suggested that the differences between children and adults result from exposure to different environments, different behaviors, and biological differences. Biological differences need to be broken down into two parts: metabolism and the windows of vulnerability. Each of these needs to be addressed differently because they may lead to different conclusions. The permanent and profound effects of exposure to diethylstilbesterol (DES) in the developing child illustrates the issue of vulnerability windows. Many of these differences noted in metabolism and biochemical sensitivity are very small differences, and may be difficult to discern using the crude tools typically available in risk assessment.

**Dr. Reigart** made several points, which he said were listed in reverse order of importance. The first of these was that children's skin is often more absorptive than adults, and that it is much greater in reference to body mass. Dr. Reigart said he had seen some assumptions in EPA risk assessments that incorrectly scaled exposure through the skin on a body weight basis when it should properly be done on a body surface basis.

He cited three differences between children and adults that were important when examining respiratory exposures: first, children have more oxygen in their blood; second, their respiratory rate is much greater than adults', when compared to body weight, perhaps twice as great in infancy; and third, the volume of air children inhale and exhale each minute is much greater.

He noted that many important systems developing in the bodies of children are fatty tissues, notably the brain. When thinking about exposure and absorption, the growth of fatty tissues and deposition of persistent chemicals in fatty tissues is very important. Dr. Reigart observed that all of the speakers and commentators agreed that children are different; he said that the real issue is determining in what ways are they different. He said it was clear that children have to be evaluated separately, and that is something that's been missing for many years.

Another difference between children and adults is that children do not die very often. He reasoned that it is therefore inappropriate to use death as an indicator of harm to children – instead, overall morbidity (disease) and morbidity in developing systems should be examined.

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[47](...continued)
Supplement 3, p. 817-820.

He discussed the belief some have that children's tissues may not be more susceptible than adults', if the tissues continue to grow after birth, as do, for example, tissues of the lung and liver. In contrast, tissues that must fully develop and stop growing prior to birth, may have little capacity to recover. However, a contrary example to this is the brain. Although it produces many cells after birth, unlike many growing tissues, the brain is still "work in progress", which if disrupted may result in significant and permanent injury. A better way to approach the issue, Dr. Reigart suggested, may be to look at tissues that recover versus those that cannot.

Dr. Reigart noted the statistics on the effect of lead exposure on IQ. If exposure causes a four-point detriment, this has the population effect of a shift in the cumulative distribution that basically removes all children with IQs above 130, and triples or quadruples the number of children with IQs below 80. So, a very small morbidity effect can have major effects on the productivity of the population.

**General Discussion**

**Dr. Lynn Goldman** (key speaker for topic 2) asked for a comment from Dr. Farland on the topic of depletion of children's reserve capacities due to environmental insults, asserting while one may see recovery of a function in a child and no morbidity in the child, that one may see an increase later in chronic diseases and perhaps earlier onset of some of the diseases associated with aging.

**Dr. Farland** agreed that children have a limited amount of reserve capacity, and insults during childhood may have some impact later in life.

**Dr. Reigart** noted that a recently published paper reported that low birth weight was associated with increased susceptibility to kidney failure, suggesting that any deficit early on does increase the risk later in life.[48]

**Dr. Donald Mattison** (key speaker for topic 3) called attention to Dr. Etzel's recently published "Green Book" as a resource (Etzel, R.A., and S.J. Balk, eds. *Handbook of Pediatric Environmental Health.* 1st edition [November 15, 1999]. Washington, DC: American Academy of Pediatrics). He noted that while mortality may be a good measure of disease impact in adults, metrics like *years of life lost* and *disability-adjusted years* may be more appropriate for children and young adults.

**Dr. Mattison** noted two lessons learned from his participation as co-chair of the 1993 National Academy of Sciences report *Pesticides in the Diets of Infants and Children*: children do not have the diverse diets that adults do, and the pharmacokinetics and pharmacodynamics of children differ from adults.[49] He indicated that researchers need to

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[48]Lackland, D.T., H.E. Bendall, C. Osmond, B.M. Egan, and D.J. Barker. Low birth weights contribute to high rates of early-onset chronic renal failure in the southeastern United States, *Archives of Internal Medicine,* v. 160, n. 10, p. 1472-1476. (2000)

[49]National Research Council. *Pesticides in the Diets of Infants and Children.* Washington, DC: National Academy Press. 386 p. (1993)

The terms "pharmacokinetics"and "pharmacodynamics" refer to the study of processes – such as

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look critically at what these differences mean and develop better models for them. Dr. Mattison expressed the belief that the nation should give careful attention to the development of a longitudinal cohort study of health in families and children.

**Dr. Jackson** (a key speaker in the afternoon session) congratulated Dr. Etzel on her presentation. He added that children in the Ukraine, who Dr. Etzel noted suffer from a much higher than typical incidence of thyroid cancer due to radiation exposure from the Chernobyl accident, are iodine-deficient. He cited this as an example of the synergistic effects of a nutritional deficiency and an environmental insult.

**Dr. Wilson** (a discussant in the afternoon session) offered three comments to Dr. Etzel regarding her paper. He noted that she might more clearly define "child" and explain whether the statistics presented were rates (e.g., per 100,000) or absolute numbers. He also suggested that she consider commenting on the effects of poverty and how these interact with environment and the availability of medical care.

**Ms. Florini** (a discussant in the afternoon session) wished to draw attention to a paper recently published by Ellen Silbergeld and colleagues on gene-environment interactions.[50] The study of maternal exposure to solvents and birth defects found a three-fold increase in certain types of defects for all children but—with the same exposures—a 15-fold increase for children with a genetic variance that affected how those solvents were metabolized. She also advocated a move from mortality to morbidity as the appropriate statistical measure for children.

**John Blodgett**, of CRS, also referred to the definition of children, noting that teenagers may have part-time or summer jobs that lead to occupational exposures. He noted that chemical exposures might occur in schools. Mr. Blodgett cautioned that differences in the age at which children may work and the occupations in which they may engage complicate the use of data from other countries and the combination of data from different countries.

**Dr. Rice** (a discussant for topic 2) noted that there are genetically programmed processes going on all through the teenage years, and that puberty is a vulnerable period. [51] She noted that there are good biological reasons why, for example, schizophrenia often manifests itself in adolescence.

**Dr. Bailar** (a discussant for topic 4) asserted that the reason that studies may focus on mortality is that there are good data on the outcome. There is a need, he said, to improve mechanisms for collecting data on morbidity.

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absorption and metabolism – that determine the concentrations of drugs in the blood and the effects of those concentrations on individuals.

[50]CRS was unable to identify this reference.

[51]See, for example, a recent review of the literature by Mari S. Golub, (2000) "Adolescent health and the environment," *Environmental Health Perspectives*, v. 108, n. 4, p. 355-362.

**Dr. Reigart** noted that there are five stages of development that pediatricians are concerned about—the pre-natal period, infancy, toddler, latency, and adolescence—and each of these have different growth and development patterns. He cited a figure in Nelson on the development of organ systems relative to age that he recommended be added to Dr. Etzel's paper.[52]

**Dr. Schierow** closed the discussion by noting that later speakers would address the questions of multi-causality of diseases and interactions among exposures.

[52]There are 16 editions of the *Nelson Textbook of Pediatrics.* The most recent edition was edited by Behrman, R.E., R.M. Kliegman, and H.B. Jenson and published in Philadelphhia by W.B. .Saunders Co. in 2000.

Lynn Goldman, M.D., a professor at Johns Hopkins School of Hygiene and Public Health, prepared the second paper. As a former Assistant Administrator of the Office of Prevention, Pesticides and Toxic Substances at the Environmental Protection Agency, she has broad knowledge of the range of chemicals regulated by the federal government. Dr. Goldman gave an overview of the chemicals and pesticides on the market today and the available information about them to assess risks to children. Her points were illustrated by case studies of lead, mercury, and polychlorinated biphenyls (PCBs). She concluded that children may be more susceptible than adults to chemicals in the environment, and that scientists now recognize a need to gather child-specific data.

Dr. Goldman and the other scientists who participated in the discussion of Dr. Goldman's paper at the CRS seminar generally agreed on the following points –

- Information about the potential toxicity to children of chemicals in U.S. commerce is very limited and usually based on indirect measures. There are few experimental data related to developmental neurotoxicity.[53]
- Data on children's exposure to chemicals, including prescription drugs, remain sparse.
- Data on childhood exposure to lead in the United States provide a sound basis for risk assessments. Lead exposure in children can lead to IQ deficits, impaired school performance, distractability, short attention spans, and impulsive behavior.
- Even when data clearly establish the toxicity of a chemical to children, such as the toxicity of methyl mercury to developing brains, exposure data for U.S. children are lacking. Epidemiological studies suggest that a small proportion of U.S. infants may be at risk due to prenatal exposure to methyl mercury.
- New data are being collected by industry and government to improve estimates of exposure and toxicity to U.S. children of pesticides, some pediatric drugs, and methyl mercury.
- Chemicals like lead and methyl mercury, that are toxic to nervous tissue in similar ways in children and adults, are more likely to harm young children (whose brains are still developing) than adults, given comparable levels of exposure.
- Where data exist on other chemicals, they are not always well exploited. For example, data gathered by the Food and Drug Administration (FDA) and EPA as part of a product registration application have not been used extensively to develop models for predicting toxicity of unstudied chemicals, often because access to such data is restricted to protect confidential business information (CBI, also known as trade secret claims).

[53]Developmental neurotoxicity is the capability of causing an alteration in an embryo, fetus, or child up to the time of sexual maturation that aversely affects growth, structure, or function of the nervous system.

# Do We Know Which Environmental Pollutants Pose a Special Health Risk to Children? Case Studies of Lead, PCBs, and Methyl Mercury

By Lynn R. Goldman, MD, MPH

It has been said that children are not little adults when it comes to health risks of environmental exposures. Children may be more exposed to chemicals in the environment than adults, because they have greater intake of air, water and food per body weight than adults do. The behaviors of young children, that involve more contact with the floor and more hand-to-mouth activity, result in greater potential exposure to contaminants in house dust or soil. Because children are rapidly growing and developing, there are "windows of vulnerability" for effects to organ systems from gestation through adolescence.[54] Finally, because children have a long life expectancy, effects with long latency have longer time to manifest themselves. On the other hand, children often are not exposed to occupational hazards, and their bodies have the strength and resilience of youth. Metabolism of pollutants as they pass through the liver and kidney changes rapidly from birth through the first few years of life. These changes mean that at various stages of development children may be more or less capable of breaking down, excreting, inactivating, or activating toxic substances.[55] In other words, the risk posed by an environmental pollutant to a child as compared to an adult depends on the pollutant and the timing of exposure.

Unfortunately, information about the toxicity of chemicals to children and their likely exposure levels is very limited. This paper gives an overview of the chemicals and pesticides that are on the market today and the information that we have about them to assess risks to children. It uses three case studies to illustrate the nature and strength of evidence underlying a conclusion that children may be more susceptible than adults to chemicals in the environment and how that evidence changed scientific views about the need to gather child-specific data.

## Chemicals and Pesticides

**Universe of Chemicals.** EPA administers two statutes that require regulation of chemicals in commerce. The Toxic Substances Control Act (TSCA, 15 USC 2601 et seq.) authorizes EPA to screen existing and new chemicals used in manufacturing and commerce

[54]Anderson, Lucy M., B.A.Diwan, N.T. Fear and E. Roman. (2000) Critical windows of exposure for children's health: Cancer in human epidemiological studies and neoplasms in experimental animal models," *Environmental Health Perspectives*, v. 108, Supplement 3, 28 p.

[55]Bearer, C.F. How are children different from adults? *Environmental Health Perspectives*, v. 103, Supplement 6, p. 7-12. (1995)

Goldman, L.R. Children – unique and vulnerable. Environmental risks facing children and recommendations for response. *Environmental Health Perspectives*, v. 103, Supplement 6, p. 13-8. (1995)

Landrigan, P.J.. Environmental hazards for children in USA. *International Journal of Occupational and Medical Environmental Health*, v. 11, n. 2, p. 189-194. (1998)

to identify potentially dangerous products or uses that should be subject to federal control. Section 8 of TSCA requires EPA to develop and maintain an inventory of all chemicals, or categories of chemicals, manufactured or processed in the United States. In 1997 there were 75,500 chemicals on EPA's inventory of industrial chemicals, but most of these have never been in commerce. Some 15,000 of these chemicals are produced or imported to the U.S. annually in amounts of 10,000 pounds or more, and about 2,800 chemicals in amounts of a million pounds or more. Chemicals in the latter group are called high production volume chemicals (HPVs). Chemicals produced in very small quantities for purposes of experimentation or research are excluded from the inventory, as are certain other chemicals regulated under other federal statutes, for example, approximately 900 pesticides that are subject to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (7 USC 136-136y), and about 8,000 chemicals regulated under the Federal Food, Drug, and Cosmetic Act (FFDCA, 21 USC 301-392). In addition, there are unknown numbers of unregulated naturally occurring substances in food and nutritional supplements.

A pesticide is defined in FIFRA as a chemical or biological agent used to control (or cause death to) a non-human organism considered by humans to be a "pest" – that is, inimical to human interest. Thus, the term pesticide encompasses insecticides, fungicides, herbicides, rodenticides, and antimicrobial disinfectants. Pesticides are applied extensively to food crops in nations around the world. Pesticides are used at all stages of food production, to protect against pests in the field, and in shipping and storage. In the United States in 1995, there were 876 pesticide active ingredients on the market, of which 489 were registered for use on food products.[56] In 1997, about 4 billion pounds of pesticides were used in the United States. Of these, some 1.2 billion pounds of "conventional" pesticides were applied in the United States, mostly for agricultural purposes, but also in home and other uses.[57] From the mid-1960s to 1980, pesticide use sharply increased from 400 million pounds to more than 800 million pounds per year – an increase largely driven by the development and use of chemical herbicides in agriculture. In contrast, non-agricultural use declined from 300 million to 200 million pounds between 1970 and the 1990s.[58] It is not known to what extent "use" reflects risk since toxicity and exposure potential can differ, pound for pound, for different pesticides.

**Risk Assessment.** Clearly, not all chemicals in commerce and not even all pesticides pose a risk to children. In fact, some chemicals are beneficial, while others, like selenium and copper, may be beneficial under some conditions but harmful under others. The challenge is to determine which chemicals under which conditions are of public health importance throughout the life span and to assure that public health attention is directed to those. Part of this challenge involves determination of risks to children, but there are other

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[56]Aspelin, A.L., and A.H. Grube. Pesticide Industry Sales and Usage: 1996 and 1997 Sales and Usage. Washington, DC: U.S. Environmental Protection Agency. Office of Prevention, Pesticides and Toxic Substances. (1999)

[57]Ibid.

"Conventional pesticides, as defined by EPA, are the pesticides commonly used in agriculture. Using the broader definition in FIFRA, the largest single pesticide use in the United States is chlorination of drinking water, which accounts for a large portion of the 4 billion pounds total U.S. use.

[58]Ibid.

life stages (for example, pregnancy and old age) that may pose unique issues. Moreover, there are factors other than age that are of potential importance. For example, we know that certain substances, such as lead, confer greater risk when children are less well nourished.[59] Theoretically, there is also the possibility of genetic susceptibility; it is anticipated that breakthroughs in genetics will result in a better understanding of when and to what extent genetic susceptibility plays a role in risks to children.

The process of evaluating risks posed by chemicals (or other agents) is called risk assessment. A framework for risk assessment, generally used in the United States, was proposed by the National Research Council in 1983.[60] This framework defines risk as a function of hazard (the inherent toxicity) of a chemical and exposure (the dosage of the chemical at the target). Ideally, to assess risks of chemicals to children, we would have full knowledge of both the toxicity and exposures at all stages of development. Also, we would understand the complete sum of exposures from all sources and we would have the capability to assess the cumulative impacts of mixtures of chemicals. The reality is that we often use surrogate measures for both exposure and hazard.

***Exposure Data.*** Exposure can be monitored along a continuum from environmental levels (e.g., amounts in food, air, water, and products) to intake levels (amounts eaten, drunk, inhaled, and absorbed by the skin) to body burdens (levels in blood, fat, bone, urine, and/or hair) to target tissue dose (amounts that enter the cells that are the targets for toxicity.) The last measure – the amount that hits the target – is what is of most interest, but that information is almost never directly available. However, as we learn about uptake and metabolism of a chemical, scientists can make estimates of target tissue dose from other available information. All too often, we have no direct measures of exposure and must rely on other measures which are drivers of exposure and which can be modeled in order to estimate exposure. Important physical and chemical parameters may be used to help model and estimate exposures, such as, solubility in water, volatility in air, persistence, ability to bioaccumulate, and so forth. Such surrogate measures include volume of chemical produced or imported, volume released and reported under the Toxic Release Inventory (TRI) and other environmental reporting systems, and estimated air emissions based on engine efficiency and incinerator combustion models. Chemicals that are persistent and bioaccumulative may continue to cause exposures and effects long after measures have been taken to reduce their production.

To fully understand exposure requires knowledge about chemical fate (i.e., where a chemical is likely to end up) and breakdown products in the environment and after uptake during metabolism. Frequently metabolites are as or more toxic than their parent compounds. Yet, we often do not know what the metabolites are, and their toxicity is often unknown. Metabolites may be different for young children, during pregnancy, or in the elderly.

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[59]National Research Council. *Measuring Lead Exposure in Infants, Children and Other Sensitive Populations*. Washington, DC: National Academy Press. (1993) p. 8.

[60]National Research Council. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: National Academy Press. (1983) p. 3.

Most data related to exposure come from industries' reports to EPA on use or release of chemicals or from monitoring of ambient air or water. There are numerous environmental reports that are filed by industry, such as the reports on routine releases to the environment of some 600 chemicals covered by the TRI and, under TSCA, reports on production levels and categories of use for industrial chemicals. However, TRI and TSCA data do not indicate the extent of direct (external) exposure to people. More useful data, from monitoring of drinking water supplies (for substances regulated under the Safe Drinking Water Act) and of ambient air (under the Clean Air Act), are more limited. For food, the USDA and FDA both monitor the food supply for pesticides, and the USDA Pesticide Data Program has provided key information on pesticide levels found during random sampling of the U.S. food supply. When analyzed in combination with the USDA food intake survey, it is possible to estimate the range of children's intakes of pesticides in food. Certain foods, like apples, peaches, pears, and milk, are more frequently eaten by children and thus often result in higher intake levels of any pesticide residues.

***Toxicity.*** Recently the U.S. EPA pesticide Science Advisory Panel adopted a "minimum data set" for assessment of risks to children. This data set includes a number of sophisticated tests for toxicity including developmental toxicity, neurotoxicity, and cancer bioassays. It incorporates a number of potential modes of action including mutation, endocrine disruption and others. In reality, other than for pesticides, pharmaceuticals, and food additives, this kind of data set is almost never available for evaluation of a chemical. An endocrine disruptor screening and testing program was developed by the EPA as directed by Congress in 1996, but it has yet to be validated and implemented.[61]

There are relatively short-term tests that can be applied to screen chemicals for toxicity. The Organization for Economic Cooperation and Development (OECD) developed the Screening Inventory Data Set (SIDS) in order to provide a rapid method to quickly screen high volume chemicals in commerce about which we have very little information. For example, recent studies indicate that we know very little about HPV chemicals.[62] In 1998, SIDS batteries were complete for only 7% of them. Around 40% had no SIDS data at all. Only about one-quarter of chemicals known to be present in consumer products had complete SIDS data. A voluntary effort by the chemical industry that is now underway should result in availability of screening level data by 2003 for all HPVs. The hope is that screening can quickly identify the chemicals of greatest potential public health concern, while minimizing the costs and animal welfare concerns associated with more complete (and definitive) assays. It is expected that in the future, even more efficient screening assays will be developed, perhaps using new microchip techniques that are on the horizon.

Modern computational procedures can also provide a significant amount of information about the toxicity of chemicals. As more is learned about mechanisms of toxicity, models of quantitative structure-activity relationships (QSARs) have been

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[61]U.S. Environmental Protection Agency. Endocrine disruptor screening program, notice. *Federal Register*, v. 63, Aug. 11, 1998, p. 42852.

[62]U.S. Environmental Protection Agency. Office of Prevention Pesticides and Toxic Substances. *Chemical Hazard Data Availability Study: What Do We Really Know about the Safety of High Production Volume Chemicals? EPA's 1998 Baseline of Hazard Information that is Readily Available to the Public*. Washington, DC: EPA. (1998)

developed and are continuing to be improved. QSARs have been used for many years by the EPA chemicals program to quickly review pre-manufacturing notices (PMNs) for new chemicals, which come into EPA with very little information.[63] However, a recent review by the U.S. EPA and the European Union (EU) found that for many chronic health effects of concern, the QSAR models are less predictive (and protective) than the SIDS data (which are required for new chemicals in the EU.)[64, 65]

Scientists base most environmental health decisions about individual pollutants on hazard information derived from animal tests. These tests assume that if a chemical is hazardous to animals, it is hazardous to humans. A related assumption is that animal testing predicts relative potency for humans. To account for the statistical bias of studies using small numbers of animals, differences in the sensitivity of individual animals (and people), and differences between animals and people, the EPA and the FDA further assume that "real" risks in each case are no more than ten times the risk observed in the study. The EPA calls the resulting estimate of a "safe" exposure level a "Reference Dose (RfD)";[66] the FDA calls the comparable standard an "Acceptable Daily Intake" (ADI).[67]

Traditionally in risk assessment, it has been assumed that risks to children are encompassed in the tenfold factor that is used to account for all the variation within the species. However, the reality is that often data are missing to inform us about risks to the child. At the EPA, modifying factors between 3- and 10- fold are applied when critical studies are missing, but in the past EPA did not have a consistent policy about which studies were "critical," so this factor often was not applied, even when data were missing.

In 1993, the National Research Council found that the EPA was not adequately accounting for children's diets and risks in setting standards for pesticides in food.[68] In response, the EPA changed its methodology for dietary exposure assessment so that it could

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[63]TSCA requires manufacturers, importers, and processors to notify EPA at least 90 days prior to producing or otherwise introducing a new chemical product into the United States. Any information or test data that is known to, reasonably ascertainable by, or in possession of the notifier, and that might be useful to EPA in evaluating the chemical's potential adverse effects on human health or the environment, must be submitted to EPA at the same time. EPA reviews approximately 1,000 new chemical manufacturing notices annually.

[64] EPA/European Community. Joint project on the evaluation of (quantitative structure-activity relationships: Final report. EPA 743-R-94-001. Washington, DC: EPA. (1993)

[65]In general, "chronic" health effects are those ailments, such as cancer or heart disease, which adversely affect health for relatively long periods of time. Chronic effects that were assessed in this case included general toxicity, neurotoxicity, developmental toxicity and reproductive toxicity (although some of these effects can be elicited with acute, short term exposures.)

[66]Barnes, D., and M. Dourson. Reference Dose (RfD): description and use in health risk assessments. *Regulatory Toxicology and Pharmacology,* v. 8, p. 471-486. (1988)

[67]Lehman, A.J., and D.G. Fitzhugh. 100-Fold margin of safety: Quarterly report to the editor on topics of current interest. *Association of Food and Drug Officials Quarterly Bulletin*, v. 18, p. 33-35. (1954)

[68]National Research Council. *Pesticides in the Diets of Infants and Children*. Washington, DC: National Academy Press. (1993)

incorporate available information about children's diets. The EPA also updated a number of test guidelines to generate more information about developmental, neurologic, and endocrine effects from pesticides. In 1996, Congress enacted the Food Quality Protection Act (FQPA), which codified several of these new changes.[69] New in FQPA were requirements for cumulative and aggregate risk assessment. Aggregate risk means considering all routes of exposure and uses of a pesticide rather than approving uses one at a time. Cumulative risk means considering all pesticides that may share a common mechanism of action. Another challenging new provision requires "an additional tenfold margin of safety to protect children." Congress went on to say "the Administrator may use a different margin of safety ... only if, on the basis of reliable data, such margin will be safe for infants and children." At the time of this writing there is still much debate about application of the tenfold FQPA factor. At the heart of the debate are two questions: First, what is the scientific (as opposed to the legal) justification to apply 10X? Second, what constitutes reliable and complete scientific data upon which to base that decision? Both of these questions have implications for establishing child protective standards across the board, not just for pesticides.

An important policy choice that has emerged from the debate about the FQPA 10X factor is whether current toxicity testing requirements and exposure information are adequate to assure the safety of infants and children, or whether EPA should routinely require additional information. One question that emerged was whether the developmental neurotoxicity test, previously conducted only if triggered by results of earlier testing, should be required by the EPA for every food use pesticide, in order to fully assess the potential for hazard to children. EPA has required that developmental toxicity be assessed for all pesticides that are neurotoxic, such as the organophosphate and carbamate pesticides.[70]

An endocrine disruptor is defined by the EPA as "an exogenous agent which interferes with the synthesis, secretion, transport, binding action, or elimination of natural hormones in the body which are responsible for homeostasis, reproduction, development, or behavior." Endocrine disruptors may act as estrogens (e.g., bisphenol A, methoxychlor, certain PCBs, or the natural compound genistein); anti-androgens (e.g., the pesticides DDT, its metabolite DDE, and vinclozolin); or may have thyroidal activity (e.g., certain PCBs). The EPA has begun a program to set priorities for endocrine disruptor screening and testing among the 15,000 chemicals produced in amounts greater than or equal to 10,000 pounds annually.[71] Once underway, this testing program should provide very important information regarding potential hazards for children. Recently, the National Toxicology Program (NTP) and the EPA conducted an expert workshop to evaluate the data on low-dose effects of endocrine disruptors, and specifically data on the plasticizer bisphenol A, for which there have been conflicting results in the literature. Some studies showed low-dose effects on development of the male reproductive tract in mice exposed *in utero*, and others did not. The workshop did not identify any reason to reject either set of studies, but did develop a number of possible explanations for the differences and recommendations for how to better

[69]Public Law 104-170.

[70]Rossi, L. Data Call-In for Developmental Neurotoxicity Testing of Specific Pesticides. Washington, DC: EPA Office of Prevention, Pesticides and Toxic Substances. (1999)

[71]U.S. Environmental Protection Agency. Endocrine disruptor screening program, notice. 63 *Federal Register* 42852, August 11, 1998.

conduct research in this area in the future. A final report from the workshop is expected in 2001.

Of much current attention are plastics additives called phthalates, plasticizers that are found in numerous products including children's toys, food, building materials, cosmetics, and medical devices. One, DEHP (diethelhexylphthalate), was removed from children's toys by the Consumer Product Safety Commission several years ago. Another, DINP, is still in many polyvinyl chloride toys. CPSC has called on manufacturers to voluntarily stop using this plastic in teethers and other toys intended for mouthing by children while scientific studies of its hazards and exposure are underway. DEHP is present in medical plastics tubing and the FDA is currently assessing whether there are exposures of concern that may result from its use. Recently, the NTP Center for the Evaluation of Risks to Human Reproduction conducted a review of phthalates. The expert panel identified phthalates as having androgen-blocking effects and was especially concerned about exposures to phthalates in medical devices among small, critically ill infants. This review is now out for public comment, and the NTP is expected to release the conclusions in early 2001.

## Case Studies

**Lead.** Lead exposure is among the most important environmental illnesses for children. Lead is a naturally occuring metal, one of the members of the periodic table of elements. Lead poisoning has been recognized since antiquity. In the second century BC, Dioscorides, a Greek physician, said "lead makes the mind give way."[72] Acute lead poisoning in adults continues to occur today, mostly as a consequence of occupational exposures. Lead is a relatively well-studied and well understood pollutant with respect to its health effects on children.

Childhood lead poisoning was described in Brisbane, Australia, in 1897. The cause of this endemic illness was identified as painted porch railings.[73] In 1920, the city of Brisbane passed the first lead paint poisoning prevention act. In the United States, poisoning from lead-based paint was described in the first decade of the 20th century. It was initially believed that if a child recovered from the acute illness, there were no sequelae.[74] Byers and Lord refuted this in 1943 in their report of 20 children who had recovered from acute lead intoxication; 19 had obvious behavior disorders or mental retardation.[75] Better designed and more sophisticated studies have been performed since that time, and there is a general

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[72]Major, R. *A History of Medicine*. Springfield, IL: Charles C. Thomas. (1954)

[73]Turner, J.A. Lead poisoning among Queensland children. *Australasian Medical Journal*, v. 16, p. 475-479. (1897)
Gibson, J.L. A plea for painted railings and painted walls of rooms as the source of lead poisoning amongst Queensland children. *Australasian Medical Gazette*, v. 23, p. 149-153. (1904)

[74]McKhann, C. Lead poisoning in children: with notes on therapy. *American Journal of Diseases of Children*. 1926. v. 32, p. 386-392.

[75]Byers, R., and E. Lord. Late effects of lead poisoning on mental development. *American Journal of Diseases of Children*, v. 66, p. 471-494. (1943)

consensus of opinion about the relationship between lead and cognitive function.[76] It should be noted that many of the same exposures for children are also important for adults.

Lead enters the body by mouth or breath (i.e., ingestion or inhalation). The relationship between exposure and blood lead level (BLL) is dynamic, changing depending on recent exposures, excretion, and equilibration with other tissues. Children deficient in iron, protein, calcium, and/or zinc absorb lead more readily. Most retained lead is stored in the bones.

Lead toxicity affects almost every organ system, most importantly, the central nervous system, peripheral nervous system, kidneys, and blood. At high BLLs (more than 70 micrograms of lead per deciliter of blood (μg/dL)), lead may cause encephalopathy (i.e., degenerative brain disease) and death in children. Survivors of encephalopathy almost always have lifelong severe disabilities, such as seizures and mental retardation.[77] Lead also interferes with enzymes that catalyze the formation of heme, the carrier for iron in red blood cells. It inhibits both prenatal and postnatal growth. Studies have shown that lead impairs hearing acuity. Lead is a carcinogen in laboratory animals, and there is some evidence for carcinogenicity in adult humans (i.e., workers), but not in children.[78]

Although the impairment of cognition in young children at the level 10 μg/dL has been established, no threshold has been identified.[79] At lower BLL values, the impact on an individual child may be undetectable. In contrast, there may be a significant impact on a population of children with such BLLs.[80] This body of literature has been examined by meta-analysis, which is a way of synthesizing data from multiple studies. The relationship between lead and IQ deficits was found to be remarkably consistent. A number of studies have found that for every increase of 10 to 15 μg/dL BLL, within the range of 5 to 35 μg/dL, there is a lowering of children's mean IQ by 2-4 points.[81]

The effects of early lead exposure appear to persist over a lifetime. Follow-up study into adulthood of a group of subjects classified by dentine lead levels in the first and second grade showed that those with high tooth lead levels as children were seven times more likely not to graduate from high school and six times more likely to have reading scores at least two grades below expected, after adjustment for a number of factors including socioeconomic status and parental IQ.[82] They also had higher absenteeism in the final year of school, lower

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[76]Cognitive function means ability to learn.
American Academy of Pediatrics. Committee on Environmental Health. Lead poisoning: from screening to primary prevention. *Pediatrics*, v. 92, n. 1, p. 176-183. (1993)

[77]Ibid.

[78]Ibid.

[79]Ibid.

[80]BLLs measure internal dose, that is, levels of lead in the boodstream.

[81]National Research Council. *Measuring Lead Exposure in Infants, Children and Other Sensitive Populations*. Washington, DC: National Academy Press; 1993.

[82]Needleman, H.L., Schell, A., Bellinger, D., Leviton, A., and Allred, E.N. The long-term effects of (continued...)

class rank, poorer vocabulary, and grammatical reasoning scores, longer reaction times, and poorer hand-eye coordination.

The most recent data published by Centers for Disease Control and Prevention (CDC) indicate that average (geometric mean) children's BLLs fell from 12.8 to 2.8 µg/dL of blood between 1976-80 and 1988-91.[83] Most significantly, during the same period, the percentage of U.S. children between 1 and 5 years of age with BLLs above 10 µg/dL (the current CDC definition of toxicity) fell from 88% to 9%. Similar drops in BLLs were seen for all age groups and income levels, and for inner city and rural residents alike. This is surely one of the most remarkable public health achievements of the decade. However, whereas 4.4% of the U.S. population had BLLs of 10 µg/dL or above in 1988-91, 11.5% of children age 1 to 2 years had BLLs in that range. Exposure was greatest to minority children, with 10% of Mexican American and 22% of black children having BLLs in this range, and to low income children, to children living in larger urban areas, and to children living in the Northeast. Thus, there was some lead exposure in all strata of society, yet there were children at much higher risk.[84]

The enormous reduction in elevated blood lead levels in the United States was largely achieved through the EPA ban of lead in gasoline.[85] In addition, CPSC, FDA, and EPA banned lead in interior housepaints, children's toys, food cans, plumbing materials, and a number of other items that led to exposures around the home, in food, and in drinking water.

Research has shown that lead paint is the major source of lead exposure for children in the United States today.[86] Prior to 1955, much house paint was so-called "white lead", 50:50 lead and linseed oil. In 1955, manufacturers adopted a voluntary house paint lead

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[82](...continued)
exposure to low doses of lead in childhood. An 11-year follow-up report. *New England Journal of Medicine,* v. 322, p. 83-88. (1990)

[83]Pirkle, J.L., D.J. Brody, E.W. Gunter, et al. The decline in blood lead levels in the United States: the National Health and Nutrition Examination Surveys (NHANES). *Journal of the American Medical Association*, v. 272, n. 4, p. 284-291. (1994)

[84]Ibid.
Brody, D.J., J.L. Pirkle, R.A. Kramer, et al. Blood lead levels in the US population. Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991) Erratum appears in JAMA, v. 272, n. 4, p. 130 (1995)]. *Journal of the American Medical Association*, v. 272, n. 4, p. 277-283. (1994)

[85]Agency for Toxic Substances and Disease Registry. (1993) *Toxicological Profile for Lead.* p. 197-199.
Bolger, P.M., C.D. Carrington, S.G. Capar, et al. (1991) Reductions in dietary lead exposure in the United States. *Chemical Speciation and Bioavailability*, v. 3, n. 314, p. 31-36.
Gunderson, E.L. (1988) FDA total diet study, April 1982-April 1984, dietary intakes of pesticides, selected elements and other chemicals. *Journal of the Association of Officials in Analytic Chemistry*, v. 71, p. 1200-1209.
Elimination of lead use in solder of canned goods also contributed to the decline in blood lead levels.

[86]National Research Council, ibid.

standard of 1%, but house paint with higher levels continued to be manufactured.[87] Seventy percent of the homes built before 1960 are estimated to have lead paint. Most dangerous are the 3.8 million homes with decaying or deteriorating lead paint in which 2 million children under the age of 6 live. Certainly any child living in a house containing lead-based paint may be at risk. Such housing and other sources of lead are found throughout the United States. A national survey of housing conducted by HUD found that age of housing, not geographic location, is the best predictor for presence of lead-based paint.

Other important sources are contaminated soil, dust, drinking water, and food. Lead may also contaminate food through uptake from soil, processing, lead soldered cans, and pottery. In the U.S., soldered cans have largely been replaced by seamless aluminum containers, but imported and large commercial-sized cans still have lead soldered seams. Ingestion of lead from ethnic folk remedies, eye cosmetics (kohl used by Moslems and surma by Hindus), hobbies (such as stained glass, artist paints, and shooting ranges), household fixtures (such as plastic miniblinds that were manufactured in lead molds), and small objects (such as fishing weights or curtain weights) can cause very severe lead poisoning.[88] Parents who are employed in the lead industry may bring lead dust home on clothing or expose children by allowing them to visit work sites.

In 1991, the CDC called for universal screening of children for lead exposure.[89] However, a national survey in 1994 showed that only one-fourth of children were screened and that only one-third of low-income children, those at most risk, were screened. Therefore, in 1997, the CDC revised its recommendation to recommend that, on a state-by-state basis, plans be developed to ensure that children who need to be screened are tested for lead exposure. The CDC has developed detailed guidance for follow-up and treatment of children with elevated blood lead levels.[90] Recently the U.S. government released a report "Eliminating Childhood Lead Poisoning: A Federal Strategy Targeting Lead Paint Hazards" that presents the federal blueprint for the elimination of childhood lead poisoning as a major public health problem over the next ten years. If it succeeds, by 2020, one hundred years after the first description of childhood lead poisoning as a disease in the U.S., we will have eliminated this disease.

In the case of lead, it was initially through the work of astute physicians that the risks of lead poisoning to children, and the long-range impacts, were identified. Eventually, it was necessary to apply the tools of modern epidemiology to fully understand the exposures and the developmental impacts of low level lead exposure to children. First, in the past it had not been understood that children ingest large amounts of contaminated house dust (relative to adults) and thereby could have greater exposures to lead and other pollutants, relative to adults. Second, it was necessary to develop the laboratory methods to measure lead

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[87]Rabin R. (1989) "Warnings unheeded: A history of child lead poisoning". *American Journal of Public Health.* v. 79, p. 1668-1674.

[88]National Research Council, ibid.

[89]Centers for Disease Control and Prevention (CDC). *Screening Young Children for Lead Poisoning: Guidance for State and Local Public Health Officials.* Atlanta: Centers for Disease Control and Prevention. (1997)

[90]Ibid.

accurately at very low levels. Much of this work was done by the laboratories at CDC. Third, it was critical that tools to measure more subtle impacts on brain function and development be developed. The NIEHS funded many of the studies that developed these tools and demonstrated the relationship between lead exposure and cognitive development.

Lead illustrates that many improvements are needed in how we assess chemical risks, if we are to accurately discover risks to children. The effects of low-level exposures to children could not have been predicted using adult studies or animal studies. In adults, effects on cognition occur at levels 100-fold higher than for children, levels at which people already are obviously very ill.[91] In animals, conventional laboratory testing methods have found effects at levels 100-1,000 times higher in animals than in humans when calculations were based on external dose, which is the standard practice. When calculations are based on body burdens (internal dose), the results are much closer, but this is not the current practice. Using sophisticated test methods not currently required by EPA, cognitive deficits as a result of lead exposure have been identified at approximately the same blood lead levels in children and animals, suggesting that changes in methodology may result in improved ability to accurately predict neurotoxicity in children based on animal studies.[92]

**Polychlorinated Biphenyls (PCBs) and Dioxins.** Dioxins and polychlorinated biphenyls (PCBs) are groups of persistent toxic chemical compounds widely dispersed in the environment. PCBs are chemical insulators that were manufactured and widely used by industry until 1976, when the U.S. Congress banned PCB manufacture and import and most PCB uses. However, several uses have been continued to this day. Because PCBs persist environmentally for many decades, contamination that resulted from past use, spills, and disposal continues to cause exposure. PCBs wind up in rivers and lakes, where they are taken up and concentrated in the food chain.

Dioxins and the similar compounds dibenzofurans were contaminants in the manufacture of PCBs and other chlorinated chemicals, including the pesticide 2,4,5-T (Agent Orange), the wood preservative pentachlorophenol, and certain clothing dyes. Dioxins also may form when such chemicals are heated or burned. They are highly persistent in the environment, and often occur together with PCBs as mixtures. Today dioxins are mostly produced by combustion processes. Dioxins and PCBs are classified by the National Toxicology Program as probable carcinogens and are considered by the EPA to be reproductive toxicants. Some PCBs are estrogenic; others may affect thyroid function.[93]

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[91]The comparisons in this paragraph are based on external doses of lead, that is, the amount of lead ingested, not on internal blood lead levels (BLLs).

[92]Rice, D.C., Evangelista de Duffard, A.M., Duffard, R., Iregren, A., Satoh, H., and Watanabe, C. Lessons for neurotoxicology from selected model compounds: SGOMSEC joint report. *Environmental Health Perspectives,* v. 104, Supplement 2, p. 205-215. (1996)

[93]Longnecker, M.P., W.J. Rogan, and G. Lucier. The human health effects of DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) and an overview of organochlorines in public health. *Annual Review of Public Health*, v. 18, p. 211-244. (1997)

Brouwer, A., U.G. Ahlborg, F.X. van Leeuwen, and M.M. Feeley. Report of the WHO working group on the assessment of health risks for human infants from exposure to PCDDs, PCDFs and PCBs. *Chemosphere*, v. 37, n. 9-12, p. 1627-1643. (1998)

Children are exposed to PCBs through breast milk, and by eating fish and other fatty foods that contain high concentrations of PCBs.[94] Children can also be exposed in the womb, as PCBs move across the placenta. The health effects of exposure to PCBs and dioxins may be estimated based on limited evidence from accidental and occupational human exposures and from animal studies.

Human exposure to high levels of PCBs has been observed as a result of two major accidents that occurred in Asia in the 1970s, in which PCB oil contaminated supplies of cooking oil (rice oil) in Taiwan and Japan. In Taiwan, such exposure was shown to interfere with many aspects of a child's cognitive development.[95]

In the U.S., the most common route of human exposure to PCBs is through large predator fish. Exposure to PCBs in concentrations attained by mothers eating fish caught in the Great Lakes has been associated with poorer neurodevelopmental function in their infants.[96] In older Dutch children, exposure to such concentrations *in utero* has been associated with decrements in their intellectual performance,[97] and in older Michigan children, with lower full-scale and verbal IQ scores.[98] Studies in both the Great Lakes area and North Carolina have shown that these decrements are greatest in children of mothers with the highest body burdens of PCBs. Figure 1 shows the results from one such study.[99] Among a group of children with PCB exposures within the normal range of background levels (that is, who did not have unusually high levels of exposure), those with the highest fetal exposures had a significant lowering of average IQ.

PCB and dioxin levels are generally higher in breast milk than in infant formula. However, an extensive review by the World Health Organization concluded that the overall benefit of breast milk consumption outweighs the risk due to dioxins, PCBs and other

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[94]Longnecker et al., ibid.

[95]Guo, Y.L., Y.C. Chen, M.L. Yu, and C.C. Hsu. Early development of Yu-Cheng children born seven to twelve years after the Taiwan PCB outbreak. *Chemosphere*, v. 29, n. 9-11, p. 2395-2404. (1994)

[96]Stewart, P., J. Reihman, E. Lonky, T. Darvill, and J. Pagano. Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. *Neurotoxicology and Teratology*, v.22, n. 1, p. 21-29. (2000)

Jacobson, J.L., S.W. Jacobson, and H.E. Humphrey. Effects of exposure to PCBs and related compounds on growth and activity in children. *Neurotoxicology and Teratol*ogy, v. 12, n. 4, p. 319-26. (1990)

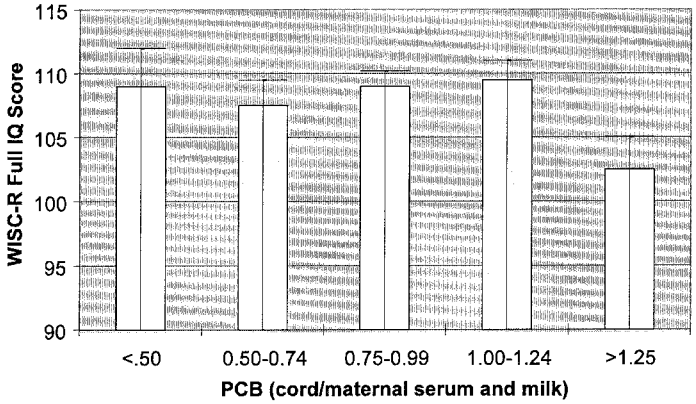
[97]Patandin, S., C.I. Lanting, P.G. Mulder, E.R. Boersma, P.J. Sauer, and N. Weisglas-Kuperus. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age [see comments]. *Journal of Pediatrics*, v. 134, n. 1, p.33-41. (1999)

[98]Jacobson, J.L., and S.W. Jacobson. Intellectual impairment in children exposed to polychlorinated biphenyls *in utero* [see comments]. *New England Journal of Medicine*, v. 335, n. 11, p. 783-789. (1996)

[99]Jacobson, J.L., and S.W. Jacobson. Dose-response in perinatal exposure to polychlorinated biphenyls (PCBs): the Michigan and North Carolina cohort studies. *Toxicology and Industrial Health*, v. 12, n. 3-4, p. 435-445. (1996)

contaminants.[100]

**Figure 1. Prenatal PCB exposure vs. 11 year IQ (adjusted)**




(nanograms/milliliter)

Human children are much more sensitive to the effects of PCBs than are adult humans or animals.[101] It has been estimated that the cognitive effects that have been demonstrated for children occur at external dose levels 10,000-fold lower than for adults. Adult effects occur only when they are so poisoned that they are very ill and cannot walk steadily. Effects for children at low levels of exposure may be so subtle that they can only be observed in large scientific studies. For animals, even testing using EPA's developmental neurotoxicity guideline or more sophisticated tests show effects at levels 1,000-fold higher than studies of cognition of children. So, while these tests are more predictive than studies in adult humans or animals, they might not be sufficiently sensitive to detect small risks to human children.[102] However, as in the case with lead, measurement of body burden (internal dose) rather than intake (external dose) of PCBs would bring these results much closer together.

**Methyl Mercury.** Mercury is a metal, a naturally occurring element on the periodic table of elements. Mercury (Hg) occurs in three forms: the metallic element; inorganic salts; and organic compounds. Solubility, reactivity, biological effects, and toxicity vary among these forms. Naturally occurring mercury sources include cinnabar (ore) and fossil fuels, such as coal and petroleum. Mercury can be released into air and water through natural weathering of rock, mining, smelting, incineration, fossil fuel burning, and industrial discharges.

[100]Longnecker et al., ibid.

[101]Ibid.

[102]Rice et al., ibid.

Organic mercury compounds include methyl mercury, ethyl mercury, and phenyl mercury. All three have been produced as industrial compounds, primarily as pesticides, preservatives, or sterilants. Methyl mercury has been used as a fungicide on seed grains and is found in industrial waste as well. In the United States, phenyl mercury (phenyl mercuric nitrate or acetate) was used in latex paint both as a pesticide (to prevent mildew growth on walls) and as a paint preservative (to prevent paint discoloration from growth of microorganisms.) Ethyl mercury, in the form of thimerosal, has been used as a preservative for killed vaccines and other biologic agents for medical therapy. Ethyl mercury was formerly used as a topical antiseptic as well (Merthiolate). Both phenyl mercury and ethyl mercury continue to be used as bacteriostatic agents for various topical pharmacological preparations. Methyl mercury is the best known because it is the predominant form of organic mercury found in the environment.

Today, consumption of fish is the primary route of exposure to organic mercury for children over the age of one. At greatest risk are children of sport and subsistence fishers who habitually catch fish from the same contaminated area.[103] The methyl mercury in contaminated waters often derives from the inorganic mercury emitted by industries. This mercury is deposited into water, where bacteria in lake, stream and ocean sediments can convert inorganic mercury to organic mercury, (e.g., methyl mercury) which then may accumulate as it moves up the food chain.[104] That is what occurred in Minamata Bay, Japan, in the 1950s, when a factory discharged large quantities of a mercury catalyst into the Bay. There were 41 deaths and at least 30 cases of profound mental injury in infants born to mothers who ingested fish from that bay during pregnancy[105]

The acute health effects of mercury exposure have been recognized for centuries, but the long-term effects of chronic exposure to lower methyl mercury levels, such as those found in fish, are still being investigated. Until recently, the best information on methyl mercury was from an extensive study of a large group of Iraqis who were poisoned when methyl mercury treated grain seeds were eaten during a famine in the 1970s. Hundreds of people were poisoned.[106] In both the Minimata Bay disaster and the Iraq epidemic, mothers who were asymptomatic or showed mild toxic effects gave birth to severely affected infants. Typically, the infants appeared normal at birth, but psychomotor retardation, blindness, deafness, and seizures developed over time.[107] Delayed development of motor skills (e.g., walking) was seen in children whose mothers were found to have mercury concentrations in

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[103]Clarkson, T.W.. The toxicology of mercury. *Critical Reviews in Clinical and Laboratory Science*, v. 34, n. 4, p. 369-403. (1997)

[104]National Research Council. *Toxicological Effects of Methylmercury*. Washington, DC: National Academy Press, (2000) p. 13.

[105]Goldfrank, L., E. Bresnitz, M. Howland, and R. Weisman. Mercury. In: Goldfrank, L., N. Flomenbaum, and N. Lewin, eds. *Goldfrank's Toxicologic Emergencies*. Norwalk, CT: Appleton and Lange, p. 641-648. (1990).

[106]Bakir, F., S.F. Damluji, L. Amin-Zaki, et al. Methyl mercury poisoning in Iraq. *Science*, v. 181, n. 96, p. 230-241. (1973)

[107]Amin-Zaki, L., S. Elhassani, M.A. Majeed, T.W. Clarkson, R.A. Doherty, and M. Greenwood. Intra-uterine methyl mercury poisoning in Iraq. *Pediatrics*, v. 54, n. 5, p. 587-95. (1974)

hair of between 10 and 20 parts per million (ppm).[108]

Because the fetus and infant appear to be more susceptible to the neurotoxic effects of methyl mercury than adults, investigators want to identify the lowest doses of mercury able to affect development adversely. This means that they must look for subtle effects among children whose mothers' diets include relatively large amounts of methyl mercury, more than is commonly consumed in the United States, but an amount that may be consumed in families that rely on fish for much of their diet.

There are three well-designed, prospective, longitudinal studies of the cognitive effects (that is, effects on the ability to learn) of chronic mercury exposure at the exposure level of interest. Two studies involve groups of scientists working with fishing populations in the Faroe Islands and the Seychelle Islands, who began to publish conflicting results several years ago. The Faroe Islands study results to date suggest that exposure *in utero* to mercury at low levels is associated with subtle adverse effects on the developing brain. Memory, attention, and language test results indicate that tested skills declined with increasing levels of methyl mercury exposure to children up to age 7.[109] Tests of coordination and visual spatial ability are less clearly associated with methyl mercury exposure. In contrast, no adverse effects on development or IQ have been found in the Seychelle study in children up to 66 months of age, even though exposures were in the same range as the Faroes study.[110]

A workshop convened by the White House in 1998 found that both the Seychelle and Faroe Island studies were well conducted studies that included appropriate measures of both exposure to methyl mercury and sensitive developmental endpoints.[111] Moreover, both studies measured and accounted for a number of important lifestyle factors (i.e., smoking, breast feeding, alcohol use, and socioeconomic status). However, the workshop noted the different findings and listed a number of potential explanations for this difference including: ethnic differences in response to methyl mercury, different measures of different intellectual

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[108]Bakir et al., ibid.
Amin-Zaki et al., ibid.
Amin-Zaki, L., M.A. Majeed, S.B. Elhassani, T.W. Clarkson, M.R. Greenwood, and R.A. Doherty. Prenatal methyl mercury poisoning. Clinical observations over five years. *American Journal of Disabled Children*, v. 133, n. 2, p. 172-177. (1979)

[109]Grandjean, P., P. Weihe, R.F. White, et al. Cognitive deficit in 7–year-old children with prenatal exposure to methyl mercury. *Neurotoxicology and Teratology*, v. 19, n. 6., p. 417-428. (1997)

[110]Davidson, P.W., G.J. Myers, C. Cox, et al. Effects of prenatal and postnatal methyl mercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study [see comments]. *Journal of the American Medical Association*, v. 280, n. 8, p. 701-707. (1998)

[111]Lucier, G., and R. Goyer. Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methyl mercury: November 18-20. Proceedings of Workshop Organized by the Committee on Environment and Natural Resources and the Office of Science and Technology Policy, The White House. Research Triangle Park, NC: National Institute of Environmental Health Sciences. (1999)

abilities, and differences in lifestyle or nutrients or other contaminants found in seafood.[112] The different findings also raised the issue of whether a single dose of methyl mercury, in a sensitive time period, is more likely to cause neurodevelopmental damage than the same total dose given gradually over several months.[113, 114]

Recently, the National Research Council of the National Academy of Sciences (NAS) reviewed available data on prenatal mercury exposure and toxicity, including a third longitudinal, prospective study in New Zealand, which previously had not been peer reviewed. The New Zealand study looked at fewer mother-infant pairs than the Faroe or Seychelles studies, but it used a broad set of standardized tests to measure cognitive effects, and the New Zealand study population was ethnically heterogeneous. The exposure pattern and research design were very similar to those in the Seychelles study, but the results agreed with those of the Faroe Island study. The NRC report, *Toxicological Effects of Methylmercury*, concluded that there could be statistical reasons for the differences among the studies, but the study conducted in the Faroe Islands provides the best estimate for methyl mercury toxicity to children at this time.[115] The NAS estimated that 60,000 children are born in the United States each year with levels of mercury that may put them at risk.[116]

## Conclusions

In the United States, physicians rarely see acute toxicity from environmental exposures to chemicals, although there are cases that occur in association with use and misuse of consumer products or industrial accidents. Rather, medical concerns are about low-level environmental exposures to chemicals and possible long-term effects, like cancer, reproductive toxicity, and neurotoxicity.

We know very little about either exposure levels or potential hazards from most chemicals in commerce in the U.S., especially the effects on the fetus and the growing child. We have much more information for pesticides, because of stricter testing and monitoring under the law. However, even pesticides often have less than the ideal data available for assessment of risks to children. Scientists are trying to generate new knowledge that will help reduce uncertainties about risks to children – knowledge of chemical toxicity to the fetus and young organism, not just to adult animals, and exposure patterns unique to children.

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[112]For example, the Faroes study had to measure and statistically account for any effects of PCB levels, because the pilot whales in the Faroe Islands contain PCBs.

[113] People in the Faroe Islands consume 1-3 meals of cod a week but have episodic feasts of pilot whale. The fish have very low mercury concentrations, but pilot whale meat has relatively high concentration of methyl mercury. In contrast, people in the Seychelles eat large amounts of fish, 12 fish meals per week on the average, but the fish have relatively low methyl mercury concentrations

[114] Davidson et al., ibid.

[115]National Research Council, *Toxicological Effects Methylmercury.*

[116]Ibid., p. 273.

PCBs, methyl mercury and lead illustrate that in many cases those toxic effects may be disproportionately borne by the very young. In the case of lead, epidemiologic studies in many parts of the world have produced consistent results that have allowed for an estimation of risk to children. In the U.S., population monitoring has allowed us to track levels of lead exposure over time, so that we can determine with a good degree of confidence the impact of lead on our children. However, efforts are still underway to understand whether there is a threshold for the adverse effects on developing brains.

In the case of PCBs, there is very little information about the levels and trends of PCBs in our children. It would be expected that levels are declining, given the ban on PCB manufacturing in the early 1980s, and indeed limited evidence indicates that to be the case. However, a number of well-conducted, prospective studies suggest neurodevelopmental effects from low levels of PCB exposure, levels seen in the general population.

Methyl mercury is a known neurotoxicant and, based on observation of accidentally exposed human populations, a developmental toxicant that interferes with the normal migration of neurons necessary to brain organization and ultimate functioning. Epidemiological studies suggest that a small proportion of infants in the United States may be at risk for adverse effects as a consequence of prenatal methyl mercury exposure.

In the case of PCBs, methyl mercury, and lead, the full extent of potential hazards to children was not understood until there were longitudinal, prospective studies that assessed exposure to children *in utero* and in early childhood, and then very carefully measured their neurological development, using sensitive tests, over the first several years of life. In all three cases, the neurodevelopmental effects of concern today have to do with subtle changes in intellectual capability that persist at least into the school years. These three cases also demonstrate that newer functional tests of developmental neurotoxicity, along with consideration of body burden (internal dose), could improve our ability to utilize toxicity testing to predict such effects on children in the future.

## Discussion

**Discussants:**

John A. (Jack) Moore, D.V.M., Center for the Evaluation of Risks to Human Reproduction; former EPA Assistant Administrator for Prevention, Pesticides, and Toxic Substances

Deborah C. Rice, Ph.D., National Center for Environmental Assessment, EPA

Michael D. Shelby, Ph.D., Chief, Laboratory of Toxicology, National Institutes of Environmental Health Sciences (NIEHS)

J. Routt Reigart, M.D., Professor of Pediatrics and Director, General Pediatrics, Medical University of South Carolina; Chair, Children's Health Protection Advisory Committee

**Dr. Moore** began by noting a recent emphasis on giving priority attention to children as a subset of the population. This, he said, is a reflection of a societal priority. However, the statutes intended to protect children's health narrow the emphasis of that societal priority by focusing on single exposures like pesticides. Dr. Moore asserted that the societal concern is exposure to chemicals, not just particular subsets of chemicals. Therefore, the issue is children's exposure, and what impact chemicals could have. He believes that the failure to recognize this difference might lead people to ignore some of the better places to get insights. He cited prescription drugs as an example, because children often have continuously high exposures to them.

Dr. Moore then discussed the SIDS international chemical screening program. He noted that if this program has a weakness, it is in its ability to detect neurotoxicity. He did not intend this as a criticism, though, since there were limitations on what could be accomplished in a screening mode. A second point he wished to make is that the "functional observation battery" – a series of activities used to measure ability to perform various tasks – used to evaluate effects of exposures, may not pick up important adverse health outcomes. The battery is typically done on an adult or a young adult animal and its sensitivity may not be sufficient to detect an adverse effect. Dr. Moore noted that, while there is some information on neurotoxicity that has been derived from humans, scientists still struggle with extrapolations from experimental systems to humans and from high dose to low dose exposure.

Dr. Moore concluded his presentation by expressing concern that there is not enough communication between pediatric neurologists and laboratory researchers, and not enough willingness of one side to accept the other's point of view. He asserted that the public is not well served when it appears that the scientific community is at odds.

**Dr. Rice** started out by noting her experience running a developmental neurotoxicology laboratory. The lab used Macaque monkeys as research subjects, employed computers to test learning, memory, attention, and similar abilities under carefully controlled conditions. Macaques were used because of the similarity of their brains to humans'. While the Macaque brain is less convoluted and smaller, it still has a relatively large and well-developed neocortex, the locus of judgment and behavior regulation. She then discussed the rat brain, noting that while we all have the sense that human behavior is more complicated than rat behavior, that humans and rats are nonetheless very similar in a number of respects. Rats and humans are both highly adaptable species that learn very well and easily, can move into new environments, and can take advantage of new situations very well. Dr. Rice gave the example of lead exposure, which produces similar effects in humans and in animal models. She explained that lead exposure in children leads to IQ deficits, impaired school performance, distractability, short attention spans, and impulsive behavior. The affected child is not able to inhibit inappropriate responses. These effects can occur when lead levels are somewhere between one and ten micrograms per deciliter of blood. She has pointed out that, if you look at the effects on a dose basis, animals models are not terribly well predictive. However, if one looks at the effects on a blood-level basis, one can find the same effects at the same levels in animal models as in children: learning deficits, distractability, short attention spans, impulsivity, perseveration (a tendency to repeat behavior with no purpose), and increased activity. There are at present no regulations that require toxicity testing using

rodents to identify such potential effects on learning of chemical exposure. Dr. Rice argued that, at least for such behavioral endpoints, there is the methodology to do so. What are needed, she asserted, are the resources and the collective will to do it, so that we are not forever stuck in the position of doing all of these "experiments" in humans.

**Dr. Shelby** began by relating the wonder he felt when considering human development and growth from an egg the size of a period at the end of a sentence to a full grown adult in about 20 years. He observed that whatever protective measures are taken for the general population will have some positive effect on children, but said further research is needed to determine whether children might be at particular risk, because they are uniquely susceptible or uniquely exposed.

In contrast to Dr. Rice, he questioned whether animal models are adequate to evaluate neurodevelopmental outcomes in humans, because effects like decrements in IQ are so subtle and complex. Dr. Shelby asserted that astute physicians have to remain an integral part of children's environmental health, because they are the front line on detecting effects. He reminded the audience that they had to accept the fact that if we were successful in identifying hazards and preventing adverse exposures we would not get any credit, since it is difficult to recognize that nothing bad has happened.

The importance of separating what is known from what is not known, with regard to low-dose exposures and long-term effects, was underlined. While DES provides a clear example of how an exposure *in utero* can lead to cancer in adults, and the neurotoxic effects of a child's exposure to lead are well recognized, Dr. Shelby noted that it is more difficult to identify examples of childhood chemical exposures that affect later ability to have children (reproductive toxicity) or to resist infection (immunotoxicity).[117]

He concluded his presentation by recommending four areas for future research efforts. First, he recommended better birth registry surveillance systems, because we do not know enough about what occurs, where it occurs, and when it occurs.[118] Second, he noted that lack of information on children's exposures limits our ability to do risk assessments on children. The third recommendation is to improve animal tests and *in vitro* methodologies to aid in evaluating exposures.[119] And, fourth, Dr. Shelby recommended more public education, especially of older children, so that people would be aware of the problem and what could be done about it.

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[117]Some scientists have suggested that human sperm counts are dropping regionally or even globally, but this notion is highly controversial. Others have raised the possibility that chemical exposures are harming our immune systems and leading to a greater incidence of ear infections or other adverse health outcomes.

[118]Epidemiologists define "surveillance" as the systematic collection, summarization, and analysis of data on newly diagnosed cases of a disease of interest for the purpose of identifying high-risk groups in the population, understanding the origin of the disease, and reducing or eliminating its transmission.

[119]Laboratory tests involving isolated tissues in test tubes or glass dishes are referred to as *in vitro*, literally meaning "in glass". Similarly, the term *in vivo* – or "in life" – refers to laboratory experiments using live plants or animals.

**Dr. Reigart** noted a difference in the effects of lead and PCB exposures. The effects of *in utero* exposure to lead are undetectable in older children and adults, while exposure in the first few years of life has more persistent effects. In contrast, PCB *in utero* exposure produces persistent neurological deficits, while post-natal exposure (through breast milk) seems less potent. Addressing the question "Which pollutants pose risks to children?" he said that lead, methyl mercury, and PCBs are three environmental pollutants that we know something about. These have been studied at great cost, he noted. However, it would be unreasonable to assume that similar chemicals and metals that have not been studied have no effect, he argued. The challenge, he asserted, was to determine how to learn about other hazards to children without bankrupting the economy, because of the many millions of dollars that such studies cost. While tools like structure-activity relationship studies exist, they are crude and better tools are needed.

**General Discussion**

**Dr. Rice** followed up on Dr. Reigart's statement concerning prenatal versus postnatal exposure to lead and PCBs. She offered a potential explanation for why the *in utero* effects of lead seem to be less influential on IQ as children age, speculating that lead levels in 2-3 year olds appear more influential, because that just happens to be when lead levels usually peak in children. This would make the observation an artifact of a more general signal-to-noise problem. Dr. Rice pointed out that studies in monkeys have shown that permanent effects can result from dosing that starts after that period. She also put a cautionary note on the suggestion that *in utero* exposure to PCBs was more potent than postnatal exposure, mentioning Dutch studies of infants and animal studies where postnatal exposure resulted in potent neurological or behavioral effects.

**Dr. Schierow** asked the attendees to address the general question of whether it is reasonable to assume that chemical exposures pose an increased risk to children, or whether it is equally reasonable to assume that there is a decreased risk. She cited differences in children's and adults' exposures as an example.

**Dr. Wilson** concurred that this was the right question to be asking, and said that what was needed was to identify the agents that were particularly toxic, because standard regulatory measures would not provide protection from them. Studying these agents also yields general information about their properties, which allows researchers to make predictions about the effects of other exposures.

**Dr. Goldman** said there were three things worth thinking about. One was that there are clues in epidemiologic studies that have not been followed through on, and that need to be. A second was that not enough is known about what is actually in children' bodies. Identifying what was actually being transmitted to them prenatally and in their first few years of life would yield a list of candidates for concern. A third was that we've not made very good use of the information we already have. She asserted that product registration information FDA and EPA already have could be exploited, using tools like quantitative

structure-activity relationships in order to do a better job with predictive toxicology.[120]

**Dr. Goldman** agreed with Mr. Redhead that this was an issue of how to get the biggest scientific bang per dollar of expenditure on research. She explained that FDA and EPA scientists tend to do their work on a product by product or chemical by chemical basis, trying to efficiently drive toward a regulatory decision, rather than trying to learn more fundamental principles that might make that whole process more efficient in the future. The latter approach is not rewarded in regulatory agencies, because it does not, at least in the short term, move decision-making forward more quickly.

**Mr. Redhead,** of CRS, asked about dioxin, as an example of a chemical on which an enormous amount of resources are being spent. He wondered what general scientific information might be gleaned from its study, beyond learning about dioxin itself.[121]

**Dr. Goldman** answered that she thought that a lot of general scientific information had flowed from the dioxin reassessment. She elaborated on her earlier comment, noting that FDA and EPA approvals require the generation of a lot of scientific information. This information is being used to address whether a particular agent will be approved and how it will be labeled. However, it could also be used to add to the body of knowledge about developmental toxicity.

**Dr. Mattison** followed up with two considerations that he identified as important for *in utero* and post-natal exposures. The first was that the fetus or child is different from the adult, because, during the course of development, there are activities that have to take place for the normal adult to be formed. If those activities are impeded, there is a range of consequences. The second relates to the concept of biologic reserve. While the term "reserve" may imply that replenishment is possible, there are circumstances in biological systems where it may be irreplaceable. He gave as an example the work of David Barker, which demonstrates that there are *in utero* exposures that influence the onset and the risk for diseases in the adult.[122] These considerations indicate that careful attention must be paid to the developmental process, including nutrition.

**Dr. Mattison** also disagreed with Dr. Reigart's comment regarding structure-activity relationships, asserting that there is a lot that could be learned from studying them. He

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[120]Both the EPA and the FDA, as a condition of production and/or marketing, require some chemical manufacturers to conduct animal and other laboratory studies to determine the toxicity of their products and chemical properties, and to report the results. In addition, companies are required to report to the federal government any complaints or other evidence they might receive with regard to adverse health effects suffered by consumers following exposure to a product.

Structure-activity-relationship (SAR) models try to explain toxicity based on the composition, shape, and reactivity of chemical molecules.

[121]The on-going EPA reassessment of dioxin risk was begun in 1991 and has cost millions of dollars. It is assessing risk from exposure to all significant forms of dioxin and some PCBs.

[122]Barker, D.J., P.D. Gluckman, and J.S. Robinson. 1995. Conference report: Fetal origins of adult disease – Report of the First International Study Group, Sydney, 29-30 October 1994. *Placenta*, v. 16, n. 3, p. 317-320.

indicated that this went to the heart of Dr. Goldman's comments that there are strategies for taking a critical look at the data that we have, and using those data to identify our areas of ignorance about chemical structures, and the impact of those structures on developmental processes.

**Dr. Portier** (a discussant for topic 4) suggested answering the question of whether it is reasonable to assume that certain chemicals pose an increased risk to exposed children as compared to adults in two ways. First he argued, because metabolism is much faster in children than adults, and ten years of a child's life is not ten years in an adult's life, knowing how a toxic substance is metabolized in the adult can help predict whether toxicity in the child is apt to be greater or less. Thus, identifying and understanding the mechanism underlying an effect is vital. The second point is that new experimental protocols are needed to evaluate chemicals for the adverse health outcomes that are unique to children.

**Dr. Kimmel** contended that where we have data on the same kinds of exposures and outcomes in animals and humans, the effects are fairly comparable, and the animal data are predictive. The problem, in her estimation, is that this sort of information is not always available, and in some cases, effects are species-specific. Neurological effects of pesticide exposures often are unique to animals that are still developing and not seen when only adult animals are used. She echoed Dr. Rice's comment that it will take the collective will of the scientific community to decide that developmental neurotoxicity studies are a priority before something will get done.

**Dr. Bailar** agreed that while we do know a great deal about some chemicals, our ignorance is still profound.

**Ms. Florini** asserted that a complementary question to the one posed by CRS for this session was: For what percentage of chemicals do we have information adequate to assess their impact on children? She called attention to Dr. Mattison's point about reserve capacity, noting that as life expectancy increases, so does the need for reserve capacity.

**Dr. Reigart** expressed the view that, more often than not, chemical exposures that have effects later in life are also developmental toxicants. This was particularly true for neurotoxic chemicals.

However, **Dr. Guzelian** countered that if this were true, then drugs would never be given to pregnant women. He said that if scientists want to make comparisons on the basis of dose or intrinsic toxicity, then the most abundant database resides in the pharmaceutical industry. This includes not only information on human testing or human experience from the development of pharmaceuticals that come to market, but also those that may be abandoned because of various problems.

**Dr. Jerome Paulson** , of George Washington University, noted that while the Food and Drug Administration (FDA) databases may be good sources of information to exploit, the agency only recently set up a special program to do research on drugs for children,

because so many drugs have in fact never been tested on children. There thus may be data on adults but not on children.

**Dr. Reigart** agreed, stating that until very recently approximately 90 percent of all pharmaceuticals used in pediatrics were off label, and that virtually all of those are also labeled to indicate usage in pregnancy is limited or should be done with great caution. However, **Dr. Goldman** added that many FDA products files may contain data about young animals even though label approval for children was not sought.

Donald Mattison, M.D., M.Sc., is the Medical Director of the March of Dimes. In the third scientific paper, he summarized the state of knowledge about birth defects and other adverse effects on growth and development to illustrate his answer to the question "Do environmental exposures to pollutants increase the rates of adverse health outcomes?" Birth defects are the leading cause of death among infants and the second leading cause of death among children generally (after motor vehicle accidents). About 150,000 babies are born each year with birth defects (at a rate of 35,714 per million births, about 1 in 28). Yet, the causes of many birth defects are poorly understood, according to Dr. Mattison. He described major difficulties encountered by scientists studying birth defects and discussed the strengths and weaknesses of various kinds of data. He also drew attention to the new *National Report on Human Exposure to Environmental Chemicals*, a new publication by the Centers for Disease Control and Prevention that "will provide an ongoing assessment of the U.S. population's exposure to environmental chemicals using biomonitoring."[123] The first edition of the report was issued in March 2001.

In general, scientists who participated in the CRS seminar agreed that –

- Exposure to certain chemicals at toxic levels during development may cause death, structural abnormality, altered growth, or functional deficits. Some effects may take years to be evident, while others may be immediate, short-lived, and reversible. Increased probability of premature birth also might be an effect of toxic exposure.
- For most chemicals, it is not known whether adverse health effects might result from prenatal, infant, or childhood exposure to low levels in the environment.
- The causes of most significant health problems in infants and children (for example, some birth defects and asthma) are only partially understood.
- The overall infant mortality rate and the rate of infant deaths due to birth defects have fallen significantly in recent years. Nevertheless, the United States has a higher rate of infant mortality than 25 other nations.
- Birth defects are the leading cause of infant mortality in the United States. Birth defects most commonly affect the cardiovascular system, respiratory system, chromosomes, and nervous system, in that order.
- Premature birth is the second most common cause of infant mortality, and the number of pre-term births has increased slightly in recent years.
- Estimates of the percentage of all birth defects that may be caused, at least in part, by environmental factors (including smoking and alcohol use) vary widely from about 3% to as much as 75%. More recent estimates are on the higher end of this range. Individual susceptibility to environmental pollutants may often be determined genetically.

[123]See the website of the National Center for Environmental Health, Centers for Disease Control and Prevention.
[http://www.cdd.gov/nceh/dls/report/default.htm]

- All known human developmental toxicants cause developmental disease in at least one species of experimental animals. Animal tests for effects on development often are accurate predictors of human developmental toxicity.
- There is no indication that background ambient levels of teratogens in the air, water, or soil have caused human birth defects in the United States.
- There is limited evidence that birth defects have increased in the vicinity of some contaminated industrial sites.
- Asthma rates in the general population have been rising in the United States for 30 years, but scientists do not know why.
- It is not clear whether the observed increase between 1973 and 1994 in rates of some types of childhood brain tumors indicates a real increase in cases or improved medical technologies.
- Generally, it is not clear whether cancer rates in children are rising.

# What Health Effects Are Associated With Environmental Risks? A Case Study of Birth Defects

By Donald R. Mattison[124,125]

## Introduction

Over the past century the United States has made remarkable progress in some areas of maternal and infant health. Infant mortality has fallen significantly (Figure 2) due predominantly to our ability to diagnose and treat infectious diseases, improved pediatric nutrition, sanitation and food safety, and more recently improvements in care for premature infants.[126] However, the United States has the worst rate of infant mortality among the G-7 industrialized nations, and ranks 26th internationally (Table 7).

As a consequence of the decrease in overall infant mortality, the leading cause of infant death in the United States and many developed countries today is birth defects, which accounts for 22% of all infant deaths (Figure 3). Prematurity and its consequences, including low birth weight (LBW) and respiratory distress syndrome (RDS), are the second leading cause of infant mortality overall. Among African-Americans, prematurity is the primary cause of infant mortality, accounting in part for the substantially higher infant mortality rates in that community.[127]

The increasing relative impact of birth defects on infant mortality is drawing increased attention to this public health problem. Unfortunately, the causes of many birth defects are poorly understood.[128] When the cause of a particular birth defect is unknown, the

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[124]March of Dimes Birth Defects Foundation, Office of the Medical Director, 1275 Mamaroneck Ave, White Plains NY 10605.

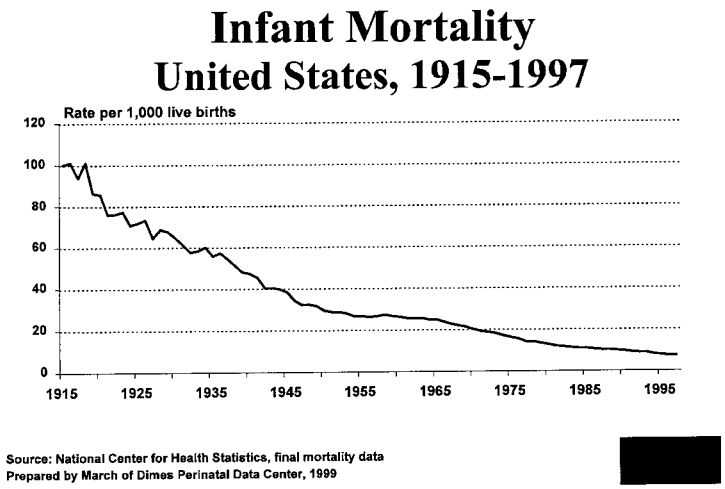
[125]I would like to thank Joann Petrini and Caroline Alter in the Perinatal Data Center for their help in analysis of data from the National Center for Health Statistics. In addition, I would like to express my appreciation to Constance A. Malpas, Program in the History of Science, History Department, Princeton University and Historical Collections, New York Academy of Medicine, for assistance in the development of this review and especially for critical discussion in formulating approaches for considering the regulation of developmental hazards. These discussions have helped sharpen the arguments presented and alerted me to potential errors in logic.

[126]McCormick, M.C. and J.E. Siegel. (1999). *Prenatal Care: Effectiveness and Implementation.* New York, NY: Cambridge University Press. 349 p.

[127]U.S. Department of Health and Human Services. (2000) *Healthy People 2010.* Washington, DC: U.S. Govt. Print. Off.
Goldenberg, R.L., J.C. Hauth, and W.W. Andrews. (2000). "Intrauterine infection and preterm delivery." *New England Journal of Medicine*, v. 342, n. 20, p. 1500-1507.

[128]Pew Environmental Health Commission. *(1999) Healthy from the Start" Why America Needs a Better System to Track and Understand Birth Defects and the Environment. 10 p.*
Schardein, James L. (2000). *Chemically Induced Birth Defects.* 3rd Edition. New York: Marcel Dekker. 1109 p.

**Figure 2. U.S. infant mortality, 1915 to 1997**




possibility that environmental or occupational exposures may play a substantial role often is suspected by health scientists.[129]

This paper reviews what is known about: 1) causes of birth defects and other adverse developmental outcomes (including death and abnormalities of function or growth); 2) levels of environmental exposure to potential developmental hazards; 3) ways to determine whether an environmental exposure to a chemical, physical or a biological agent may be capable of producing embryo or fetal death, structural malformations, functional abnormalities, or alterations in growth; and 4) the level of certainty (or uncertainty) with regard to various data and risk assessments.[130]

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[129]Akhurst, R.J., R.J. Kavlock, and G.P. Daston. (1997). *Drug Toxicity in Embryonic Development: Advances in Understanding Mechanisms of Birth Defects.* Berlin; New York: Springer.

Daston, G.P. (1997). *Molecular and Cellular Methods in Developmental Toxicology.* Boca Raton: CRC Press. 284 p.

Neumann, D.A., and C.A. Kimmel, (1998). *Human Variability in Response to Chemical Exposures: Measures, Modeling, and Risk Assessment.* Washington, DC: ILSI Press. 257 p.

Kimmel, C.A., and J. Buelke-Sam. (1994) *Developmental Toxicology.* New York: Raven Press. 479 p.

Olshan, A.F. and D.R. Mattison (1994). *Male-Mediated Developmental Toxicity.* New York: Plenum Press. 406 p.

Lie, R.T., A.J. Wilcox, and R. Skjaerven. (1994). "A population-based study of the risk of recurrence of birth defects [see comments]." *New England Journal of Medicine*, v. 331, n. 1, p. 1-4.

[130]National Research Council, Committee on Risk Assessment of Hazardous Air Pollutants. (1994).

(continued...)

**Table 7. Comparison of infant mortality rates (death/1,000 live births) and international rankings for 1996 for selected countries**

| Country | Infant Mortality Rate | International Ranking |
|---|---|---|
| Australia | 5.8 | 16 |
| Belgium | 5.6 | 13 |
| Canada | 6.1 | 20 |
| Denmark | 5.7 | 14 |
| England and Wales | 6.1 | 20 |
| France | 4.9 | 9 |
| Germany | 5.0 | 10 |
| Japan | 3.8 | 1 |
| Sweden | 4.0 | 3 |
| United States | 7.3 | 26 |

Data from Health, United States 2000, National Center for Health Statistics 1997 and 1999.

## Background on Birth Defects

Developmental diseases may be described in terms of origins or outcomes.

**Origins of birth defects.** Some birth defects occur because an embryo or fetus is destined to develop abnormally from the time of fertilization. These are called malformations. The risk of developing a malformation sometimes can be reduced. For example, folic acid supplements taken prior to fertilization (conception) can decrease the risk of neural tube defects in infants, a serious and common malformation, up to 70%.[131]

Other developmental diseases occur because fetal growth is physically restricted (deformation). An infant with a deformation would have been normal if the physical restriction of growth had not occurred during intrauterine development. One example of a deformation is Potters Syndrome, a deformation produced by inadequate formation of amniotic fluid, resulting in abnormal skeletal and lung development.

An infant who might have been normal at birth but instead is born with a developmental disease because of exposure to a chemical, physical, or a biological agent has a preventible developmental disease called a disruption. Examples of disruptions include

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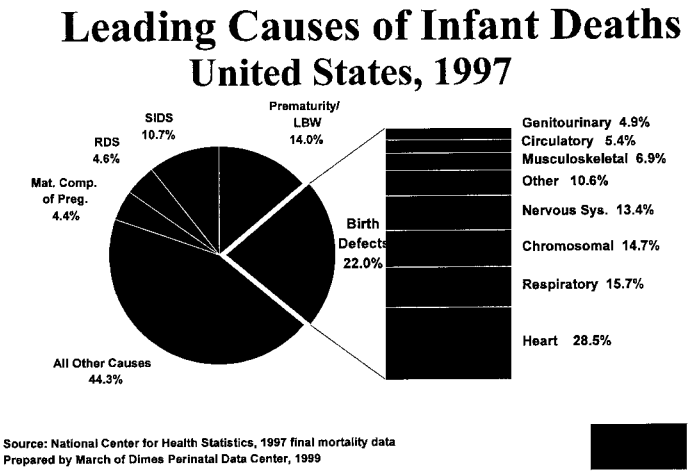
[130](...continued)
*Science and Judgment in Risk Assessment.* Washington, DC: National Academy Press.

[131]Berry, R.J., Z. Li, and J.D. Erickson et al. (1999) "Prevention of neural-tube defects with folic acid in China," China-U.S. Collaborative Project for Neural Tube Defect Prevention [corrected; erratum to be published]. *New England Journal of Medicine*, v. 341, n. 20, p. 1485-1490. #66? Botto, L.D. C.A. Moore, and M.J. Khoury, et al. (1999) *New England Journal of Medicine,* v. 341, n. 20, p. 1509-1519.

**Figure 3. Leading causes of infant mortality in the United States during 1997.**




congenital rubella syndrome, neurodevelopmental abnormalities produced by exposure to lead, and those produced by exposures to ionizing radiation.[132]

Estimates of the percentage of birth defects that might be related to environmental risks have evolved over time as scientists' understanding of developmental processes and causes of disease have progressed (Table 8). However, all estimates are problematic, when one considers that many birth defects may have more than one cause.

Earliest estimates by Wilson et al. (1965), Wilson and Fraser (1977), and Brent and Beckman (1986) suggested that about 10% of birth defects were due to teratogens and 65% were of unknown origin.[133] These estimates were widely cited in most publications about

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[132]Barker, D.J., P.D. Gluckman, and J.S. Robinson. 1995. Conference report: Fetal origins of adult disease – Report of the First International Study Group, Sydney, 29-30 October 1994. *Placenta*, v. 16, n. 3, p. 317-320.
Schardein, ibid.

[133]Wilson, J.G. (1965) Embryologic considerations in teratology. *Annual New York Academy of Sciences*, v. 123, p. 219-227.
Wilson, J.G. and F. C. Fraser. (1977) *Handbook of Teratology: General principles and etiology.* New York: Plenum Press. 476 p.
Brent, R.L. and D.A. Beckman. (1986). "Teratology." *Clinics in Perinatology,* v. 13, n. 3, p.491-
(continued...)

the origin of developmental abnormalities, until a 1989 study by Nelson and Holmes estimated that about 3% of birth defects are due to teratogens, 37% due to gene-environment interactions, and 43% of unknown origin.[134] Each of these estimates was consistent with the scientific understanding at the time, which suggested that single factors were important causal agents (e.g., infectious agents, physical factors, chemicals, or maternal conditions responsible for most birth defects).

Our current scientific understanding has evolved. Thus, while earlier estimates of etiology or causation of developmental abnormalities represented by those from Wilson emphasized the small number of birth defects caused by known teratogens (less than 10%), more recent estimates have included an increasing percentage of birth defects produced by gene-environment interactions. Gene-environment interactions mean that the individual carries genetic factors which modify the susceptibility of the fetus to the disruptive effect of an environmental agent that produces the birth defect or developmental abnormality observed. This leads to a model for developmental disease like that illustrated in Figure 4, in which the risk for a developmental disease is a consequence of an interaction between environmental, social, and biological factors. Recently, Shaw, using data from the California Birth Defects Monitoring system, estimated that most birth defects (up to 75%) are due to gene-environment interactions.[135] In contrast, estimates of structural malformations of unknown origin have decreased from 65% to 43% to 25%, suggesting an increase in knowledge. However, there remains much uncertainty about the diseases thought to be caused through gene-environment interaction.

**Table 8. Estimates of the environmental impact on birth defects.**

| Reference | Genetic or chromosomal | Teratogen | Gene-Environment | Unknown | Comment |
|---|---|---|---|---|---|
| Wilson, 1965; Wilson and Fraser, 1977; Brent and Beckman, 1986 | 25% | 10% | Not estimated | 65% | These estimates were based on hospital data and inadequate population data. |
| Nelson and Holmes, 1989 | 17% | 3% | 37% | 43% | Hospital based survey |
| Shaw, 2001 | Not estimated | Not estimated | 75% | 25% | Estimate based on research birth defects program |

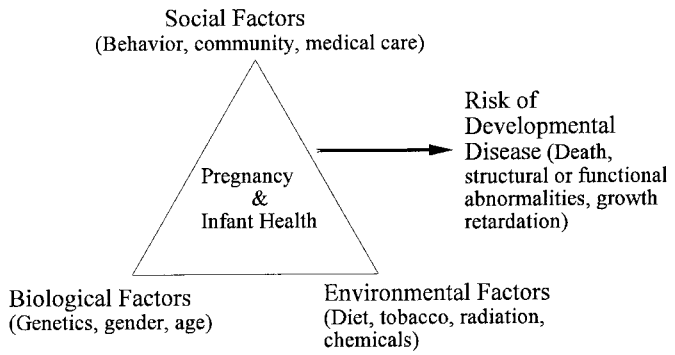
Why do scientists think environmental factors play any role in birth defects? Studies by experienced investigators have demonstrated that animals treated with chemicals found in the environment, and for which there is human exposure, produce birth defects in the animals, and human epidemiological studies have also demonstrated an association between

[133](...continued)
693. Philadelphia: Saunders.

[134]Nelson, K. and L.B. Holmes. (1989). "Malformations due to presumed spontaneous mutations in newborn infants." *New England Journal of Medicine*, v. 320, n. 1, p. 19-23.

[135]Shaw, Gary M., 2001, personal communication, California Birth Defects Monitoring Program.

**Figure 4. Interactions between social, biological, and environmental factors and the expression of developmental abnormalities.**




Source: Modified from the The Pew Environmental Health Commission (1999).

such exposures and developmental disease.[136] Additionally, epidemiologists have attempted to explore the relationship between the environment and birth defects with results that suggest that the environment appears to play a significant but poorly defined role, in part due to inadequate investment in epidemiological research.[137] The material summarized in Table 9 suggests increasing complexity in our understanding of the causes of birth defects.

**Outcomes.** At least four health outcomes result from birth defects: death, structural abnormalities, functional abnormalities, and alteration of growth.[138] A fifth outcome, premature birth, also is discussed briefly, although it is not usually categorized as a birth defect. Each outcome is illustrated below.

***Death.*** One class of drugs used to treat hypertension acts by inhibiting the angiotensin converting enzyme (ACE inhibitors). When experimental animals are treated with ACE inhibitors, fetal death rates increase. Similar observations have been made in women treated with ACE inhibitors during pregnancy. It is thought that fetal death results from a substantial reduction in renal blood flow produced by these drugs. Because of the

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[136]Shepard, Thomas. (2001) *Catalog of Teratogenic Agents.* 10th edition. Baltimore, MD: Johns Hopkins University Press.
Schardein, ibid.

[137]The Pew Environmental Health Commission, ibid.
Lie et al., ibid.
Schardein, ibid.

[138]U.S. EPA. "Guidelines for developmental toxicity risk assessment," 56 *Federal Register* 63798-63826, Dec. 5, 1991.
http://www.epa.gov/nceawww1/raf/pdfs/devtox.pdf

impact on fetal renal blood flow, despite the potential benefit for management of hypertension in some pregnant women, it is recommended that ACE inhibitors not be used during the second and third trimesters of pregnancy.[139]

***Structural malformation.*** It has been estimated that there are approximately 75 chemicals and drugs which are known to produce human structural malformations.[140] One well known chemical that is associated with structural malformations of both male and female reproductive systems is diethylstilbestrol (DES).[141] DES was used to treat women early in pregnancy because it was thought that it would prevent miscarriage and other pregnancy complications. Unfortunately, not only was DES unable to prevent pregnancy complications, it produced malformations of the male and female reproductive systems, and increased the risk for vaginal cancer. Some investigators believe that the structural malformations were unlikely to have been identified if a randomized clinical trial had not been conducted to determine the therapeutic effectiveness of DES.

***Functional abnormality.*** Over the past three decades there has been increased recognition that in addition to structural malformations produced by agents which are developmental hazards, functional abnormalities may also be produced.[142] Areas of oncern include: intelligence, behavior, or performance of various tissues, organs and systems. Prevention of functional abnormalities will require understanding of exposures known to modify the functional parameter which is being studied. One clear example is lead, which has been demonstrated to lower intelligence and produce behavioral abnormalities.[143]

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[139]Koren, Gideon. (2001). *Maternal-fetal Toxicology: A Clinician's Guide*. New York: Marcel Dekker.

[140]Schardein, ibid.

[141]Herbst, A.L. (1981). "Diethylstilbestrol and other sex hormones during pregnancy." *Obstetrics and Gynecology*, v. 58, n. 5 Suppl., p. 35S-40S.

Herbst, A.L. (1987). "The effects in the human of diethylstilbestrol (DES) use during pregnancy." *Princess Takamatsu Symp* v. 18, p. 67-75.

Wilcox, A.J. (1995) Age at menarche among diethylstilbestrol granddaughters. *American Journal of Obstetrics and Gynecology*, v. 173, n. 3, Pt 1, p. 835-836.

Hornsby, P.P., A.J. Wilcox, et al. (1995). "Onset of menopause in women exposed to diethylstilbestrol in utero." *American Journal of Obstetrics and Gynecology*, v. 172, n. 1, p. 92-95.

Hornsby, P.P., A.J. Wilcox, et al. (1994). "Effects on the menstrual cycle of in utero exposure to diethylstilbestrol." *American Journal of Obstetrics and Gynecology*, v. 170, n. 3, p. 709-715.

[142]Kavlock, R.J., C.T. Grabowski, et al. (1983). *Abnormal Functional Development of the Heart, Lungs, and Kidneys: Approaches to Functional Teratology: Proceedings of a Conference Held in Asheville, North Carolina, May 11-13, 1983.* New York, N.Y.: A.R. Liss.

Riley, E.P. and C.V. Vorhees (1986). *Handbook of Behavioral Teratology*. New York: Plenum Press.

[143]Bellinger, D., and H.L. Needleman. (1994) The Neurotoxicity of Prenatal exposure to lead: Kinetics, mechanisms, and expressions. In: Bellinger, D., and H.L. Needleman (eds.) *Prenatal Exposure to Toxicants: Developmental Consequences*, p. 89-111. Baltimore: Johns Hopkins University Press.

**Working Definitions**[144]

**Birth Defect.** A physical/structural, functional, or metabolic abnormality in an embryo and fetus that results in physical or mental disability, or is fatal; it may be manifested at any time, from just before or after birth through sexual maturation

**Deformation.** A structural and functional developmental abnormality (birth defect), resulting from physical forces acting on the fetus.

**Development.** The process of growth and maturation from an immature to a more mature stage.

**Developmental Disease.** Any alteration in an embryo, fetus, or child up to the time of sexual maturation that adversely affects growth, lifespan, structure, or function.

**Developmental Hazard.** A chemical, biological, or physical agent that produces developmental disease, when exposure occurs to a parent prior to conception, a mother following conception, or the infant or child.

**Disruption.** A birth defect caused by an exposure to a developmental hazard.

**Environment.** Most broadly, includes the social, chemical, physical, economic, infectious, and cultural exposures experienced by an individual.

**Functional Abnormality.** An alteration in the function (e.g., behavior, intelligence, kidney, or lung function) of an individual which occurs as a consequence of exposure to a developmental hazard.

**Gene.** A specific portion of an inherited pattern of chemicals repeated in every cell of an animal or plant, which is transmitted from parent to offspring, and which may determine development, structure, or function of the organism.

**Gene-Environment Interaction.** Interactions between chemical, physical, social, biological and other influences within an organism so as to modify gene expression.

**Infant Mortality.** Death within the first year of life.

**Low Birth Weight (LBW).** Birth weight less than 2500 grams.

**Malformation.** A birth defect resulting from intrinsically abnormal developmental processes, for example, due to a genetic abnormality (e.g., Down syndrome).

**Prematurity.** Birth before 37 completed weeks of gestation.

**Reproductive Disease.** Impairment of male or female reproductive structure or function produced by exposure to a chemical, physical, or a biological agent and leading to decreased fertility, completely preventing conception or survival of the fertilized egg, or preventing implantation.[145]

**Reproductive Toxicology.** The study of the impact of chemical, physical or biological agents on the reproductive processes, including; formation, release and interactions of the gametes, the sperm and egg. Reproductive processes are generally considered to end when fertilization takes place.

**Teratogen.** A chemical, physical or biological agent capable of producing a disruption in an embryo or fetus (see also developmental hazard).

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[144]Schardein, ibid.
Wilson and Fraser, ibid.
Kimmel and Buelke-Sam, ibid.

[145]Korach, K.S. (1998). *Reproductive and Developmental Toxicology*. New York: Marcel Dekker. 722 p.
Thomas, J.A., K.S. Korach, and J.A. McLachlan. (1985). *Endocrine Toxicology*. New York: Raven Press. 404 p.

***Growth.*** Growth, including birth weight and rate of weight gain after birth, appears to be a sensitive indicator of various insults during pregnancy and early postnatal development. While measures of growth are thought to be sensitive, they are not specific to chemical exposures, because many different factors can influence growth both before and after birth. Prenatal exposure to tobacco smoke and alcohol are known to decrease fetal growth and increase the incidence of low birth weight.

***Prematurity.*** While premature birth is not traditionally included in the spectrum of adverse outcomes considered as developmental toxicology, there is growing evidence that it should be included. Premature birth is the second leading cause of death during the first year of life, and there is growing evidence that environmental exposures may play a role in premature delivery. For example, it is known that smoking is associated with premature birth, some agricultural chemicals have been suggested to decrease the length of gestation, and recently it was suggested that there are potential interactions between minor variations in the structure of genes (polymorphisms) and length of gestation.[146] Recent data from Wang and her coworkers suggest length of gestation is decreased due to interactions between polymorphisms in genes involved in metabolism (cytochrome P-450 and glutathione s-transferase) and benzene exposures that are below the permissible exposure limit set by the Occupational Safety and Health Administration.[147] In addition, there is mounting evidence that air pollution also may play a role in prematurity.[148]

It is not necessary that all of these endpoints of developmental toxicity be present or produced by an agent that causes developmental disease; the presence of one endpoint in humans, identified in an epidemiological study or observed in an animal experiment, is sufficient to identify the agent as a developmental hazard.

**Exposure.** To what agents (drugs, chemicals, biologicals, physical agents) are people exposed, at home or work, outside, or while pursuing hobbies? What are the levels and duration of exposures? What do we know about developmental toxicity produced from agents that may be released into the environment, or to which humans may be exposed? Unfortunately, until recently we had little or no data on the amounts of any industrial chemicals in our bodies. However, an innovative and important program to track the concentrations of chemicals in the U.S. population has just been initiated by the Center for

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[146]Chen, D., S.I. Cho, C. Chen, et al. (2000). "Exposure to benzene, occupational stress, and reduced birth weight [In Process Citation]." *Occupational and Environmental Medicine*, v. 57, v., 10, p. 661-667.

Loch-Caruso, R. (1999). "A mechanistic-based approach for assessing chemical hazards to parturition." *Journal of Womens Health,* v. 8, n. 2, p. 235-248.

Wang, X., D. Chen, T. Niu, Z. Wang, L. Wang, L. Ryan, T. Smith, D.C. Christiani, B. Zuckerman, and X. Xu. (2000). "Genetic susceptibility to benzene and shortened gestation: evidence of gene-environment interaction," *American Journal of Epidemiology*, v. 152, n. 8, p. 693-700.

Wen, S.W., R.L. Goldenberg, G. R. Cutter, et al. (1990). "Smoking, maternal age, fetal growth, and gestational age at delivery." *American Journal of Obstetrics and Gynecology,* v. 162, n. 1, p. 53-58.

[147]Wang, X. et al., ibid.

[148]Bobak, M. (2000) Outdoor air pollution, low birth weight, and prematurity. *Environmental Health Perspectives*, v. 108, n. 2, p. 173-176.

Environmental Health at CDC.[149] It may begin to help us understand the impact of environmental chemicals on birth defects.

Because birth defect surveillance systems are incomplete in most communities, it is difficult to get well-defined estimates of the actual number of pregnancies affected.[150] Inadequacies in birth defects tracking systems also impair our ability to define human developmental hazards. For example, if there are differences in exposure to an industrial, agricultural, or household chemical in various regions of the United States, comparing differences in birth defect rates with differences in body exposure levels may help describe the causal relationship (if any). This task has been complicated by the recognition that many birth defects may be a consequence of complex interactions (e.g., gene-environment interactions) rather than a single agent. However, over the past six decades it has been possible to identify some single agent exposures that produce birth defects and developmental disease in humans. Examples are described below.

## Selected Agents and Their Human Developmental Consequences

Clinical and epidemiologic studies of humans exposed to chemicals, physical agents, drugs, or infectious agents, that found evidence of developmental toxicity, provide some insight into human vulnerability to developmental toxicants.[151]

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[149]National Center for Environmental Health, Centers for Disease Control and Prevention. (2001) *National Report on Human Exposure to Environmental chemicals.* http://www.cdc.gov/nceh/dls/report/default.htm

[150]The Birth Defects Prevention Act of 1998 (Public Law 105-168) authorized CDC to collect, analyze, and make available data on birth defects. The Children's Health Act of 2000, enacted October 17, 2000, established a National Center on Birth Defects and Developmental Disabilities (NCBDDD) at the Centers for Disease Control and Prevention on April 12, 2001. CDC provides funding to address problems that hinder birth defect surveillance programs. It has supported establishment of birth defects registries in four states (Maine, Montana, Nevada, and New Hampshire); existing new programs (Florida, Kentucky, Missouri, New Mexico, North Carolina, South Carolina, and Utah); and established surveillance programs (Arkansas, Colorado, Hawaii, Iowa, Michigan, New York, and Oklahoma).

[151]Cunningham, F.G., and J.W. Williams (2001). *Williams Obstetrics.* 21st edition. New York: McGraw-Hill. 1668 p.

Reece, E.A. and J.C. Hobbins (1999). *Medicine of the Fetus and Mother.* Philadelphia: Lippincott-Raven Publishers.

Murray, C. J. L. and A. D. Lopez (1998). *Health Dimensions of Sex and Reproduction: the Global Burden of Sexually Transmitted Diseases, Hiv, Maternal Conditions, Perinatal Disorders, and Congenital Anomalies.* Cambridge, Ma., Harvard School of Public Health.

Murray, C. J. L., A. D. Lopez, et al. (1996). *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020.* Cambridge, MA: Harvard University Press.

Murray, C. J. L., A. D. Lopez, et al. (1996). *Global Health Statistics: A Compendium of Incidence, Prevalence, and Mortality Estimates for over 200 Conditions.* Cambridge, MA: Harvard University Press.

Gabbe, S.G., J.R. Niebyl, et al. (2001). *Obstetrics: Normal & Problem Pregnancies.* New York, Churchill Livingstone.

**Infectious agents that produce developmental defects.** Table 9 summarizes data on four selected infectious agents known to produce human developmental disease.[152]

**Table 9. Infectious agents that are known to produce human developmental disease[153]**

| Infectious Developmental Hazard | Developmental Defect(s) Observed Following Maternal and Fetal Infection | Estimated Risk |
|---|---|---|
| Cytomegalovirus | Deafness<br>Brain damage<br>Eye disorder | Up to 8% of fetuses develop the indicated developmental defects from an infected pregnancy |
| Rubella | Eye and heart defects<br>Deafness<br>Brain damage | Up to 90% of fetuses develop a develop-mental abnormality after confirmed infection of mother in first 10 weeks of pregnancy |
| Toxoplasmosis | Brain damage<br>Eye disorder<br>Deafness | 30-40% of fetuses will be infected and develop developmental disease or abnormalities after maternal seroconversion in pregnancy without treatment |
| Varicella-zoster | Brain damage<br>Eye disorder<br>Cutaneous scara | Up to 2% become infected and develop defects after varicella infection of mother |

Source: Modified from global burden of disease – reproduction volume.

***Cytomegalovirus.*** Up to 2% of newborns are infected *in utero* with Cytomegalovirus (CMV). Of those infected, as many as 10% are symptomatic at birth.

[152]American Academy of Pediatrics, Committee on Infectious Diseases. (1994). *Red Book: Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics.

[153]In all instances the mother is infected and then transmits the infection to the fetus. Prevention strategies focus on decreasing the number of women who are susceptible or exposed during pregnancy. Note that while these infectious agents are known to produce developmental disease, not all fetuses in which the mother is infected will develop developmental disease. It is not known if those that do are more susceptible to infection, are exposed to a larger number of infectious agents or more susceptible to damage once infected. It is interesting to note that many of the defects observed in this selected group of infectious agents are functional - altering sensory organs or the central nervous system.

Characteristic effects include growth retardation and central nervous and cardiovascular system damage. Additional long-term consequences include hearing and neuro-developmental impairment. As there is currently no treatment for an infected fetus, prevention focuses on minimizing maternal CMV exposure when possible.[154]

***Rubella.*** Prior to the development of the rubella vaccine in the mid-1960's, rubella epidemics occurred every 6 to 9 years resulting in fetal death and congenital rubella syndrome in thousands of pregnancies. Infection in the first trimester is associated with spontaneous abortion. Fetal infections later in pregnancy are associated with organ damage resulting in hearing loss, cardiovascular impairment, mental retardation, and eye abnormalities. Vaccination of all children and women of childbearing age prevents infection and consequently congenital rubella syndrome.

***Toxoplasmosis.*** *Toxoplasma gondii*, a protozoan parasite, can infect the fetus, with the risk of congenital toxoplasmosis increasing as pregnancy progresses. Exposure occurs most frequently via cat feces and infected undercooked meat. Fetal infection is associated with spontaneous abortion, premature delivery, growth retardation, and central nervous system damage. Current treatments are not completely effective, prevention of exposure with hygienic measures appears to the best approach.

***Varicella Zoster.*** Varicella, or chickenpox, is highly contagious. Most infections and consequent immunity are acquired during childhood. Women, who have not acquired immunity during childhood are susceptible and at risk of pneumonia, especially if pregnant. Maternal Varicella pneumonia during pregnancy is serious and life threatening. Fetal infection is associated with spontaneous abortion, growth retardation, central nervous system damage and scarring of skin. A vaccine is available.

**Medications which produce developmental abnormalities.** There are medications which are known to produce developmental abnormalities, some of which are summarized on Table 10. Medications used during pregnancy are typically used to treat a specific disease, either in the mother, the fetus or in rare cases the placenta. In all cases it is essential to critically consider the benefit of the medication for the disease being treated, whether the disease is maternal, fetal or placental.[155] In these instances it will be necessary to define the interaction of pregnancy and the disease and subsequently how the complex physiological alterations of pregnancy influence the use of the medication chosen to treat the disease of interest. While the full discussion of obstetrical risk-benefit analysis is beyond the scope of this review, the interested reader is referred to the standard obstetrical texts which

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[154]Bright, K.A., and K. Calabro. (1999). "Child care workers and workplace hazards in the United States: Overview of research and implications for occupational health professionals." *Occupational Medicine*, v. 49, n. 7, p. 427-437.

[155]Koren, ibid.
Polifka, J.E. and J.M. Friedman. (1999) "Clinical teratology: identifying teratogenic risks in humans. *Clinical Genetics*, v. 56, n. 6, p. 409-420.
Cunningham and Williams, ibid.
Reece, E.A., and J.C. Hobbins. (1999). *Medicine of the Fetus and Mother.* 2nd Edition. Philadelphia: Lippincott-Raven Publishers.

consider this issue.[156] One advance in clinical care relevant to this topic is preconception counseling.[157] Given that there may be several different therapeutic strategies to treat a chronic maternal disease (e.g., hypertension, seizure disorder), it is important to adjust medications prior to pregnancy to assure the best possible outcome. Because most treatment in pregnancy currently is for maternal disease that exists prior to conception, it is important for the physician caring for the reproductive age couple to carefully counsel on the need for treatment and benefits, as well as risks prior to pregnancy.

### Table 10. Selected drugs associated with developmental disease

| Chemical Developmental Hazard | Developmental Defect(s) Observed Following Maternal Treatment | Estimated Risk of Developmental Abnormality |
|---|---|---|
| Anticonvulsants | Spina bifida after valproate<br>Oral clefts<br>Cardiovascular defects | The risk of developmental defect is about 4% overall, but varies with number and nature of anticonvulsant(s) used. As the number of anticonvulsant drugs used to control the seizure disorder increase the risk of developmental defect in the fetus also increases. Some teratologists believe that the risk of developmental abnormalities is increased in women with seizure disorders irrespective of treatment |
| Warfarin derivatives | Nasal hypoplasia<br>Epiphyseal stippling<br>Brain damage | Nasal hypoplasia and epiphyseal stippling occur in 8% after use in first trimester; brain damage in 5% after use in second trimester |
| Diethylstilbestrol | Genital anomalies; in females includes small intrauterine volume, abnormal cervix, substantially increased risk for premature delivery; and increased risk of vaginal adenocarcinoma | Up to 20% of males and 40% of females after increasing doses between 7 and 34 weeks, with greatest effect in the first trimester of pregnancy. |

***Anticonvulsants.*** The use of anticonvulsants by women of childbearing potential clearly illustrates the utility of preconception counseling as well as the risk-benefit analysis which is needed to determine which medications should be used.[158] Seizure disorders occur in about 800,000 to 1.1 million U.S. women of childbearing age. Most of these women need to use an anticonvulsant to control their seizures, which can be life threatening.[159] Exposure to various anticonvulsants during pregnancy results in the risk of developmental disease approximately doubling.

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[156]Shepard, ibid.

[157]Cefalo, R.C. and M.-K. Moos. (1995). *Preconceptional Health Care: A Practical Guide.* St. Louis: Mosby.

[158]Morrell, M.J. (1996) Hormones, reproductive health, and epilepsy. In: Wyllie E, ed. *The Treatment of Epilepsy*, 2nd Edition, p. 179-187. Baltimore: Williams & Wilkins.

[159]North Pacific Epilepsy Research website for "A North American Registry for Epilepsy and Pregnancy". [ http://seizures.net/articles_other/Registry_text.html ]

However, among the medications available for the treatment of the various types of seizure disorders, the risk for malformations appears to vary substantially. Note that there is also disagreement among some investigators about the impact of the seizure disorders on development. It has also been suggested that gene-environment interactions may play a significant role.

***Warfarin derivatives.*** The warfarin derivatives (coumarin, warfarin sodium, marevan, Panwarfin, Coumadin, Sofarin) include a group of compounds which are anticoagulants and act by interrupting the vitamin K dependent clotting factors, and as a consequence are used to treat disorders of coagulation. These disorders are found among women of reproductive age, and so women are frequently treated with these medications. Treatment is necessary because untreated coagulation disorders can be life threatening. Use of these drugs has demonstrated increased risk for selected developmental abnormalities, including underdevelopment of the baby's nose, growth retardation, and vertebrae abnormalities. As a result, women who are attempting pregnancy typically switch to another anticoagulant, heparin, which appears to have no adverse effect on the developing fetus.

***Diethylstilbestrol.*** During the 1940's and 1950's it was thought that spontaneous abortion or miscarriage occurred among some women because of insufficient estrogen production by the placenta.[160] As a consequence, some clinicians began to treat women who had previously had a pregnancy which ended in a miscarriage with a synthetic estrogen, diethylstilbestrol (DES). It was suggested by these clinicians that the use of this synthetic estrogen would decrease the risk that a subsequent pregnancy would end with a miscarriage. To test the hypothesis that DES decreased the risk of miscarriage a group of creative investigators at the Chicago Lying-In Hospital designed a randomized control trial.[161] The outcome of this study demonstrated clearly that DES had no effect on the risk of spontaneous malformation, and subsequent studies of this population demonstrated that the use of DES during pregnancy actually increased the risk of abnormal development of the genitalia in both female and male children.[162] In addition, among the women there was an increased risk of developing an unusual vaginal carcinoma, as a consequence of the abnormal development of the vagina.[163]

These examples of drugs which produce developmental abnormalities have taught us several important lessons concerning the identification of developmental toxicants. A key lesson is that in every case of known human developmental abnormality, the drug has been observed to also produce developmental toxicity in an animal model. A second lesson is that a history of exposure to a chemical or of human chemical use does not necessarily

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[160]Dieckmann, W.J., M.E. Davis, L.M. Rynkiewicz, et al. (1953) Does administration of diethylstilbestrol during pregnancy have therapeutic value? *American Journal of Obstetrics and Gynecology*, v. 66, p. 1062-1081.

[161]Ibid.

[162]Bibbo, M., W.B. Gill, F. Azizi, et al. (1977) Follow-up study of male and female offspring of DES-exposed mothers. *Obstetrics and Gynecology*, v. 49, n. 1, p. 1.8.

[163]Kaufman, R.H., M.O. Korhonen, T. STrama, et al. (1982) Development of clear cell adenocarcinoma in DES-exposed offspring under observation. *Obstetrics and Gynecology*, v. 59, n. 6, Supplement, p. 68S-72S.

demonstrate safety with respect to fetal development. As an example, consider the effects of alcohol on fetal development. While alcohol has been used by human populations for thousands of years, it was only in 1973 that data demonstrating fetal developmental toxicity was published. (See below for more discussion of this topic.)[164]

## Environmental Exposure Levels

We have very little data on the potential for most chemicals to produce developmental toxicity, even in experimental animals. As a consequence, we know little about their ability to interfere with human development. It is still more difficult to identify the impact of environmental levels of exposure to chemicals on developmental processes. Nevertheless, there are some data on selected chemicals which are summarized in Table 11.

***Methyl mercury.*** When mercury is dumped into seawater it is metabolized by aquatic organisms to methyl mercury. Methyl mercury is fat soluble and concentrated in the fatty tissues of sea animals. When consumed by humans it is concentrated in fat rich tissues including the brain. Two acute accidental human exposures to methyl mercury provide information about its developmental effects. Iranians were exposed when they accidentally consumed seed grain that had been treated with methyl mercury to repel rodents. Japanese villagers were exposed to methyl mercury when they consumed fish and other aquatic species living in Minimata Bay. The bay was polluted with industrial releases of mercury, which aquatic animals converted to methyl mercury. The mercury concentrated in the fatty tissue of fish. Children exposed *in utero* displayed the neurodevelopmental effects predominant when there is damage to the central nervous system.

***Hypoxia.*** There are several different types of hypoxia (oxygen deprivation) which may occur during pregnancy. In communities at high altitude, the amount of oxygen in the air is less than found in the atmosphere of communities at sea level. In the communities at high altitude, it has been observed that there are selected pregnancy complications related to oxygen deprivation.[165] Lack of oxyugen most often results from carbon monoxide exposure, frequently a consequence of a faulty combustion device -- an unventilated space heater, for example. Carbon monoxide displaces oxygen from hemoglobin in the bloodstream and decreases the amount of oxygen available to the mother, as well as the fetus. Carbon monoxide exposure, depending on level and duration, may produce headache, nausea, and ultimately unconsciousness. At the level producing unconsciousness, carbon monoxide can clearly produce damage to the fetus with impact on the developing nervous system. [166]

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[164]Schardein, ibid.
Friedman and Polifka, ibid.

[165]Giussani, D.A., P.S. Phillips, S. Anstee, et al. (2001) Effects of altitude versus economic status on birth weight and body shape at birth. *Pediatric Research*, v. 49, n. 4, p. 490-494.

[166]Koren, G., T. Sharav, A. Pastuszak, et al. (1991) A multicenter, prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy. *Reproductive Toxicology*, v. 5, n. 5, p. 397-403.

***Ethyl Alcohol.*** While alcohol has been used socially for thousands of years, and its adverse effect on embryonic and fetal development suggested,[167] it was not until the early 1970's that the impact on fetal development was defined.[168] Exposure to ethyl alcohol occurs as a consequence of ingestion in social settings – but is considered to be environmental exposure in the broadest sense. It is currently thought that alcohol produces abnormal development of the face and central nervous system in a dose dependent fashion across multiple species including humans. At the present time it is not known what the safe dose of alcohol is during pregnancy or what the largest safe dose during development is. However, it is known that alcohol is the most significant preventible cause of mental retardation during pregnancy.[169]

### Table 11. Environmental exposures associated with developmental disorders in humans

| Teratogen | Developmental Defect(s) Observed in Infants Exposed *in utero* | Estimated Risk |
|---|---|---|
| Methyl mercury | Brain damage | 6% of infants in fishing village where seafood was contaminated |
| Hypoxia | Persistent ductus arteriosus | 1-5% of schoolchildren born and living > 4km above sea level |
| Ethyl alcohol | Brain damage<br>Cardiac and joint defects | 30% of infants of women with manifest chronic alcoholism |

For most other chemicals and health outcomes, available information on developmental toxicity at environmentally relevant levels of exposure is not available. Some situations and chemicals that have been associated with, or suspected to produce developmental defects, are shown in Table 12.

## Classes of Evidence for Developmental Toxicity

This section will review the four general classes of data that are available for predicting that an agent might be a developmental hazard, and as a consequence be capable of producing human developmental disease. The classes of evidence include human data, animal data, *in vitro* data, and theoretical data, identified in Table 13 as SAR, an acronym for Structure-Activity Relationship. Within each class of data, the evidence supporting the

[167] Judges 13:7, pregnant women were admonished to "drink no wine nor strong drink, and eat no unclean food."

[168] Stratton, K., C. Howek, and F.C. Battaglia (eds.) (1996) *Fetal Alcohol Syndrome: Diagnosis, Epideiology, Prevention, and Treatment*, Institute of Medicine. Washington, DC: National Academy Press. 230 p.
Streissguth, A.P., S. Landesman-Dwyer, J.C. Martin, and D.W. Smith. (1978) Teratogenic effects of alcohol in humans and laboratory animals. *Science*, v. 209, p. 353-361.

[169] Stratton et al., ibid.

assertion of developmental safety or risk is variable. In some instances, high-quality, well-designed and conducted animal studies may have considerably more certainty in predicting human risk than anecdotal human observations.

**Table 12. Summary of situations and substances that have been associated with or suspected to produce developmental defects**

| SUBSTANCE/SITUATION | BIRTH WEIGHT | GESTATION LENGTH | BIRTH DEFECT |
|---|---|---|---|
| TOXIC SUBSTANCES | | | |
| Electronics assembly | X | | |
| Hair dye | | | Cardiac defects |
| Lead | X | X | Total anomalous pulmonary venous return |
| Polychlorinated biphenyls (PCBs) | X | | "Yusho" syndrome |
| Soldering | | | Cardiac defects |
| Styrene monomer | X | | |
| SOLVENTS | X | | Anencephaly, gastroschisis |
| Paint/paint stripping | | | Total anomalous pulmonary venous return, anencephaly |
| Benzene | X | | Neural tube defects and major cardiac defects |
| Carbon tetrachloride | X | | Central nervous system defects, neural tube defects, and oral cleft defects |
| Toluene | X | | Microcephaly, CNS defects |
| Tetrachloroethylene | | | Oral cleft defects |
| Trichloroethylene | | | Central nervous system defects, neural tube defects, and oral cleft defects |
| PESTICIDES | | | |
| Agricultural work | X | | Total anomalous pulmonary venous return, anencephaly |
| Triazine herbicides | X | | Orofacial clefts |
| POLLUTANTS | | | |
| Carbon monoxide | X | | |
| Chloroform and other trihalo-methanes | X | | Central nervous system defects, oral cleft defects, and major cardiac defects |
| Hazardous waste | X | X | Cardiac and circulatory defects, neural tube defect, hypospadias, gastroschisis |
| Methyl mercury | | | Central nervous system defects, cerebral palsy, cleft lip and palate |
| Particulate matter (PM) | X | | |

**Human data.** Human data on the developmental impact of an agent, whether chemical, biological or physical, generally is thought to provide the strongest evidence demonstrating either safety or harm in well-designed and conducted studies. This is because the data are gathered in the relevant species. There frequently are difficulties in obtaining adequate human data, however. For example, it is generally considered unethical to experimentally expose women prior to or during pregnancy to uncharacterized agents to determine developmental hazard. The cost of human studies can be quite high, and the time and effort required to complete those studies can be very long. Confounding factors, such as other exposures (for example, women who smoke are also frequent coffee drinkers, and women who consume drugs of abuse typically consume more than one drug, for example, narcotics and alcohol) may also weaken the evidentiary nature of the epidemiological study.

However, it is possible to get relevant information from studies in which women are treated with a drug for its therapeutic effect during pregnancy.[170] In addition, it may be possible to observe the outcome of pregnancy among women accidentially exposed to the agent of concern.[171]

While the predictive value of data gathered from epidemiological studies is high, it is important to note that even if an agent has been demonstrated to produce developmental disease in humans, not all those either exposed or treated will get the disease. For example, among women treated with ACE inhibitors during pregnancy, an agent which increases the

**Table 13. General qualities of various types of evidence for evaluating developmental risks to human health.**

| Data | Price | Predictive Value | Certainty | Health Protective |
|---|---|---|---|---|
| Human | High | High | High | No |
| Animal | Moderate | Moderate | Moderate | Yes |
| *In vitro* | Low | Low | Low | Yes |
| SAR | Very Low | Low | Low | Yes |
| Animal + *In vitro* + SAR | Moderate | High | Moderate to high | Yes |

risk of fetal death, there will be infants born who are unaffected.[172] That is also the case for infectious agents like rubella[173] and environmental exposures like methyl mercury.[174] In addition, there are clear effects of dosage, with smaller doses producing lower risk for

[170]Baird, K.L. (1999) The new NIH and FDA medical research policies: targeting gender, promoting justice. *Journal of Health Politics, POlicy, and Law*, v. 24, n. 3, p. 531-565.

[171]Kline, J., B. Levin, Z. Stein, et al. (1981) Epidemiologic detection of low dose effects on the developing fetus. *Environmental Health Perspectives*, v. 42, p. 119-126.

[172]Steffensen, F.H., G.L. Nielsen, H.T. Srensen, et al. (1998) Pregnancy outcome with ACE-inhibitor use in early pregnancy. *Lancet*, v. 351, n. 9102, p. 596.
Buttar, H.S. (1997) An overview of the influence of ACE inhibitors on fetal-placental circulation and perinatal development. *Molecular and Cellular Biochemistry*, v. 176, n. 1-2, p. 61-71.

[173]Katow, S. (1998) Rubella virus genome diagnosis during pregnancy and mechanism of congenital rubella. *ntervirology*, v. 41, n. 4-5, p. 163-169.

[174]Semczuk, M., and A. Semczuk-Sikora. (2001) New data on toxic metal intoxication (Cd, Pb, and Hg in particular) and Mg status during pregnancy. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, v. 7, n. 2, p. 332-340.
Clewell, H.J., J.M. Gearhart, P.R. Gentry, et al. (1999( Evaluation of the uncertainty in an oral reference dose for methylmercury due to interindividual variability in pharmacokinetics. *Risk Analysis*, v. 19, n. 4, p. 547-558.

adverse developmental consequences, as seen with fetal alcohol syndrome and fetal alcohol effects.[175]

Even when data are gathered in humans, there are critical questions which must be asked about the nature of the evidence gathered. For example, because human research usually involves relatively small numbers of human subjects, who have been exposed or who have health effects of interest, one critical question is the statistical power of the study – that is, how large an effect would have had to be before the study could have detected it. This is especially important when reviewing a study which suggests that exposure to the agent of concern produces no adverse developmental effect. Some investigators believe that it is important to indicate that there are actually no truly negative studies of adverse developmental consequence among humans. Rather the negative studies are unable to demonstrate an effect, within the designed statistical power of the study. For example, small studies may only be able to identify agents which substantially increase the risk for abnormal development by as much as ten or a hundred fold, but we know that many agents increase the risk for developmental disease by several fold at most. So, while such a small study might be characterized by some as "negative", it is clearly only negative for agents whose potency for producing developmental disease is greater than the power of the study. The study cannot inform decision makers about the safety of an agent with lower or smaller impacts on abnormal development.

Another item of concern with respect to interpreting data from human studies is exposure characterization, especially time, duration, amount, and timing with respect to pregnancy and the developmental stages of the fetus. Relationship of exposure to fetal development also may affect the biological plausibility of exposure being a cause of an adverse health effect.

Finally, a significant critique of the utility of relying on human studies to evaluate safety is the moral concern that data demonstrating human developmental abnormalities only become available when enough people have been sufficiently harmed to be measured at a scientifically acceptable level of certainty, usually 95%. Contrary to public health principles and to the ethics of medical practice, reliance on scientific proof of harm to human health means relying on the failures of preventive medicine.

**Animal Data.** Animals are integrated biological systems which generally respond developmentally in ways relevant to human toxicity. Animal data on developmental hazards are clearly inferior to human data as a basis for judging the potential effects on humans of chemical exposure, if the data are of similar quality and quantity. However, the quantity and quality of animal data frequently are far superior, and therefore, animal data have many advantages over human epidemiological data. For example, it is possible to design animal experiments with exposure only to the agent of concern, removing the issue of confounding that occurs in human studies. It also is possible to treat groups of animals with measured and increasing doses of the agent. Control groups are more easily formed and better matched to

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[175]Kline et al., ibid.
Little, R.E. (1981) Epidemiologic and experimental studies in drinking and pregnancy: the state of the art. *Neurobehavioral Toxicology and Teratology*, v. 3, n. 2, p. 163-167.

tested animals. Various doses and duration and timing of exposures can be manipulated to delineate the sensitive periods during development, which are frequently difficult to identify using human data. Moreover, animal data can generally be collected relatively quickly and at substantially lower cost than human data using epidemiological studies.

The quality of data from animal experiments varies. To test for developmental effects of animal exposure, generally it is necessary to expose sexually mature animals throughout at least one egg and sperm production cycle prior to mating. At least three doses and one control group are used. The highest dose should be selected to produce evidence of maternal toxicity, generally a 10% reduction in weight during the course of gestation. Choice of lower doses will depend on knowledge of toxicity of the agent. Exposure continues during mating, and throughout gestation for the female. Just prior to birth, the female is sacrificed (killed) and the young delivered.[176] Some of the young are sacrificed to examine the skeleton and internal organs; others are allowed to grow and develop. Examination of the skeleton and internal organs should carefully evaluate weight, size and macroscopic, microscopic and ultrastructural anatomy. In some instances, it may be necessary to evaluate the functional characteristics of individual organs or tissues in the intact (live) animal. Young raised by foster parents should be evaluated for functional characteristics at various stages of life. In some instances, or for some agents, it may be necessary to conduct multigeneration treatments to characterize the full impact of a chemical on genetic and developmental processes.

Key criteria for evaluating the quality of animal data include the number of animals in each treatment group, number of treatment groups, number of variables evaluated, number of control groups, species used, appropriateness of the species used for the chemical considered, appropriateness of the route of exposure considered or used in the animal model, the route of exposure relative to likely route of human exposure, and the number of generations exposed.

Research conducted by Brown and Fabro, and by Hashemi et al. have described the utility of animal data in estimating human risk for developmental toxicity.[177] In general, these studies have demonstrated that all known human developmental toxicants are developmental toxicants in at least one experimental animal, but they are not positive in all animal test species.[178] Animal tests also are quite accurate in identifying chemicals that are not developmental toxicants. A detailed analysis by Schardein found that approximately

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[176]Generally, rodents (i.e., rats or mice) are bred and selected for laboratory use to ensure homogeneity of the experimental and control groups and a known level of sensitivity to the health effect of interest.

[177]Brown, N.A., and S. Fabro. (1983). The value of animal teratogenicity testing for predicting human risk, *Clinical Obstetrics and Gynecology*, v. 26, n. 2, p. 467-477.
Hashemi, R.R., F.R. Jelovsek, and M. Razzaghi. (1993). Developmental toxicity risk assessment: A rough sets approach, *Methods of Information in Medicine*, v. 32, n. 1, p. 47-54.

[178] Hashemi, Jelovsek, and Razzaghi determined that chemicals that tests have shown to be toxic in animals have a 75% - 100% chance of being toxic to humans. Chemicals that are not toxic in animal experiments have a 64% - 91% chance of being non-toxic for people. The overall accuracy of animal tests for predicting human toxicity is between 63% and 91%.

3,300 chemicals have been tested for developmental toxicity in experimental animals.[179] Among that group, 63% (2078) were not developmental toxicants, the remaining 1,223 (37%) were either clearly teratogenic (236 or 19%), probably teratogenic (693 or 57%), or possibly teratogenic (294 or 24%).[180]

***In vitro* data.** Over the past 50 years, developmental biology has benefitted from the emergence of a broad array of *in vitro* models for exploring the effects of chemical, biological, and physical agents on cells and cellular constituents.[181] *In vitro* models subject isolated organs, tissues, cells, or sub-cellular fragments to possibly harmful agents in a laboratory (e.g., in a glass plate or test-tube).

These *in vitro* model systems have been useful in exploring mechanisms of normal development using either animal or human cells and the impact of an agent on that developmental process. Depending on the nature of the *in vitro* experiment, a scientist can consider a single chemical interaction, such as chemical binding to a particular type of receptor, with a high degree of control of concentration. Using *in vitro* data, chemicals can be classified depending on their structure, which determines their physical properties. Some examples of chemical classes include: water soluble or fat soluble; acidic or basic; volatile or nonvolatile. Other examples of chemical classes that are especially relevant to developmental toxicity include: estrogenic or nonestrogenic (depending on whether a chemical interacts with estrogen receptors on cells), or similar to vitamin A or not (depending on whether the chemical interacts with retinol receptors). In this manner, *in vitro* tests are useful screening tools for excluding clearly innocuous chemicals from further scrutiny, at least with regard to specific classes of health impact. There might remain concern about nonspecific toxicity, however.

Another benefit of collecting *in vitro* data is that it can provide support for the relevance of animal testing for human developmental risk. Two important advantages of these laboratory approaches to toxicity testing is low cost and speed with which they can be established and provide data.

There are also disadvantages to use of *in vitro* data. For example, it is more difficult to extrapolate to human populations from *in vitro* data, and any risk estimate made on that basis will be highly uncertain, in part because tissue cultures do not behave like whole animals. Although the data can be used to determine that a chemical is or is not likely to have a particular effect in humans, and to infer whether there is a need to understand how the chemical acts in an intact biological system, *in vitro* data are not sufficient to conduct a full risk assessment, unless a chemical clearly will not interact with human tissues, regardless of exposure.

**Theoretical data.** There are a variety of theoretical data which may be of value

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[179]Schardein, ibid.

[180]Ibid.

[181]Riecke, K., and R. Stahlmann. (2000) Test systems to identify reproductive toxicants. *Andrologia*, v. 32, n. 4-5, p. 209-218.

in predicting whether a chemical is likely to be a developmental toxicant. Perhaps the best known and most useful is the study of chemical structure-activity relationships.[182] It has been known for many years that the biological impact of a chemical is dependent on its structure. Knowledge of chemical structure and of how structure relates to cellular activity, therefore, provides information about chemical class and mechanism of action. Scientists use structure-activity relationships (SAR) to evaluate the potential toxicity of chemicals for which other data are lacking. Structure may be used to predict the impact of a previously unsynthesized or untested chemical on the biological process of interest. Like many *in vitro* tests, SAR data probably are most useful for predicting chemicals of interest for further analysis.

The main drawback to SAR data with respect to characterizing human developmental toxicity is the uncertainty of any risk estimate. Certainty may be high if analysis identifies chemicals as belonging to a known class of developmental toxicants, but most often, classification is tentative and risk estimates highly uncertain.

Several chemical classes have been characterized through SAR. For example, Kavlock explored the structure and activity of chemicals called phenols.[183] His data subsequently were re-analyzed by Hansch, who also evaluated aniline mustards, another chemical group.[184]

A group of investigators at the University of Pittsburgh and Case-Western Reserve University has developed a unique approach to SAR, which they used to analyze a broad range of effects, beneficial as well as toxicological, in developing the evaluation of chemicals associated with developmental disease.[185] They created a database of chemicals associated with developmental toxicity in humans, as well as in specific animals, then developed an extensive database of human developmental impacts of chemicals and drugs.[186]

## Conclusions - How Do We Know a Chemical Can Produce a Birth Defect?

There are testing systems available for identification of agents that are likely to cause

[182]McCormick and Siegel (1999)

[183]Kavlock, R.J. (1990) Structure-activity relationships in the developmental toxicity of substituted phenols: in vivo effects. *Teratology*, v. 41, n. 1, p. 43-59.

[184]Hansch, C., B.R. Telzer, and L. Zhang. (1995) Comparative QSAR in toxicology: examples from teratology and cancer chemotherapy of aniline mustards. *Critical Reviews in Toxicology*, v. 25, n. 1, p. 67-89.

[185]Klopman, G., and H.S. Rosenkranz. (1995) Toxicity estimation by chemical substructure analysis: the TOX II program. *Toxicology Letters*, v. 79, n. 1-3, p. 145-155.

[186]Ghanooni, M., D.R. Mattison, Y.P. Zhang, et al. (1997) Structural determinants associated with risk of human developmental toxicity. *American Journal of Obstetrics and Gynecology* v. 176, n. 4, p. 799-805.
Rosenkranz, H.S., Y.P. Zhang, O.T. Macina, et al. (1998) Human developmental toxicity and mutagenesis. *Mutation Research*, v. 422, n. 2, p. 347-350.

human developmental disease. Clearly, the highest degree of certainty (or the smallest degree of uncertainty) in the likelihood that a chemical, physical or a biological agent is a human teratogen comes from studies in which it is shown that a substance produces birth defects in human populations. However, human data usually are available only when accidental exposure already has occurred, and birth defects have been discovered. Medical ethics do not allow public health practitioners to wait to evaluate potential chemical toxicity until human data are available.

In all but a few cases, human epidemiological research data, experimental animal research data, *in vitro* experimental data, and theoretical data based on SAR are too sparse to support chemical risk assessments for developmental toxicity. Thus, conclusions cannot be drawn about the likelihood that birth defects are due to environmental hazards. However, given the number of known developmental toxicants relative to the number of chemicals that have been tested for developmental toxicity, and the number of chemicals in commerce for which there is no toxicity data, it is likely that additional developmental toxicants remain to be identified.

## Discussion

**Discussants:**

Jonathan M. Samet, M.D.,M.S., Professor and Chair, Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health

Carole Kimmel, Ph.D., National Center for Environmental Assessment, EPA

Michael D. Shelby, Ph.D., Chief, Laboratory of Toxicology, NIEHS

**Dr. Samet** first addressed the question: how would we know if an epidemic caused by an environmental exposure was in progress? Asthma, for example, has been extensively researched, yet the most honest answer is that we do not know why its frequency is rising in the general population. While there are some birth defect registries in place, and the Surveillance, Epidemiology and End Results Reporting (known as the SEER) program tracks data on childhood cancer incidence, there are no analogs in place in the United States for this most common of chronic childhood diseases. As a result, it was surprising when research revealed that the rise in asthma rates had been going on for some 30 years.

In the absence of prospectively gathered data, retrospective analysis through epidemiological studies and surveys is the primary tool for studying asthma, and the lack of longitudinal information on problematic exposures makes such work difficult.[187] Dr. Samet

[187]Dr. Samet is referring to various analytic methods of studying the origins of disease in human populations. Both retrospective and prospective case-control and cohort studies are observational rather than experimental, because the scientist does not control the level of exposure to chemicals experienced by the population being observed. Retrospective case-control studies observe exposures of people diagnosed with a disease and compare them with exposures of persons who do not have

(continued...)

suggested that the message that may be conveyed based on a review of asthma research is that simple, straightforward, public health principles have not been applied to asthma. He noted that this same point had been made in the May 2000 Pew Environmental Health Commission report *Attack Asthma: Why America Needs a Public Health Defense System to Battle Environmental Threats,* which was authored by Dr. Goldman and others. What is needed, he asserted, is the development and application of public health surveillance of asthma, standardized tracking of asthma morbidity (asthma mortality is tracked), a better understanding of children's exposures, and more information on how risks from environmental agents may have changed over time.

**Dr. Kimmel** began by addressing the issue of how well animal testing predicts developmental disorders in children. To date, most of this work has been done on birth defects. In evaluating predictiveness, the dose, duration, and timing of exposure must be considered, because effects may be highly dependent on all of these factors. One cannot easily conclude that a particular chemical does not cause effects in humans, because it may be that there has not been a sufficiently large animal population exposed to a high enough dose level at the right time of development to manifest an adverse effect. There are good qualitative predictions based on animal studies for chemical effects in humans, and these have been examined, but the health effect that occurs in humans is not always the same as the effect in animals. There are some good data for neurotoxicity (e.g., for lead), but comparable data for animals and humans are not available in all cases. Dr. Kimmel opined that there are three areas where data are needed to detect or prevent the effects of environmental exposures to children. The first of these, as Dr. Samet mentioned, is nationwide surveillance of birth defects and other kinds of disorders in children, exposure factors, and sociological and other kinds of factors that might relate to the disorders. Support is also needed for studies to evaluate the effects of environmental factors, with particular attention paid to circumstances where there is a time lag between exposure and effects. Finally, there is a need for continued improvement of strains of animals prone to specific health effects that can be used as models of humans who contract particular diseases. At this time, some data are available through, for example, FDA's pharmaceutical database, but she believes it is not clear whether the initial testing or screening studies that are done on animals predict the ultimate health effects that you see in humans.

**Dr. Shelby** stressed several points. The first of these is the high value of the human data. Given this value, birth registry surveillance systems are critical, and well worth their costs. Exposure assessment, he asserted, is vital to understanding effects on children's health. Information on lifestyle, diet and the like are also important pieces of the puzzle. Serious consideration needs to be given to the means – *in vitro* testing or structure-activity relationships, for example – to be used for prioritizing chemical testing, because all organs, all tissues, all cells, all organelles, and all molecules are potential targets for developmental

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[187](...continued)
the disease. Prospective cohort studies begin with a group of healthy people who vary in the levels of exposure they have experienced. The health of these people is observed over a number of years to determine whether there is a relationship between the levels of chemical exposure experienced and the rate at which disease develops. A prospective cohort study design generally provides stronger scientific evidence than a retrospective case-control design, if all other study design elements are the same.

toxicants.[188] Dr. Shelby seconded Dr. Mattison's assertion that research on mechanisms (that is, how a chemical exerts its effects on the body) is important, because toxicity testing alone is insufficient for understanding health effects like birth defects. There is also a real need for improved and refined toxicity testing methods, because toxicity testing methods are out of date, and the information that they provide is limited. Epidemiology has to play a role in the search for problematic exposures, as does frontline vigilance by physicians. Lastly, more information on gene-environment interaction is needed, in order to help explain why some exposures are problematic only to subsections of the population.

**General Discussion**

**Dr. Schierow** began the general discussion by noting there were several audience members who appeared to be greatly disagreeing with some of the presentations. She invited them to voice their objections.

**Dr. Bailar** asked whether a rise in preterm births might be due to increased survival of premature babies, and corresponding decline in fetal deaths or still births.

**Dr. Mattison** replied that there has been no change in the definition of preterm birth – that is, delivery before the 37th completed week of gestation – so he did not think this was a definitional issue. While there is no question that survival of infants born after too short a period of gestation has improved, the health problems resulting from preterm birth are still troubling.

**Dr. Goldman** agreed this was an issue, observing that still births are included in death records. She pointed out that sustaining a pregnancy for even a short additional span of time may make a huge difference in survival. Fertility technologies may also have an effect, since there are now more multiple births, and multiple births tend to be preterm.

**Dr. Mattison** added that the increase in multiple births is due to not only the increased use of assistive reproductive technologies (that is, fertility treatments) but also the greater number of births to older mothers. As age increases, the likelihood of multiple births increases.

**Dr. Wilson** asked for an example that better explains the term "gene-environment interaction."

**Dr. Mattison** cited three of these. One is a hypothesized interaction between environmental exposure to petrochemicals and certain P450 polymorphisms that appear to

[188]See footnotes 119 and 120 above.

increase the risk for shortened gestational length in a population studied in China.[189,190] A second is polymorphisms in particular genes that appear to increase the risk of cleft palate and cleft lip formation in the children of cigarette smokers.[191] The third is a genetic polymorphism that allows one to identify individuals who are susceptible to eighth nerve damage from particular kinds of antibiotics.[192]

**Mr. Redhead** asked what the relationship was between the incidence of birth defects and the age of the mother, since in the past 100 years there has been a dramatic reduction in the incidence of birth defects and the average age of mothers at birth has gone up as well.

**Dr. Mattison** noted that there are certain kinds of abnormalities that do change with the age of both the mother and the father. The age of the mother has the greater influence, predominantly errors in chromosome numbers that occur with increased frequency with advancing maternal age. This has been recognized for some time and there are screening programs to help identify those particular pregnancies and give families options for dealing with these outcomes.

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[189]Polymorphisms are mutually exclusive forms of the same gene, governing the same biochemical and developmental process.

[190]Xu, S., S-I Cho, and C. Padungtod, et al. 1998. Association of petrochemical exposure with spontaneous abortion. *Occupational and Environmental Medicine*, v. 55, n. 9801, p. 31.

[191]Hickman, Todd A. 1998. *The assocation of specific EPHX1 and GSTM1 gene polymorphisms with phenytoin- or smoking-associated birth defects.*

[192]Guan, M.X., N. Fischel-Ghodsian, and G. Attardi. 2000. A biochemical basis for the inherited susceptibility to amino glycoside ototoxicity. *Human Molecular Genetics*, v. 9, n. 12, p. 1787-1793.

Andrew Olshan, Ph.D., is a professor in the Department of Epidemiology, School of Public Health at the University of North Carolina. His paper examining the state of research on children's environmental health is the fourth and final paper in the scientific portion of this report. Dr. Olshan used his own research on the relationship between brain cancer in children and pesticide exposure to portray the more general issues in children's environmental health research.

In general, scientists who participated in the CRS seminar agreed that –

- The environmental factors that might increase childhood cancer rates generally are not known, with a few exceptions, most notably ionizing radiation.
- A very large increase is needed in chemical testing to support risk assessments for potential health effects in children due to environmental exposure to chemicals.
- Better chemical exposure data are needed for parents and children. Currently, most studies estimate pesticide exposure levels for all pesticides as a group, rather than for particular products, and estimates almost always are based on indirect measures of uncertain validity.
- Although data on pesticide exposure are limited, we believe that home, lawn, and garden uses of pesticides are larger sources of pesticide exposure to most parents and children than agriculture.
- The biologic mechanisms by which pesticide exposure might lead to cancer in children remain speculative and should be investigated.
- The totality of epidemiologic evidence is not sufficient to conclude causal association of pesticide exposure and brain cancers, though the data are suggestive.
- Public health surveillance of asthma morbidity and other disorders in children is needed.
- There is a need for much more screening of chemicals for environmental risks to children's health. New research methods, including toxicogenomics and bioinformatics, should be developed to screen chemicals.[193]
- Research should take into account the effects of age at exposure, timing, and duration of chemical exposure. There is a need for better experimental data on the health effects of pesticides on offspring of laboratory animals.
- New methods are needed for toxicological testing, and for evaluating existing databases, especially for factors that determine toxicity, allergenicity, and for non-cancer endpoints like developmental immunology. Structure-activity relationships (SAR) among chemicals might be used to evaluate absorption, distribution, metabolism, and interaction with cells, but a need remains for new animal strains suitable for testing.

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[193]Toxicogenomics is an emerging scientific discipline that combines genomics (the study of genes and their function) and bioinformatics (the management and analysis of biologic research data using advanced computing techniques) to identify and describe the ways that chemical molecules affect and are affected by human bodies.

# Pesticides and Childhood Brain Cancer: A Review and Perspective

By Andrew F. Olshan*

I have chosen to present pesticides and childhood brain tumors as a case study of environmental influences on children's health. Pesticides are one of many important classes of environmental exposures, yet they have been of particularly great interest to scientists, policy makers, regulatory bodies, and the public. This widespread interest in pesticides and their effect on a wide array of health endpoints has resulted in a number of toxicological and epidemiological studies. I believe that the findings on pesticides and childhood cancer accurately represents the patterns of results, state of knowledge, strengths, and limitations of the epidemiologic approach to studying how environmental exposures might affect different aspects of children's health.

## Background

**Childhood Brain Cancer.** Childhood brain tumors are rare with an estimated annual incidence of 39 cases per million children (<15 years of age) in the United States.[194] A total of 1,700 new cases are expected in the United States this year. They are the second leading cause of cancer incidence and mortality during childhood. Using data gathered by the National Cancer Institute between 1984 and 1994, the overall percent of children surviving brain cancer for 5 years was 67%. Survival for some types of brain tumors was poorer.

National cancer statistics have shown an increase in the incidence of some types of childhood brain tumors during the mid-1980s (1983-1986).[195] A 35% increase in incidence from 1973 to 1994 has been reported, with rates remaining stable.[196] Some scientists argue that the apparent increase is due to improvements in medical technology (e.g., introduction of magnetic resonance imaging, or MRI), and changes in diagnostic criteria, disease classification, and neurosurgical methods.[197] Other scientists maintain that if the improved

[194]Gurney, J.G., M.A. Smith, and G.R. Bunin. CNS and miscellaneous intracranial and intraspinal neoplasms. In: Ries, L.A.G., M.A. Smith, J.G. Gurney, et al. *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995.* Bethesda, MD: National Cancer Institute, SEER Program, NIH Pub. No. 99-4649, p. 51-63. (1999)

[195]Linet, M.S., L.A. Ries, M.A. Smith, R.E. Tarone, and S.S. Devesa. Cancer surveillance series: Recent trends in childhood cancer incidence and mortality in the United States. *Journal of the National Cancer Institute,* v. 91, p. 1051-1058. (1999)

[196]Smith, M.A., B. Freidlin, L.S. Ries, R. Simon. Trends in reported incidence of primary malignant brain tumors in children in the United States. *Journal of the National Cancer Institute*, v. 90, p. 1269-1277. (1998)

[197]Linet et al., ibid.

(continued...)

ability to detect brain tumors were responsible for the increased incidence, the rates should then have returned to the earlier baseline levels.[198] They suggest that the increased incidence is real and compatible with an unidentified carcinogen introduced into the environment.[199] Additional monitoring of trends in brain cancer incidence and investigation of environmental risk factors are warranted.

Several exposures and factors have been described as known risk factors for childhood brain tumors. These include gender (incidence is higher in males for some types of brain cancer); therapeutic doses of ionizing radiation, such as in children treated for tinea capitis or cancer; and certain genetic conditions such as neurofibromatosis.[200] A number of other factors have been suggested as possible causes of childhood brain tumors, but the evidence is not conclusive. These factors include maternal diet during pregnancy, especially consumption of cured meats; family history of brain cancer; electromagnetic fields; history of head injuries or epilepsy; and paternal occupational exposures.[201]

**Pesticides.** Pesticides are chemical or biologic agents designed to kill insects (insecticides), weeds (herbicides), rodents (rodenticides), fungi (fungicides), and other undesired plant and animal life.[202] The International Agency for Research on Cancer (IARC) has classified 26 pesticides as carcinogenic in animals.[203] Agriculture is the major pesticide use in the United States.

There are many ways in which parents and children may be exposed to pesticides. Farmers, their spouses, and children can be directly exposed to pesticides in the field and through home pesticide contamination. Pesticides from agricultural runoff can contaminate community drinking water supplies. Exposure of children can also occur through food. Occasional single food items have been shown to contain pesticide residues. However, it has been shown that the largest source of most children's exposure is home, lawn, and garden

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Smith et al., ibid.
Legler, J.M., L.A. Ries, M.A. Smith, J.L. Warren, E.F. Heineman, R. S. Kaplan, and M.S. Linet. Cancer surveillance series [corrected]: brain and other central nervous system cancers: recent trends in incidence and mortality. *Journal of the National Cancer Institute,* v. 91, p.1382-1390. (1999).

[198]Schechter, C.B. Re: Brain and other central nervous system cancers: recent trends in incidence and mortality. *Journal of the National Cancer Institute*, v. 91, p. 2050-2051. (1999)

[199]Ibid.

[200]Gurney et al., ibid.
Little, J. *Epidemiology of Childhood Cancer.* Lyon: IARC Scientific Publications No. 149. (1999).

[201]Ibid.

[202]Pesticide is defined more broadly in the Federal Insecticide, Fungicide, and Rodenticide Act to include non-lethal substances used to control pests, for example, insect repellants.

[203]IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 53: Occupational exposures in insecticide application, and some pesticides. Lyon: International Agency for Research on Cancer. (1991)
IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 1-69: Lyon: International Agency for Research on Cancer (1972-1997).

pesticide use.[204] Recent studies have estimated that 78% to 97% of families in the mid-western United States use pesticides in or around the home.[205] Application of indoor and outdoor pesticides can lead to household carpet contamination. Carpet contamination can be persistent and poses a greater exposure potential to children, since they spend considerable time on the floor, and have frequent hand-to-mouth contact with objects on the floor.[206] Children can also be exposed to pesticides in delousing shampoo and pet-care products, such as flea and tick collars and sprays.

The biologic mechanisms by which pesticide exposure might lead to cancer in children remain speculative. However, hypothetically cancer might result from exposure directly to a child or to a developing fetus through the mother. In addition, if a pesticide were to mutate, or genetically alter, the father's sperm or mother's eggs prior to the child's conception, the child might become more susceptible to developing cancer.[207] If the mother were exposed to pesticides during her pregnancy, either direct genetic alterations or changes in hormonal regulation or immunologic function in the fetus could lead to the later development or progression of cancer.[208] Direct exposure to pesticides during childhood could change normal cells to cancerous cells, or decrease the child's immunologic function and allow pre-cancerous cells to progress to malignant brain cancer. Laboratory studies have not yet provided direct evidence about how pesticides might act through these possible pathways, although animal studies have shown that cancer can be induced in offspring by

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[204]Grossman, J. What's hiding under the sink: dangers of household pesticides. *Environmental Health Perspectives,* v. 103, p. 550-554. (1995)

[205]Davis, J.R., R.C. Brownson, and R. Garcia. Family Pesticide Use in the Home, Garden, Orchard and Yard. *Archives of Environmental Contamination and Toxicology*, v. 22, p. 260-266. (1992)

[206]Gurunathan, S., M. Robson, N. Freeman, B. Buckley, A. Roy, R. Meyer, J. Bukowski, and P.J. Lioy. Accumulation of chlorpyrifos on residential surfaces and toys accessible to children. *Environmental Health Perspectives*, v. 106, n,. 1, p. 9-16. (1998)

[207]Tomatis, L., S. Narod, and H. Yamasaki. Transgeneration transmission of carcinogenic risk. *Carcinogenesis,* v. 13, p.145-151. (1992)

Anderson, L.M., K.S. Kasprzak, and J.M. Rice. Preconception exposure of males and neoplasia in their progeny: Effects of metals and consideration of mechanisms. In: *Male-Mediated Developmental Toxicity* (Olshan, A.F., and D.R. Mattinson, eds.). New York:Plenum Press, p. 129-140. (1994)

Anderson, L.M., B.A. Diwan, N.T. Fear, and E. Roman. Critical Windows of Exposure for Children's Health: Cancer in Human Epidemiological Studies and Neoplasms in Experimental Animal Models. *Environmental Health Perspectives,* v. 108, Supplement 3, p. 573-594. (2000)

[208]Anderson, L.M., B.A. Diwan, N.T. Fear, and E. Roman, ibid.

Brooks, B.O., and J.B. Sullivan. Immunotoxicology. In: *Hazardous Materials Toxicology: Clinical Principles of Environmental Health* (Sullivan, J.B., and G.R. Krieger, eds.). Baltimore:Williams and Wilkins, p. 190-214. (1992)

Lotzova, E. Immune Surveillance and Natural Immunity. In: *Developmental Immunology,* (Cooper, E.L., and Nisbet-Brown, eds.). New York:Oxford University Press, p. 401-425. (1993)

Steen, R.G.. Cancer and the Immune System. In: *A Conspiracy of Cells: The Basic Science of Cancer.* New York:Plenum Press, p. 129-146 (1993)

Colborn, R., F.S. vom Sahl, and A.M. Soto. Development effects of endocrine-disrupting chemicals in wildlife and humans. *Environmental Health Perspectives*, v. 101, p. 378-384. (1993)

some chemicals (that are not pesticides) and by radiation.[209]

Previous reviews of epidemiologic studies have revealed a number of associations between pesticides and childhood cancers.[210] This paper reviews the methods and results of published studies of occupational and residential pesticide use and the risk of childhood brain cancer.

## Epidemiologic Studies of Cancers of the Brain and Central Nervous System

**Methods.** Table 14 presents the characteristics of the studies of pesticides and childhood brain tumors that I have reviewed. Because of the rarity of childhood brain cancer, most of the epidemiologic studies have been retrospective, case-control studies, in which a group of persons with a disease is compared with a control group without the disease of interest.[211] Cancer cases have primarily been identified through population-based or hospital tumor registries. Controls have been derived from a variety of sources including census records, telephone random-digit dialing, birth certificates, friends of cases, and children with other cancers or illnesses. Most studies of parental occupation inferred pesticide exposure based on job title and industry, rather than by direct measurement. Employment history information was obtained through interviews and from birth and death records. Residential exposure (which refers to pesticide use in the home and in the lawn and garden) has been assessed only by parental recall. Few studies obtained information about both occupational and residential exposure.

**Findings.** A total of 15 epidemiologic studies have been conducted that have investigated the relationship between pesticide use and the risk of childhood brain tumors. These studies have examined various sources of pesticide exposure including father's occupational exposure, farm residence, and home and garden pesticide use. Table 15 summarizes the study results.

A few epidemiologic studies have reported that fathers' employment in agriculture

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[209]Tomatis, ibid.
Anderson et al., 1994, ibid.
Anderson et al., 2000, ibid.

[210]Daniels, J.L., A.F. Olshan, and D.A. Savitz. (1997) Pesticides and childhood cancers. *Environmental Health Perspectives,* v. 105, p. 1068-1077.
Zahm, S.H., and W.H. Ward. (1998) Pesticides and childhood cancer. *Environmental Health Perspectives,* v. 106, Supplement 3, p. 893-908.

[211]The prevalence of the exposure level is compared between the case and control groups and quantified by an "odds ratio" statistic, which estimates the relative risk. The odds ratio is the risk of disease, given exposure, relative to risk without exposure. If an odds ratio is equal to 1.0, there is no difference in exposure between cases and control groups. A ratio greater than 1.0 indicates that cases have greater exposure; if the ratio is less than 1.0, exposure is less frequent among cases. In assessing the importance of the results, I will interpret the strength of association as the magnitude of the odds ratio, paying particular attention to ratios greater than 1.5. The precision of the risk estimate will be indicated by the span of the 95% confidence interval for each odds ratio.

**Table 14. Characteristics of Studies Evaluating Pesticide Exposure and Childhood Brain Cancer (modified after Daniels et al., 1997)**

| Setting and Study Period[a] | Case Group[b] | Upper Age Bound | Number of Cases | Source of Cases[c] | Source of Controls[c] | Data Source, Period of Interest[d] | Adjusted Variables | Reference |
|---|---|---|---|---|---|---|---|---|
| Baltimore 1965-1975 | Brain | 19 | 84 | H | BC, C | Interview PG, CH | age, race, sex | Gold, 1979 |
| Finland 1950-1975 | Brain | 14 | 948 | T | BC | BC PG | age | Hemminki, 1981 |
| Baltimore 1965/1969-1974 | Brain | 19 | 7043 | T, DC | BC, C | Interview PG, CH | age, race, sex, Dx date | Gold, 1982 |
| Los Angeles 1972-1977 | Brain | 24 | 209 | TF | – | Interview PG, CH | – | Preston-Martin, 1982 |
| Ohio 1959-1978 | Brain: deaths | 19 | 491 | DC | BC | BC PG | age, race, sex, paternal age, birth order, birth weight, % cty. farmed | Wilkins, 1988 |
| Ontario 1977-1983 | Brain | 19 | 74 | H | PR | Interview CH | age, sex, Dx age, region | Howe, 1989 |
| Ohio 1975-1982 | Brain\ CNS | 19 | 110 | H | RD | Interview PC, PG, CH | age, race, sex, region | Wilkins, 1990 |
| PA, DE, NJ 1980-1986 | Brain: AG | 14 | 163 | H | RD | Interview PC, PG, CH | age, race, region | Kuijten, 1992 |
| Missouri 1985-1989 | Brain | 10 | 45 | T | F, C | Interview PG, CH | age, sex, smoke, income, education, time Dx to interview | Davis, 1993 |
| U.S. & Canada 1986-1989 | Brain: AG & PNET | 5 | 321 | CCG | RD PG, CH | Interview | age, race, region, income | Bunin, 1994 |
| Denver 1976-1983 | Brain | 14 | 252 | T | RD | Interview PG, CH | age, sex, region, maternal age, maternal race, maternal smoke, education, EMF, Dx age, income | Leiss, 1995 |
| Norway 1965-1991 | Brain | 39 | 182 | T | – | Agricultural registry CH | age, calendar year, birth year | Kristensen, 1996 |
| California & Washington | Brain | 19 | 540 | T | RDD | Interview | age, sex, birth year, region | McKean-Cowdin, 1998 |

| Setting and Study Period[a] | Case Group[b] | Upper Age Bound | Number of Cases | Source of Cases[c] | Source of Controls[c] | Data Source, Period of Interest[d] | Adjusted Variables | Reference |
|---|---|---|---|---|---|---|---|---|
| England & Wales | CNS | 14 | 109 | DC | DC | DC | age, year of death, social class | Fear, 1998 |
| Los Angeles | Brain | 19 | 224 | T | RDD | Interview PG, CH | sex, birth year | Pogoda, 1997 |

*(a)* All studies reviewed were case-control studies except Kristensen, 1996.

*(b)* Cancer type abbreviations: AG-astrocytic glioma, PNET-primitive neuroectodermal tumor, CNS-Central Nervous System

*(c)* Source of cancer cases or controls: H- hospitals, T- tumor registry, BC- birth certificate or registry , DC- death certificate, C- child with another cancer type, I- child with non-cancer illnesses, F-friend or neighborhood, RDD- Random Digit Dialing, CCG- Children's Cancer Study Group, PR- population registry/census

*(d)* Exposure period: PC-pre-conception, PG-pregnancy, CH-childhood

*Other abbreviations:* Dx-diagnosis, (–)=information not available or not applicable to the study design

in the period prior to conception of their child was related to an increased risk of childhood brain tumors.[212] Paternal employment in agricultural occupations or in an occupation that typically uses pesticides during pregnancy was associated with an elevated risk in some, but not all studies.[213] Maternal employment in agricultural occupations was not reported in any publications.

Some studies of occupational pesticide exposure to fathers reported that such exposure more than doubled a child's likelihood of having cancer. For example, a study from the Philadelphia area found that paternal employment in agricultural occupations had an odds ratio of 1.8 (95% confidence interval = 0.6 - 6.0) for astrocytoma.[214] However, interpretation of these findings is limited by the fact that the number of exposed cases was small in most studies. This also leads to statistical imprecision (wide confidence intervals), indicating that the results are unstable. Further, pesticide exposure was not directly measured in these studies, but presumed given parental employment in agriculture.

Farm residence also has been used to infer potential pesticide exposure of the father, pregnant mother, or child. In general, most of these studies relied on farm residence as a proxy for both occupational and residential pesticide exposures, but did not measure direct exposure to individuals. Residence on a farm has been associated with an increased risk for two specific forms of childhood brain cancer in two studies.[215] Relative risk estimates ranged

[212]Wilkins, J.R., and T. Sinks. Parental occupation and intracranial neoplasms of childhood: Results of a case-control interview study. *American Journal of Epidemiology*, v. 123, p. 275-292. (1990)
Kuijten, R.R., G.R. Bunin, C.C. Nass, and A.T. Meadows. Parental occupation and childhood astrocytoma: Results of a case-control study. *Cancer Research*, v. 52, p. 782-786. (1992)

[213]Wilkins, J.R., and R.A. Koutras. Paternal occupation and brain cancer in offspring: A mortality-based case-control study. *American Journal of Industrial Medicine*, v. 14, p. 299-318. (1988)
Wilkins and Sinks, ibid.
Kuijten et al., ibid.

[214]Kuijten et al., ibid.

[215]Bunin, G.R., J.D. Buckley, C.P. Boesel, L.B. Rorke, and A.T. Meadows. Risk factors for (continued...)

**Table 15. Case-control studies evaluating the risk of childhood brain cancer associated with parental occupational and residential exposure to pesticides prior to conception, during pregnancy, and during childhood (modified after Daniels et al., 1997)**

| Exposure Type & Frequency | Cancer Type[a] | Pregnancy OR | Pregnancy 95% CI/ p-value | Age[e] | Childhood OR | Childhood 95% CI/ p- value | Reference |
|---|---|---|---|---|---|---|---|
| **Occupation-Father** | | | | | | | |
| Agriculture | AG | 1.3 | 0.7-2.6 | | | | McKean-Cowdin, 1998 |
| Agriculture | PNET | 0.5 | 0.3-2.9 | | | | McKean-Cowdin, 1998 |
| Agriculture | | 0.8 | 0.7-1.0 | | | | Fear, 1998 |
| Agriculture | | 2.4 | 1.2-4.9 | child | | | Wilkins, 1988 |
| Agriculture | | 1.6 | 0.4-6.1 | child | 0.9 | 0.3-2.9 | Wilkins, 1990 |
| Agriculture | | 2.7[b] | 0.8-9.1 | | | | Wilkins, 1990 |
| Agriculture | | 1.8[b] | 0.6-6.0 | | | | Kuijten, 1992 |
| Agriculture | | 1.0 | 0.2-4.3 | 0-1yr Pre-Dx | 1.3 | 0.7-6.3 | Kuijten, 1992 |
| Farmer | | (1/0)[d] | | | (1/0)[d] | | Gold, 1982 |
| Farmer | | 1.2 | – | | | | Hemminki, 1981 |
| **Farm Residence** | | | | | | | |
| Horticulture | | 1.3 | 0.9-1.8 | | | | Kristensen, 1996 |
| Pesticide | | 1.4 | 1.0-1.9 | | | | Kristensen, 1996 |
| Grain Farm | | 1.3 | 1.0-1.8 | | | | Kristensen, 1996 |
| Horticulture | NAG | 1.5 | 0.9-2.7 | | | | Kristensen, 1996 |
| Grain Farm | NAG | 1.7 | 1.1-2.8 | | | | Kristensen, 1996 |
| Pest purchase-low | NAG | 2.0 | 0.9-4.7 | | | | Kristensen, 1996 |
| Pest purchase-medium | NAG | 2.9 | 1.5-5.6 | | | | Kristensen, 1996 |
| Pest purchase-high | NAG | 3.3 | 1.4-7.8 | | | | Kristensen, 1996 |
| Farm, unspecified | | | | | 4.0 | p=0.04 | Gold, 1979 |
| Farm, unspecified | | | | | 1.0[c] | p=0.98 | Gold, 1979 |
| Farm, unspecified | AG | 0.5 | 0.1-1.8 | | 0.4 | 0.1-1.6 | Bunin, 1994 |
| Farm ≥ 1 year | PNET | 3.7 | 0.8-23.9 | | 5.0 | 1.1-46.8 | Bunin, 1994 |
| **Garden** | | | | | | | |
| Pesticide | | 0.6 | 0.3-1.1 | 0-2yrs | 0.5 | 0.4-0.9 | Leiss,1995 |
| Pesticide | | | | 0-2yrs | 0.5 | 0.4-0.8 | Leiss,1995 |
| Insecticide | | 1.5 | 0.6-3.9 | 0-6mo | 2.3 | 0.7-8.3 | Davis,1993 |
| Insecticide | | | | 7mo-Dx | 1.6 | 0.7-3.6 | Davis,1993 |
| Insecticide | | 1.2[c] | 0.5-3.0 | 0-6mo | 1.2[c] | 0.4-3.8 | Davis,1993 |
| Insecticide | | | | 7mo-Dx | 2.6[c] | 1.1-3.9 | Davis,1993 |
| Herbicide | | 1.1 | 0.5-2.5 | 0-6mo | 1.7 | 0.7-3.9 | Davis,1993 |
| Herbicide | | | | 7mo-Dx | 2.4 | 1.0-5.7 | Davis,1993 |

(...continued)

astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: A report from the Children's Cancer Group. *Cancer Epidemiology, Biomarkers & Prevention,* v. 3, p. 197-204. (1994)

Kristensen, P., A. Andersen, L.M. Irgens, A.S. Bye, and L. Sundhem. Cancer in offspring of parents engaged in agricultural activities in Norway: Incidence and risk factors in the farm environment. *International Journal of Cancer*, v. 65, p. 39-50. (1996)

| Exposure Type & Frequency | Cancer Type[a] | Pregnancy OR | Pregnancy 95% CI/ p-value | Age[e] | Childhood OR | Childhood 95% CI/ p- value | Reference |
|---|---|---|---|---|---|---|---|
| Herbicide | | 1.0[c] | 0.4-2.4 | 0-6mo | 3.4[c] | 1.2-9.3 | Davis,1993 |
| Herbicide | | | | 7mo-Dx | 1.7[c] | 0.7-3.9 | Davis,1993 |
| Herbicide | | | | Pre-Dx | 0.9 | 0.5-1.9 | Howe, 1989 |
| **Home Extermination** | | | | | | | |
| Ever | | 1.3 | 0.7-2.1 | 0-2yrs | 1.4 | 0.6-2.7 | Leiss,1995 |
| Ever | | | | 2yrs-Dx | 1.1 | 0.4-3.0 | Leiss,1995 |
| Often | | 1.0 | p=0.59 | | 0.9 | p=0.29 | Preston-Martin, 1982 |
| Ever | AG | 0.7 | 0.4-1.4 | | | | Bunin, 1994 |
| Ever | PNET | 1.0 | 0.6-1.9 | | | | Bunin, 1994 |
| Insects | | | | unk | 2.3 | p=0.10 | Gold, 1979 |
| Insects | | | | unk | 1.2[c] | p=0.84 | Gold, 1979 |
| Insecticides | | 1.3 | 0.7-2.4 | | 1.2 | 0.8-2.0 | Pogoda, 1997 |
| Snail | | 1.1 | 0.6-2.1 | | 1.0 | 0.6-1.8 | Pogoda, 1997 |
| Flea/Tick | | 1.7 | 1.1-2.6 | | 1.0 | 0.7-1.4 | Pogoda, 1997 |
| Spray, Fogger | | 10.8 | 1.3- 89.1 | | | | Pogoda, 1997 |
| Termites | | 2.7 | 0.5- 14.2 | | 0.7 | 0.4-1.3 | Pogoda, 1997 |
| Termites, father | | 2.9 | 1.3-7.1 | 7mo-Dx | 1.4 | 0.5-3.9 | Davis, 1993 |
| Chlordane, father | | 1.5 | 0.5-4.9 | | | | Davis, 1993 |
| **Pesticide-general** | | | | | | | |
| Ever | | 1.8 | 0.8-4.0 | 0-6mo | 1.9 | 0.8-4.3 | Davis, 1993 |
| Ever | | | | 7mo-Dx | 3.4 | 1.1-10.6 | Davis, 1993 |
| Ever | | 1.2[c] | 0.5-2.9 | 0-6mo | 1.9[c] | 0.8-4.4 | Davis, 1993 |
| Ever | | | | 7mo-Dx | 1.7[c] | 0.5-5.4 | Davis, 1993 |
| Ever | AG | 1.5 | 0.8-2.7 | | | | Bunin, 1994 |
| Weekly | AG | 2.2 | 0.6-7.4 | | | | Bunin, 1994 |
| Ever | PNET | 0.7 | 0.4-1.4 | | | | Bunin, 1994 |
| Weekly | PNET | 1.0 | 0.2-4.9 | | | | Bunin, 1994 |
| Ever | | 1.5 | p=0.08 | | 1.1 | p=0.44 | Preston-Martin,1982 |
| **Bombs** | | | | | | | |
| Ever | | 2.1 | 0.5-8.3 | 7mo-Dx | 1.1 | 0.3-3.7 | Davis, 1993 |
| Ever | | 6.2[c] | 1.4-28.4 | 7mo-Dx | 0.6[c] | 0.2-2.0 | Davis, 1993 |
| **No-Pest Strip** | | | | | | | |
| Ever | | 1.5 | 0.9-2.4 | 0-2yrs | 1.4 | 0.7-2.9 | Leiss, 1995 |
| Ever | | | | 2yrs-Dx | 1.8 | 1.2-2.9 | Leiss, 1995 |
| Ever | | 5.2 | 1.2-22.2 | 0-6mo | 3.7 | 0.9-15.2 | Davis, 1993 |
| Ever | | | | 7mo-Dx | 3.7 | 1.0-13.7 | Davis, 1993 |
| Ever | | 1.9[c] | 0.6-5.9 | 0-6mo | 2.5[c] | 0.7-9.4 | Davis, 1993 |
| Ever | | | | 7mo-Dx | 2.0[c] | 0.6-6.3 | Davis, 1993 |
| **On Pets, Insects** | | | | | | | |
| Shampoo/Dip | | 1.2 | 0.6-2.5 | | | | Pogoda, 1997 |
| Shampoo/Dip | | 1.9 | 0.7-5.4 | 0-4 yrs | | | Pogoda, 1997 |
| No. Pets >1 | | 2.0 | 1.0-4.0 | | | | Pogoda, 1997 |
| No. Pets >1 | | 3.5 | 1.1-11.4 | 0-4 yrs | | | Pogoda, 1997 |
| Hr/day with Pet >3 | | 1.9 | 0.9-4.2 | | | | Pogoda, 1997 |
| Hr/day with Pet >3 | | 3.2 | 0.8-12.2 | 0-4 yrs | | | Pogoda, 1997 |
| Ever | | 0.6 | 0.2-1.5 | 0-6mo | 4.8 | 0.9-24.7 | Davis, 1993 |
| Ever | | | | 7mo-Dx | 1.4 | 0.6-3.1 | Davis, 1993 |
| Ever | | 0.4[c] | 0.1-1.0 | 0-6mo | 1.8[c] | 1.8-6.6 | Davis, 1993 |

| Exposure Type & Frequency | Cancer Type[a] | Pregnancy OR | Pregnancy 95% CI/ p-value | Age[e] | Childhood OR | Childhood 95% CI/ p- value | Reference |
|---|---|---|---|---|---|---|---|
| Ever | | | | 7mo-Dx | 0.7[c] | 0.3-1.5 | Davis, 1993 |
| **Pet Collar, Flea** | | | | | | | |
| Ever | | 1.1 | 0.5-2.1 | | | | Pogoda, 1997 |
| Ever | | 0.9 | 0.4-2.1 | 0-6mo | 5.5 | 1.5-20.0 | Davis, 1993 |
| Ever | | | | 7mo-Dx | 2.4 | 1.1-5.6 | Davis, 1993 |
| Ever | | 0.6[c] | 0.2-1.3 | 0-6mo | 4.4[c] | 1.4-14.3 | Davis, 1993 |
| Ever | | | | 7mo-Dx | 1.3[c] | 0.6-2.9 | Davis, 1993 |
| **Shampoo, Lice *(Kwell)*** | | | | | | | |
| Ever | | | | 7mo-Dx | 1.9 | 0.6-6.9 | Davis, 1993 |
| Ever | | | | 7mo-Dx | 4.6 | 1.0-21.3 | Davis, 1993 |

*a* - General brain cancer unless specified: AG-Astrocytic Glioma, NAG-non-astrocytic neuroepithelial tumor, PNET- Primitive Neuroectodermal Tumor

*b* - Exposure prior to conception

*c* - Cancer Controls

*d* - Reported data insufficient to calculate OR; shown is number of cases exposed/number of controls exposed

*e* - If not reported, the age of exposure during childhood was not specified

*Other abbreviations:* Dx=diagnosis

from 1.5 to 3.7 (with 95% confidence intervals of 0.9 - 2.7 and 0.8 - 23.9, respectively). One study used Norwegian agricultural census information to classify possible pesticide exposure levels based on the amount of pesticides purchased for each farm.[216] The results suggested a dose-response trend: the risk of childhood brain cancer increased with increasing level of pesticides purchased (rate ratios = 2.0, 2.9, 3.3).[217] Because the census information was obtained every 5 years, this study could not determine exposure at specific points relative to pregnancy and childhood. Nonetheless, the Norwegian study provides some suggestive evidence for an association between pesticides and childhood brain tumors.

Residential pesticide use includes use of professional extermination services; lawn and garden use; home use of sprays, foggers, and no-pest strips; application of pesticides to pets; and shampoo application to children for lice. Table 15 shows that most studies simply asked whether pesticides were used or not (indicated in the first column of the table by "ever"). These studies did not find an increased risk with use of garden pesticides during pregnancy; one study noted higher risks for use of garden pesticides during childhood.[218]

Two studies reported an elevated risk for use of a variety of home extermination products by the mother or father during pregnancy. These include flea/tick products,

[216]Kristensen, ibid.

[217]Ibid.

[218]Davis, J.R., R.C. Brownson, R.B. Garcia, B.J. Bentz, and A. Turner. Family pesticide use and childhood brain cancer. *Archives of Environmental Contamination and Toxicology*, v. 24, p. 87-92. (1993)

spray/foggers, and pesticides used to kill termites.[219] Although the risk estimates were elevated, they were rather imprecise as evidenced by the wide confidence intervals (e.g., odds ratio = 10.8, confidence interval 1.3 to 89.1).

Other types of home pesticide products, including bombs and no-pest strips, showed increased risks.[220] Pet-related pesticide products were also associated with risks in two studies.[221] Interestingly, one study that asked more details about the use of the product reported higher risks when precautions were not taken (evacuating the home, following label instructions) and with a greater number of pets and more hours a day spent with the pet.[222] The use of shampoo (Kwell) on the child to kill lice had an increased risk.[223]

Concerns about many of the residential pesticide studies include the small study sizes (e.g., the Davis et al. study was based on 45 cases),[224] and the limited amount of detailed information collected about the specific pesticide products, application methods, frequency of use, and safety measures. It is interesting that the studies that reported positive effects of residential pesticide exposure were those with greater detail on the timing, frequency, and form of pesticide use.[225]

**Discussion.** Taken together, the studies do provide some epidemiologic evidence for a possible relationship between pesticides and childhood brain tumors. Suggestive associations are seen for residence on a farm and use of certain home pesticides. Particularly interesting is the population-based study that included the most detailed data collection instrument.[226] This study reported higher risk estimates for childhood brain tumors in association with factors that indicate exposures of a greater magnitude. For example, number of pets treated and lack of precautions taken during pesticide use. Nonetheless, the totality of the epidemiologic evidence is not sufficient to conclude causal association of pesticide exposure and brain cancers for a number of reasons. First, the magnitudes of many of the relative risk estimates are moderate (around 1.5 - 2.0). Second, as has been previously noted, many of the studies are small, basing their results on only a few exposed cases. The resultant statistical imprecision also provides less confidence in interpreting the effect of pesticides.

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[219]Ibid.
Pogoda, J.M., and S. Preston-Martin. Household pesticides and risk of pediatric brain tumors. *Environmental Health Perspectives*, v. 105, p. 1214-1220. (1997)

[220]Davis et al., ibid.
Leiss, J.K., and D.A. Savitz. Home pesticide use and childhood cancer: A case-control study. *American Journal of Public Health*, v. 85, p. 249-252. (1995)

[221]Davis et al., ibid.
Pogoda and Preston-Martin, ibid.

[222]Pogoda and Preston-Martin, ibid.

[223]Davis et al., ibid.

[224]Ibid.

[225]Bunin et al., ibid.
Pogoda and Preston-Martin, ibid.

[226]Pogoda and Preston-Martin, ibid.

One of the biggest difficulties in interpreting the current epidemiologic data relates to the ascertainment and assessment of pesticide exposure.

There are several aspects to this broader issue that warrant discussion. Studies do not always distinguish between herbicides, insecticides, fungicides, or other types of pesticides, which are not always mutually exclusive categories.[227] Also, the chemical properties of various pesticides, the methods of application, the exposure pathways (dermal, ingestion, or inhalation), frequency and duration of exposure are not usually evaluated in most studies.[228] All of these factors affect the type and degree of exposure. Pesticide exposure determination in all studies was indirect, based on parents' self-report of job titles, industry, and residential pesticide use. Information collected about home and occupational pesticide exposure has often been limited to a few general questions in an interview or questionnaire, rarely solely designed to collect detailed information about pesticide exposure. Three studies obtained exposure data from birth or death certificates, sources that may not accurately represent the actual job, exposure, or time period of interest.[229]

Even when detailed exposure assessment instruments are used, it is likely that parents would have had difficulty remembering details about the frequency and timing of pesticide use prior to and during the pregnancy of interest, especially when this may have been many years in the past. Thus, one can assume that such information about past pesticide use is prone to error. If the error in information provided by parents of children with brain tumors is similar in level to that of parents of the comparison (control) parents, this will incorrectly tend to reduce the magnitude of the effect (as measured by the odds ratio) towards no association (odds ratio = 1.0). In other words, the risk estimates may have underestimated the true effect. However, in studies of childhood disease, there is a concern that case parents may be more motivated than control parents to find a reason for their child's illness, and differential recall may result. This difference in recall and reporting of exposure between

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[227]Davis et al., ibid.

[228]Gold, E., L. Grodis, J. Tonascia, and M. Szklo. (1979) Risk factors for brain tumors in children. *American Journal of Epidemiology*, v. 109, p. 309-319.

Hemminki, K., I. Saloniemi, T. Salonen, T. Partanen, and H. Vainio. (1981) Childhood cancer and parental occupation in Finland. *Journal of Epidemiology and Community Health*, v. 35, p. 11-15.

Gold, E.B., M.D. Diener, and M. Szklo. (1982) Parental occupations and cancer in children. *Journal of Occupational Medicine*, v. 24, p. 578-584.

Wilkins and Koutras, ibid.

Howe, G.R., D. Burch, A.M. Chiarelli, H.A. Risch, and B.C.K. Choi. (1989) An exploratory case-control study of brain tumors in children. *Cancer Research,* v. 49, p. 4349-4352.

Wilkins and Sinks, ibid.

Kuijten et al., ibid.

Davis et al., ibid.

Leiss, J.K., and D.A. Savitz. (1995) Home pesticide use and childhood cancer: A case-control study. *American Journal of Public Health* v. 85, p. 249-252.

[229]Hemminki et al., ibid.

Wilkins and Koutras, ibid.

Fear, N.T., E. Roman, G. Reeves, and B. Pannett. (1998) Childhood cancer and paternal employment in agriculture: the role of pesticides. *British Journal of Cancer*, v. 77, p. 825-829.

case and control parents could result in an overestimation of effect.[230] At present there are few data available to estimate the amount of pesticide recall error and potential differences between parents of children with cancer and parents of healthy children.

Finally, the assessment of the epidemiologic evidence is complicated by the lack of supporting experimental studies that would provide biologic plausibility. There has not been sufficient laboratory research on the potential for specific pesticides to induce cancer in offspring after exposure *in utero* or exposure of the father.

In sum, there is an array of epidemiologic evidence indicating that parental and childhood exposure to pesticides might increase the risk of childhood brain tumors in offspring. The current literature would also suggest an increased risk for other childhood cancers such as leukemia.[231] However, the causal interpretation of these findings is complicated by deficiencies in the published studies and lack of experimental research to provide a biologic framework. Therefore, in my opinion, regulatory action based on epidemiologic evidence is premature at present.

## Future Directions

Indirect exposure assessment based on parental recall of the chemicals used remains one of the major limitations of case-control studies that is not easily corrected. There have been recent advances in methods to obtain improved occupational exposure data in community case-control studies.[232] Also, several new approaches to estimating general environmental, household, and personal pesticide exposure have been proposed. These include house dust sampling, biologic monitoring, and remote sensing and geographic information systems.[233] However, until reliable and affordable markers of direct pesticide

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[230] Werler, M.M., B.R. Pober, K. Nelson, and L.S. Holmes. (1989) Reporting accuracy among mothers of malformed and nonmalformed infants. *American Journal of Epidemiology*, v. 129, p. 415-421.

[231]Daniels et al., ibid.
Zahm and Ward, ibid.

[232]Stewart, P.A., W.F. Stewart, E.F. Heineman, M. Dosemeci, M. Linet, and P.D. Inskip. A novel approach to data collection in a case-control study of cancer and occupational exposures. *International Journal of Epidemiology*, v. 25, p. 744-752. (1996)

[233]Ward, M.H., J.R. Nuckols, S.J. Weigel, S.K. Maxwell, K.P. Cantor, and R.S. Miller. Identifying populations potentially exposed to agricultural pesticides using remote sensing and a Geographic Information System. *Environmental Health Perspectives,* v. 108, p. 5-12. (2000)
Colt, J.S., S.H. Zahm, D.E. Camann, and P. Hartge. Comparison of pesticides and other compounds in carpet dust samples collected from used vacuum cleaner bags and from a high-volume surface sampler. *Environmental Health Perspectives,* v. 106, p. 721-724. (1998)
Edwards, R.D., and P.J. Lioy. The EL sampler: a press sampler for the quantitative estimation of dermal exposure to pesticides in housedust. *Journal of Exposure Analysis and Environmental Epidemiology*, v. 9, p. 521-529. (1999)
Loewenherz, C., R.A. Fenske, N.J. Simcox, G. Bellamy, and D. Kalman. Biological monitoring of organophosphorus pesticide exposure among children of agricultural workers in central

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exposure are developed to capture historical periods of interest, epidemiologic studies must continue to improve indirect exposure assessment tools. Improved structured questionnaires with job- and exposure- specific questions may substantially improve the quality of information obtained from interviews with parents.[234] For example, questions on the type of crop and purpose for use have been helpful in studies of occupational pesticides.[235] Information from new pesticide-exposure databases and reference literature could also be incorporated with the information from the questionnaires to improve exposure classification.[236] Questionnaires that include detailed items on household pesticide application methods and other exposure determinants, as in the Pogoda et al. study, may be helpful. Validation studies, including household and biologic sampling, are needed to evaluate the accuracy of questionnaire responses.

There are examples of epidemiologic studies that have identified important environmental hazards for children, such as lead and mercury; nonetheless, obtaining definitive evidence for other agents has been difficult. Conclusive evidence regarding the risk to parents and children posed by environmental exposures to agents, such as solvents, metals, electromagnetic fields, and air pollution, has remained elusive. Many of the epidemiologic study design issues illustrated in this case study of pesticides and childhood brain tumors apply to these other exposures as well. The need for innovations in exposure assessment and additional parallel laboratory research is paramount to improve the scientific basis of risk assessment and subsequent policy decisions.

## Discussion

**Discussants:**

Christopher J. Portier, Ph.D., Chief, Laboratory of Computational Biology and Risk Analysis, and Associate Director, National Toxicology Program, NIEHS

John Bailar, M.D., Ph.D., Professor, University of Chicago; retired PHS officer, formerly at National Cancer Institute (NCI), former editor of the Journal of

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Washington State. *Environmental Health Perspectives,* v. 105, p. 1344-1353. (1997)

[234]Bunin et al., ibid.
Stewart et al., ibid.
Blair, A., and S. H. Zahm Methodologic issues in exposure assessment for case-control studies of cancer and herbicides. *American Journal of Industrial Medicine*, v. 18, p. 285-293. (1990)

[235] Nanni, O., M. Ricci, C. Lugaresi, D. Amadori, F. Falcini, and E. Buiatti. Interactive use of *a priori* exposure matrices to improve the characterization of chemical exposures in agricultural work studies. *Scandinavian Journal of Work, Environment and Health*, v. 19, p. 191-199. (1993)

[236]Leighton, T.M.,and A.P. Nielsen. The United States Environmental Protection Agency, Health Canada, and National Agricultural Chemicals Association Pesticide Handlers Exposure Database. *Applied Occupational and Environmental Hygiene*, v. 10, p. 270-273. (1995)
Sexton, K., S.G. Selevan, D.K. Wagener, and J.A. Lybarger. Estimating human exposures to environmental pollutants: Availability and utility of existing databases. *Archives of Environmental Health*, v. 47, p. 398-407. (1992)

the NCI, former statistical consultant to the New England Journal of Medicine; MacArthur Fellow, 1990-1995; Institute of Medicine member

William H. Farland, Ph.D., Director, National Center for Environmental Assessment, EPA

**Dr. Portier** focused on the three questions posed for this topic. (See the seminar program on page 191. The questions posed were: 1. Based on available scientific evidence about environmental health risks to children, what can we conclude? 2. To what extent do we have consensus? 3. To resolve the areas of disagreement, what types of research would be most helpful?) His answer to the first was that the available scientific evidence allows us to conclude that environmental health risks to children exist, that they are something to be concerned about, and that these risks may be both qualitatively and quantitatively different than those seen in the adult population. What is perceived as a higher risk for the young may simply be a "faster" risk, because effects may occur or manifest more quickly. Age, time, and duration of exposure also play important roles.

Dr. Portier proposed that the desire for improved screening for environmental risks to children's health was an area of consensus, and pointed to the table on cost and health protectiveness that Dr. Mattison presented in his talk as a guide. (See Table 13.)

He had two suggestions for new research directions, both new technologies. The first was "toxicogenomics", the term used to describe an emerging scientific discipline that combines genomics (the study of genes and their function) and bioinformatics (the management and analysis of biologic research data using advanced computing techniques) to identify and describe the ways that chemical molecules affect and are affected by human bodies.[237] Toxicogenomics, Dr. Portier said, should be used to explore how interactions between genes, the age of the subject, and environmental exposures affect whether and how an adverse effect manifests itself. Exposure to an environmental agent at an age where a gene is being expressed may, for example, have a much larger impact than otherwise. Investment in research and in the tools of toxicogenomics — notably microarray and protein chip technologies — is very important, he stated.[238]

The second area for new research cited was improved toxicological testing methods. Dr. Portier suggested that structure-activity relationships (SAR), which have been used to directly evaluate toxicologic potential, should be applied to examine the major drivers of toxicity: the absorption, distribution, metabolism, and eventual interaction of chemical agents with important targets inside cells. Dr. Portier asserted that SAR could yield this information, if large databases were exploited. Toxicological testing could also be improved by being expanded to include information about periods when children are potentially more vulnerable to damage from chemical exposure, like during the perinatal and prenatal periods.[239]

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[237]Definitions adapted from "The Genomics Lexicon" < http://209.52.56.28/lexicon/index.html>.

[238]These two types of computer chips can be used for simultaneous monitoring of the expression levels of hundreds or thousands of genes.

[239]Perinatal means "around the time of birth" and includes the period from the 28th week of gestation

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Determining whether a particular agent crosses the placenta, for instance, supplies important clues.

Dr. Portier argued that special emphasis is needed for the non-cancer endpoints, such as damage to brain function or the immune system, where there are not presently good testing systems. Developmental immunology and immunotoxicity is yet another area where more information is needed, he stated. Within these disciplines, there is particular need to develop good tests for allergenicity.

Dr. Portier echoed the comment of several other discussants about the desirability of removing restrictions on the use of FDA's and EPA's information databases on the toxicology of compounds, noting that NIEHS's National Toxicology Program database is routinely used to address big-picture questions. Toxicology research still concentrates on studies of individual chemicals administered to single species, evaluating specific outcomes. The challenge is to look across multiple compounds and numerous animal species to draw conclusions about general patterns; to apply large mechanistic models and good statistical techniques to link the available data; and test reasonable mechanism-based hypotheses.

**Dr. Bailar** focused his presentation on cancer. He noted that cancer is a biologic process and, if it were possible, it would be assessed in terms of the behavior of that process. Such information could be used to assess all aspects of cancer: its cause, prevention, early detection, diagnosis, treatment, follow up, and ultimate outcome. However, we lack good measures for how masses of cells act, and must instead rely on imperfect substitutes, like microscopic appearance. This can lead to confusion over cancer trends, because a change in the way an indirect indicator is used (e.g., whether we count a particular mass of cells as a tumor) or in how its findings are interpreted (e.g., whether a benign tumor indicates a greater risk of developing cancer) may give the appearance of a change in incidence rate of disease, whether or not a change has actually taken place. For example, there has been a substantial expansion in the search for cancers and a substantial increase in sensitivity to the issue. New screening methods may in some cases identify cancers that would never have resulted in adverse health consequences (for example, because they grow too slowly or do not interfere with a vital organ) and would therefore remain unrecognized, were it not for the screen. Data suggest that this has occurred for breast, prostate, and lung cancers, and may be true for cancers of the thyroid and ovary. A screening program in Japan resulted in the detection of about a three-fold increase in the apparent incidence of neuroblastoma, one of the more important forms of malignant neoplasm in young children. The tumors that were found were in their early stages. They were treatable, and patients had excellent survival rates, but there was virtually no impact on the population-wide mortality rate, because of this enhanced detection phenomenon.

The bottom line, Dr. Bailar maintained, is that cancer incidence rates cannot be used as a measure of the change in risk. This does not mean that environmental causes are unimportant in childhood cancer or that specific agents do not cause cancer in children, he cautioned, but it does suggest that there is little, if any, evidence for a broad increase in

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before birth through the first 7 days after delivery. "Prenatal" means "before birth".

cancer in children.

**Dr. Farland** began by noting that, although the seminar's discussions clearly suggest that environmental health risks exist for children, examples of manifestations of children's susceptibility to environmental health hazards are limited. A basic problem is that many existing studies show deficiencies when measured against the traditional criteria used by epidemiologists to judge causality.[240] These criteria include the consistency of the results across studies, timing (whether or not the exposures occurred before the effect), and the presence of a dose-response relationship (whether the effects increase when exposure increases). Because one of the more important issues to consider when examining causality is biological plausibility, the need to understand how chemicals interact with the body is key.

Dr. Farland observed that, because childhood cancer and birth defects are relatively rare events, there is a risk that scientific studies will fail to detect adverse health effects. EPA is continually required to explain why studies that show no adverse effect (so-called "negative results") are not good evidence that there is no effect, because they were not designed with the statistical power to detect relatively small increases in population risk that may result from some exposures.[241] Therefore, studies need to place emphasis on better exposure estimates and other changes that will yield more power.

A final point raised was that epidemiologic studies are most appropriate for the evaluation of human responses to exposures (e.g., to determine whether there are any adverse health effects detectable in a population exposed to a spill of a chemical that has not been adequately characterized in terms of toxicity); are largely useful in hazard identification (i.e., in answering the question "Is this chemical a possible hazard?"); but are less useful for risk assessment for either individuals or populations (because there are too many differences, that cannot be controlled experimentally, among people in their exposures and physiologies to permit accurate assessment of precisely how much exposure leads to how much risk). The critical needs are for better ways of measuring exposure, improved understanding of which exposures are critical to particular health effects, and the use of early indications of possible disease (called biomarkers) in studies. One example of the use of early markers is Dr. Frederica Perera's work on polyaromatic hydrocarbons (PAHs) and air pollution.[242] Some of the research on polymorphisms shows increased risks for people with certain genetic variations, while other work shows that certain subpopulations may be less susceptible to some exposures. It's also true that having a lower risk for one outcome may produce a higher risk for another.

With regard to scientific consensus, Dr. Farland said that he hoped the scientific

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[240]Specifically, the Bradford-Hill criteria (Bradford-Hill, A. 1971. *Principles of Medical Statistics*, 9th edition. New York: Oxford University Press).

[241]Often, statistical power is weak because the number of animals or people observed is too small to allow generalization to the exposed population. However, poor data also can weaken statistical power.

[242]For example, Perera, F.P., W. Jedrychowski, V. Rauh, and R.M. Whyatt. 1999. Molecular epidemiologic research on the effects of environmental pollutants on the fetus. *Environmental Health Perspectives,* v.107, Supplement 3, p. 451-460.

community — particularly through independent peer review — would collectively identify and validate areas of consensus and work together to compile data.

**General Discussion**

**Dr. Goldman** asked if too sharp of a focus on prenatal and perinatal cancers might result in missing an increased risk of cancer later in life. Dr. Olshan conceded that this was a concern, but asserted that childhood cancers were in and of themselves an important outcome to study. **Dr. Portier** added that a crucial piece of information missing from many studies is the effect of pattern of exposure as a function of age. Adding such measures to a chronic cancer study or a neurological or immunological assay increases the number of animals required, which in turn increases the time, effort and cost of the study. However, the information that could be derived could, in the long run, seriously reduce the reliance on animals and the need to study each and every chemical of concern, because it would generate a better picture of the effects of age, dose, and pattern of response.

**Dr. Schierow** noted that the increased use of experimental animals has been raised as an objection to some of the recent testing protocols. **Dr. Portier** indicated that there is a trade off between optimizing the number of animals used in a study that looks for a specific effect, and using a greater number in a more generalized study that covers multiple possible endpoints.

**Dr. Schierow** asked about alternative tests that do not require the use of animals. These are useful, **Dr. Portier** replied, but there is insufficient information on how to translate the results of such tests to humans. Animal tests are still needed to anchor and validate non-animal alternatives, although techniques and understanding are improving, and the need for animal tests is diminishing.

**Rabbi Swartz** asked the audience to comment on the contradictory studies on whether cancer rates were increasing.

**Dr. Bailar**, who organized and directed the national cancer survey that evolved into the SEER program, reiterated his earlier skepticism about the meaning of the changes seen in incidence rates, given the changes over the past several decades in how cancer is detected, diagnosed, and reported.

**Dr. Schierow** then called the morning session to a close.

## Policy Opportunities

Given the state of the science, policy experts were asked to advocate a particular policy approach in response to the question "What, if any, is the appropriate role of the federal government (as opposed to state or local government) in managing children's environmental health risks?" Four individuals who had publicly expressed diverse views on this subject were asked to prepare scholarly papers describing the approach they favored and discussing its strengths and weaknesses. CRS asked each author to reference statements of fact to published, peer-reviewed research or to an independent authority. Matters of personal opinion were to be identified as such, according to CRS policy. None of the policy paper authors wrote on behalf of an organization; each expressed personal views. Authors retain responsibility for the accuracy and balance of their final papers. CRS assumes responsibility for the balance of the overall report.

Drafts of policy papers were presented in the afternoon session of the May 22, 2000 seminar. Final versions of these papers are included below, followed by a summary of the discussion which followed presentation of the four draft papers.

Convergence, rather than divergence, of opinion again is evident among the authors and discussants of policy papers: authors seem unanimously to favor governmental action in the form of research. The following statements of consensus have been approved by participants in the May 22, 2000, seminar.

- The federal government should identify research priorities and conduct and sponsor basic medical, biological, environmental, and public health research to improve scientific understanding of children's health and development.
- The federal government should organize, fund, and evaluate monitoring programs to collect data on chemicals in the environment, children's health trends, and children's exposure to chemicals.
- The federal government should help shape, manage, and support a public health infrastructure capable of preventing and responding to significant children's environmental health risks, with special attention to children with limited access to medical care.
- Federal policies should recognize that economic status, environment, and health interact, and that diseases usually are caused by a confluence of genetic and environmental factors.
- Federal policies for research and risk management related to children's health should recognize the significance of morbidity, although no satisfactory metric is available for quantitative comparisons.[243]

Differences of opinion lie in more detailed prescriptions for public policy.

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[243]Participants discussed the advantages and disadvantages of various health benefit measures in use today, such as lives saved, life-years saved, quality-adjusted life-years (QALYs) saved, and disability-adjusted life-years (DALYs) saved, but disagreed about their utility.

Because a key issue concerned whether environmental health risks to children are significant or not relative to other health risks, and mortality rates were used to indicate such risks, a table is provided (Table 16) showing selected major causes of death and death rates per million in 1997 for infants and children and, for comparison, the U.S. population as a whole.[244] The age of 19 years is used as the upper bound of childhood, because growth and development continue throughout adolescence.

A key counterpoint to the argument that death rates indicate relatively low risk to children from exposure to environmental pollutants was the recognized importance of non-fatal disabilities and illnesses that might result from chemical exposure. Because few children die, mortality risks are not very useful indicators of children's health, it was argued. (This argument also is made more generally: mortality risks are too small a piece of the picture of public health even for evaluating the health of adults.)

Unfortunately, neither the method nor the data exist to allow construction of a second table comparing rates of morbidity due to various health conditions. Only a few reliable figures are available. For example, about 12,400 cases of cancer are diagnosed in children and adolescents younger than 20 years each year.[245] Birth defects occur at a rate of about 1 in 28 births, affecting (to various degrees) approximately 150,000 babies annually.[246] Asthma is the leading chronic illness in children of the United States and the leading cause of school absenteeism due to chronic illness. About 150,000 children are hospitalized due to asthma each year. An estimated 4.8 million children under 18 years of age have asthma.[247] Unfortunately, we know remarkably little about the contribution that environmental factors make to these childhood illnesses.

EPA claims that nearly one million U.S. children are lead poisoned, probably due to exposure to lead-based paint. But even in the case of lead poisoning, factors other than chemical exposure influence disease rates. In almost all cases, only suggestive data exist to link environmental chemicals exposure to adverse health effects, and genetics are likely to play a significant role in causation.

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[244] Many causes of death have been omitted here, including all those associated with birth or unique to prenatal or postnatal conditions, such as Sudden Infant Death Syndrome. Some that were omitted are leading causes of death in one or more age groups. For example, septicemia (a blood infection) caused a total of 22,396 deaths in the U.S. population, including 196 infant deaths and 164 deaths in childhood (ages 1 - 19), while benign neoplasms (tumors) caused a total of 7,659 deaths in the population, including 198 deaths to children and 25 deaths among infants. The top 10 causes of childhood deaths are included above and are listed in order from most to least childhood deaths.

[245] Klausner, R.D. (1999) Foreward. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995.* National Cancer Institute, Bethesda, MD. p. iii.

[246] March of Dimes. Factsheet on Birth Defects.
http://www.modimes.org/HealthLibrary2/FactSheets/Birth_Defects.htm

[247] Centers for Disease Control and Prevention, National Center for Environmental Health, Asthma Facts
[http://www.cdc.gov/nceh/asthma/factsheets/asthma.htm]

**Table 16. Numbers of deaths and death rates (per million) for selected causes of death in the United States in 1997**[248]

| | Infants and Children, 0 to 19 Years (Population = 77,079,882) | | U.S. Population (Population = (267,720,362) | |
|---|---|---|---|---|
| Cause of Death | Number of Deaths | Crude Death Rate | Number of Deaths | Crude Death Rate |
| All | 55,879 | 725 | 2,314,245 | 8,644 |
| Motor vehicle accidents | 7,814 | 101 | 42,340 | 158 |
| Birth defects | 7,431 | 96 | 11,912 | 44 |
| Homicide | 3,767 | 49 | 19,425 | 73 |
| Cancer | 2,261 | 29 | 539,577 | 2,015 |
| Suicide | 2,109 | 27 | 30,535 | 114 |
| Heart disease | 1,564 | 20 | 726,974 | 2,715 |
| Flu & pneumonia | 836 | 11 | 86,449 | 323 |
| Fire/burns | 773 | 10 | 3,601 | 13 |
| Cerebrovascular | 467 | 6 | 159,791 | 597 |
| Asthma, bronchitis, emphysema | 316 | 4 | 109,029 | 407 |
| Human Immuno-deficiency Virus (HIV) | 211 | 3 | 16,516 | 62 |
| Accidental fall | 208 | 3 | 11,858 | 44 |
| Medical treatment | 108 | 1 | 3,043* | 11 |
| Bathtub drowning | 104 | 1 | 329 | 1 |
| Appendicitis | 26 | <1 | 395 | 1 |
| Lightning | 13 | <1 | 58 | <1 |
| Cold weather | 11 | <1 | 501 | <1 |
| Dog bite | 11 | <1 | 19 | <1 |
| Whooping cough | 6 | <1 | 6 | <1 |
| Fireworks | 3 | <1 | 8 | <1 |
| Lack of food | 1 | <1 | 114 | <1 |
| Venomous plant or animal | 1 | <1 | 3 | <1 |

[248]Many causes of death have been omitted here, including all those associated with birth or that are unique to prenatal or postnatal conditions, such as Sudden Infant Death Syndrome. Some that were omitted are leading causes of death in one or more age groups. For example, septicemia (a blood infection) caused a total of 22,396 deaths in the U.S. population, including 196 infant deaths and 164 deaths in childhood (ages 1 - 19), while benign neoplasms (tumors) caused a total of 7,659 deaths in the population, including 198 deaths to children and 25 deaths among infants. The top 10 causes of childhood deaths are included and are listed in order from most to least childhood deaths.

| | Infants and Children, 0 to 19 Years (Population = 77,079,882) | | U.S. Population (Population = (267,720,362) | |
|---|---|---|---|---|
| Cause of Death | Number of Deaths | Crude Death Rate | Number of Deaths | Crude Death Rate |
| Antibiotics (reaction) | 0 | 0 | 11 | <1 |
| Botulism | 0 | 0 | 2 | <1 |

Source: Data are from the ninth revision of the International Classification of Diseases (ICD-9) Title and Code Cross Reference File, which can be found at the Centers for Disease Control and Prevention (CDC), National Center for Health Statistics website [http://www.cdd.gov/nchs/data/qmwki_97.pdf].

* These are reported instances of death due to medical treatment. The National Academy of Sciences estimated in November 1999 that 44,000 to 98,000 Americans die each year from medical errors.

Kenneth Chilton, Ph.D., presented the first policy paper in the afternoon session of the CRS seminar on May 22, 2000. Dr. Chilton, a Distinguished Senior Fellow and Manager of Environmental Research at the Center for the Study of American Business at Washington University in St. Louis, Missouri, argued that environmental risks to children's health are not large relative to other risks, and were exaggerated by the Clinton Administration. He expressed concern that this exaggeration might distort priorities in public health programs, diverting public resources away from programs targeting greater risks. He urged restraint in public resource allocations and in public communication about children's environmental health risks, tempering pronouncements about risks with acknowledgments of associated benefits that may justify risks.

Dr. Chilton described current federal research efforts as "considerable" and "adequate." He said he would either broaden or rescind President Clinton's Executive Order 13045, which mandates development of child-centered programs. Environmental protection legislation, Dr. Chilton stated, should be written to include consideration of costs, benefits, and other risks when regulating environmental contaminants.

Finally, Dr. Chilton recommended that a broadly focused public health agency, rather than EPA, should lead any children's environmental health initiative on the part of the federal government. This arrangement would be more likely to preserve an appropriate balance among programs devoted to various risks.

Rabbi Daniel Swartz, Executive Director of the Children's Environmental Health Network (CEHN), emphasized the importance of social, ethical, and political values, in addition to biological and economic factors, in determining what federal policies should be with respect to children's environmental health, particularly in light of the uncertainty of scientific estimates of risk. He argued that equity, liberty, and justice were values Americans hold in common. He expressed a preference for policies aimed at prevention, as opposed to treatment after exposure. Reductions in poverty should be pursued along with reduced environmental hazards, according to Rabbi Swartz. He admired the example set by the Food Quality Protection Act standard for protecting children in which pesticides are not assumed to be completely safe for children, but are not assumed to be dangerous at all levels in all circumstances, either: data drive the decision whether to provide an extra margin of precaution in standard setting.

Rabbi Swartz provided several suggestions for federal action to protect children's environmental health, including more protective standard setting, consideration of cumulative and aggregate risks to children in risk assessments and rule development, development of national monitoring and research strategies, establishment of a broad parental right to know about potential risks to their children, better intragovernmental and intergovernmental coordination of relevant programs, support for a moral code that protects children, and responsible behavior with respect to children. Finally, Rabbi Swartz warned of the limitations of economic analyses and advised the federal government to revise economic assumptions that he alleged are incompatible with protection of children's environmental health. Rabbi Swartz said he would retain and support Executive Order 13045 on Children's Environmental Health, establish a White House Council on Children's Environmental Health and Safety, and employ whatever means are appropriate at the federal level to achieve protection of children's health, including regulation, voluntary programs, grants, demonstration programs, outreach and education, and legislation.

Kimberly Thompson, Sc.D., Assistant Professor of Risk Analysis and Decision Science at Harvard University's School of Public Health, gave the third policy paper. Dr. Thompson provided an overview of the recent history of federal agency involvement in children's health issues. She argued that the most significant risks to children's health were not the focus of recent initiatives on children's environmental health, but noted the lack of data that would permit relative risk assessment. She summarized research needs identified by various workgroups in recent years.

The federal government should evaluate and address environmental risks, she urged, in light of more certain risks of equal or greater magnitude, such as children's risk of dying in automobile accidents, gun violence, and child abuse. She argued that both exposure to, and toxicity of, chemicals in the environment must be assessed chemical-by-chemical, because the quality and quantity of health effects are variable. Dr. Thompson concluded that sparse data do not provide a solid scientific basis for rulemaking.

She urged policy makers and researchers to clearly define terms, identify inequities, and target policies to relatively high risks. The role of the federal government should be to coordinate programs concerned with child welfare, address children's health issues of national or international scope, support medical and public health research, regulate multinational industries, provide resources to meet children's needs, and monitor children's health, according to Dr. Thompson. She questioned our national commitment to improving children's health, however, and expressed special concern about the health of uninsured children and the congressional failure to ratify the International Convention on the Rights of the Child.

Dr. Thompson stated that federal support and oversight are needed for traditional local public health programs, such as immunization and food stamp programs, and she argued that a more analytic approach is needed to ensure accountability and efficient use of federal resources available for children's health programs. A prerequisite to analysis, she claimed, is more transparency in how resources are allocated to research and risk management programs. Dr. Thompson criticized policy decisions that fail to consider tradeoffs among risks and benefits, and she concluded that future research should collect data

on costs and benefits of alternative risk management policies as well as information needed to put environmental risks in perspective.

Richard Jackson, M.D., M.P.H., Director of the National Center for Environmental Health at the Centers for Disease Control and Prevention (CDC), contributed the final major policy paper in which he argued that federal responses to chemical risks historically have been delayed pending data collection and analysis, resulting in unnecessary suffering and permanent disabilities. He urged vigorous enforcement of existing regulations and aggressive promulgation of "child-centered, science-based, prevention-oriented environmental health and safety policies that protect children now and in the future." The special role of the federal government should include public health surveillance, data collection and analysis, and development of national goals for children's health, he stated.

Much more funding for research is needed, Dr. Jackson claimed, in order to fully understand the health effects resulting from exposures to environmental toxicants, particularly when those health effects appear only many years after exposure. Dr. Jackson praised the Food Quality Protection Act provision mandating addition of up to a 10-fold safety factor to federal standards limiting pesticide residue levels on food eaten by children. He argued that the FQPA forces manufacturers of pesticide products to prove their safety, an approach which he favored. Swift implementation of the FQPA provisions is needed, he said. He also urged continued and increased funding for the existing interagency task force on children's environmental health.

Discussants raised a number of significant issues. For example, Dr. Trudy Cameron, a professor of economics at the University of California at Los Angeles, noted that the policy papers all seemed to recommend selection of measurable public health goals prior to decisions about how to allocate federal resources. She advised selection of rather broad measures, so that goal attainment would not be impeded. In addition, Dr. Cameron argued that the federal government should intervene to manage the availability of public goods like health protection, because preventive measures in particular are unlikely to attract much private investment.

Many speakers expressed concern about the focus on mortality when illnesses are so much more prevalent in children. It was noted that by defining children's risk in terms of deaths during childhood would miss any increase in death rates during the adult years due to childhood exposure to environmental contaminants.

Dr. James Wilson, Senior Fellow at Resources for the Future, stated that most federal laws governing chemicals and the environment protect women of child-bearing age and children, making additional chemical regulations unnecessary. The key lesson of the seminar, he alleged was that the effect of poverty on the health of children is a more significant problem than environmental pollution.

Ms. Karen Florini, a Senior Attorney with Environmental Defense, argued that the United States is rich enough to be both safe and healthy, that is, to address injuries as well as environmental risks to children. What she termed a "lack of political will" to address

poverty, guns, and smoking does not excuse delays in addressing environmental health hazards for which political will does exist, she said. In addition, Ms. Florini claimed that at least some progress in reducing environmental risks to children may be relatively inexpensive or even profitable for the regulated industries.

Ms. Florini added that data are too sparse to rule out children's exposures to environmental chemicals as causes of chronic diseases in adulthood. Until data can be collected, she urged use of conservative, protective assumptions to fill in any scientific gaps.

Ms. Sandra Tirey, an Assistant Vice President of the Chemical Manufacturers' Association (now the American Chemistry Council), suggested that a key role for the federal government should be in communicating accurate children's health risk information to the general public. She also favored federal incentives for collaboration "among government, academic, industry, and other stakeholder interests."

The ultimate purpose of research sponsored by the federal government seemed to be at issue, according to Mr. Jim O'Hara, formerly with the Food and Drug Administration and now directing Health-Track (a project supported by The Pew Charitable Trusts through a grant to Georgetown University). He noted that some policy advocates want research to inform regulations, while others seem to see research only as a tool to inform the public. He urged integration of public health and environmental protection approaches in federal policies.

CRS-111

# Placing Children's Environmental Health Risks in Perspective

By Kenneth W. Chilton, Ph.D.

## Introduction

Children's health is an issue of concern to all parents and even to those who aren't parents. It is trite to say that our children are America's future, but it is still true. Healthy children are better able to develop into strong contributors to the society that responsibly nurtures them.

This is a pragmatic view of the importance of protecting children's health, whereas parents are motivated by stronger ties of love. They know that the word "dependent" is more than a line item on an IRS 1040 form. Children depend on their parents to see that they eat healthy meals, dress appropriately for weather conditions, are protected with seat belts and bicycle helmets, don't play in the streets, are taken to the doctor when they have health problems and for myriad other actions that protect and nurture them.

Children's environmental health could be defined broadly enough to take into account nearly all threats to a child's well-being. And perhaps it should be. Nonetheless, when most Americans think of "environmental health" they think of pollution or contaminants as the threat being addressed.

In this context, increasing emphasis is being placed on the fact that children are not just small adults. Children (ages 0 to 14 for the purposes of this paper) may have different exposures and responses to environmental contaminants. For example, adults are not likely to suffer the effects of lead poisoning from eating lead-based paint or putting lead dust in their mouths while crawling on the floor in an apartment with lead paint. In other instances, it is a different reaction in immature enzyme systems or other developmental processes that makes the risk to children greater than for adults. It is not true that children are more at risk from *all* environmental contaminants, however.

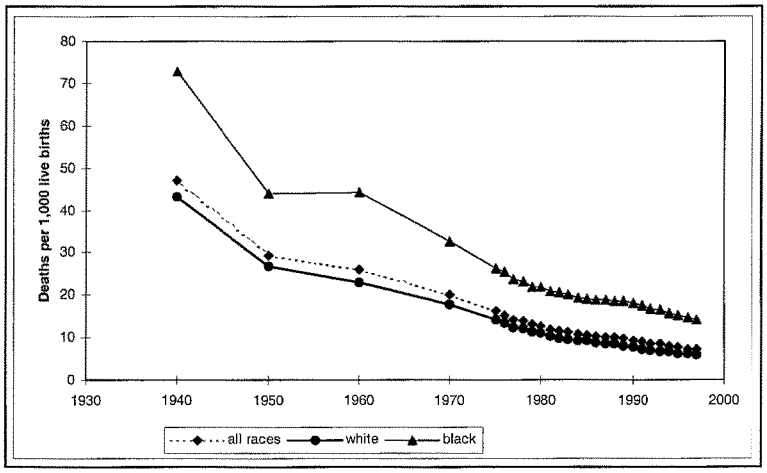
Is the increased emphasis on children's environmental health really justified by the significance of the risks presented by environmental contaminants? This paper argues that environmental threats to children's health are not large relative to other risks, and are being exaggerated by the White House and the Environmental Protection Agency. As a result, federal research programs that are designed to improve overall public health (and children's health, as well) are in danger of having their priorities shifted in ways that make them less – not more – effective.

## Significance of Children's Environmental Health Risks

### Environmental Health Risks Relative to Other Risks to Children's Health: Missing the Forest for the Trees.

***The Under-reported Good News.*** The heightened concern for children's environmental health is receiving disproportionate media attention compared to the under-reported good news about overall children's health improvements. Trends in infant mortality and life expectancy at birth provide simple indicators of trends in children's health. These trends (shown in Figures 5 and 6) show dramatic and unmistakable improvements for the average American, though infant mortality rates and life expectancy for African Americans continue to lag behind white Americans.

**Figure 5. Infant Mortality Rate: 1940-1997**

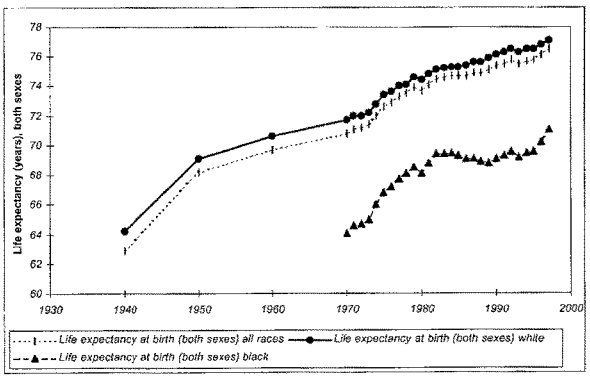



Source: Hoyert, Donna L., Kenneth D. Kochanek, and Sherry L. Murphy (1999), "Deaths: Final Data for 1997," National Vital Statistics Reports, Vol. 47, No. 19 (Centers for Disease Control, National Center for Health Statistics, June 30), p. 86.

Infant mortality (deaths within the first year of life) fell in the period 1940 to 1997 from 43.2 deaths per 1,000 live births to 6.0 for whites, and from 72.9 to 14.2 deaths per 1,000 for blacks. (See Figure 5.) Cure or prevention of infectious diseases such as smallpox, polio, diphtheria, rubella and measles; earlier detection and better treatment for diseases such as cancer; better sanitation and better drinking water purification methods; increased availability of fresh fruits and vegetables; and numerous other scientific, medical, and public health advances are responsible for this highly favorable trend.

Life expectancy at birth is another important indicator of overall health and welfare. (See Figure 6.) From 1970 to 1997, this indicator rose from 64.1 years to 71.1 years for African Americans. This is a substantial improvement of 11% in just over two and one-half decades. Data for Caucasians extend as far back as 1940 when life expectancy at birth was 64.2 years compared to 77.1 years in 1997.

**Figure 6. Life Expectancy at Birth: 1940-1997**




Source: Hoyert, Donna L., Kenneth D. Kochanek, and Sherry L. Murphy (1999), "Deaths: Final Data for 1997," National Vital Statistics Reports, Vol. 47, No. 19 (Centers for Disease Control, National Center for Health Statistics, June 30), p. 23. For 1971-1974, Anderson, Robert N., Kenneth D. Kochanek, and Sherry L. Murphy (1997), "Report on Final Mortality Statistics, 1995," Monthly Vital Statistics Report, Vol. 45, No. 11, Supp. 2 (Centers for Disease Control and Prevention, National Center for Health Statistics, June 12), p. 19.

Of course, these overall indicators do not mean that there are not particular threats to children's health that are on the rise. Asthma and some rare forms of cancer appear to be increasing. As we shall see in a moment, however, most of the reported rising trends in more common childhood cancers are questionable. In addition, improved treatment is reducing childhood mortality from most forms of cancer.

***Comparing Health Risks from Environmental Contaminants to Other Risks.*** Data on childhood deaths, published in *National Vital Statistics Reports,* help to illuminate the leading causes of death in children. Table 17 shows the 10 leading causes of death in 1997 for two different age groups – children 1 to 4 years of age and those 5 to 14 years old.[249] For both age groups, "accidents and adverse effects" are the leading causes

[249]Causes of infant mortality (0-1 year olds) are rather different from causes of deaths for 1-to-4 year olds. The death rate is much higher – 723 deaths per 100,000 – and includes such factors as: disorders relating to short gestation and low birth weight, sudden infant death syndrome, respiratory distress syndrome, newborn affected by maternal complications of pregnancy, etc. Not surprisingly,

(continued...)

of childhood mortality. Accidents represent 37% of deaths in the 1-to-4 age group and 42% of those in the 5-to-14 grouping. Leading causes of accidental death include suffocation, drowning, motor vehicle occupant injury, fire and burns, and pedestrian and bicycle injuries. Accidents also cause approximately 246,000 hospitalizations, 8,700,000 emergency room visits, and 11,000,000 visits to physicians annually.[250]

Many of the deaths and injuries from accidents are preventable. In his May 1998 testimony before a Senate Labor and Human Resources Committee hearing, Dr. C. Everett Koop, former U.S. Surgeon General, claimed that 90% of childhood injuries and deaths are preventable.[251] And the good news is accidental deaths in the 14 and under age group are falling. Childhood deaths due to accidents declined 18% from 1987 to 1995, from 8,069 to 6,611 annually.[252] This progress is likely due to many factors – increased use of seat belts, child safety seats, bicycle helmets, smoke detectors, and many other safety innovations.

Malignant neoplasms (cancers) are the second and third leading cause of death among 5-to-14 year olds and 1-to-4 year olds, respectively. However, they account for roughly one-fifth as many deaths as accidents for 1-to-4 year olds and about one-third as many deaths as accidents in 5-to-14 year olds. Cancer deaths occur 20% more frequently than homicides for the 1-to-4 age group. Congenital anomalies (birth defects) are the second leading cause of deaths for 1-to-4 year olds (about 11% of the total).

***EPA's Designation of Top Environmental Threats to Children's Health.*** In September 1996, EPA published *Environmental Health Threats to Children* to outline its agenda to protect children's health and to identify what the agency considers to be the top environmental threats to children.[253] EPA's seven-step national agenda includes the following:

- Ensure that all standards set by EPA protect children.

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[249](...continued)
congenital anomalies (birth defects) are the leading cause of infant deaths, making up 22% of the total. Accidents and adverse effects represent slightly less than 3% of infant deaths. (Hogert, D.L., K.D. Kochanek, and S.L. Murphy, *National Vital Statistics Reports*, v. 47, n. 19, Hyattsville, Md.: Centers for Disease Control and Prevention, National Center for Health Statistics, June 30, 1999. p. 88.)

[250]National Safe Kids Campaign, *The National Safe Kids Campaign Injury Fact Sheet*, September 1997.
<http://www.safekids.org/fact97/ci97.html>

[251]U.S. Congress, Senate Committee on Labor and Human Resources, *Hearing on unintentional childhood injuries and death*, 105th Cong. 2nd Sess., May 5, 1998.

[252]National Safe Kids Campaign, *The National Safe Kids Campaign Trends in Unintentional Childhood Injury Prevention Since the Launch of the National Safe Kids Campaign*, Fact Sheet, September 1997.
<http://www.safekids.org/fact97/trends97.html>

[253]U.S. Environmental Protection Agency, *Environmental Health Threats to Children*, EPA 175-F-96-001, September, 1996.

**Table 17. Ten Leading Causes of Death, Annual Number of Deaths, and Rates per 100,000 U.S. Children in 1997**

| Ages 1-4 | | | | Ages 5-14 | | | |
|---|---|---|---|---|---|---|---|
| **Rank** | **Cause of death** | **Annual number** | **Rate** | **Rank** | **Cause of death** | **Annual number** | **Rate** |
| 1 | Accidents and adverse effects | 2005 | 13.1 | 1 | Accidents and adverse effects | 3371 | 8.7 |
| 2 | Congenital anomalies (birth defects) | 589 | 3.8 | 2 | Malignant neoplasms | 1030 | 2.7 |
| 3 | Malignant neoplasms (cancer) | 438 | 2.9 | 3 | Homicide and legal intervention | 457 | 1.2 |
| 4 | Homicide and legal intervention | 375 | 2.4 | 4 | Congenital anomalies | 447 | 1.2 |
| 5 | Heart disease | 212 | 1.4 | 5 | Heart disease | 313 | 0.8 |
| 6 | Pneumonia and influenza | 180 | 1.2 | 6 | Suicide | 307 | 0.8 |
| 7 | Conditions originating in perinatal period | 75 | 0.5 | 7 | Pneumonia and influenza | 141 | 0.4 |
| 8 | Septicemia | 73 | 0.5 | 8 | Chronic obstructive pulmonary disease | 129 | 0.3 |
| 9 | Benign neoplasms, carcinoma in situ | 65 | 014 | 9 | Human Immuno-deficiency Virus | 102 | 0.3 |
| 10 | Cerebrovascular disease | 56 | 0.4 | 10 | Cerebrovascular disease /Benign neoplasms | 76 | 0.2 |
| Other causes | | 1433 | 9.3 | Other causes | | 1612 | 4.2 |
| All causes | | 5501 | 35.8 | All causes | | 8061 | 20.8 |

[1] Age-adjusted death rate per 100,000 children in this age group.

Source: Hogert, D.L., Kochanek, K.D., Murphy, S.L., National Vital Statistics Report, Vol. 47, No. 19 (Hyattsville, Maryland: Centers for Disease Control and Prevention National Center for Health Statistics, June 30, 1999) p.27.

- Expand research on child-specific susceptibility and exposure to environmental pollutants.

- Develop new, comprehensive policies to address cumulative and simultaneous exposures faced by children (as opposed to the chemical-by-chemical approach used in the past).

The agency also pledged "to provide the necessary funding to address children's environmental health issues *as a top priority among relative health risks"* (emphasis added). The shortcoming of the EPA approach is that environmental health risks have not been established to be among the top risks to children's health.

Table 18 lists the top environmental risks to children's health as EPA judges them to be. Cancer morbidity and mortality are important medical end points for many of these threats (lead poisoning and asthma being notable exceptions). Indeed, EPA has sought to link childhood cancer to environmental contaminants in a variety of forums.

### Table 18. Top Environmental Threats to Children's Health Identified by the EPA

| *Threat* | *EPA Comment* |
|---|---|
| Lead poisoning | Affects up to 1.7 million children age five and younger. |
| Pesticides | Children eat more fresh produce than adults. Some pesticides can cause cancer, nervous system damage, or respiratory illness. More than 100,000 children accidentally ingest pesticides each year. |
| Asthma | Deaths due to asthma in children and young people increased 118 percent from 1980 to 1993. |
| Drinking water contaminants | In 1995, 30 million Americans drank water from systems that violated at least one public health standard. |
| Polluted water | Mercury contamination in fish is a major threat. |
| Toxic waste dumps | Ten million children younger than age 12 live within four miles of a toxic waste dump. |
| Polychlorinated biphenyls (PCBs) | PCBs were banned by EPA in 1976 but are still present in the environment. PCB exposure during pregnancy is reported to cause learning disabilities. |
| Secondhand tobacco smoke | Can cause acute and chronic respiratory conditions in children. |
| Overexposure to ultraviolet light | Sunburns during childhood increase the risk of developing malignant melanoma. In the United States in 1995, there were an estimated one million new cases of skin cancer. |

Developed from: U.S. Environmental Protection Agency, *Environmental Health Threats to Children*, (September 1996) EPA 175-F-96-001.

At EPA's September 15, 1997, Conference on Preventable Causes of Children's Cancer, Administrator Carol Browner acknowledged that the death rate from childhood cancer has declined dramatically but went on to say:[254]

> But an equally dramatic rise in the overall number of kids who get cancer threatens to overshadow the gains we have made.
>
> In the past two decades, we have seen higher rates of acute lymphoblastic leukemia in children, higher rates of a type of brain cancer in children, and higher rates of Wilms' Tumor of the kidney... And we don't know exactly why.
>
> Many leading health experts suspect that toxins found in our environment may very well play a role in the growing incidence of certain childhood cancers. The world that our children are born into now includes tens of thousands of new chemicals that simply were not around just a few decades ago — substances that are present in our air, in our water, in our homes, in our foods.

Until about a year and a half ago, the website for EPA's Office of Children's Health Protection (OCHP) cited cancer incidence rates for the under 15 age group compiled in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) data base in order to buttress the agency's statement that childhood cancer rates for some types of cancer are on a dramatic rise.[255] The OCHP fact sheet on children's health stated that, for the 1973-to-1994 period, the incidence of acute lymphocytic leukemia was up by about 5%, brain cancer up about 40%, and Wilms' tumor up by about 46%.

But these findings were fundamentally flawed for two reasons: (1) they were based on a simple end-point analysis comparing incidence rates for 1973 to 1974 to those for 1994 to 1995; and (2) they provided no sense of the baseline frequency of these cancers. The correct way to analyze this data is by ordinary least squares regression to determine if there is a significant trend taking place rather than just a good deal of random variation in the data.

When the analysis is done properly, it shows that acute lymphocytic leukemia (ALL) is increasing at a rate of 3 added cases per 10 million 0-to-14 year olds each year (1973 to 1995). The base rate for ALL in 1973 was about 270 per 10 million for the 0-to-14 age group. Childhood brain cancers rose at an annual rate of 5 cases per 10 million over the period. The 1973 base rate was 240 cases annually per 10 million 0-to-14 year olds. Kidney and renal pelvic tumors (a broader category than Wilms' tumor) show no trend. These types of cancers occurred at a rate of 70 per 10 million children in 1973.

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[254]Browner, Carol, "Children's Health and The Environment: The EPA Commitment," U.S. EPA Conference on Preventable Causes of Cancer in Children, September 15-16, 1997). <http://www.epa.gov/children/document/minutes.htm>

[255]U.S. Environmental Protection Agency, Office of Children's Health Protection, *Some Facts on Children's Cancers*, Fact Sheet, December 1997.

A more detailed analysis of the SEER data by Martha S. Linet and her colleagues at the National Cancer Institute reached the following conclusion:[256]

> There is no substantiated change in incidence for the major pediatric cancers, and rates have remained relatively stable since the mid-1980s. The modest increases that were observed for brain/CNS cancers, leukemia, and infant neuroblastoma were confined to the mid-1980s. The patterns suggest that the increases likely reflected diagnostic improvements or reporting changes.

In short, EPA misinterpreted the modest increases in childhood cancer incidence, if there has been any change at all.

Interestingly, the OCHP fact sheet also cited a 1981 paper by Richard Doll and Richard Peto which estimates that exposure to environmental pollutants may be responsible for 1 to 5% of all (including children's) cancer deaths.[257] A 1996 paper by Doll concludes:[258]

> Pollution, which is popularly thought to be a major hazard, must cause some cases, but the risks that can be quantified — those of polycyclic aromatic hydrocarbons, trace metals and benzene from the use and combustion of fossil fuels in industry and transport, dioxins from the combustion of waste, pesticide residues in food, and discharge from the nuclear industry — all appear to be so minute that the social cost of trying to reduce them further may well outweigh any benefit from reduction in the incidence of cancer.

A recent report from the Harvard Center for Cancer Prevention estimates that just 2% of cancer incidence in the United States may be caused by environmental pollution. Food additives and contaminants may explain another 1% of cancer cases, but it is salt, not pesticide residues, that is the confirmed cancer risk (stomach cancer).[259]

Clearly childhood cancer is not of epidemic proportions. Moreover, we should not expect to see significant improvements in its rather modest baseline incidence or mortality rate by focusing on reducing environmental contaminants.

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[256]Linet, Martha S., Lynn A.G. Ries, Malcolm A. Smith, Robert E. Tarone, and Susan S. Devesa, "Cancer Surveillance Series: Recent Trends in Childhood Cancer Incidence and Mortality in the United States," *Journal of the National Cancer Institute*, v. 91, n. 12 (June) 1999. p. 1051-1058.

[257]Doll, Richard and Richard Peto, "The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today," *Journal of the National Cancer Institute*, v. 66, n. 6 (June) 1981. p. 1191-1308.

[258]Doll, Richard, "Nature and Nurture, Possibilities for Cancer Control," *Carcinogenesis*, v. 17, n. 2. 1996. p. 177-184.

[259]"Harvard Report on Cancer Prevention, Volume 1: Causes of Human Cancer," In: Coldity, Graham A., H. William DeJong, David J. Hunter, Dimitrios Trichopoulos, and Walter C. Willett (Eds). *Cancer Causes & Control*, Vol. 7, Supp., Table 1, p. 1. Nov. 1996. <http://www.hsph.harvard.edu/organizations/canprevent/summary.html>

EPA also has emphasized the effects of air pollution, primarily ozone, on children with asthma and other respiratory problems. Approximately 15 million Americans have asthma, including 5 million children.[260] EPA's September 1996 report *Environmental Health Threats to Children* states:

> Many of the most common air pollutants can cause or contribute to respiratory illnesses, including asthma, which is now the leading cause of hospital admissions for our nation's children. More than 25% of the nation's children live in areas that don't meet national ambient air quality standards.[261]

Figures 7 and 8 put the most serious health end point for childhood asthma — mortality — into better perspective. When a stepwise linear regression is run with data on annual death rates from asthma for 0-to-4 year olds and for 5-to-14 year olds, two things become clear: (1) the problem is really with 5-to-14 year olds and (2) a decade and a half favorable trend was suddenly reversed for 5-to-14 year olds in 1976 and leveled off for 0-to-4 year olds at that time.

For 0-to-4 year olds, death rates from asthma fell from 1961 to 1976 at a rate of 0.2 deaths a year — from 4.5 per million to about 1.4 per million. After 1976, there is a very slight rise of 0.03 deaths a year, but this latter trend has only marginal statistical significance.

For 5-to-14 year olds, the asthma death rate trend was also favorable from 1961 to 1976, falling at a rate of 0.09 per million a year. From 1976 to 1994, however, death rates increased annually by 0.14 per million 5-to-14 year olds — rising from about 1.1 per million to approximately 3.7 per million. Thus, while 0-to-4 year olds experienced asthma death rates more than twice the rates of 5-to-14 year olds in 1961, by 1994 this relationship was virtually reversed — the asthma death rate for children in the 0-to-4 age range is about half that for 5-to-14 year olds. The causes of these unfavorable trends in childhood asthma remain a mystery.

Outdoor air pollution appears to be a poor candidate for providing an explanation for these trends, however. As Table 19 shows, the trend in air pollution has been downward during virtually the same period (1978 to 1997) that asthma death rates have been rising for 5-to-14 year olds. To further rule out ambient air pollution as a cause for unfavorable asthma death trends one would need to perform linear regressions on more localized data for asthma deaths and air pollution levels. Because childhood asthma deaths are rare, it would be difficult to validate (or invalidate) a relationship between air pollution and asthma deaths in childhood. Elevated ozone and particulate levels certainly do trigger asthma attacks, some

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[260] Centers for Disease Control and Prevention, National Center for Environmental Health, "CDC's Asthma Prevention Program," Apr. 1997. http://www.cdc.gov/nceh/pubcatns/97tsheet/asthma/asthma.htm.

[261] U.S. Environmental Protection Agency, *Environmental Health Threats to Children*, EPA 175-F-96-001. September; 1996.

**Figure 7. Rates of death from asthma per 1,000,000 infants and children aged 1 to 4 years.**

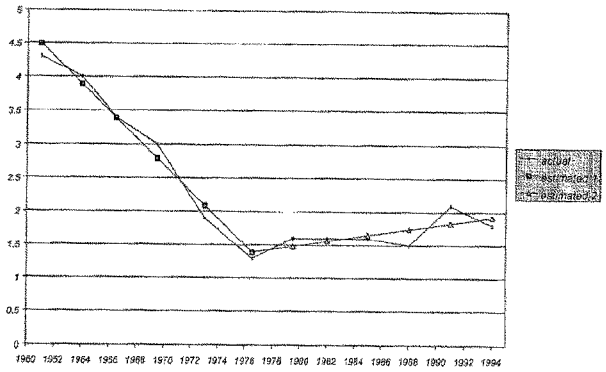


**Figure 8. Rates of death from asthma among children aged 5 to 14 years (1961-1995)**

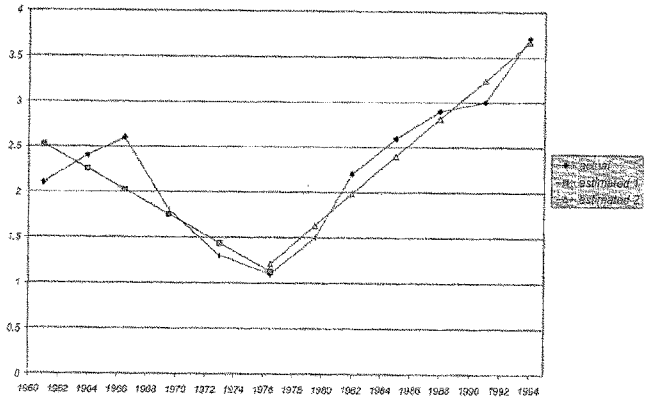

**Table 19. Change in U.S. Air Quality–Concentrations (1978-1997) and Emissions (1970-1997)**

| Criteria Pollutant | Change in Concentration (%) | Change in Emissions (%) |
|---|---|---|
| Carbon monoxide | -60 | -32 |
| Lead | -97 | -98 |
| Nitrogen dioxide | -25 | +11 ($NO_x$) |
| Ozone | -30 (1 hour) | -37 (VOC) |
| $PM_{10}$* | -55 | -35 |

Notes: * Particulate matter measuring 10 micrometers or less in diameter

Includes only directly emitted particles. Secondary PM formed from $SO_x$, $NO_x$, and other gases comprise a significant fraction of ambient PM.

Source: U.S. Environmental Protection Agency, office of Air Quality Planning and Standards, *National Air Quality and Emissions Trends Report, 1997* (Research Triangle Park, N.C., December 1998), p. 9.

of which can even lead to death. But I believe that other factors play more important roles in higher incidence of childhood asthma and deaths due to asthma.

***Conclusion.*** Children's health is significantly improving, not worsening, according to such broad measures as infant mortality rates and life expectancy at birth. When causes of childhood mortality are examined, malignant neoplasms are the third leading cause of death in 1-to-4 year olds but far less of a threat than accidents and only slightly more common than homicide. In the 5-to-14 age group, cancers are the second leading cause of death but, again, far behind accidents, though more than twice as frequent as homicides. According to researchers at the National Cancer Institute, there has been no substantial change in incidence for major pediatric cancers since the mid-1980s.[262] Further, the Harvard Center for Cancer Prevention estimates that just 3% of cancer incidence (for all ages) may be attributable to environmental pollution and additives or contaminants in food — 1% of this total being attributed to salt.[263]

Deaths related to asthma are increasing in frequency, particularly for 5-to-14 year olds. A decade and a half of declining asthma death rates was abruptly reversed for 5-to-14 year olds in 1976 and leveled off for 0-4 year olds at that time. Ambient air pollution may be a poor candidate for explaining these trends, however, because ozone and particulate levels have been improving over this same period.

When a high profile agency such as the Environmental Protection Agency indicates that introduction of "tens of thousands of new chemicals" is a likely cause of higher rates of childhood cancer, it distracts policy makers from considering other possible causes and from

[262]Linet, Martha S. et al., p. 1051.

[263]"Harvard Report on Cancer Prevention, Volume 1: Causes of Human Cancer," ibid.

addressing more serious threats. Because accidents are far and away the greatest risks to children, and in many instances preventable, drawing the attention of parents and policy makers away from these greater risks can actually harm children's health.

This is not to say that EPA should not continue its efforts to see how children might be differentially impacted by environmental contaminants. It does argue for some restraint in assigning large amounts of new resources to these efforts and for considerable restraint with regard to public pronouncements about the relative hazard presented by environmental contaminants.

**"Contaminants" May Provide Benefits As Well As Risks.** Many so-called environmental contaminants play beneficial roles that far outweigh their threats to children's health. A reasonable approach, therefore, is to weigh benefits along with threats. This follows the standard approach for medicines and vaccines, where some level of side effects (even including at times death) is considered acceptable because of the much greater saving of human lives from using the drug or vaccine. This sensible approach is notably absent in most efforts to reduce health threats from environmental contaminants.

***Example of Pesticide Regulation.*** Take, for example, the case of pesticide regulation. The 1993 report by the National Research Council, *Pesticides in the Diets of Infants and Children,* analyzed the possible special effects of pesticide residues on America's children. The report examined quantitative and qualitative differences between adults and children, with regard to toxicity of pesticides. Quantitative age-related differences in absorption, metabolism, detoxification, and excretion of xenobiotic compounds as well as physical and biological differences — body size and the maturity of body systems — were considered. Qualitative differences due to brief periods in early development of an organ system were also analyzed.

In addition, the study examined differing exposures of children to pesticide residues compared to adults. Children 1 to 5 years old eat three to four times more food than adults in proportion to their mass and have less variety in their diets. A one-year old drinks 21 times more apple juice and 11 times more grape juice and eats two to seven times more grapes, bananas, pears, carrots, and broccoli than the average adult.[264] According to the NRC study, most of the differences in pesticide-related health risks result from this second factor — exposure -- not physical differences between adults and children.

The report led to a chain of events that has placed children's health in the forefront of special concerns about environmental contaminants. It had a major impact on the Food Quality Protection Act (FQPA) of 1996. FQPA requires that residues in food must be at levels that exhibit a "reasonable certainty of no harm." The Act amends the two statutes that regulate pesticides — the Federal Insecticide, Fungicide and Rodenticide Act, and the Federal Food, Drug and Cosmetics Act.

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[264]Landrigan, Philip J., et al. "Children's Health and the Environment: A New Agenda for Preventive Research," *Environmental Health Perspectives*, v. 106, supp. 3 (June) 1998. p. 787-793.

FQPA specifically requires that pesticides be evaluated for potential effects on children. If the data on risks to children are not available, EPA can use up to a tenfold safety factor to lower allowable pesticide residues. The Act also requires the agency to consider cumulative risks posed by *all* exposures to pesticides of similar classes.

But what about the *benefits* to children's health resulting from judicious use of pesticides? The NRC was not charged with examining this side of the equation and the report clearly acknowledges this fact. Nonetheless, diet is reported to be one of the largest controllable risk factors for cancer. The rate of most types of cancer (lung, larynx, oral cavity, esophageal, stomach, colorectal, bladder, pancreatic, cervical and ovarian) is roughly *twice* as high in the quarter of the population with the lowest intake of fruits and vegetables as in the quarter with the highest.[265]

Synthetic pesticides are one of the key factors in producing an abundant supply of fresh fruits and vegetables. Public policies that restrict the *judicious* use of these pesticides, or potentially ban them, based on the very tight standards on pesticide residues spelled out in the Food Quality Protection Act, could actually *harm* children's health, if they reduce children's consumption of fruits and vegetables.

A Texas A&M study suggests that a 50% reduction in pesticide used on crops of nine fruits and vegetables (apples, grapes, lettuce, onion, oranges, peaches, potatoes, sweet corn, and tomatoes) would reduce yields by nearly 40%. Former Food and Drug Administration Commissioner, pediatrician David Kessler, remarked on the occasion of the Clinton Administration's 1993 plan to reduce pesticide use:

> We are not saying that food is unsafe... There is no reason for a scare... There is no doubt that the benefits of fruits, vegetables and grains far outweigh the risks of residues of pesticides in these products.[266]

As this example illustrates, there are potentially serious public policy consequences to only looking at the harm that environmental agents may cause without considering the benefits at the same time.

***Example of Global Control of Aflatoxin.*** Another example of the problem with taking too narrow a view of risk is global control of aflatoxin to reduce liver cancer rates. A recent article in *Science* outlines the problems that can be created for developing nations' health, if developed nations are overly restrictive in regulating aflatoxin levels in their food imports.[267]

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[265] Ames, Bruce, and Lois Swirsky Gold, *Misconceptions About Environmental Pollution, Pesticides and the Causes of Cancer*, Policy Report 213. Dallas, Tx.: National Center for Policy Analysis. (March) 1998), p. 3, 4.

[266] Kenworthy, Tom, and John Schwartz, "3 U.S. Agencies Announce Joint Commitment to Cut Pesticide Use," *Washington Post*, June 26, 1993.

[267] Henry, Sara Hale, F. Xavier Bosch, Terry C. Troxell, and P. Michael Bolger, "Reducing Liver (continued...)

According to the *Science* article, liver cancer is the fifth most frequently occurring cancer worldwide, responsible for 427,000 deaths in 1990. "Incidence rates in developing countries are estimated to be approximately 2 to 10 times those in developed countries; 76% of cases are found in Asia ... There are many risk factors for liver cancer, including exposure to hepatitis B or C ... and to aflatoxins."[268]

Aflatoxins are contaminants in food "as a result of fungal contamination during growth and after harvest ... Aflatoxins are most commonly associated with peanuts, corn, rice, cottonseed, dried fruits, tree nuts, spices, figs, crude vegetable oils, cocoa beans, and copra," and dairy products if dairy cattle have eaten contaminated feed.[269] There are several types of aflatoxins with the most toxic of these being designated aflatoxin B1. In high doses, aflatoxins "are among the most potent hepato-carcinogens known, as well as being mutagenic and hepatotoxic." Effects of long-term exposure to low doses are not well established at present.[270]

Recently, Codex Alimentarius, a United Nations organization funded by the World Health Organization and the Food and Agriculture Organization, requested a quantitative risk assessment of the health risk posed by aflatoxin-contaminated foods moving in world trade. Codex sets standards for food additives, residues of veterinary drugs and pesticides, naturally occurring toxicants, and human-derived contaminants.[271]

Henry et al. reported that the risk of liver cancer from aflatoxin B1 consumption was 30 times higher for individuals exposed to hepatitis B as for those persons not exposed. Thus, the proportion of persons exposed to hepatitis B in the population and the levels of aflatoxin are both critical for the risk assessment. Canada and the United States have set aflatoxin B1 standards of 15 to 20 parts per billion (ppb) in finished food products; France and the Netherlands have standards of 4 ppb, and India set its standards at 30 ppb. (Ten micrograms per kilogram is equivalent to 10 ppb.) The typical Western European diet results in less than 19 nanograms (ng) aflatoxin B1 consumption daily, whereas the typical Far Eastern diet is 103 ng a day.[272]

The Codex advisory group conducting the risk assessment estimated that, for countries where daily aflatoxin B1 consumption is less than 19 ng, and the proportion of persons exposed to hepatitis B is about 1%, reducing the aflatoxin standard from 20 to 10 ppb would reduce liver cancers annually by just two cases in a population of 1 billion — an undetectable change by epidemiological methods. In other countries with higher consumption of aflatoxin and higher percentage of population exposed to hepatitis B (e.g.,

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[267](...continued)
Cancer — Global Control of Aflatoxin," *Science*, v. 286, Dec. 24, 1999. p. 2453-2454.

[268]Ibid., p. 2453.

[269]Ibid.

[270]Ibid.

[271]Ibid.

[272]Ibid.

25%), reducing the standard from 20 to 10 ppb would reduce the annual risk of developing liver cancer to approximately 0.3 per million, arguably a marginally significant risk reduction.[273]

As a result of the risk assessment, Codex adopted a standard of 15 ppb for aflatoxin B1 in raw peanuts. However, concern about possible exposure of children to a metabolite of aflatoxin in milk and dairy products (aflatoxin M1) led Codex to propose lowering its limit in these products from 0.5 to 0.05 ppb, even though the metabolite is only one-tenth as toxic as aflatoxin, and no measurable reduction in liver cancer risk would be expected to result from lowering the standard.[274]

The risk assessment concluded that a more substantial reduction in liver cancer would result from vaccination against hepatitis B in developing nations. A significant decline in liver cancer incidence has been shown among cohorts of vaccinated newborns and children in Taiwan and vaccinated adults in Korea despite no change in aflatoxin standards, according to Henry et al.[275]

This global regulatory example demonstrates how important it can be to consider all options in reducing health risks. Stringent regulatory standards on global contaminants may produce no discernable health benefit to developed nations and far less benefit than other risk-reduction options for developing nations.

## Federal Research Priorities

Of all the activities where the federal government can make a difference in children's health, research on health trends and their causes would seem to be the areas where it has a comparative advantage over state and local government or non-profit and profit-making institutions in the private sector. Federal agencies have the authority and resources to gather data and conduct analyses to identify important health effects and trends. These analyses help focus attention on key health threats and serve to raise questions about the possible causes for those whose incidence may be rising. Numerous public and private institutions such as hospitals and state and local public health authorities cooperate in these efforts, of course.

The federal government also has an advantage in pursuing answers to questions raised in the data gathering and analysis activity. Some of the research may be performed within federal agencies but much of it is conducted at medical schools and other research facilities in the private sector. Federal funding and oversight of basic research on causes of important health risks are vital steps in leading toward their reduction.

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[273]Ibid., p. 2454.

[274]Ibid.

[275]Ibid.

**Key Federal Research Programs.** The Department of Health and Human Services (HHS) is the key federal repository for health trend data. The Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) are the key data collection agencies within HHS. Within CDC, the National Center for Health Statistics and the National Center for Environmental Health are important sources for data on children's environmental health trends. The National Vital Statistics Reports are issued by the National Center for Health Statistics, for example.

The National Institutes of Health is the principal biomedical research agency in the federal government. NIH funds more than 40,000 research grants annually from its $20 billion budget (Fiscal Year 2001). The federal government, primarily through NIH, funds approximately 36% of all U.S. medical research.[276] Within NIH, the National Cancer Institute, is collecting data through its Surveillance, Epidemiology and End Results (SEER) program that is particularly valuable in identifying trends in childhood cancer. In addition, there is the National Institute for Child Health and Human Development and a National Institute for Environmental Health Sciences (NIEHS), one of the few federal agencies that investigates the role of environmental agents in causing adverse effects in children, according to a draft EPA report.[277, 278]

Several key EPA offices and programs share responsibility for planning environmental research with special relevance for children, including the Office of Research and Development (ORD), the Office of Water, the Office of Children's Health Protection (OCHP), and the Office of Prevention, Pesticides, and Toxic Substances (OPPTS). By and large, research is driven by legislative requirements, and children's health is only mentioned explicitly in the Food Quality Protection Act of 1996 (Public Law 104-170) and Safe Drinking Water Act Amendments of 1996 (Public Law 104-182). In addition, children's health has been implicit in the setting of national ambient air quality standards and hazardous waste site cleanup. Otherwise, children's environmental health must be treated as a subtopic of existing priorities.

Current federal research efforts are considerable and, I argue, adequate to meet the challenge. If the top environmental threats to children's health, as defined by the Environmental Protection Agency, become the focus of government efforts, many more beneficial activities may be ignored. It is beyond the scope of this paper to evaluate the host of research programs which could have a children's environmental health component. Instead, it considers how President Clinton's Executive Order (EO) 13045: "Reduce Environmental Health and Safety Risks to Children" (April 21, 1997) might be expected to affect the balance of research on children's health. The specific response by the EPA's Office of Research and Development will be used to infer how this EO might impact other federal health research programs.

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[276]U.S. Congress, Joint Economic Committee, "The Benefits of Medical Research and the Role of the NIH." Washington, DC: U.S. Govt. Print. Off. May 2000.

[277]U.S. Environmental Protection Agency, Office of Research and Development, "Strategy for Research on Environmental Risks to Children," External Peer Review Draft. Aug. 3, 1999. Washington, DC: U.S. Environmental Protection Agency. p. 19.

[278]Ibid., p. 20.

**Effects of Executive Order 13045.** The provisions of EO 13045 appear reasonably straightforward:

> [T]o the extent permitted by law and appropriate and consistent with the agency's mission, each Federal agency:
>
> (a) shall make it a high priority to identify and assess environmental health risks and safety risks that may disproportionately affect children; and
>
> (b) shall ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks.

But how might this directive influence the research agendas of the federal agencies that attempt to comply?

EPA's ORD would seem to be an agency whose research priorities might be more readily adapted to the new emphasis on children's environmental health. Examining EPA's "Strategy for Research on Environmental Risks to Children," circulated in draft form in August 1999 for peer review, sheds some light on some of the challenges faced in responding to EO 13045.[279] The Strategy draft was written by a scientific team, led by EPA's Director of the National Center for Environmental Assessment in EPA's Office of Research and Development, Dr. William Farland.[280]

In developing the strategy document, the team considered the major end points and environmental health problems shown in Table 20. The primary objective of ORD's Children's Health Program is "to conduct the research needed and provide the methods to reduce uncertainties in EPA risk assessments for children, leading to effective measures of risk reduction."[281]

The science team broke the strategy down into 5 main topics covering a total of 13 research areas. The team then ranked each research area as "high," "medium," or "low" priority based upon how feasible they seemed to be, given the current state of scientific knowledge and ORD's ability to perform the research, along with the potential of the research thrust to improve EPA risk assessments or to reduce childhood health risks. Table 21 shows how these research areas were ranked within the five main topics.

The draft research strategy document is too detailed to discuss at length, but several key statements in the draft provide valuable insights into the challenges faced by agencies attempting to better evaluate environmental risks to children's health.

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[279]Ibid.

[280]The other members of the science team producing the strategy document were from ORD's laboratories and centers and from the Office of Prevention, Pesticides, and Toxic Substances (OPPTS), the Office of Water, and the Office of Children's Health Protection (OCHP).

[281]U.S. EPA, "Draft Strategy for Research," p. EX-2.

**Table 20. Children's Risk Topics Considered in the Research Strategy of EPA's Office of Research and Development**

| Health End Points | Environmental Health Threats |
|---|---|
| Cancer | Outdoor and Indoor air pollution |
| Neurotoxicity | Pesticides |
| Immune system effects | Environmental tobacco smoke |
| Asthma and other respiratory effects | Microbes and other drinking water contaminants |
| Other birth defects (e.g., death, malformation, growth alteration) | Specific compounds such as lead, mercury, PCBs, vinyl chloride |
| | Mixtures |

ORD attempted to place the research strategy in the context of EPA's overall Strategic Plan, which was written to comply with the 1993 Government Performance and Results Act (GPRA, Public Law 103-62).[282] ORD's research document fits under EPA's goal to: "Provide sound science to improve the understanding of environmental risk and develop and implement approaches for current and future environmental problems."[283] The six high-priority research areas in ORD's portion of the GPRA Strategic Plan are: 1) safe drinking water, 2) high-priority air pollutants (especially particulates), 3) emerging environmental issues (endocrine disruptors as a near-term focus), 4) research to improve ecological risk assessment, 5) research to improve health risk assessment, and 6) pollution prevention and new technology for environmental protection. ORD's children's environmental health research is identified as a subtopic of the human health risk assessment area. A very interesting conclusion was reached by the team:[284]

> The Science Team decided that a research strategy directed at specific environmental problems and end points would not provide sufficient flexibility and might impede the development of new approaches to risk assessment. Issues surrounding children's environmental health are too numerous to address individually in this Strategy, and current knowledge is limited, making it difficult to foresee emerging issues and future directions.

[282]The 1993 Government Performance and Results Act (GPRA) requires federal agencies to adopt the principles of performance-based management: a five-year strategic plan that includes a mission statement, a set of goals, measurable objectives to achieve those goals, and performance measures to identify progress against the objectives.

[283]U.S. EPA, "Draft Strategy for Research," p. 5.

[284]U.S. EPA, "Strategy for Research," p. 27.

**Table 21. Research Area Priorities of EPA's Office of Research and Development**

| Research Area by Main Topics | High Priority | Medium Priority | Low Priority |
|---|---|---|---|
| Development of data to reduce uncertainties in risk assessment | | | |
| - Mode of action research | X | | |
| - Exposure field studies | X | | |
| - Activity pattern and exposure factor studies | X | | |
| - Epidemiology studies | | X | |
| Development of risk assessment methods and models | | | |
| - Methods and models for assessing dose-response relatioships in children | X | | |
| - Methods and models for using exposure data in risk assessment | X | | |
| Experimental methods development | | | |
| - Methods for hazard identification | | X | |
| - Methods for measuring exposures and effects in children and to aid in extrapolations between animals and humans | | X | |
| Risk management and risk communication | | | |
| - Reduction of exposure buildup of contaminants indoors | X | | |
| - Communication of risk | X | | |
| - Multimedia control technologies | | | X |
| Cross-cutting issues | | | |
| - Variation in human susceptibility | | X | |
| - Effects of mixtures and cumulative risk | | X | |

ORD's Science Team was not able to apply criteria set out in its strategic plan submitted in response to GPRA requirements to measure its performance of the objectives of EO 13045. The research strategy document stated:[285]

> The ORD criteria were found to be specific to a particular health effect, a particular method or model for assessing risk, or a particular risk management technique.

[285]U.S. EPA, "Strategy for Research," p. 28.

They are problem-specific and do not apply well to research areas that are broadly defined.

The research priorities that the ORD science team identified, the 5 topic areas and 13 research areas shown in Table 21, were meant to cut across environmental problems. However, the ranking scheme is a concession to reality, since ORD cannot set strategy or command research resources for other federal agencies. The priorities were set based partly on the research capabilities of ORD scientists as principal investigators, possibly in collaboration with scientists at other agencies, in academia, or with private firms (the Intramural Program), or with academic scientists as principal investigators through ORD's Science to Achieve Results (STAR) program.

Of course, the team did not attempt to consider what the priorities might be if other federal agencies took the lead. But by excluding activities where ORD is not the lead agency, the rankings are biased in comparison with rankings based only on the cost and value of the information to be gained. Similarly, within each agency, one would expect to see, at best, this type of sub-optimal priority-setting taking place in response to executive orders. In some agencies, existing programs may be unaffected but re-labeled to make them *sound* as if they address children's environmental health.

Further appreciation for the constraints within which any given agency must attempt to respond to a new directive from the Oval Office can be obtained by examining the criteria that ORD used to rank the broad topic areas as shown in Table 22. Items 2, 3, 4, and 5 are all institutional constraints, not really the type of professional/ technical criteria like items 1 and 6 that one would hope would drive research strategies in a more perfect setting.

## Table 22. ORD Science Team Criteria for Ranking Research on Children's Environmental Health

1. Importance of the research to reducing uncertainty in risk assessment and protecting children from environmental health threats.
2. Feasibility of conducting the research in the ORD Intramural or STAR Programs.
3. Availability of resources including the capacities and capabilities of ORD's Laboratories and Centers and the extrmural resources.
4. Opportunities to develop and maintain scientific expertise in ORD to enable use of research results in EPA risk assessments.
5. Opportunities for collaboration with other Federal Agencies and with other ORD research programs.
6. Maintenance of a balance between short-term research that will reduce major uncertainties in risk assessment and long-term, more speculative research, that may identify previously unknown hazards and exposures to children or change EPA's way of doing risk assessments and ultimately produce more accurate and less costly assessment procedures.

This is not an indictment of ORD's "Strategy for Research on Environmental Risks to Children." The draft document is a thoughtful response to EO 13045. The particular research projects that the science team identifies as high priority will, no doubt, help improve

risk assessments for environmental contaminants that might affect children's health. The point is that it is easier to establish a new cross-cutting policy concern by Executive Order 13045 in principle than it is to fit it in with existing organizational structures and activities.

As noted above, the problem of how to implement executive orders, given priorities and programs designed to fit existing, and sometimes inconsistent, statutory authorities, is not unique to ORD or even to EPA. Other federal health agencies have broad missions "to document the occurrence and explain the causes of childhood development disorder and disease." Their missions are to improve children's health rather than to focus narrowly on environmental pollutants or contaminants as likely causes of health problems. Compliance with Executive Order 13045 forces many agencies to place greater emphasis on environmental health risks in their research agendas. This could result in giving environmental threats higher priorities than they deserve.

Alternatively, it could cause environmental research to focus on a few chemicals or conditions known to affect children. This may explain the agendas of eight Children's Environmental Health and Disease Prevention Research Centers sponsored jointly by EPA and NIEHS. This joint effort provides a high profile involvement of non-governmental institutions focusing, essentially, on environmental threats from EPA's list.

Five of the EPA/NIEHS centers are studying the influence of the environment on asthma and other respiratory diseases in groups of children. Three centers are examining the relationship between development disorders and exposures to neurotoxicants, especially organophosphate pesticides in groups of highly exposed children, such as children of farm workers. While there is nothing inherently wrong with this approach to research on environmental threats to children's health, it is a little discomforting to see these centers so narrowly focused on EPA's "usual suspects." It is somewhat hard to imagine that findings of little or no significant harm from these environmental sources will be broadly publicized.

## Recommendations

Many federal agencies have been working for decades to improve children's health. Judging from data on infant mortality and life expectancy at birth, staff at these federal agencies along with a host of private sector scientists, medical professionals, public health officials and others have been very effective.

The following recommendations focus on what might be the consequences of placing greater emphasis at the federal level on the effects of environmental contaminants on children's health; they have little to say about the roles of non-federal institutions in enhancing children's health. This is not meant, however, to imply that their roles are unimportant.

Research addressing children's environmental health issues appears to be the one area in which the federal government holds a comparative advantage over state and local government or non-profit and profit-making institutions in the private sector. The federal

government has the resources and authority to collect valuable data on trends in children's health, to fund research on causes and treatments for more serious threats, and to disseminate information that will help parents take actions that will protect their children.

Nonetheless, a serious review of these activities leads to ideas for improving the federal role in protecting children from health risks. Here are suggestions for doing so:

**Rescind Executive Order 13045 or replace it with a broader mandate to improve children's health and safety.** The case for a separate emphasis on children's environmental health risks is not strong. Children's health statistics provide little support for assertions that environmental pollution or contaminants are significantly increasing childhood cancer incidence or asthma-related deaths. This is not to say that environmental sources don't play a role in the health of America's children, only that this role has, by and large, been exaggerated by agencies like the EPA and by the popular press, in the author's opinion.

Ideally, EO 13045 should be rescinded by President Clinton's successor. Doing so would not stop research on environmental health threats to children; but it would not place undue emphasis on this one aspect of children's health or redistribute health research funding among age groups regardless of the public health benefits of doing so.

A second-best alternative is to broaden the mandate of Executive Order 13045. Given the political implications of rescinding an executive order that places greater emphasis on the well-being of children, broadening the directive may be the only realistic alternative. This broader perspective would keep from distorting the priorities of the many federal agencies seeking to improve public health. The subset of those agencies that do focus on environmental health would continue to do so and would continue to pay special attention to children's differing exposures and responses to contaminants.

An executive order may be effective for introducing a new requirement for federal agencies to address a new issue such as cost-benefit analysis, but it is less effective when it adds a new cross-cutting concern that does not fit well within the organizational structures of the affected agencies. In the case of environmental risks to children's health, the response by the agency most focused on environmental issues — the Environmental Protection Agency — is constrained by its orientation toward specific programs resulting from individual statutes. Funding and staffing a new cross-cutting activity is simply easier said than done.

Lastly, EO 13045 creates two public expectations that will likely lead to disappointment. As discussed above, the public expects the President's directive to be executed and has little appreciation for the organizational difficulties in doing so. Secondly, and more importantly, the attention given children's environmental health risks might cause parents to believe that environmental contaminants are more significant health threats than they truly are. As a result, the public may demand that greater resources — public and private — be devoted to reducing environmental health risks. Greater taxpayer dollars for

increased federal programs or higher prices paid by consumers to cover the costs of more stringent regulations will likely produce disappointing results in improving children's health.

**When environmental legislation is crafted it needs to be more balanced, considering costs and benefits and risk tradeoffs of regulating environmental contaminants.** The Clean Air Act is an example of an important environmental statute that would benefit from a requirement to conduct cost-benefit analysis and for the results to be a part of the decision making process in setting air quality standards under Section 109.[286] The ground-level ozone standard has, in the past, been established at levels where costs greatly exceed benefits.[287] The new eight-hour standard arguably makes this tradeoff even more unfavorable.[288]

The Food Quality Protection Act is an example of legislation that has a one-sided view of risk. FQPA adds requirements to specifically consider risks of pesticide residues to children and to add up to a ten-fold safety factor when information on these risks is not available for a specific pesticide or class of pesticides. The Act does not require EPA to consider, however, the health *benefits* of fresh fruits and vegetables that could be foregone as a result of overly stringent regulation of pesticides.[289]

**Multi-agency cooperation can improve children's health, but the lead agency should be the one with the broader perspective.** In the specific case of children's environmental health, it is imperative that "children's health" be emphasized over "environmental health" in order to prevent potentially counterproductive reordering of priorities (as discussed above). Though the temptation is to defer to EPA because of its

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[286]Some sections of the Clean Air Act, as amended, (CAA; 42 U.S.C. 7401-7626) expressly allow consideration of costs (e.g., in the control of emissions of air pollutants from major *new* stationary sources, Section 111(a)(1)). However, under Section 109 EPA is required to set ambient air quality standards for pollutants such that their attainment and maintenance "are requisite to protect the public health" based on air quality criteria and allowing an adequate margin of safety. Air quality criteria are compilations of information reflecting the latest scientific knowledge relevant to the assessment of risks to public health or welfare posed by the presence of criteria pollutants in the ambient air [Section 108(a)(2)]. This statutory provision only authorizes consideration of environmental and human health risks, and was interpreted by the Court of Appeals for the District of Columbia Circuit in 1980 as prohibiting consideration of costs (Lead Industries Association v. EPA, 647 F.2d 1130, 1149 (D.C. Cir. 1980)). Similarly, the Supreme Court ruled February 27,2001, in *Whitman v. American Trucking Associations* that the Clean Air Act bars EPA from considering implementation costs when it sets primary national ambient standards. The case challenged EPA's promulgation in 1997 of revised primary national ambient air quality standards for ozone and particulate matter.

[287]Sholtz-Vogt, Anne, and Kenneth Chilton, "Battling Smog". In: Chilton, Kenneth, and Melinda Warren (eds.), *Environmental Protection: Regulating for Results*, Boulder, CO: Westview Press. 1991. Table 3.2, p. 62.

[288]Huebner, Stephen, and Kenneth Chilton, *EPA's Case for New Ozone and Particulate Standards: Would Americans Get Their Money's Worth?* (St. Louis, MO: Center for the Study of American Business, Policy Study 139, June 1997).

[289]The FQPA does allow some consideration of costs, but it strictly limits their nature and influence in tolerance setting.

charge to protect the public from pollutants, when units of HHS team with EPA, in general, the HHS unit might be the better agency to take the lead.

## Conclusion

The possibility that environmental contaminants adversely affect the health of our nation's children has led to widespread concern. Exposures to pesticides and other synthetic chemicals is a hypothesized risk factor for childhood diseases including cancer, birth defects, and developmental abnormalities. Such risks are being greatly exaggerated by the White House and the Environmental Protection Agency, and as a result, federal research programs that are designed to improve overall public health (and children's' health, as well) are in danger of having their priorities shifted in ways that make them less – not more – effective.

This paper argues that restraint and balance are necessary when addressing children's environmental health risks, and that regulation should be a last resort, fully justified by substantial net benefits. Given the limited impact of environmental pollution on public health, a shift of federal resources to emphasize environmental risks may not be necessary, or even desirable.

Furthermore, it is vitally important that each environmental risk be considered in its full context. Often there are offsetting benefits that can outweigh the risks of the environmental contaminant. For example, very small risks are more than offset by the positive effects of judicious use of chemicals to increase the quality and quantity of fresh fruits and vegetables and to provide safe drinking water. In a broader context, any government activity — especially regulation — that generates more costs than benefits decreases the economic well-being of families, thus, reducing their ability to spend their own resources to protect the health of their children. Greater family resources arguably can improve health care services, provide for more safety features in the home, and so on.[290]

Many questions remain unanswered, and the extent to which environmental contaminants may adversely affect the health of our nation's children is not clear. More information on the causes of childhood diseases is needed. This quest for information should be broadly defined. Whether federal funding should be increased to accelerate research on children's health is a decision for Congress and the White House to make. Unless better evidence is presented that "environmental" health threats to children are more significant than they presently appear to be, there is little reason to devote a larger piece of the federal public health research pie to these risks.

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[290]Other factors also may deserve consideration, such as political feasibility, technological capacity, or ecological risks.

# The Role of the Federal Government In Protecting Children's Environmental Health

By Daniel Swartz

What role should the federal government play in protecting children from environmental conditions and substances[291] that might harm their health? One's answer, I suspect, depends a good deal on the general role one envisions for the federal government. As we look specifically at protecting children's environmental health, however, there are a number of fundamental principles that even those with differing views of government might see eye to eye on. I want to start by identifying three key areas of agreement, and then taking off from them, outline some possible implications for a federal role in children's environmental health, including recommendations that, while not consensus, are supported by many leading public health organizations.

Our shared fundamental principles begin with science. I think we can all agree that decisions in this area should use the best current scientific knowledge – though, as I will outline below, we might differ on how to use that knowledge. We also all realize that even the best current knowledge is not good enough, and so our policies should also encourage scientific progress – and that progress here means not only applied science directly relevant to specific children's environmental health concerns, but basic science from biochemistry to genetics as well.

Second, science, even in those instances when all agree with its conclusions, often cannot in and of itself determine policy. While we might not all agree on all the additional factors to be weighed, we all probably realize that concerns for equity, justice, and liberty do and should play fundamental roles in our government's decision-making processes.

Third, children are not merely biologically different from adults – as a society, we view children in a different moral, even theological, light. Some of this difference in perspective is self-interested. After all, your children and grandchildren will pay for my Social Security; similarly, a well-educated populace has general benefits, while raising a generation of criminals would be deleterious to us all. But of course, our interest in children is not merely self-interest. Children are the best synecdoche for the future, in that they indeed determine much of the course of our future and represent the rest. For a species that often has trouble thinking of others or long-term, children give us the opportunity to do both simultaneously. That is why, although one of the chief blessings of our country is the diversity of its religious traditions, these traditions all ascribe special value to children and place a special duty on society to protect the most vulnerable – a category for which children serve as the exemplar par excellence. Thus, figuring out the proper role for the federal government in protecting children from environmental health hazards means not only

[291] "Environmental conditions and substances" are here defined as alterations to living and non-living planetary and local systems caused, directly or indirectly, by humans.

measuring biological vulnerabilities, but also factoring in economic and political vulnerabilities and the way our society values children.

That is what we potentially hold in common. Now to two more difficult tasks: first, trying to take general agreed-upon values and applying them to specific situations vis-à-vis children's environmental health, and second, trying to make decisions about values that each of us individually might hold to be fundamental, but which we are also in fundamental disagreement about. As an example of the first, by equity do we mean protecting all children, including those with special vulnerabilities, to the extent that they all have equal health outcomes? Or perhaps by equity we mean that we will set one equal standard that is protective of most children in most circumstances? As to the second, we might agree on the ethical value of protecting the common good or the most vulnerable – but disagree completely about what the federal government's role is in such protection.

So how do we apply shared values? And how do we mediate among conflicting beliefs about other values, or even commonly held values that in particular circumstances are in conflict with each other? Unfortunately, we can not run a peer-reviewed experiment to determine these answers. As a country, however, we do have a long history of trying to come to grips with such problems – and I want to use a bit of that history to outline my views, as well as some alternatives, on six key aspects of the proper federal role in protecting children from environmental health hazards. This bit of history is one of the best, most concise summations of federal roles in general – the preamble to the U.S. Constitution. For those who have not recited it recently, it goes like this:

> We the People of the United States, in Order to form a more perfect Union, establish Justice, insure domestic Tranquility, provide for the common defense, promote the general Welfare, and secure the Blessings of Liberty to ourselves and our Posterity, do ordain and establish this Constitution for the United States of America.

Through these six key phrases, I will try to delineate an appropriate federal role in addressing children's environmental health concerns.

## A more perfect union –The proper role for science

For the last two hundred years, we have witnessed the steadily increasing impact that science has had on every person on this planet. And as that impact, primarily positive, has escalated, our political leadership has confronted an ever-growing dilemma: how should decisions about complicated, technical scientific issues be best made in a democracy? How do we combine the expertise of science with not only the interests but also the involvement of the public? Tensions around science-based policy have arisen in our courts, our legislatures, and, most of all, our administrative agencies. All are busy trying to form a more perfect union between science and the institutions of our republic.

Many have written extensively about precisely these struggles – let me just briefly sum up a few key points others have raised.[292]

First, it is critical to realize that science measures; it does not value. Science may be able to tell us the probability of a particular health outcome; it cannot tell us how to treat that probability, how to weigh that consequence. The decisions about how to interpret science results are policy decisions; even the prioritization of which science questions are asked first is in large part a policy decision. We may be able to measure the prevalence of risk through science – but such measures will never provide us with an automatic calculus for deciding which risks we as a society consider to be the most important – for, as I will discuss below, many factors besides the sheer probability of the risk should play an important role in such decisions.[293] Thus, while a formula that tries to rank risks simply by probability might initially sound attractive, in the real world, such an approach ends up being not only overly simplistic but also counterproductive. Furthermore, in many if not most cases dealing with environmental health hazards, we must acknowledge the limitations of the present state of science in accurately measuring risk. This is a relatively new field, with many large questions still unanswered.

Second, good scientists are comfortable with uncertainties – policy makers seldom are, and communications offices almost never like to deal with uncertainty. Scientific uncertainty should not mean that no policies should be implemented – for there is always, to a greater or lesser extent, uncertainty in science. And even when major questions are not fully answered, there are often preliminary answers that cry out for immediate actions. Let us avoid assuming that uncertainties about risks indicate that these uncertain risks are not significant in scope. If this seminar helps provoke greater attention to the difficulties of weighing uncertainties in policy decisions and communicating those uncertainties to the general public, it will have served a very useful function.[294]

Third, we sometimes deal preferentially with certain kinds of science over others. Both as individuals and collectively, we, for example, invest much more heavily in cures than in prevention, I would argue. Cures may be more dramatic (and also more profitable, as prevention tends to be a public good while cures are typically private goods)[295] – but especially when considering problems with long potential time horizons, as is the case with children's environmental health concerns, I believe prevention needs a greater emphasis.

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[292]See, for example, Faigman, David L., *Legal Alchemy: the use and misuse of science in the law*, Freeman and Co., 1999.

[293]Rabbi Swartz uses the term "risk" to mean "hazard" or perhaps "adverse effects." In other contexts the term risk is defined to mean "probability."

[294]For interesting discussions of these topics, see, for example, James G. March. *A Primer on Decision Making: How Decisions Happen*. New York: Free Press, 1994.
Reinhardt, U.E., "Making economic evaluations respectable." Social Science and Medicine 45 (4); 555-562, 1997.
White, Renee T., Putting Risk in Perspective: Black Teenage Lives in the Era of AIDS. New York: Rowman & Littlefield Pub, Inc. 1999.

[295]I am indebted to Dr. Trudy Cameron for pointing out the public/private distinction during the oral presentation of this paper.

Arguably, public health has consistently contributed most to public welfare through prevention – whether that prevention has come in form of vaccinations, sewage treatment, or the elimination of lead from gasoline. Public environmental health should heed these lessons from history and steer closer to a preventative model. Since a market left on its own tends to under-invest in public goods, the federal government can be an important sponsor of prevention-oriented research, as well as play a key catalyzing role in encouraging the development of prevention-oriented technologies.

Finally, the federal government can and, I believe, should play an active role in bridging the science and policy communities – not only by bringing researchers and health care practitioners to Washington through fellowship programs, but also by ensuring that key policy makers have adequate science training. The Children's Environmental Health Network has over a decade of experience bringing these communities together to collaborate on setting policy and research agendas, and we would be happy to assist our government in any way with this task.[296]

## To establish justice – Examining disproportionate burdens

Science can help us measure risks. Economics can try to translate those risks into monetary terms – although the accuracy of such translation efforts sometimes leaves much to be desired, as I will discuss below. But even if we could know exact costs and benefits, that would not be enough information – for if we are to establish justice, we need to know who pays costs and who receives benefits.

This is one key reason why we cannot simply set policy priorities by probability of risk, despite the easy appeal of such a simplified approach, for it can and should matter to us as we make policy who is doing what to whom and for what reason. Risks that people take on voluntarily, or at least receive some direct benefit from, should be regulated differently than risks imposed on a population by someone else, who is making a profit that is not shared with those at risk. And, we might also decide differently about risks if they are in the service of manufacturing life-saving medicines, as opposed to enabling us to produce additional colors of swizzle sticks. For these reasons, analogies between, for example, risks from pesticides and side-effects from medicines are, at their core, misleading and false. Significant uses of pesticides and herbicides, including, for example, aesthetic uses on lawns and flowers, confer no public health value. And, in direct contrast to the distribution of costs and benefits from life-saving drugs with significant side-effects, children at risk from chemical exposures are rarely those who benefit most from the use of these chemicals, nor do they take on these risks voluntarily, as do patients with medicines.[297] For example, a child exposed to pesticide residues through food is rarely saved from nutritional illness by the application of that particular pesticide to that particular crop. Even were that the case, one

[296]See our website [www.cehn.org], for further details. Please note that this paper and the opinions in it, while generally consistent with the positions of the Network, are solely the author's.

[297]Rabbi Swartz probably is referring here to exposures to environmental pollution.

should remember that life-saving drugs are forcibly removed from the market when safer alternatives are found.[298]

True, trying to measure the social utility of a product can be difficult – and can lead us away from the efficiencies of a market economy toward unduly centralized, command and control economics. But I do not believe that our society should leave critical health and safety concerns solely to the ever-changing currents of the market place, especially when it comes to protecting children.

Thus, to establish justice by crafting scientifically sound child-protective policies, the federal government should look beyond aggregate cost-benefit analysis. Furthermore, because children cannot make economic or sophisticated risk-based decisions for themselves, society and all levels of government need to take an extra measure of caution on their behalf. A market needs consumer choice to function properly – and so when that choice is non-existent or meaningless, as is the case with children and environmental health risks, forces outside the market, such as the federal government, need to play a lead role in providing a measure of safety.

But just how large should that measure be? Who do we protect as we try to establish justice? How do we take account of the differing levels of environmental hazards in different parts of this country? Or the fact that children are not only different from adults biologically and physiologically, but that not all children are the same? Do we set standards to protect biologically "average" or "sensitive" children? The 1993 Cryptosporidium outbreak in Milwaukee severely affected only those with other health impairments – but, for them, it too often proved fatal. Should all biological sensitivities receive equal weight in our decision making process – or should we, for example, set ambient air quality standards protective of most children, and expect asthmatic children to stay inside and breathe filtered air? Similarly, should we set pesticide residue standards based on "typical" or "most-burdened" populations – on exposures faced by suburban soccer kids or the children of farm workers? And, given the present health care system of our nation, should standards take into account likely inequities in the level of health care different types of children receive?

Clearly, different informed, well-meaning people could have greatly differing views on these questions. Nonetheless, I want to close this section with a plea for greater consideration of one set of problems – the interactions between poverty, environment, and health. We have, for example, successfully eliminated between 90 and 95% of the lead poisoning in this country – yielding better lives for millions of children. But not all children are receiving this benefit – and, it turns out, those most in need, those who routinely receive the worst health care and have the fewest economic, political, and educational resources available, suffer the most. I believe that our federal government can and should play a key role in reducing the linked burdens of poverty and environmental health hazards for our children.

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[298]The Food and Drug Administration (FDA) may remove a product from the market (that is, withdraw its approval of the drug) only when the safety of that drug is not adequately established through scientific studies, regardless of the existence of "safer" alternative products. However, some would argue that the FFDCA allows FDA to exercise discretion in evaluating whether a product is "safe."

## Insure domestic tranquility –What is "acceptable" risk? Where is the burden of proof?

Insure domestic tranquility – a poetic if not necessarily extremely clear phrase, redolent with images from our pastoral past, with farmer-citizens serving as the backbone of a young nation. But I grew up in a farming community, and I know that behind the apparent tranquility lies a life of risk. Will the rains come? What will the market for corn be this year? Next year? Farmers realize that most decisions come with risk – but also know that taking the wrong risks can ruin lives, families, even communities. Insurance against risks is constantly on one's mind.

Thus, delineating the proper federal role in protecting children from environmental health hazards means, to a great extent, clarifying how and/or when our government should get involved in the risk management process. There are many potential models for such roles – I want to outline here two endpoints of what I believe to be a key spectrum.

At one extreme would be an assumption that chemicals are inherently safe. At the other extreme is the assumption that chemicals pose potential danger. From a standpoint of pure science, neither one is inherently more accurate than the other is – but from a policy standpoint, this initial assumption drives many, many results down the line. An initial assumption of chemical safety presumes, for example, that chemicals are innocuous until proven toxic. The advantage of this approach is that societal resources are not wasted mitigating presumed risks that are in fact non-existent. The disadvantage is that such an approach may lead to some negative health consequences while proof is being accumulated. And when effects are subtle or long-delayed, as was the case with low-level lead poisoning and many other environmental health hazards, a full-blown crisis can erupt before "proof" kicks in. After all, finding a smoking gun sometimes means that one has also found a dead body.

An assumption of safety may be better in situations when decisions are made with good initial information and a history of accurate decision making. Unfortunately, we have seen far too many cases, from DDT to ozone-depleting aerosols, from generations of lead poisoning to DES babies, where decisions were made with inadequate information.

The approach at the other extreme, assuming a need for caution and giving preference to prevention over coping after the fact, holds that all actions involving chemicals are potentially harmful and asks for proof of zero-harm before proceeding on a given course. The advantage of this approach is that harmful actions are much more likely to be prevented than with the above approach. The downsides are two-fold – first, that harmful inactions become more likely, and second, that society may expend resources preventing trivial hazards.

My own personal preference is to err on the side of caution – but in a large country with a dynamic economy but limited governmental resources, that is not always possible. Nor am I completely of one mind even about whether strict precaution is in fact the ideal, whatever its practical shortcomings. But, I think, we do already have enough evidence to

show that strict presumptions of chemical safety have put children's health and lives at risk far too often.

The Food Quality Protection Act, as presently written,[299] provides an intriguing model for balancing these approaches. Because we already know that children's eating habits differ significantly from adults, because, due to their size, children take in more food, water, and air per pound of body weight than adults; because, due to hand-to-mouth behavior and the fundamental attraction between kids and dirt, children's non-food exposures to pesticides may also significantly differ; because children have generally longer life-spans and therefore longer time-horizons for an exposure to cause harm; and because, according to the best research currently available, children may be more sensitive to some effects of some pesticides – e.g. developmental neurotoxicity – we have many well-researched reasons to suspect that pesticide residue standards that protect adults may not always protect children.[300] And so, in the absence of data that contradicts our assumption of precaution, FQPA adds the admittedly arbitrary 10x factor. The burden of proof is thereby shifted; in this limited set of circumstances, pesticides, which are, after all, designed expressly to be toxic, are not assumed to be completely safe for children. On the other hand, they are not assumed to be dangerous at all levels in all circumstances, either – and if data proves that the 10x factor is not necessary, it can and should be reduced. To date, for example, EPA has applied the full 10x factor in 10% of cases, and it has subsequently reduced factors when additional data were submitted.[301]

One could easily imagine analogous mixtures of safety vs. precautionary assumptions in other child-health related environmental standards. The federal government could assume, for example, that in the absence of other data, chemicals to which people are more likely to be exposed should receive greater scrutiny – as is the case with the voluntary high production volume chemical-testing program. We could further assume that in the case of chemicals that we know children are exposed to – such as those found in human biomonitoring – more thorough testing is required. Conversely, since biomonitoring thus becomes a key trigger for raising precautionary procedures, increased and increasingly accurate biomonitoring may become a necessity – both for setting priorities for caution and for potentially showing that certain chemicals do not raise immediate health concerns.

The federal government could require that the licensing fee for the introduction of new chemicals include either more complete exposure and human hazard testing or funds sufficient to undertake such testing – and we could also require periodic relicensing, based on timelines mutually agreeable to regulated industries and public health interest groups, for chemicals already in production that were never subject to such testing. Such proposals

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[299]At the time of this writing, Congress was considering radical revisions to the FQPA, revisions that arguably would have, in effect, eliminated the child-protective assumptions described above. That legislation was not enacted.

[300]While hundreds of studies show these increased risks, the best known – and the one in part responsible for the crafting of FQPA – is the National Academy of Sciences 1993 study, *Pesticides in the Diets of Infants and Children*, National Academy Press, 1993.

[301]U.S. General Accounting Office. *Children and Pesticides: New Approach to Considering Risk Is Partly in Place.* HEHS-00-175. Washington: U.S. Govt. Print. Off. Sept. 11, 2000. 23 p.

sound quite modest when compared to strict precautionary models – which might, for example, require a temporary ban on any chemical that has not been thoroughly tested, no matter what the predicted exposure level or commercial significance of the product is. Another alternative would be to require a private bond to be issued at the time each new compound is introduced – to cover any potential liability from harmful effects discovered in the future. This, however, moves us from prevention back to coping after the crisis has occurred.

Public health is also best served when the assumptions behind regulations match real world situations and not convenient simplifications. For example, it may be appealing to rank childhood risks by mortality before leaving childhood – because such mortality is clear, simple, easy to measure – and also potentially quite deceiving. For such an assumption not only misses all non-fatal morbidity, it also ignores later mortality caused by childhood exposures. Through this over-simplification, Dr. Chilton's charts (e.g., Figures 5, 7, and 8, and Table 17) miss the fact that, over U.S. children's lifetimes, for example, 75% of their mortality risks come from chronic disease, and we do not yet know how much of that 75% is linked to environmental hazards.[302]

Focusing on risks because they are easier to measure makes as much sense as the old story of a man, late at night, seeing his friend crawling around beneath a lamp pole. "Charlie," he asks, "what are you doing?" Charlie replies, "Looking for my car keys, Fred." To which Fred responds, "I'll help you look. You figure you dropped them right here?" "No, actually I dropped them on the other side of the street – it's just that the light is better over here." The light is better on the childhood mortality side of the street – but risks that are presently inadequately characterized may hold the key to our children's healthier future.

Furthermore, not knowing the exact dimension of a risk does not mean that that dimension is small. A look at what we do and do not know about cancer rates illustrates this point. The proportion of cancers in which environmental hazards play a role is simply not known at present. Dr. Chilton's figure of 3% is controversial.[303] A number of studies of particular classes of pollution and their effects on particular types of cancer have given rise to figures more than an order of magnitude greater. For example, there is some evidence that air pollution may cause 10% of lung cancers, while water-borne pollutants may cause between 20% and 40% of bladder and possibly rectal cancers.[304] All are estimates, based on epidemiological findings – but the jury, or in this case, the consensus among researchers is still out. And as we understand more about the complexities and importance of gene-

[302]The Pew Environmental Health Commission's series of reports (on asthma, birth defects, etc) chronicle both the overall burdens of chronic diseases and the potential role of environmental health hazards in various health outcomes.

[303]See, for example, Schmahl, D., R. Preussmann, and M.R. Berger. *Causes of Cancer – An Alternative View to Doll and Peto (1981).* Klinische Wochen-schrift, Springer-Verlag, 1989.
Epstein, SS., J.B. Swartz, et al. Carcinogenic risk estimation, *Science*, v. 240, May 20, 1988, p. 1043-1045.

[304]Davis, D. L., and C. Muir. Estimating avoidable causes of cancer, *Environmental Health Perspectives*, v. 103, Supplement 8, Nov. 1995, p. 301-306.
Zahm, S. H., and S.S. Devesa, "Childhood cancer: Overview of incidence trends and environmental carcinogens, *Environmental Health Perspectives*, v. 103, Supplement 6, Sept. 1995, p. 177-184.

environment interactions, environmental factors may be seen to be an increasingly important part of the equation. So, in the meantime, as estimates change, what should the federal government do – simply assume that our children are safe? I doubt that many parents would prefer that role for our federal government to play.

Similarly, false simplifying assumptions that each child is only exposed to one potentially harmful chemical at a time, from only one exposure pathway are so contrary to the real world as to do a great disservice to our children. Yet these assumptions govern much of our present environmental regulations. It is only with the passage of FQPA that more realistic estimations for exposures have begun to be incorporated.

## Provide for the common defense –Government as data-gatherer/ data-user

The "common defense" is an over-used phrase. It has been invoked to justify everything from physical education to the building of highways. But the federal government's potential role as data gatherer/analyzer/front-line user truly can play a significant defensive function in protecting our children from environmental health hazards. And the federal government can perform a critical role precisely because this is a common defense – one that must be national in scope to effectively and accurately monitor health trends and exposures.

The first important aspect of this role is to help identify and prioritize data/research gaps. Obviously, this should not be undertaken solely by the federal government – but since such an analysis, to be complete, should cut across governmental levels, involve many potentially competing public and private institutions, bring together leading researchers and practitioners, and create partnerships with and between public interest groups, regulated industries, and concerned parents, only the federal government has the power and scope to play adequately the role of convenor. I expect that a comprehensive list of such gaps would include exposure data, the tracking of key illnesses, biomonitoring, and improved/simplified testing protocols, as well as further basic medical and biological research to help clarify various developmental processes and key windows of vulnerability. The longitudinal cohort study proposed to examine links between environmental exposures and children's diseases is another example of a data gap that can best be addressed at the federal level.[305]

As gaps are identified, we will need to rebuild the public health infrastructure necessary to gather, analyze and act upon appropriate data. As was documented in earlier papers, asthma rates are increasing rapidly – but we do not have good data on just where, how, and when. Certain types of birth defects, such as hypospadias, are on the rise – but we do not really know by how much, or what other birth defects we might be missing. Our ability to monitor which compounds are actually found in human bodies has increased considerably over the past decade. Not only could and should it increase further, however, but we are not even fully using present techniques. For example, there is no comprehensive

[305]The reference is to the longitudinal cohort study authorized by the Children's Health Act of 2000. [http://www.nichd.nih.gov/despr/cohort/about.htm]

national database to tell us what synthetic chemicals are found in breast milk – clearly an issue of concern to children's health.

But our common defense requires more than the right environmental health intelligence. We also need to be able to respond to what we find. We do not need another report that sits on the shelf of overworked county or state public health officials, because they do not have the resources to address the report's conclusions. For example, we have known for centuries that lead is toxic – and the nation's public health community warned about lead additives in gasoline beginning in the 1920s. Yet these reports were not much acted on until 1979 – and even then, the action was not initially spurred by public health concerns. Once problems are identified, the federal government should have a clear, central, and active role to play both in mitigating the immediate concern and establishing methods for preventing its recurrence.

## Secure the blessings of liberty – Beyond prevention to true health

Liberty means more than freedom from – more than escape from the tyrant's grasp. True liberty means also freedom to grow, develop, choose, and learn. Similarly, health should mean more than simply the absence of illness. It can and should mean the presence of full opportunities. A healthy child is one whose health does not hold him or her back in body or mind. For such a child, health includes not only soundness of body but wholeness of spirit.

If we try to evaluate how the United States has done in terms of this broader definition, it is clear that we have made much progress over the past century. And clearly some aspects of this broader definition do not and should not lie within the purview of the federal government. I am not expecting a federally mandated "medi-soul" program to address wholeness of spirit, for example. But even when examining only those areas that the federal government should address, such as, in my opinion, children's environmental health, we are still far from an ultimate goal of a nation of truly healthy children, whose health helps lead them from strength to strength. If this is to be our goal, then the progress to date is not enough.

Let me turn the discussion briefly to the question of rights vs. goals. Some would state the above not as a goal but as a right – stating, as a broad coalition of groups have, that "All children have the right to clean air, to safe drinking water and food, and to consumer and commercial products free of environmental health and safety threats; all children have the right to healthy homes, child care facilities, schools and communities."[306] I don't in any way disagree with such statements – but I am not convinced that the language of "rights" is particularly helpful here. Rights-language always raises questions – rights from whom? Inherent human rights? Rights from our creator? Rights granted – or denied – by our system of government? More troubling still are some common American assumptions about rights – that all rights are absolute, making it difficult to adjudicate between competing rights, or

[306]At present, over 100 public health, children's, medical, faith, and community organizations have signed on to these principles as part of a "Partnership for Children's Environmental Health."

that rights are highly individualistic, separating us from our neighbors rather than creating shared bonds of responsibility.

I believe it is simpler and clearer to discuss national goals, rather than get bogged down in a sometimes-convoluted philosophical, philological debate. Our federal government has a, if not the, key role to play in not only articulating but actualizing these expansive pediatric environmental health goals. Here are a few candidate federal actions I would propose, some of which I have already mentioned above:

- The setting of all environmental health standards so as to protect children as well as adults, including subpopulations that are especially vulnerable due to multiple exposures, income levels, or racial/ethnic makeup.
- The enactment of standards that consider aggregate and cumulative exposures and pathways of exposure to children.
- The full incorporation of children's special sensitivities into all appropriate risk assessments.
- The implementation of national research strategies designed to fully investigate the environmental components of children's health, including long-term and latent effects.
- A national structure of monitoring and biomonitoring to accurately measure childhood exposures and diseases, and a public health system capable of addressing those exposures.
- Broad-based parental right-to-know, including clear labeling, improved reporting and testing of chemicals, and transparent avenues for parental and community participation in decisions affecting children's environmental health.
- Systemic cooperation between government agencies overseeing aspects of children's environment.
- An underlying government-wide ethos that understands children's special health concerns, as well as the unique moral standing children have in our society.
- The encouragement of government and industry practices, standards, and values that consider children's environmental health concerns in every aspect of the design process and embrace the responsibility to prevent environmental health hazards.

I believe that such a platform of goals would take us well on our way toward true health.

## To ourselves and our posterity – Economics and our responsibility to the future

A market economy is the most productive economic system humans have yet devised. Markets lose efficiency, however, as reality fails to meet some basic assumptions of classical economic theory – assumptions such as full and accurate information, consumer sovereignty

and choice, and no significant externalities from the market. When we look not only at ourselves but also at our posterity, as is the case with children's environmental health concerns, we must realize that classical economics gives us at best approximate answers – and that present market forces alone, no matter how economically productive, will not be enough to protect our children.

This does not mean that economic analysis is not needed. After all, we may agree that no one, no individual, business, organization, or governmental body should operate in a fashion that directly or indirectly threatens the health of children. But I am sure that we would also agree that, in the near-term future, it is unlikely that we will reach that ideal – and so, in the meantime, we have to prioritize. Good economic analysis can help us with that task. The federal government can play a useful role both in correcting key market deficiencies and in enhancing economic analysis and thus our ability to take long-term effects into consideration. Let me outline briefly a few of the deficiencies I perceive that our federal government might address.

First there is the standard economic practice of discounting – of devaluing the future at a set percentage rate to compensate for factors such as future opportunities, investment growth, and so on. In some circumstances, discounting accurately measures how real people behave – that is why so many people are willing to pay for their car over 60 months and their house over 30 years. But discounting may not always be appropriate – and the far-future health of our children and our children's children is a key case in point. For example, under OMB's standard discounting rate of 7%, children lose more than half their value in just 10 years. I doubt any parent – even parents of unruly teenagers – would agree with that, or behave in the marketplace as if that were so. And yet such figures guide our policy-determining cost-benefit analyses – and so systematically undervalue prevention of environmentally-related disease in children. One could argue that such practices encode systematic discrimination against children.

Systematic undervaluation is a broader problem when applying standard cost-benefit procedures (such as contingent valuation) to children's environmental health. How could we calculate a child's willingness to pay to prevent lead poisoning, if the child can neither pay nor fully realize the import of his or her decision? If we measure worth by wages or consumer spending, children have little to no value. If we measure how children affect parental decisions, we miss the broader societal value of children I outlined above. And when we just look at the adult perspective, we may miss the true cost to children, for example, of not being able to play outside because of pollution-related asthma triggers.

EPA's Office of Child Health Protection is examining a number of similar issues, based on recommendations from the Children's Health Protection Advisory Committee, Economics Working Group on which Dr. Cameron and I sit. In addition to broad questions about discounting and measuring costs and benefits among children, we have raised more specific questions about such issues as the value of a statistical life and the impact of using such measures on children's health protection. Current assumptions hold that any life saved is of one, set value. This has the advantage of preventing the undervaluation of the elderly – but it may also cause us to undervalue the long-term benefits of protecting children from environmental health hazards that have life-long effects.

Which brings us to questions of monetization and morbidity vs. mortality. In order to try to compare the value of saving a life in an auto accident to preventing the onset of a non-fatal asthma attack, we currently monetize both possibilities and compare them in dollar terms. In many cases, this obscures rather than clarifies. Rather than giving policy makers our artificial attempts at figuring out how many asthma attacks equal one death, perhaps we would better serve them by more clearly outlining actual health outcomes rather than dollar equivalents. This still provides useful information – after all, knowing that one program might prevent 5 hospitalizations from asthma per million dollars spent while another might prevent 500 for that same million should influence policy – while leaving explicit those hard decisions about trade-offs. Traditional cost-benefit analysis also obscures distributional effects – who pays and who benefits. As noted above, especially when we talk about children, such effects should be considered as we decide policy – and so again there is a need for explicit figures without the obscuring equalization of monetization.

Economic analysis can serve as a tool to make choices and set priorities. But it is neither helpful nor accurate to declare that significant economic tradeoffs are commonplace between environmental health and public safety concerns. There is not one unitary pot of resources to deal with all childhood problems. Requiring the testing of chemicals to evaluate if they pose risks as developmental neurotoxins, for example, has essentially no impact on childhood accident rates. In fact, many policies, such as those designed to make cities safer for pedestrians, simultaneously reduce environmental health and safety risks. Nor, despite overstated claims from Rachel Carson's day down to our own, has any study ever shown <u>any</u> nutritional deficits caused by EPA regulation of pesticides. Some who criticize an emphasis on environmental health hazards say it "distracts policy makers from considering other possible causes and from addressing more serious threats." Are they asserting that other risks pose a greater threat than asthma, the number one cause of school absenteeism, affecting 14 million Americans, killing 5,300 each year in the United States, let alone all the other significant environmental health hazards facing children, from environmental tobacco smoke to lead and mercury poisonings?[307] These are not distractions – and they keep no parents from addressing safety concerns ranging from bicycle helmets to crib safety.

Finally, there is the difficulty of weighing in strictly economic terms the notion of irreversibility. We are not the first generation to attempt risk analysis. For example, in the Jewish tradition, there is a fundamental precept that no lives – including one's own, since God is regarded as the ultimate owner of all – may be risked without reason, or merely to make a profit. So rabbis for centuries have been trying to answer the question, what is an unreasonable risk? About two hundred years ago, Rabbi Jacob Ettinger came up with a calculus not unlike many used today. According to Rabbi Ettinger, an unreasonable risk is one that an individual informed of three key factors would not wish to take. Those three factors are: the likelihood of the risk, the scope of the potential effect (e.g., death vs. discomfort), and whether or not that effect is reversible. Even in cases where likelihood is relatively low, when a potential effect might be irreversible, Ettinger argues, we need to act with additional caution.[308] In other situations, economists often assume infinite opportunities

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[307]Mannino DM, Homa DM, Pertowski CA, et. Al, "Surveillance for asthma – United States, 1960-1995, Morbidity-Mortality Weekly Report, Centers for Disease Control Summary, 1998; 47:1-27

[308]Rav Jacob Ettinger, *Responsa Binyan Zion,* #137

of choice – but irreversible effects, ranging from cancer deaths to infertility, strip children of choice, permanently.

On all these issues, the federal government can help us correct market deficiencies through better, more child-centered, economic analyses. Some of the tools for conducting such improved analysis already exist and need merely to be implemented. Others have not yet been devised – and so it is important to note that when we talk about necessary research to protect children from environmental health hazards, some of that research should be into econometric techniques.

## Conclusion

Children are unique biologically – and morally. Protecting them from environmental health hazards will require both additional scientific research and actions taken based on current knowledge. Above, I have outlined a number of key areas where, I believe, the federal government can and should take the lead both in promoting research and in promulgating protective standards, as well as general principles to help guide potential federal actions. I hope that these recommendations will prove to be of long-term value.

I wish to conclude by offering four more immediate recommendations of my own, ones designed to be implemented during the transition to the next Administration.

## Executive Order 13045 and EPA's Office of Children's Health Protection

Much of the recent focus on children's environmental health can be attributed, directly or indirectly, to Executive Order 13045, Protection of Children From Environmental Health Risks and Safety Risks (April 21, 1997),[309] and the establishment of EPA's Office of Children's Health Protection (OCHP). In my experience, Executive Order 13045 and OCHP have been models of how the government should work – seeking flexibility; setting short, medium, and longer term priorities; establishing collaboration between government agencies and partnerships with stakeholder communities ranging from public health groups to industry leaders; changing, albeit sometimes slowly, the basic operational ethos of significant agencies; and, most importantly of all, beginning to address important environmental health hazards facing children in an appropriate, child-focused fashion. In other words, both the Executive Order and OCHP have accomplished many of their original goals. Now comes the slow and steady work of systematically reviewing environmental health policies to ensure that every one takes into account the unique susceptibilities of children. To accomplish this larger task, Congress and the next Administration should give full support to Executive Order 13045 and OCHP.

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[309] 62 *Federal Register 19885-19888.*

## A New White House Council on Children's Environmental Health and Safety

One reason for the Executive Order's success has been the creative collaborations established through the inter-agency task force designed to implement the Order. In many ways, the task force has been a model of how government agencies should work together. Nonetheless, the task force is an informal, ad hoc locus of cooperation – and as the work of protecting children moves forward, it might be best both to raise its profile and establish it more firmly. One way to accomplish these tasks simultaneously would be for Congress and the Administration to establish a White House Council on Children's Environmental Health and Safety. This Council could, among its other activities:

- Play the chief coordinating role in cross-agency implementation of policies.
- Host White House Summits biennially on the issue, involving appropriate federal, state, and local officials and policy makers as well as stakeholder leadership in the crafting of an ongoing child-protective agenda, and discussing key policy concerns, from data gaps to discount rates, as noted above.
- Publish an annual report on the state of children's environmental health and safety, which would provide a valuable tool for evaluating progress and identifying future priorities
- Undertake an awards/recognition program to highlight successful community efforts across the country and increase the replicability of model programs.

## Policy Tools for Protecting Children

To date, a wide variety of policy tools has been utilized in reducing risk to children from environmental health hazards. These have included voluntary self-regulation by industries, key research grants, funding for model programs, citizen outreach and education, and federally mandated legislation and regulation. All of these have played key roles in protecting children, and all should continue to be utilized during and after the transition to the next Administration. An a priori, ideologically based commitment for or against one tool or another does a disservice to our children. The most appropriate criteria for choosing which policy tool to use are those which examine impact on childhood risks. Thus, for example, viewing regulation as a "last resort" misses the importance of regulation in protecting public health and safety over the past century. Congress and the Administration should continue to put children above ideology and use whatever means are appropriate for protecting them from environmental health hazards.

## FQPA as a Model for Balance

As noted above, FQPA strikes an interesting, generally effective balance between presuming that pesticides pose no harm to children unless specific data already show such harm, and protecting our children with an added measure of prevention and caution. It also

seeks to adjust old, inaccurate simplifying assumptions about how children and adults are exposed to pesticides, to reflect the real-world phenomena of aggregate and cumulative exposures. EPA has shown great flexibility in implementing FQPA, using added measures of safety when initial data raise concerns and not rigidly applying the 10x factor in all cases. Most fundamentally, FQPA for the first time explicitly recognizes the biological fact that children have different, and often greater, environmental susceptibilities than adults. If the federal government is to craft policies that protect our children through the 21st century, it would do well to use FQPA as a model for future legislation.

# Navigating the Maze: Federal Activities to Address Children's Environmental Health Risks

By Kimberly M. Thompson, Sc.D.

## Introduction

As the researchers, artists, leaders, teachers, and parents of future generations, today's children represent one of our nation's most valuable resources, and the U.S. government shares responsibility with parents and other levels of government for protecting the health and well-being of children. Throughout the last century, American children as a whole enjoyed the benefits of parental and governmental commitment to improving their lives, and of amazing strides in scientific understanding. As a result, most American children today experience impressively high-quality lives compared to their predecessors.[310] The devastating toll of once-common epidemic infectious diseases (e.g., malaria, dysentery, measles, whooping cough, diphtheria, and small pox) represents a largely forgotten history in the United States.[311] The efforts and observations of early scientists and engineers laid the foundation for successful public health measures like vaccination, water disinfection, isolation, and pasteurization that led to huge improvements in children's health, much of this in the last century. The remarkable decrease in the infant mortality rate and increase in the average life expectancy that occurred since 1900 provide evidence of this significant progress.[312]

In spite of the progress, however, children continue to be injured and killed by hazards that have persisted throughout American history, particularly from firearms, poisoning, drowning, violence, and burns. In addition, children now face the relatively new challenges associated with other diseases (e.g., sexually-transmitted diseases, AIDS, childhood cancers) and broadly defined environmental hazards (e.g., motor vehicles, illicit drugs, smoking, toxic substances). While national indicators show important recent improvements in some aspects of children's health,[313] health risks still cause a significant

[310]King, C.R. (1993) *Children's Health in America.* New York, NY: Macmillan Publishing. For some additional comparisons also see Thompson, K.M. (2000) Kids at risk. *Risk in Perspective*, v. 8, n. 4, Boston, MA: Harvard Center for Risk Analysis. http://www.kidsrisk.harvard.edu

[311]Ibid.

[312]See Figures 5 and 6 in the paper by Dr. Kenneth W. Chilton that appears in these proceedings.

[313]Federal Interagency Forum on Child and Family Statistics (FIFCFS). "America's children: Key

(continued...)

amount of premature mortality and morbidity, and they compromise healthy child development.[314] Given the progress yet to be made, it is not surprising that improving children's lives emerged as a priority on the national agenda in the 1990s.[315]

What is surprising, however, is the lack of focus on the most significant threats to children's health – those that measurably diminish the quality and/or length of the lives of American children – and the lack of appreciation of the importance of putting the various threats to children in perspective, so that we can efficiently and effectively target resources at the interventions that will lead to the greatest improvements. The emphasis on children in the last decade includes significant focus on children's environmental health. This paper suggests that the focus on children's environmental health is currently poorly defined, and argues that the federal government must play a critical role in evaluating the relative risks to children, promoting and supporting cost-effective programs to reduce risks, and insuring that the laws and policies of the United States produce the greatest degree of health, happiness and safety to the nation's children.[316]

## Perceptions of Children's Risks

Risks to children, by this I mean the probability and severity of bad outcomes occurring for Americans under the age of 21 years, concern Americans.[317] Table 23 shows the top ten responses to a 1997 survey that asked Americans with children to name the two or three most serious problems facing U.S. children today.[318] While this list indicates concern about risks, researchers remarked that two problems that many experts consider among the most serious problems for children, poverty and lack of adequate health care, did not make the list.[319] Nearly 20% of Americans under the age 18 live in poverty, and nearly

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[313](...continued)
national indicators of well-being, 2000." Washington, DC: Forum on Child and Family Statistics. (2000)
http://www.childstats.gov/index.htm.

[314]National Commission on Children, 1991. *Beyond Rhetoric: A New American Agenda for Children and Families.* Washington, DC: National Commission on Children.

[315]Ibid.
Executive Order 13045. Protection of Children From Environmental Health Risks and Safety Risks. 62 *Federal Register* 19885, April 23, 1997.

[316]"Government is, or ought to be instituted for the common benefit, protection, and security of the people, nation, or community; of all the various modes and forms of government, that is best which is capable of producing the greatest degree of happiness and safety, and is most effectually secured against the danger of maladministration" (George Mason, Article 1, Virginia Bill of Rights, 1776).

[317]For a compelling and hopeful perspective see Schorr, L.B. (1988) *Within Our Reach: Breaking the Cycle of Disadvantage.* New York, NY: Doubleday.

[318]Blendon, R.J., J.T. Young, M.C. McCormick, M. Kropf, and J. Blair. (1998) Americans' views on children's health. *Journal of the American Medical Association* , v. 280, n. 24, p. 2122-2127.

[319]Ibid.

5% of Americans under age 18 suffer from moderate or severe hunger.[320] In spite of the federal Children's Health Insurance Program (CHIP), many American children remain underinsured or uninsured.[321]

| **Table 23. Most Serious Problems Facing Children (ties indicated)[322]** | |
|---|---|
| 1 | Drugs/drug abuse |
| 2 | Crime |
| 3 | Breakdown of home life |
| 4 | Poor quality education |
| 5 | Alcohol abuse |
| 5 | Peer pressure |
| 7 | Lack of discipline |
| 8 | Influence of media |
| 9 | Unwanted teen pregnancy |
| 10 | Sexual freedom |

When researchers asked respondents to identify the most serious health problems facing American children today, they found these to be of relatively low salience; nearly one-fourth of the respondents could not name a single health problem, and nearly one-half could not name two problems.[323] Table 24 shows the results of the health problems most named. A key conclusion of the study authors is that:

> [T]he public is unaware of which problems actually affect the most children or affect them most severely.... [Neither] the leading causes of childhood deaths – unintentional or intentional injuries – nor other problems such as poverty and limited access to health care are salient enough to Americans to be listed at the top of the nation's agenda for children today.[324]

Indeed, I believe that, as a nation, we lack a comprehensive, authoritative resource that quantifies the risks that American children face.

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[320]See current statistics from FIFCFS, 2000 supra note.

[321]Edmunds, M., M. Teitelbaum, and C. Gleason. (2000) *All Over the Map: A Progress Report on the State Children's Health Insurance Program (CHIP).* Washington, DC: Children's Defense Fund.

[322]Ibid.

[323]Ibid.

[324]Ibid, p. 2126.

| Table 24. Most Serious Health Problems Facing Children as Indicated by Americans with Children in Their Homes (ties indicated)[325] | |
|---|---|
| 1 | AIDS |
| 2 | Infectious/communicable diseases |
| 3 | Drugs |
| 4 | Cancer |
| 5 | Smoking |
| 6 | Dietary concerns |
| 7 | Alcohol-related problems |
| 8 | Cannot get or pay for medical care |
| 8 | Asthma |
| 10 | Teenage pregnancy/unwanted pregnancy |

## Assessing Children's Environmental Risks

Given available statistics on mortality, unintentional injuries kill more Americans between ages 1 and 21 years than any other cause of death.[326] For context, a breakdown of the general category of unintentional injuries provides estimates of annual mortality risks due to specific causes for children under age 10 as shown in Table 25. While Table 25 shows the data for only half of the range of childhood and for only one year, it is instructive, because it provides a clear sense of the magnitude of some of the leading threats to children today, and context for considering the commonly used regulatory criterion of a risk of "one in a million." Other similar tables could be presented for different age categories of children. This range is used as an example.

These mortality risk estimates show that, on average, risks to children exceed 1 in a million *annually* for these injury related causes of death. Further, based on these numbers alone for the first 10 years of life, the mortality risks from motor vehicles, drowning, fire, and suffocation exceed a *lifetime* risk of 1 in a million.[327] If we include the period of adolescence

[325]Ibid.

[326] See Table 17 in the paper by Dr. Kenneth W. Chilton that appears in these proceedings.

[327]This can easily be seen by multiplying the average number of deaths per million children under age 10 per year in Table 25 by 10 years and dividing the result by 75 years to approximate a lifetime.

(continued...)

(for example, through age 19), when guns become a more significant killer, then the risks associated with guns also exceed a lifetime risk of one in a million. That Americans do not recognize the single largest killer of kids - motor vehicles - as a health problem for children given these results clearly indicates to me the need for improved information about children's risks. By "improved information" I mean both a synthesis of the existing data, so that better information is available, but also education about relative risks and risk reduction strategies.

**Table 25. Estimated Annual Mortality Risk for Children Under Age 10 (Number of deaths per million children)[328]**

| | | | |
|---|---|---|---|
| Motor vehicles | 46 | Guns | 5 |
| Drowning | 20 | Poisoning | 2 |
| Suffocation | 17 | Bicycles | 2 |
| Fire | 16 | Medical care | 2 |

Environmental risks are more uncertain than the risks of accidents, because they usually cannot be estimated based on past experience and mortality statistics. In many cases, and particularly in the context of environmental risks of illness or death, assessors must rely on mathematical models to estimate potential public health risks as a function of exposure. To estimate the potential risk posed by a substance in the environment, an analyst must combine information about exposure to the substance and the substance's toxicity to those exposed. For children, these estimates are very uncertain, because children represent a group that is relatively understudied.

Estimates of toxicity are difficult, because analysts generally must extrapolate from limited data on potential health effects at high doses to potential health effects at low doses. Indeed, the few cases of existing data that demonstrate causal and differential effects on children compared to adults largely come from cases where high exposures led to significant numbers of cases of relatively rare diseases that could be detected.[329] Children's risks from exposure to toxic substances can differ from adults' risks in outcome (often referred to as a qualitative difference) and/or in severity (often referred to as a quantitative difference). The relative toxicity of substances for children and adults must be assessed on a case-by-case

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[327](...continued)
Thus, even if the risks associated with these hazards ended at age 10, which they do not, the lifetime risk associated with these hazards would still exceed 1 in a million.

[328]Based on 1997 data from the National Center for Injury Prevention & Control, Centers for Disease Control and Prevention and population estimates from Statistical Abstract of the United States for 1997.
http://www.cdc.gov/ncipc/osp/usmort.htm
http://www.census.gov/statab/freq/99s0014.txt

[329]Rogan, W.J. (1995) Environmental poisoning of children – Lessons from the past. *Environmental Health Perspectives*, v. 103, Supplement 6, p. 19-23.

basis.[330] Historically pediatric populations have not been the subject of sufficient pharmaceutical trials for various reasons[331] or epidemiological studies due to the relative rarity of disease.[332] In a few cases, extrapolation may be required to estimate the effects on children based on limited evidence from a cohort of occupationally exposed adults. In most cases, however, the best available evidence might be that the substance might cause adverse health effects in animals, and risk assessors must extrapolate toxicological data between species as well as for age. Specific examples exist of cases where exposures of children resulted in health effects that did not occur in exposed adults (e.g., vaginal and cervical cancer from fetal exposure to diethylstilbestrol) and vice versa (e.g., sterility following adult exposure to mumps).[333] Examples also exist of cases where adults are more sensitive to exposure than children for the same effect (e.g., liver toxicity from exposure to acetaminophen) and vice versa (e.g., neurological damage from exposure to lead or hexachlorophene).[334]

As with toxicity, children's exposures can also differ from those of adults. Childhood represents a period of rapid growth, and due to their higher metabolic activity children have higher daily requirements for food, water, and oxygen per unit of body weight than adults.[335] In addition, children's activities may differ significantly from those of adults, and consequently, some exposure scenarios or conditions that apply to one group might not apply to the other (e.g., occupational exposure, extended periods of time crawling, high soil ingestion rates, large consumption of apples or grapes). The available evidence suggests that exposure of and risk to children, relative to adults, must be assessed on a case-by-case basis.[336]

The enormous challenge for risk assessors focused on environmental risks arises in causally linking the environmental hazards to outcomes of concern (i.e., to causes of mortality or morbidity like cancer, birth defects, and respiratory airway diseases). This becomes particularly challenging for chronic health effects. The war on cancer reveals a

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[330]Guzelian, P.S., C.J. Henry, and S.S. Olin (eds). (1993) *Similarities and Differences Between Children and Adults: Implications for Risk Assessment.* Washington, DC: ILSI Press.

[331]Department of Health and Human Services, Food and Drug Administration. Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients, 62 *Federal Register* 43900. (1997)

[332]Grufferman, S. (1998) Commentary: Methodologic approaches to studying environmental factors in childhood cancer. *Environmental Health Perspectives,* v. 106, Supplement 3, p. 881-886.

[333]Wilson, J.D., E. Braunwald, K.J. Isselbacher, R.G. Petersdorf, J.B. Martin, A.S. Fauci, and R.K. Root. (1991) *Harrison's Principles of Internal Medicine*, 12th Edition. New York, NY: McGraw-Hill, Inc.

[334]See Guzelian et al. supra note.

[335]Ibid. See also Bearer, C.F. (1995) How are children different from adults? *Environmental Health Perspectives,* v. 103, Supplement 6, p. 7-12.

[336]See Guzelian et al. supra note. See also International Life Sciences Institute (ILSI) 1996 "Research needs on age-related differences in susceptibility to chemical toxicants: Report of an ILSI Risk Sciences Institute Working Group." Washington, DC: ILSI. Finally, also see Goldman, L.R. (1998) Chemicals and children's environment: What we don't know about risks. *Environmental Health Perspectives,* v. 106, Supplement 3, p. 875-880.

critical insight that we should take into account in doing research on other large categories of diseases Cancer is more than one disease, with more than one cause. We should expect this to be true for other health concerns as well (like asthma or autism).

## The Focus on Children

Several factors have led to an increased focus on children in the last decade, ranging from President Clinton's political agenda to medical research on child brain development. The increase in concern about children in the 1990s can be seen from the list of federal activities aimed at children shown in Table 26.

**Table 26. U.S. Federal Governmental Focus on Children's Environmental Risks in the 1990s[337]**

| | |
|---|---|
| 1992 | Congress enacts the Housing and Community Development Act, Title X, mandating new requirements for managing residential lead-based paint hazards |
| 1995 | EPA Administrator releases *Environmental Health Threats to Children* report and an agency-wide "Policy on Evaluating Health Risks to Children; U.S. Congress, Office of Technology Assessment (OTA), releases *Risks to Students in Schools* |
| 1996 | Congress enacts the Safe Drinking Water Act Amendments and Food Quality Protection Act with provisions specific to children; ATSDR launches a child health initiative; Children's Environmental Protection Act of 1996 introduced (first legislation focused on children's environmental health) |
| 1997 | EPA establishes Office for Children's Health Protection; numerous acts specific to children introduced in both houses of Congress; President Clinton issues Executive Order 13045, "Protection of Children from Environmental Health Risks and Safety Risks;" G7 declaration on children's health signed by EPA Administrator and other environmental leaders; ATSDR releases *Report on Healthy Children - Toxic Environments: Acting on the Unique Vulnerability of Children Who Dwell Near Hazardous Waste Sites*; the Food and Drug Administration proposes a rule to require pediatric studies of certain new drugs and biological products; Interagency Task Force on Protecting Children from Environmental Health Risks and Safety Risks issues first annual report *America's Children: Key National Indicators of Well-Being;* President Clinton proclaims October 6 National Child Health Day; Office of Science and Technology Policy releases *Report on Investing in Our Future* |

[337]This non-comprehensive list of examples of the growth of activities focused on children's environmental health is created in part based on information compiled by the American Industrial Health Council's "Chronology of Events: Children's Health Issues" and the Children's Environmental Health Network's "Chronology of Children's Environmental Health" (available at: http://www.cehn.org/cehn/Chronology.html).

| | |
|---|---|
| 1998 | Introduction of legislation related to children's environmental health continues; Centers for Disease Control and Prevention (CDC) and EPA request roughly $10 million for FY 1999 for assessing health risks to children; Consumer Product Safety Commission (CPSC) issues guidance for manufacturers to refrain from filling children's products with hazardous chemicals; EPA announces agenda for the Children's Health Test Rule; EPA issues the Children's Environmental Health Yearbook; EPA and Department of Health and Human Services (DHHS) create eight national research centers to address children's environmental health; EPA issues the Child Health Champion Resource Guide; CPSC adopts a policy on lead |
| 1999 | Introduction of legislation related to children's environmental health continues; President's Task Force on Environmental Health Risks and Safety Risks to Children releases report *Asthma and the Environment: A Strategy to Protect Children*; EPA announces reevaluation of five existing standards to protect children's environmental health; EPA announces the "Kids First" voluntary chemical testing program; Children's Environmental Health and Safety Inventory of Research becomes available on the Internet; National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) report on statistical trends and risk factors for childhood cancers for 1975-1995 becomes available on the Internet; NIOSH proposes activities under the Childhood Agricultural Injury Prevention Initiative |

The concern about children's environmental health risks led to several major conferences that focused on identifying data gaps and research needs for improving characterization of these risks (summarized in Table 27).

Not surprisingly, the call for more children's environmental risk research led to a growth in the resources committed, although this growth is difficult to quantify. Specific examples of the funding commitment can be found, however, in the appropriation of millions of dollars to create new academic research Centers for Children's Environmental Health and Disease Prevention.[338]

[338]See National Institute of Environmental Health Sciences Press Release #15-98 (August 10, 1998) that indicates the annual cost of $10 million dollars to support eight centers (http://www.niehs.nih.gov/oc/news/niehsepa.htm).

## Table 27. Recommendations to address data gaps that inhibit better characterization and valuation of children's health risks[339]

**General Issues**

- Coordinate laboratory science, human and animal clinical, and population epidemiological studies to understand the long-term, delayed, and potential cross-generational health effects resulting from environmental exposures.
- Collect specific data for children (particularly for vulnerable sub-populations such as low income and racial/ethnic communities) related to: differences between children and adults, the unique susceptibilities of children and critical periods of vulnerability in development, the influence of environmental exposures on developing physiology of adolescents, impacts of early exposures on later life disease outcomes, and the effects of cumulative, multiple, and synergistic exposures.
- Create cost-effective data banks of exposure information (data and biological specimens) and resource and referral systems for health professionals that provide information about disease/cancer clusters, prevention, and interventions.
- Develop better and more cost-effective research tools including systemic and new approaches for exposure screening and monitoring, for assessing population-based adverse developmental outcomes, and for toxicity testing.
- Develop a coordinated research and policy program that involves all affected communities more effectively using a prevention-oriented, child-centered paradigm and promoting education about preventable causes of environmental disease.
- Address the ethical, social, and scientific issues associated with using and developing genetic and biomarker information, and increase development and use of many types of biomarkers in risk assessment and clinical settings.
- Develop and administer toxicity tests to infantile animals and possibly *in utero* to follow the entire life spans of the animals, better mimic the human condition of exposure in childhood, and detect unanticipated outcomes of early exposures. Based on the test results develop new and refined dose-response models for child-specific health effects.
- Develop exposure assessment methods to evaluate fetal exposures and the contribution of parental exposures, to characterize exposure during critical periods and to highly exposed populations, and to evaluate and improve protocols for child exposure assessment, if needed.
- Improve exposure assessments for epidemiological studies, including large international efforts, and examine the association between cancer incidence and birth defects.

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[339]Table 27 paraphrases and summarizes the recommendations from four conference reports: Carlson, J.E., and K. Sokoloff. (1995) "Introduction: Preventing child exposures to environmental health hazards: Research and policy issues." *Environmental Health Perspectives,* v. 103, Supplement 6, p. 3-5.

Carlson, J.E. (1998) "Children's environmental health research – An introduction." *Environmental Health Perspectives* v. 106, Supplement 3, p. 785-786.

Carraquino, M.J., S.K. Galson, J. Licht, R.W. Amler, F.P. Perera, L.D. Claxton, and P.J. Landrigan. (1998) "The US EPA conference on preventable causes of cancer in children: A research agenda." *Environmental Health Perspectives,* v. 106, Supplement 3, p. 867-873.

Landrigan, P.J., J.E. Carlson, C.F. Bearer, J. Spyker Crammer, R.D. Bullard, R.A. Etzel, J. Groopman, J.A. McLachlan, F.P. Perera, J. Routt Reigart, L. Robinson, L. Schell, and W.A. Suk. (1998) "Children's health and the environment: A new agenda for prevention research." *Environmental Health Perspectives, v.* 106, Supplement 3, p. 787-794.

**Disease-specific research**

**Asthma**

- Design studies to understand and characterize the linkages between: (1) air pollutants (outdoor, indoor, bioaerosols and chemicals) and asthma; (2) good medical care and the course and severity of disease; (3) differences in susceptibility and risk factors of individual children; (4) prevention strategies for pregnant women and mothers of young children and reductions in the incidence of asthma; and (5) interactions among exposure and infection history and the development of allergy, asthma, and airway reactivity (particularly for inner city and affluent environments).

**Neurobehavioral effects (both acute and delayed)**

- Explore neurotoxicological mechanisms of action and health effects of neurotoxicant mixtures;
- Develop multigenerational neurotoxicity tests and techniques to assess genetic-environment interactions in neurotoxicity; and
- Study long-term social and behavioral responses to neurotoxicants.

**Endocrine and sexual disorder effects**

- Study exposure to potential endocrine disruptors (perinatal and *in utero*) and their role in the incidence of hypospadias, cryptorchidism, testicular, breast, and prostrate cancers, endometriosis, and premature onset of menarche.

**Cancer**

- Initiate methods to map patterns of incidence and generate hypotheses;
- Begin major biomarker-based epidemiological studies to evaluate these hypotheses;
- Conduct prospective longitudinal studies of children with known exposures to carcinogens in childhood or *in utero*;
- Study genetic bases for childhood cancer;
- Develop a national children's cancer registry;
- Develop animal models to explore toxicological differences between children and adults and to evaluate toxicity for developing organ and immune systems;
- Conduct research on developmental changes and susceptibility related to immune function, metabolism, dietary factors, obesity, and cell proliferation;
- Study the differences in DNA repair for adults and children; and
- Study the role of maternal nutrition and immune protection.

The fact that all of the calls for increased research and funding for children's environmental health risks fail to mention the need for studies designed to place the significance of these risks into broader context remains a significant error of omission, in my opinion. As a nation we must ask whether we are investing the limited resources we allocate toward improving the lives of our children in the ways that will benefit them the most, and whether these resources are sufficient to meet the needs of our children.

## Definitions Matter

The absence of a single governmental entity (or private entity with sufficient authority) charged with quantifying children's risks and defining key terms makes it impossible to

understand the relative significance of environmental health risks and to set priorities for interventions and research targeted at improving the lives of American children. As a beginning, it is imperative to appreciate that terms and definitions matter.

For example, almost everyone will agree with the statement that environmental factors are important determinants of a child's well being. However, people clearly differ in their definition of the term "environmental factors" ranging from socio-economic status, stress in the home, and all factors external to the child's body,[340] to the much more limited definition of the quality of the air, water, and other elements of the physical, chemical, and perhaps biological media experienced by the child.[341]

A recent survey that focused on public perceptions of environmental health risks found that the majority of respondents believed that "environmental factors like pollution and toxic wastes" were very important in causing disease, presumably including diseases that impacted children.[342] Unfortunately, even though the survey specifically indicated "air pollution, water pollution, drinking water that has harmful chemicals or other materials in it, pesticides in the food people eat, and toxic waste"[343] as examples of environmental risks in other questions, it is still difficult to know what respondents included in their definitions of "environmental factors" and what they thought each of those terms meant. Further, given the use of the words "toxic" and "harmful," which provide strong affective cues, it is not surprising that respondents expressed concern.[344]

Another definition that emerges as critical in the discussion of children's health is the definition of child. The amazing growth and development process of childhood occurs in stages, and children's risks change dramatically as they age. However, review of the existing laws and risk assessment methods suggests a current lack of standard definitions for the different stages of childhood.[345]

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[340]For example, see Schorr, 1988 supra note.

[341]This is essentially the definition used for the May 22, 2000 meeting for the term environment as the air, water, solid surfaces, plants, and animals, or the portion of the environment under the regulatory arm of the Environmental Protection Agency.

[342]Princeton Survey Research Associates, 2000. "National Survey of Public Perceptions of Environmental Health Risks." Washington, DC: Princeton Survey Research Associates. (Available at http://health-track.org/reports/survey0620/survey0620.pdf).

[343]Ibid.

[344]Slovic, P., M. Fincane, E. Peters, and D.G. MacGregor. (2000) "The affect heuristic." Chapter in T. Gilovich, D. Griffin, and D. Kahneman (eds.) *Intuitive Judgment: Heuristics and Biases.* Cambridge, UK: Cambridge University Press.

[345]The statement referring to review of the existing laws comes from currently unpublished work in progress by the author. The statement referring to risk assessment methods is based on Thompson, K.M. (2000). "Changes in children's exposure as a function of age and the relevance of age definitions for exposure and risk assessment." In Appendix E in the Report on the Workshop on Issues Associated with Selecting Age Groups for Assessing Exposure to Children from the Washington, DC: US EPA, Risk Assessment Forum.

Definitions also matter in the context of risk management. In particular, the authority, abilities, and resources of the decision maker and how the issues are framed determine whether, how, and who manages the risks. In this process, focusing on risks experienced by individual children (presumably at high-risk) versus the risk to the entire population of children or both can impact both the policy and the outcome. For example, if the risk management focuses on high-risk children, this might lead to targeted interventions that impact only these children, but leave the risks to the remaining children in the population unchanged. In contrast, if the focus is on the entire population of children, strategies that decrease risks for all children may be more likely to be favored over those that reduce risks to the few at highest risk.

Recognizing the potential for distinct health risks to children and evaluating those risks in the regulatory process can help identify risk inequities and target policy options that may lead to improved health outcomes for children. For example, consider the tens of children killed in minor automobile accidents by the force of deploying passenger-side airbags that were designed to protect unbelted adult men. A recent cost-effectiveness analysis that explored the magnitude of the tradeoff found that passenger airbags kill one child on net for every 5 to 10 adults they save.[346] Retrospective analysis suggests that early assessments of the risks and benefits of airbags failed to adequately consider the uncertainty about the effectiveness of airbags and variability in risk for different age groups.[347] Incorporation of child-specific risk assessment results into the airbag cost-benefit analysis might have resulted in identifying a way to mitigate the dangers of airbags to children while still maintaining the benefits of airbags for adults. At the very least, it would have fully informed the decision makers of some of the risk tradeoffs associated with air bags.[348] (Note that the National Highway Traffic Safety Administration now requires compliance tests with a range of crash test dummy sizes).[349] This example serves as an important lesson about the need to focus beyond an identified "sensitive subpopulation" (in this case, unbelted adult men),[350] to explore the impacts of a risk management strategy on all members of the population (in this case, including children and small adults).

The metric we use to count progress or make comparisons also matters. For example, if we move away from lives saved to life-years saved as the metric, this effectively places

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[346]Graham, J.D., K.M. Thompson, S.J. Goldie, M. Segui-Gomez, and M.C. Weinstein. (1997) "The cost-effectiveness of airbags by seating position." *Journal of the American Medical Association,* v. 278, p. 1418-1425.

[347]Thompson, K.M., M. Segui-Gomez, and J.D. Graham. (1998) "Validating engineering judgments: The case of the airbag's lifesaving effectiveness." *Reliability Engineering and System Safety,* v. 66, n. 1, p. 57-68.

[348]Graham, J.D., and J.B. Weiner. (1995) *Risk vs. Risk: Tradeoffs in Protecting Health and the Environment.* Cambridge, MA: Harvard University Press.

[349]See National Highway Traffic Safety Administration standard at [http://www.nhtsa.dot.gov/airbag/proposed/advbag.html#adv21].

[350]Unbelted adult men were identified as the "sensitive" population in this case because their lack of restraint use and relatively higher weight placed them at the highest risk for impacting the interior surface of a crashing vehicle. The perception was that if airbags could stop an unbelted adult male from impacting the interior surface of the car, then they could stop anyone, including a child.

more weight on the child who has relatively more years of productive life ahead compared to the adult, and it allows acknowledgment that the same life can be saved more than once.[351] More subtly, the use of quality-adjusted life-years (QALYs) ( a metric widely used in the U.S. medical community) is not differentially weighted as a function of age over the lifespan. In contrast, disability-adjusted life-years (DALYs) (a metric widely used internationally in the assessments of the global burdens of disease) are weighted lower for children and the elderly than for middle-age adults.[352] In particular, a DALY lived at age 2 is valued as worth only 20% of a DALY lived at the peak utility age of 25, and above age 25 DALY values decrease.[353]

Finally, definitions influence the allocation of resources. With the passage of the Government Performance and Results Act and expectations of measurable benefits for expended costs, regulators and researchers focus their efforts on identified problems. In spite of any expectations, however, we lack a well-defined methodology for evaluating and monitoring the performance of national activities (environmental and otherwise) aimed at improving the lives of American children. This may not be surprising given the complexity of the problem and the number of different stakeholders involved in the process (including policy makers, parents, teachers, physicians, and children). However, in my opinion, no excuse justifies failing to use an analytically rigorous approach to inform individual and societal decisions, to establish national goals for children, and to require coordination of the myriad programs and policies affecting children. Currently the web of policies targeted at children show important inconsistencies with respect to risk that will require governmental action to be resolved.

## The Role of Government

**Commitment and Coordination.** For all children's health issues that are national or international in scope, I believe the federal government is the logical manager of these risks. For example, issues that involve federal action include global climate change and energy policy, product and substance testing, support for expensive research that improves interventions for prevention, detection, and treatment of injury and disease, and regulation of multinational industries in a global economy. Federal programs need to insure the health and welfare of the nation's children by securing the resources required to meet the needs of today's children and those of future generations, by conducting and sponsoring research that improves their lives, and by monitoring children's health. In sum, when it comes to protecting children in today's world, the federal government must play a role.

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[351]Wright, J.C. and M.C. Weinstein. (1998) "Gains in life expectancies from medical interventions – Standardizing data on outcomes." *New England Journal of Medicine*, v. 339, p. 380-386.

[352]Murray, C.J.L. (1994) "Quantifying the burden of disease: The technical basis for disability-adjusted life years." *Bulletin of the World Health Organization*, v. 72, p.429-445.

[353]Anand, S., and K. Hanson. (1997) "Disability-adjusted life years: A critical review." *Journal of Health Economics*, v. 16, p. 685-702.

While raising healthy and happy children may be within our reach,[354] sadly, we appear to lack the national commitment to achieve this goal; a commitment that must occur at all levels of government. The lack of commitment at the national level is apparent in the surprising fact that the United States is one of only two nations that has not yet ratified the 1989 Convention on the Rights of the Child; Somalia, which lacks a functional government, is the other.[355] While ratifying this Convention would lead to domestic issues associated with its implementation, the fact that we have not ratified it may send a message to the world and to our children about the lack of importance that we place in protecting children. Thus, while the role of the federal government as our representative to the world is critical, we currently appear to have a long way to go with respect to protecting children in the increasingly globalized society.

Nationally, governmental programs continue to serve children in what appears to be an uncoordinated and single-symptom approach, and they fail to address the needs of the nation's most needy children. For example, we continue to struggle with providing health insurance to children. Although recent passage of the Children's Health Insurance Program (CHIP) provides some hope that we might move in the right direction, recent evidence suggests that uninsured children are not yet fully benefitting from CHIP.[356]

I believe that the federal government's critical role with respect to the implementation of programs that provide benefits to children at the state, local, and ultimately the family level is one of support and oversight for the programs that work. The federal government should establish an expectation for coordination of the myriad programs that benefit children (e.g., including the CHIP, Food Stamp Program, Women, Infants, and Children Program, and Head Start). At the local level, communities play a major role in injury prevention, vaccination programs, and local disease control, and within the family, parents and others play the most critical role of caring directly for children.

Coordination within and among these levels is critical, because a lack of consistency among standards of risks experienced by American children may lead to emphasis on the costly reduction of small risks, while inexpensive programs that reduce larger risks fail to receive necessary support. Table 25 showed a number of common causes of death that lead to lifetime risks above one-in-a-million with much more certainty than some environmental risks that are regulated at the one-in-a-million risk level (including pesticides under the 1996 Food Quality Protection Act). The lack of a coordinated and comprehensive effort that assesses the economic and health ramifications of choices made based on differential standards of risk management means that our limited resources may not be spent as effectively as possible, and that years of healthy children's lives might be squandered as a result. Clearly, other important values should be considered, but this should be done explicitly. Congress needs to ask some tough questions, like does it make sense that the EPA lacks authority to reduce what I believe is probably the most significant chemical risk to

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[354]Schorr, 1988 supra note.

[355]The text of the Convention can be found at: http://www.unicef.org/crc/crc.htm. I am grateful to Professor Stephen Marks of the Harvard School of Public Health for pointing out to me that only the U.S. and Somalia had yet to ratify the Convention.

[356]Edmunds et al., supra note.

children – environmental tobacco smoke?[357] If we really intend to address the needs of all children, we should insure that environmental risks are placed in perspective, that the actions taken make children better off overall, and that we focus on implementing the most cost-effective strategies for reducing or eliminating children's risks. If additional resources need to be allocated to improve the lives of American children, this should be done, but Americans should be confident that investing these resources will lead to the promised improvements.

**Investing Transparently and Wisely.** The efforts to improve children's lives require resources. The 1997 *Investing in Our Future* report from the Office of Science and Technology Policy (OSTP) estimated that all levels of government spent $500 billion on children and adolescents in fiscal year 1995.[358] Of this $500 billion, OSTP estimated that two-thirds goes to K-16 education and the remainder goes primarily toward social welfare (including health). The OSTP report concluded that only $2 billion was aimed at research and development for children and youth, which was less than 0.4% of the total government expenditures on children and youth and less than 3% of total Federal research enterprise. Based on these results, the OSTP Report suggested that current Federal research investments for child and adolescent health and development may not be consistent with investments in other research areas and may be inadequate to support informed policies and decision making.[359]

Unfortunately, in the years since this report, while the commitment of resources toward research on children has probably grown, we still lack good information about their allocation and sufficiency. Surprisingly, the Children's Environmental Health and Safety Inventory of Research database, a comprehensive new information resource about children's research, fails to provide any information about the expected financial costs and the benefits of the research. We do not know how we are spending our research resources for children or what we expect to receive for those expenditures. I believe that Congress should demand this information and use it in making decisions about its investments in interventions and research.

With respect to interventions that aim to reduce environmental risks to children, the transparency is equally poor, or perhaps slightly worse. No database exists to provide information about expenditures on interventions for American children. A review of the pediatric cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA) literature published in peer-reviewed journals reveals a lack of common metrics and attention to

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[357]DiFranza, J.R., and R.A. Lew. (1996) Morbidity and Mortality in children associated with the use of tobacco products by other people. *Pediatrics*, v. 97, n. 4, p. 560-568.

According to the article, smoking-related illnesses and fires cause approximately 136 to 212 deaths of children under age 18 annually. However, it is even more discouraging from a public health perspective that, although our laws prohibit children under age 18 from purchasing cigarettes, 8% of 8th-graders, 16% of 10th-graders, and 23% of 12th-graders reported smoking cigarettes daily in the previous 30 days, see FIFCFS supra note.

[358]Office of Science and Technology Policy (OSTP). (1997) *Investing in Our Future: A National Initiative for America's Children in the 21st Century.* Washington, DC: Executive Office of the President.

[359] Ibid.

assessing the economic costs and benefits of pediatric interventions.[360] This same review shows that there are no existing studies in the peer-reviewed literature for children's environmental risk management interventions.[361] In sum, we lack a means for comparing the "bang for the buck" of the various programs targeted at children.

Several factors may explain the lack of information on interventions. For example, environmental interventions tend to be characterized by shared costs and benefits and it may be difficult to perform CBAs and CEAs of environmental interventions specifically for children. For some environmental hazards, children may not be particularly identified as the sensitive subpopulation because both children and adults benefit significantly from control (e.g., criteria air pollutants). Even in the historical case of removing lead from gasoline, the EPA's analysis of the benefits included significant benefits for adults that exceeded the benefits for children.[362] Myopic focus on the benefits to children could potentially lead to perverse outcomes, and in general we should learn from the case of airbags that we need to consider variability in risk over the entire population.[363] Alternatively, the absence of published economic evaluations of pediatric interventions may reflect a lack of demand to perform such analyses or be an indication that any such analyses that are performed do not make their way into the peer-reviewed literature. While the long and uncertain latency periods associated with environmental disease may impair efforts to capture the presence and timing of health benefits from environmental interventions, methodological strategies to deal with these uncertainties should be explored along with issues associated with assumptions used in valuation. Again, I believe that Congress should demand this information and improvement in the analytical methods for characterization of the costs and benefits of children's programs.

**Recognizing Trade-offs Under Conditions of Uncertainty.** The national debate about pesticides provides a clear case where uncertain science and concerns about children's well-being continue to lead to the need for Congressional action to fix previous mistakes and where greater appreciation of the uncertainties is needed.

In 1989, public concern about children's exposure to pesticides in food followed the release of risk assessment results for Alar in apples that emphasized children's increased exposure compared to adults and led to questions about whether existing pesticide regulations were sufficient to protect children. In 1993, the National Academy of Sciences *Pesticides in the Diets of Infants and Children* report concluded that "the current regulatory system does not, however, specifically consider infants and children.... It looks only at the average exposure of the entire population."[364] The Report also stated:

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[360]Thompson, K.M. and E.B. Elkin. "A synthesis of pediatric cost-effectiveness and cost benefit analyses." Submitted.

[361]Ibid.

[362]Schwartz, J. (1994) Societal benefits of reducing lead exposure. *Environmental Research*, v. 66, p. 105-124.

[363]See Thompson et al. supra note.

[364]National Research Council. (1993) *Pesticides in the Diets of Infants and Children.* Washington,

(continued...)

> Three 10-fold uncertainty factors are now applied to the NOEL to develop the RfD: 10 to account for interspecies differences, 10 to account for intraspecies differences, and 10 when there is evidence of developmental effects as demonstrated by toxicological testing and metabolic/disposition studies. Thus, a 10-fold factor has been applied by the EPA whenever toxicity studies have shown fetal developmental effects. Because of specific periods of vulnerability that exist during development, the committee recommends that an uncertainty factor up to the 10-fold factor traditionally used when there is evidence of fetal developmental toxicity should also be considered for postnatal developmental toxicity and when data from toxicity testing are incomplete. The committee wishes to emphasize that this is not a new, additional uncertainty factor but, rather, an extended application of a [sic] uncertainty factor now routinely used by the EPA for a narrower purpose.[365]

In 1996, Congress incorporated many of the recommendations of the NAS Report in the Safe Drinking Water Act Amendments and the Food Quality Protection Act (FQPA). Overnight, the FQPA dramatically changed the requirements for risk assessment and risk management for pesticides. Notably, the FQPA placed emphasis on protecting children, and required what sounds like an *additional* safety factor of 10 to protect children in the context of assessing the risks from health effects other than cancer, unless sufficient evidence existed to justify a lower factor. The Federal Food, Drug, and Cosmetic Act (FFDCA), as amended, now requires:

> In the case of threshold effects ... an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for 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. Notwithstanding such requirement for an additional margin of safety, 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.[366]

In my opinion, one of the biggest problems with the entire debate about pesticides is the presumption that a factor of 10 will lead to increased protection of children, and the absence of expectations to assess the trade-offs associated with this and other pesticide policies.

Like any other substance, pesticides in high amounts can have harmful effects. Pesticide poisoning from improper use should always be of concern and, like all potentially hazardous substances, pesticides should be kept out of children's reach. However, we have no compelling scientific basis for believing that the small amounts of pesticide residues typically found on food are harmful. In contrast, however, we have good scientific evidence that a diet

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[364](...continued)
DC: National Academy Press, p 2.

[365]Ibid, p. 361. The EPA Integrated Risk Information System Glossary defines a No-Observed-Effect-Level (NOEL) as "an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control." The EPA defines a Reference Dose (RfD) as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." Definitions available from the EPA at: http://www.epa.gov/iris/gloss8.htm.

[366]FFDCA §408(b)(2)(C).

rich in fresh fruits and vegetables is critical to good health and is recommended by the U. S. Department of Agriculture (USDA). We do not know how parents will respond to the messages they receive about pesticides. However, if they reduce the amounts of fresh produce they give to their children, this could have important health consequences. The option to buy "organic" produce does provide consumers who can afford them another option. However, I am unaware of any scientific evidence to suggest that produce grown with organic farming methods is safer or more nutritious than the same produce grown conventionally.

With such large uncertainties about the relative costs and benefits of farming methods, the fact that EPA lacks the authority to examine the risks associated with organic produce and to weigh the trade-offs that may occur associated with different growing methods (natural toxins, food-borne pathogens) is striking. Are people trading off relatively small pesticide associated risks for smaller, equivalent, or larger risks of produce grown without pesticides? We don't know. Also, given that approximately 20% of American children live in families with incomes below the poverty level, how does any increase in concern about pesticides affect them, particularly if parents feel compelled to buy the more expensive "pesticide-free" produce or none at all?

A 1997 report called *Food Safety from Farm to Table: A National Food Safety Initiative* begins by stating:

> While the American food supply is among the safest in the world, there are still millions of Americans stricken by illness every year caused by the food they consume, and some 9,000 a year – mostly the very young and elderly – die as a result. The threats are numerous and varied, ranging from *Escherichia coli* (*E. coli*) O157:H7 in meat and apple juice, to *Salmonella* in eggs and on vegetables, to *Cyclospora* on fruit, to *Cryptosporidium* in drinking water – and most recently, to hepatitis A virus in frozen strawberries.[367]

Under current statutes these "natural toxins" do not get included as "environmental" factors but as food contaminants. In sum, because we know a lot less than we should about the impacts of pesticide policy on children, Congress should be concerned about insuring that the policies lead to more good for children than harm.

**Better Data.** While the need for better information is clear, the data collection process requires careful design. The idea that we should simply measure body burdens or environmental levels of substances and do everything that we can to reduce them fails to consider the toxicology, the trade-offs, and the baseline levels of risk, which are not and can never be zero. Imagine taking that approach in other contexts. For example, it is possible that a plane will fall out of the sky and kill you, and if you have planes flying over your head, then you are exposed. Does this mean we should do everything that we can to eliminate planes flying? Doesn't it matter that the risk for most people is so small as to be negligible under current standards of risk management, even though there are certainly some people at

[367]Institute of Medicine and National Research Council. (1998) *Ensuring Safe Food: From Production to Consumption*. Washington, DC: National Academy Press, p. 163.

a much greater risk than others?[368] What about the fact that substituting to other modes of transportation could induce other risks and would come with other disadvantages? I agree with the recommendations of the NAS report *Science and Judgment in Risk Assessment*, and I believe we must do a better job characterizing variability and uncertainty in risk. Although different factors associated with the risks might lead us to rationally implement different risk standards, the lack of explicit consideration of differential standards may lead to perverse situations and, in my opinion, it deserves serious attention.

## Conclusion

In my opinion, President John F. Kennedy captured the goals of environmental protection overall, when he said, "It is our task in our time and in our generation to hand down undiminished to those who come after us, as was handed down to us by those who went before, the natural wealth and beauty which is ours." So far, the historical record of each generation being better off than its predecessor with respect to life expectancy appears to hold.[369] We continue to improve our understanding of science and nature and to develop technologies that increase both the length and quality of our lives. More impressively, we are accomplishing these improvements with an ever increasing population. Given that each human life requires support from the environment to survive, that we believe that environmental resources are currently limited to this planet (although we continue to explore beyond planetary boundaries), and that humans appear to be changing the planet on all scales (from locally with construction to globally with climate change), the importance of sound policies that protect the environment are imperative to the survival of our species. If we are to offer Kennedy's promise to generations of future children, we must manage our resources well and strive to better manage environmental risks.

Compared to other risks that children face, American children's environmental risks (narrowly-defined) currently appear to be relatively small, although it is difficult to make this comparison given the lack of a comprehensive, authoritative source that quantifies the risks that American children face. It is time for Congress to take a cross-cutting analytical look at the risks to children and how they are managed under existing federal policies. These comments should not be taken to imply that we should ignore opportunities to reduce these risks even further when cost-effective options exist, or to imply that these risks might not be the most significant ones for some children. However, any strategies implemented to reduce children's environmental risks should fully consider the trade-offs involved and insure that the uncertain benefits of the actions are worth the costs and any future data collection efforts made to better understand children's environmental risks should include provisions to put these risks in perspective.

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[368]Thompson, K.M., R.F. Rabouw, and R.M. Cooke. (2001) "The risk of grounding fatalities from unintended airplane crashes" *Risk Analysis* v. 21, n. 6, p. 1025-1037.

[369]See Figures 5 and 6 in the paper by Dr. Kenneth W. Chilton that appears in these proceedings.

# The Role of the Federal Government in Protecting Children's Environmental Health

By Richard Joseph Jackson, MD, MPH, FAAP

## Introduction

In 1991, data from the Third National Health and Nutrition Examination Survey (NHANES III), a population-based health survey of the American people, showed dramatic declines in the blood lead levels of U.S. children.[370] These declines were primarily the result of regulations requiring the removal of lead from gasoline and soldered food cans. My view is that after nearly a half century of obstruction and outright denials of lead's deleterious effects by industry officials and of foot dragging by various government commissions and agencies,[371] the federal government, supported by irrefutable data, finally "did the right thing" and acted to protect the nation's children by banning lead from gasoline and food cans. By then, however, millions of U.S. children may have been exposed to lead, and many of them were victims of its most disastrous effects, including lowered IQs, severe behavior problems, seizures, coma, and death.[372]

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[370]Brody D.J., J.I. Pirkle, R.A. Kramer, et al. Blood lead levels in the U.S. population; phase I of the third National Health and Nutrition Examination Survey (NHANES III, 1988-1991). *Journal of the American Medical Association*, 1994, v. 272, p. 277-283.

[371]Markowitz, G., and D. Rosner. Cater to the children: the role of the lead industry in a public health tragedy, 1900-1955. *American Journal of Public Health*, 2000, v. 90, n. 1, p. 36-46.

[372]Fulton, M., G. Raab, G. Thompson, D. Laven, R. Hunter, and W. Hepburn. Influence of blood lead on the ability and the attainment of children in Edinburgh. *Lancet*, v. i, p. 1221-1226.
Needleman, H.L., and C.A. Gastoris. Low-level lead exposure and the IQ of children. *Journal of the American Medical Association*, 1990, v. 263, n. 5, p. 673-678.
Lansdown, R., W. Yule, M. Urbanowicz, and I.B., Millar. Blood lead, intelligence, attainment and behavior in school children: overview of a pilot study. In: Rutter, M., and R.R. Jones (eds.) *Lead versus Health*, p. 267-296. 1983. New York: John Wiley and Sons.
Lyngbye, T., O.N. Hansen, A. Trillingsgaard, I. Beese, and P. Grandjean. Learning disabilities in children: significance of low-level lead exposure and confounding effects. *Acta Pediatrica Scandinavia*, 1990, v. 79, p. 352-360.
Needleman, H.L., C. Gunnoe, A. Leviton, H. Peresie, C. Maher, and P. Barret. Deficits in psychological and classroom performance of children with elevated dentine lead levels. *New England Journal of Medicine*, 1979, v. 300, p. 689-695.
Bergomi, M., P. Borella, G. Fantuzzi, G. Vivoli, N. Sturloni, G. Cavazutti, et al. Relationship between lead exposure indicators and neuropsychological performance in children. *Developmental Medical Child Neurology*, 1989, v. 31, p. 181-190.
Bellinger, D., A. Leviton, C. Waternaux, H. Needleman, and M. Rabinowitz. Longitudinal analyses of prenatal and postnatal exposure and early cognitive development. *New England Journal of Medicine*, 1987, v. 316, p.1037-1043.
Bellinger, D., J. Sloman, A. Leviton, M. Rabinowitz, H. Needleman, and C. Waternaux. Low-level exposure and children's cognitive function in preschool years. *Pediatrics,* 1991, v. 87, p. 219-227.
Lansdown, R., W. Yule, M.A. Urbanowicz, and J. Hunter. The relationship between blood-level

(continued...)

The tragedy of lead poisoning in America in my opinion underlines the importance of protecting children from environmental health and safety risks, so that they can live full and productive lives unencumbered by preventable disease or injury. Further, I believe it speaks to the federal government's responsibility to enforce existing health and safety regulations and to develop and promulgate child-centered, science-based, prevention-oriented environmental health and safety policies that protect children now and in the future.

Obviously, state and local governments also have a role in this task, serving often as arenas where new ideas are tested and innovative programs are developed and replicated. However, their roles are different from that of the federal government, which I believe must set the pace in protecting children's environmental health and safety by using its expertise in public health surveillance, data collection and analysis, and policy development to develop national goals that address both immediate and long-term child-health issues and making certain that those goals are in the best interest of children nationwide.

## The Federal Role in Public Health

In 1988, the Institute of Medicine (IOM) published *The Future of Public Health*,[373] a pivotal document that addressed concerns about the role of public health in America. IOM articulated the government's role as constituting three functions: assessment, policy development, and assurance. These functions reflect how public health does its job—by identifying problems, mobilizing the effort and resources needed to combat those problems, ensuring that essential components are in place so that the public receives crucial services, and evaluating the effectiveness of those interventions or services. The IOM asserts that "federal leadership in matters of public health is especially critical if scientific and professional expertise is to play its proper role in the policy process, offsetting the influence of special interests that tend to be especially decisive in smaller-scale public affairs."[374] The IOM also points out that the public health knowledge base, which is what is used to protect the health of the nation, depends on the advocacy of the federal government to function most effectively; it finds the federal role in developing national data and conducting research is

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[372](...continued)
concentrations, intelligence, attainment, and behaviour in a school population: the second study. *International Archives of Occupational and Environmental Health*, 1986, v. 57, p. 225-235.

Hawk, B.A., S.R. Schroeder, G. Robinson, D. Otto, P. Mushak, D. Kleinbaum, et al. Relation of lead and social factors to IQ of low SES children: a partial replication. *American Journal of Mental Deficiency,* 1986, v. 91, p. 178-183.

Hatzakis, A., A. Kokkevi, C. Marovelias, K. Katsouyanni, F. Salaminos, A. Kalandidi, et al. In: Smith, M., L. Grant, and A. Sors (eds.) *Lead Exposure and Child Development: An International Assessment.* Dordecht: Kluwer Academic Publishers, 1989, p. 211-223.

Schwartz, J., C. Angle, and H. Pitcher. Relationship between childhood blood lead levels and stature. *Pediatrics,* 1986, v. 77, n. 3, p. 281-288.

Schwartz, J., and D. Otto. Blood lead, hearing thresholds and neurobehavioral development in children and youth. *Archives of Environmental Health,* 1987, v. 42, n. 3, p. 153-160.

[373]Institute of Medicine. *The Future of Public Health.* Washington, DC: National Academy Press, 1988. p. 42-43.

[374]Ibid.

irreplaceable.[375] The functions that the IOM assigns to the federal government for protecting the general public health apply as well, I believe, in protecting the environmental health and safety of this nation's children.

## Children Are Not "Little Adults"

Any discussion of pediatric environmental health requires at least a brief review of the differences between children and adults. Children can be more susceptible than adults to the adverse effects of many of these chemicals, environmental, and safety risks due to factors peculiar to childhood. Through their normal behavior, children are often at greater risk for exposure to chemical and biological hazards and toxicants and physical hazards, and due to their complex physical development and rapid growth, may be more susceptible than adults to the adverse effects of many of these exposures. Their small size and weight arguably make them less likely to withstand injuries or to be protected by standard features, such as a seat belt, that protect adults.

Children grow rapidly, and their exposure to and their absorption, distribution, metabolism, and excretion of various substances change over time, affecting how their bodies deal with environmental contaminants. Although the formation of organs occurs *in utero,* the ultimate size and function of various organ systems are determined at various points in childhood. At birth, children's nervous, respiratory, reproductive, and immune systems are not fully developed. For example, the air sacks of the lungs are not complete until adolescence; the area of gas exchange in the lungs increases more than 20-fold from infancy to adulthood. Young children also breathe more rapidly and inhale more air in proportion to their body weight than do adults. Additionally, children have higher metabolic rates, drink more fluid, and consume more calories per kilogram of body weight than do adults.[376] Thus, if the air children breathe or the food or liquid they consume contains a toxicant, children will receive a larger dose of the toxicant per pound of body weight than would an adult; consequently, their potential relative exposure to ingested toxicants such as pesticides is greater than that of adults. Additionally, the ability of children to detoxify and excrete toxic substances differs from that of adults, because children's metabolic systems are immature. Finally, children's physical environments vary with their age and developmental stage and present different opportunities for and patterns of exposure over time. For instance, infants and toddlers generally will have more exposure to substances in or on floors or carpeting and in dust or soils that may contain toxic chemicals or pesticide residues.

## Need for Human Health Data in Making Good Decisions for Children

Decision makers depend on "good" science to develop sound public health policies, yet they are often hampered by a lack of human data on children's health issues. With the possible exception of data on childhood lead poisoning, we lack adequate information on the

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[375]Ibid.

[376]Guzelian, P.S., C.J. Henry, and S.S. Olin (eds). *Similarities and Differences Between Children and Adults: Implications for Risk Assessment.* Washington, DC: National Academy Press, 1993, 283 p.

human health effects of other environmental exposures to children. Much more funding for research in this area is needed if we are to understand fully the health effects resulting from exposures to environmental toxicants.

Another major stumbling block to our work in environmental health is that diseases potentially caused by toxic exposure during fetal development or childhood might appear only years or decades later. For example, from the late 1930s to the late 1960s, diethylstilbestrol (DES), a synthetic estrogen, was used to prevent miscarriages. In fact, some physicians prescribed DES routinely for all pregnancies, and an estimated 4.8 million pregnant women received the drug during that period.[377] The positive effects of DES were disproved in the early 1950s, indicating that DES had no effect on pregnancy loss.[378] Nonetheless, physicians continued to prescribe the drug for pregnant women until 1971, when DES was identified as the cause of a rare clear-cell vaginal and cervical cancer found among teenaged girls and young women exposed to DES *in utero*.[379] As the population of DES-exposed women ages, studies are under way to determine what the potential health effects of DES are on women at menopause and whether DES exposure increases the rate of hormonally related cancers among women who took DES. Concerns remain about the adverse effects of DES, including possible problems among the sons of mothers who took DES and among those with "third-generation" exposure (i.e., the male and female grandchildren of women who took DES during pregnancy).[380]

Although this use of DES was banned in 1971,[381] children potentially are continually exposed to thousands of new synthetic chemicals whose toxicity has yet to be analyzed, and whose potential hazards are unknown. We lack information about the effects of exposure to hazardous substances on children; in the past, the vulnerability of infants and young children was not considered when testing chemicals for their toxicity. Rather, risks of adverse effects were assessed by testing exposures on adult animals. Little has been done to study the effects of early exposure or of multiple or cumulative exposures on the appearance of disease later in life. Clearly, in my opinion, it is vital to the decision-making process that we conduct additional research in this area and continue federal funding for research that will evaluate human exposures. It is vital to the decision-making process that we collect data on how environmental hazards affect various subpopulations of children, and

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[377]Guisti, R.M., K. Iwanoto, and E.E. Hatch. Diethylstilbestrol revisited: A review of the long-term health effects. *Annals of Internal Medicine,* 1995, v. 122, n. 10, p. 778-788.

[378]Dieckmann, W.J., M.E. Davis, L.M. Rynkiwwicz, and R.E. Pottinger. Does the administration of diethylstilbestrol during pregnancy have therapeutic value? *American Journal of Obstetrics and Gynecology*, 1953, v. 66, p. 1062-1081.

[379]Herbist, P.L., H. Ulfelder, and D.C. Poskanzer. Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. *New England Journal of Medicine*, 1971, v. 284, p. 878-881.

[380]Newbold, R.R., R.B. Hanson, W.N. Jefferson, B.C. Bullock, J. Haseman, and J.A. McLachlan. Increased tumors but uncompromised fertility in the female descendants of mice exposed developmentally to diethylstilbestrol. *Carcinogenesis*, 1998, v.19, p. 1655-1663.

[381]U.S. Food and Drug Administration. Diethylstilbestrol contraindicated in pregnancy. Washington, DC: FDA Drug Bulletin, U.S. Department of Health, Education, and Welfare, 1971.

we must determine, through biomonitoring—the direct measurement of chemicals in human blood, serum, or urine—background levels of these chemicals in our population.

Public health's role is to assess the health of various populations, reporting on causes and rates of morbidity and mortality for diseases, and determining whether the body burden of toxic substances has increased, remained the same, or decreased. But it's not enough simply to identify possible causes of disease; we must intervene to reduce or eliminate them, and then must evaluate our interventions to determine whether or not they have been successful. Certainly, as the NHANES data showing lowered blood lead levels demonstrated, the ban on lead in gasoline and food cans was a highly successful intervention, although, in my opinion, it was unjustifiably delayed by the decades-long tactics of the lead and petroleum industries to deny lead's effects or to place blame for those effects on workers, consumers, or the children themselves, and which dimmed the future for many children and cost others their lives.[382]

## The Food Quality Protection Act

In many ways, however, we have made significant progress in protecting children's health. In 1996, federal lawmakers took another long-overdue step, I believe, to protect children's environmental health, when Congress unanimously passed the first piece of environmental legislation that specifically addresses children's exposure to pesticides. The landmark Food Quality Protection Act (FQPA), which amended two earlier laws—the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)—provides for a health-based safety standard for pesticide residues in food and includes special provisions for children.[383] FQPA fundamentally changed the way that the EPA regulates pesticides. The law requires the agency to review, by 2006, the safety of all existing tolerances–the legal limits for pesticide residues on certain food crops –that were in effect when FQPA passed, and those pesticides that appear to pose the greatest risk must be given priority. The Act requires an explicit determination that pesticide tolerances are safe for children, mandating the addition of up to a 10-fold safety factor to these tolerances, consideration of children's sensitivity and exposure to pesticides, and the caveat that the benefits derived from a pesticide cannot override the risks it poses to children. EPA can add the 10-fold safety factor if uncertainty exists concerning available data about a particular pesticide, or if the potential for exposure to a particular pesticide increases. EPA must also collect better data on food-consumption patterns of infants and children, levels of pesticide residues, and pesticide use.

The FQPA puts the burden of proof of a product's safety squarely where it belongs, in my opinion—on the manufacturer of the product.

FQPA's passage was a victory for those fighting to protect children's health. Consumer advocates hailed its passage, and industry generally supported the law. However, in 1998, when it appeared as though the 10-fold safety margin was in jeopardy, child-health

[382]Markowitz and Rosner, ibid.

[383]Food Quality Protection Act of 1996, Public Law 104-170 (Aug, 3, 1996).

advocates, whose voices for protecting children's environmental health have grown stronger in recent years, provided key testimony before Congress. J. Routt Reigart, M.D., Chair of the Children's Environmental Health Network, pressed for immediate implementation of FQPA, particularly for the 10-fold margin of safety provision, arguing that adequate data are lacking for "virtually every pesticide," and urging that the 10-fold safety factor not be scuttled or delayed pending the outcome of further studies.[384] He pointed out that respected studies already demonstrate the need to provide additional protections for children and that actions to protect children from exposure to pesticides should not be delayed or subject to "regulatory hoops that will add an additional 5 or10 years before children will benefit from FQPA."[385] The very fact that this testimony was necessary, in my opinion, emphasizes the need for vigilance about children's health issues to make certain that agencies are in fact implementing and enforcing laws, such as FQPA, that protect children's health. However, until sufficient and reliable data exist to address other complex environmental exposures, I believe that we must take a preventive approach that establishes health-based standards for protecting children, particularly those most at risk as a result of their socioeconomic status, race, or ethnicity; I think industry should bear responsibility for proving that these chemicals are indeed safe.

## Task Force on Environmental Health Risks and Safety Risks to Children

I also believe that the combined efforts of many federal agencies are needed, working in partnership with state and local governments and community groups, to address children's environmental health and safety issues in the years ahead. Anticipating that need and responding to calls for a coordinated federal approach to formulating policies and activities that protect children, President Clinton issued Executive Order 13045, "The Protection of Children From Environmental Health Risks and Safety Risks," on April 21, 1997.[386] This directive sought to ensure that protecting the nation's children from environmental and safety threats would become an important goal of all federal agencies. The order signaled an opportunity to raise awareness of federal health agencies about environmental issues and of sister agencies about child-health issues.

The order also established a Task Force that was charged with recommending strategies for protecting children's health and safety. To that end, the Task Force has developed a database of all research which the U.S. government either conducts or funds that is related to adverse health effects to children as a result of their exposure to environmental health or safety risks. Known as CHEHSIR, this database gives researchers, federal agencies, the general public, and others access to this valuable information.[387] The database contains information about approximately 550 federally funded projects. Its primary purpose is to

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[384]Reigart, J.R. Food Quality Protection Act; Testimony submitted to the Subcommittee on Department Operations, Nutrition and Foreign Agriculture, 25 June 1998. <http://www.cehn.org/cehn/testimony.html. Accessed July 10, 2000>

[385]Ibid.

[386]62 *Federal Register* 19883-19888, April 23, 1997.

[387]<http://www.epa.gov/chehsir>

facilitate communication among researchers studying children's environmental health and safety issues.

The Task Force also focused on four priority areas, each of which is associated with high levels of morbidity or mortality among America's children: asthma, unintentional injuries, cancer, and developmental disorders (lead poisoning is included in this area). The Task Force established work groups to address each of the priority areas.

**Asthma.** Asthma, currently the most common chronic disorder among U.S. children, has reached epidemic proportions, affecting nearly 5 million children younger than 18 years of age.[388] In fact, during the past 15 years, asthma rates have skyrocketed, increasing 160 percent among children younger than 5 years of age.[389] The mortality rate for children with asthma also increased threefold during the period from 1977 through 1995,[390] and for minority populations the mortality rate is also higher. For example, in 1995, the rate among black children in the United States was four times higher than it was for white children (11.5 per million compared with 2.6 per million, respectively.)[391] The work group recommended these actions, which are designed to reduce environmental risks to children who have asthma: 1) expanded research into those environmental factors that potentially contribute to the onset of childhood asthma, 2) expanded and accelerated research to develop and evaluate strategies for improving the quality of life for children with the disease, 3) implementation of nationwide public health programs that improve the use of scientific knowledge to prevent and reduce the severity of symptoms by reducing environmental exposures, and 4) establishment of a coordinated, nationwide asthma surveillance system that collects, analyzes, and disseminates data about health outcomes and risk factors at state, regional, and local levels.[392] These recommendations lay out a distinctive national plan of action that provides much sought-after direction for dealing with this major public health problem.

**Unintentional Injuries.** Unintentional injuries are the leading cause of death and hospitalization among U.S. children and teenagers and account for almost 44 % of all deaths after the first year of life.[393] Because of the high incidence of deaths resulting from traumatic brain injuries (about 9,000 annually) and the high number of nonfatal injuries with debilitating consequences (approximately 60,000 per year), the work group focused its

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[388]Massey, J.T., T.R. Moore, V.L. Parsons, and W. Tadros. Design and estimation for the National Health Interview Survey, 1985-1994. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, CDC, National Center for Health Statistics, 1989. DHHS Publication No. PHS89-1384. (Vital and health statistics: Series 2, No. 110.)

[389]Mannino, D.M., D.M. Homa, C.A. Pertowski, et al. Surveillance for asthma—United States, 1960-1995. *Morbidity and Mortality Weekly Report*, 1998, v. 47, n. SS1, p. 1-28.

[390]Ibid.

[391]National Center for Health Statistics. *Vital Statistics of the United States, 1990.* Vol. II: Mortality, part a. Technical appendix. Washington, DC: Public Health Service, 1994. DHHS Publication No. PHS95-1101.

[392]Task Force on Environmental Health Risks and Safety Risks to Children. Biennial report. In press.

[393]Ibid.

attention on this class of injuries.[394] Many federal agencies are collaborating with private and corporate partners to promote safety in homes, schools, communities, on the playground—anywhere children are likely to be at risk for these injuries. The Task Force has recommended implementing a series of interventions to increase awareness of traumatic brain injuries and how to prevent them, including establishing safety programs in Atlanta, Detroit, Minneapolis, and Dallas, and expanding surveillance activities so that all trauma is included in the database of the National Electronic Injury Surveillance System.[395] With the expanded system, we can develop national estimates of the number of these injuries from all causes among children who are treated in hospital emergency departments and will be better able to direct resources and prevention activities. Efforts to strengthen communication among agencies and organizations and to deliver prevention messages to the public are also key, and the work group has addressed the need for these groups to link Web sites and hotlines and to distribute safety information through a variety of channels.

**Cancer.** The Task Force addressed gaps in understanding about the causes of childhood cancer and possible environmental causes of the disease. Among children aged 1-14 years, cancer is the most common cause of disease-related mortality; each year in the United States, about 1,600 children in this age group die of cancer.[396] The work group addressing this priority issue proposed several areas for study to improve our understanding of the causes of childhood cancer. These include 1) understanding the role the environment plays in childhood cancer; 2) identifying potentially preventable environmental causes of cancer; 3) identifying the role of gene-environment interactions for specific childhood cancers; 4) developing strategies for reducing children's exposure to carcinogens, such as tobacco smoke, that cause adult onset of the disease; 5) promoting toxicologic research and exposure assessment associated with environmental carcinogens, and 6) educating the public about cancer and possible risk factors.[397] The work group further recommended these actions: 1) establish a national network for research on cancer in children that will include a central registry of cases of childhood cancer in this country, 2) establish a national childhood cancer registry tissue bank, 3) convene a workshop on childhood leukemias and brain tumors, and 4) develop and implement a model cancer-inquiry response system as a means of establishing a systematic approach to cancer surveillance.[398]

**Developmental Disorders.** Developmental disorders cover a broad range of neurologic, reproductive, and immunologic deficits. Task Force recommendations for this priority area focused on research, including developing and implementing a prospective cohort study that would examine environmental effects on parents and children, and would be similar to the approach used in the elegant Framingham study, which looked at chronic

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[394]Ibid.

[395]Ibid.

[396]Reis, L., C. Kosary, B. Hankey, et al. SEER *Cancer Statistics Review, 1973-1995*. Bethesda, MD: National Cancer Institute, 1998.

[397]Task Force on Environmental Health Risks, ibid.

[398]Ibid.

health conditions of adults in the United States.[399] The children's study would help researchers gain a better understanding of how the complex interaction of genes and the environment operates in the developing fetus and child, and would provide critical opportunities for improving public health surveillance and developing effective interventions.

Another key piece in this priority area is eliminating childhood lead poisoning as a major public health problem by 2010. Despite all the successes in reducing lead poisoning among U.S. children, close to 890,000 children still have blood lead levels that may cause serious harm to their developing brains and bodies[400] and permanently affect their ability to function well in society. In general, these children are the poorest in the country; they often live in deplorable housing that contains deteriorating lead-based paint or lead-contaminated dust, and prospects for moving them to lead-safe housing are bleak indeed. The work group proposed an integrated, large-scale, multiple-agency primary prevention strategy to eliminate exposure to lead-based paint or dust.[401] Some aspects of this push involve increasing the abatement of lead hazards in housing and ensuring tougher enforcement of existing regulations; others involve policy issues related to screening and Medicaid reimbursements for environmental and case management services, and still others deal with research and surveillance and monitoring issues.

Although the effort needed to accomplish the goals of the Task Force in these four priority areas is daunting, the collaboration of federal agencies in this major endeavor to protect children's environmental health and safety is both gratifying and compelling to me. From the start, federal agency and department heads were enthusiastic supporters of the Task Force goals. Agencies began to appreciate their common goals and soon realized that they could join forces to protect children in ways they had not previously considered. Many issues remain, not the least of which is adequate funding to implement Task Force recommendations, but I believe there is now a uniform goal across agencies and a mechanism for communication and collaboration that had not existed previously.

## Conclusion

We have made impressive gains in protecting children's health and safety in this country, particularly within the last 50 years, but I believe we must act more vigorously than we have in the past to address the problems that remain. Our nation is the richest on earth, yet given our immense wealth and massive technologic resources, we have not faced squarely our environmental responsibilities to our children, in my opinion. At a minimum, I believe that not only must we base policy decisions and protections on rigorous, independent science, but also that we must enforce the letter of existing laws that protect children's health. It means that we back up our words with deeds, including implementing aggressive policies to protect

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[399]Ibid.

[400]Centers for Disease Control and Prevention. Screening young children for lead poisoning: Guidance for state and local public health officials. Atlanta: U.S. Department of Health and Human Services, Public Health Service, 1997.

[401]Task Force on Environmental Health, ibid.

children's health and safety. It means funding programs, research, public health surveillance, and data collection and analysis at levels that will allow us to accomplish our work. It means that we consider protecting children's health and safety a mandate, one that is as important as protecting our national security.

## Discussion

**Discussants:**

Trudy Ann Cameron, Ph.D., Professor, Department of Economics, University of California at Los Angeles

James D. Wilson, Ph.D., Senior Fellow, Resources for the Future

Karen L. Florini, Senior Attorney, Environmental Defense

Sandra L. Tirey, Assistant Vice President for Regulatory Affairs, Chemical Manufacturers Association

Jim O'Hara, M.A., Executive Director of Health-Track, a project supported by the Pew Charitable Trusts through a grant to Georgetown University

**Dr. Cameron** began by noting that economists are not simply corporate cost accountants. The broad mandate of the profession is instead to consider how best to allocate scarce resources amongst competing end uses. For her allotted time (the scarce resource for presenters), she selected five points to make (a subset of the competing end uses for the limited time.) The first was to observe that a common theme in most of the policy papers is that one must define a measurable goal ("objective function") before arguing how society ought ultimately to allocate its resources. Among the choices in this case are:

- minimize children's environmental risks;
- maximize children's health;
- maximize children's welfare, which includes criteria beyond health; and
- maximize society's welfare.

It's necessary to decide what to minimize or maximize before any informed choices can be made, and to keep in mind that too narrowly defined an objective function may mean that we fail to achieve our desired goal.

Her second observation was that people are sometimes prone to adapt their behavior in a way that blunts or negates the effect of any intervention taken by a government. A classic example of this phenomenon is the hypothesized tendency of people to drive more recklessly when they are wearing seat belts because of the added safety protection that belts provide. Seat belt laws may thus prevent fewer injuries and accidents than they would if people did not alter their driving habits. Relating this to a potential environmental risk, one can presume that food producers choose to use pesticides in food production, because this practice increases their profits. If less pesticide were used, this might increase the cost of producing the same output, which might then be passed along to consumers in the form of higher prices. If prices go up, it is possible that some people may consume less of what is being produced. The potential for offsetting behavioral adaptations needs to be considered, since unintended adverse consequences may result if there is too narrow a focus on a principle like "less pesticide is good." In this example, we need to know what will happen

to food prices and how people will respond to these price changes, before we can be sure of the overall consequences of limiting pesticide use.

Dr. Cameron's third observation was that public support for costly programs to deal with risks depends on public perceptions rather than science. She did not find it irrational for people to decide that they are more worried about environmental risks to children than traffic accidents, even though traffic accidents may pose a higher and more tangible risk. She noted a distinction between risks that are voluntarily assumed and those that are involuntarily imposed, and that environmental risks are often perceived as involuntary. She believes that people fear involuntary risks more and are willing to pay more to avoid them. Dr. Cameron believes that this means that there is a vast need for disseminating accurate information about risks, so that the policy decisions that would be supported by the populace are consistent with the actual science involved.

A fourth observation addressed the use of cost-benefit analysis (CBA). It is important to understand that, whenever a decision is made, Dr. Cameron argued, a CBA has been done. The only issue is the extent to which it was done explicitly and transparently. Despite what some people think, CBA is an aid to decision making — it does not make decisions. It is not useful to look only at the bottom line of a cost-benefit analysis. What you need to know is how that bottom line was arrived at. Economic theory teaches that you could, in principle, rely on the bottom line alone, but only if everyone affected by the decision subscribed to the same set of utilitarian beliefs about what constitutes the best social and economic goals. However, Kenneth Arrow got a Nobel Memorial Prize for pointing out that it's impossible to come up with one universally acclaimed definition of social welfare. Dr. Cameron believes that thus, it is immensely important to do CBAs explicitly, rather than implicitly, to specify the assumptions that underlie the analysis, and substantiate the sometimes numerous analytical choices that have to be made to get to the bottom line.

Unfortunately, the information supplied to the people who do CBA is not always the information that is the most useful for CBA. Individuals who want to know the costs and benefits of a regulatory alternative often provide inputs in the form of single numbers (point estimates) meant to represent, for example, an unhealthful level of air pollution, because this is the easiest way to express this information. However, the real world is seldom that simple. There is often great variability or uncertainty in things like the level of a pollutant in the environment or the dose that causes adverse health effects. A proper economic analysis requires information about how health benefits and other potential policy impacts are likely to be distributed across time and across people, and about scientific uncertainties underlying any of these projections.

Dr. Cameron's final comment on policy approaches for managing risks to children's environmental health warned against an oversimplified view of who the good and bad guys are, and why they do what they do. She opined that a marketplace is not just a corporation full of faceless directors and managers looking to maximize profits. Rather, Dr. Cameron sees the market as an interaction of all buyers and sellers, including consumers who want lower prices, stockholders who want good returns on their investments, and workers who want higher wages. All of these groups have a hand in creating problems that are outside the influence of market forces (that is, externalities such as pollution), which impose costs on

society at large (or some portion of it). For example, pollution may result from the use of a technology that increases productivity and thus leads to higher wages, better investment returns, lower prices, and greater profits.[402] Externalities are a classic example of why government is needed to intervene to make things work out better for society as a whole. Governments intervene (through laws or regulations or taxes) to make people behave as though they fully recognize all the external social costs and benefits that go along with a particular decision.

The government also has a role, Dr. Cameron advised, in managing the availability of public goods.[403] Health protection involves both public and private goods. A cure for an illness, for example, may be a private good that the market will bring about, because profit-maximizing firms have an incentive to develop it. On the other hand, preventive programs are more likely to produce public goods, such as group immunity or clean neighborhoods, which are likely to be much less viable business enterprises for a private profit-maximizing firm. These are much less likely to be provided by the free market.

Finally, Dr. Cameron addressed the economic practice of discounting – adjusting costs and benefits to reflect the relatively greater value they are believed to have in the present as opposed to some point in the future. There are a great number of different discount rates that various government bodies and others use in various circumstances. What needs to be recognized is that none of these is the "right" rate. All are subjective and all simplify an inherently complex set of issues that may be best discussed in the open.

**Dr. Wilson** first addressed an aspiration expressed by Rabbi Swartz in his presentation, arguing that, in almost all cases, environmental standards are already being set so as to protect children. The legal standard that is imposed on the FDA and EPA — "reasonable certainty of no harm" in the case of pesticide residues, for example — does not just mean no harm to adult white males. It means no harm for the entire population, including women of child-bearing age and children. The cases where standards do not protect children are the exceptions, Dr. Wilson explained, and he noted that there are exceptions to any rule.

The other point emphasized by Dr. Wilson was the numerous references in the earlier presentations to the effects of poverty on the environment of children. The message he took from the presentations of Drs. Thompson and Chilton is that there are far more important things for Congress to focus on than the "tweaking of the regulations of chemicals." If there was any one lesson that should come out of this workshop, he said, it is that the more significant problem for children's health is the effect of poverty on their environment.

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[402] An externality is said to occur when the action of one decision maker has an effect on someone or something that is not directly involved in the action. Externalities, which can be positive or negative, are typically ignored by the decision maker.

[403] Economists define a public good as something that can be consumed by more than one individual at a time and whose consumption cannot be denied to an individual who desires it. Thus, there is typically not a profit to be made in producing a public good, even though it can be in everyone's self interest to have it.

**Ms. Florini** focused on some implicit assumptions and assertions she believed were made through the course of the seminar, and why she disagreed with at least some of them. The first of these was the notion that America cannot afford to be both safe and healthy. She pointed out that the United States is the richest country in the history of civilization, and that lack of political will to deal with health hazards like poverty, guns, and smoking is not an excuse to forego additional progress in dealing with other health hazards where that will exists.

A second implicit assumption identified by Ms. Florini was that all the inexpensive and easy environmental protection steps have already been taken, and that any additional interventions would be very costly. To illustrate that this is not necessarily the case, and, she believes, is almost certainly wrong, she cited a recent collaboration between Dow Chemical and the Natural Resources Defense Council. Working together, these parties found ways to reduce nearly 7 million pounds of waste and emissions of toxic chemicals from a plant in Michigan, while saving the company over $5 million annually and yielding an overall return rate of 180%.[404] There is also a long history of regulatory compliance costs being overstated, according to Ms. Florini.[405]

The third assumption, one also refuted by several others speakers during the day, is that mortality rather than morbidity should be the focus of concern and regulatory action. Asthma is a good example of why this is not necessarily the case, Ms. Florini explained. The fact that asthma is the number one cause of school absences means that it has long-term and perhaps profound effects that are not reflected in mortality statistics. In addition, a focus on deaths in childhood misses the fact that early childhood experience is the major risk factor for asthma later in life. What matters is the rapid upward trend and prevalence for children.

**Ms. Florini** identified the fourth implicit assumption that she finds incorrect as the belief that environmental interventions will have little impact on children's health. This assumption presupposes that we know enough about the causes of the chronic diseases to exclude environmental factors. In fact, the causes of most chronic disease are not known, according to Ms. Florini. Because the absence of evidence is not evidence of absence, it is not appropriate to suggest that the environment can be disregarded as an important factor in health. Advances in areas like gene-environment interactions and efforts to generate more information on the toxicity of industrial chemicals in widespread use are starting to fill at least some of the data gaps. At this time, however, the data do not exist that would rule out environmental agents, particularly for those effects of greatest concern for children: developmental impacts on the nervous, reproductive, and immunologic systems. Ms. Florini ended on a point of agreement with other speakers, that better exposure characterization data for children are needed. She observed that no one has ever done a complete analysis of the full range of contaminants in human breast milk, and that there is almost no data available on which chemicals are present in children's toys, utensils, and other items. EPA is making

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[404]<http://www.nrdc.org/cities/manufacturing/ilgdow.asp>

[405]Goodstein, Eban, and Hart Hodges. Polluted data: Overestimating environmental costs, *The American Prospect*, n. 35, Nov.-Dec., 1997, p. 64-69.

Harrington, Winston, R.D. Morgenstern, and P. Nelson. On the accuracy of regulatory cost estimates. Discussion paper 99-18. Washington, DC: Resources for the Future. (1999)

progress on this issue through a voluntary children's testing initiative that examines chemicals for which biomonitoring data are available.[406] There are still numerous data gaps to fill. In the absence of data, Ms. Florini advocated the use of "conservative defaults," assumptions that will err on the side of caution by being protective of children's health. These not only offer protection in the face of inadequate information, but also create incentives for additional data generation. Without conservative defaults as the fallback position, information gaps tend to get enshrined, because there is no incentive to pursue information needed to justify changing them. Conservative defaults also reduce the incentive to avoid action through "paralysis by analysis." Where incentives exist to develop environmentally friendlier products, a way is usually found to do so, according to Ms. Florini.

**Ms. Tirey** set the stage for her remarks by noting that she came to the seminar with two biases that were rooted in her background. The first was as an individual who works for an industry that is grounded in science; the second, as an individual — and more importantly, a mother — who is schooled in the field of public health. Both biases, she said, informed her values and her approach to the questions posed to the seminar participants. In addressing the question of the appropriate role for the federal government in managing children's environmental health risks, she first noted that the chemical industry is a global industry and that her remarks apply on a global as well as a local scale.

Her initial recommendation was that the federal government should employ a definition of environment that is more inclusive. This definition would include the psychosocial, economic, biological, physical, and chemical aspects of the environment. The examples raised by other speakers of the impact of poverty and the interaction among factors in creating or causing disease illustrate that a broader definition of environment is needed. Without one, we may miss or stop too soon in seeking solutions. One corollary to this recommendation is that there needs to be incentives for crosstalk among the disciplines concerned with children's health. Multi-factorial problems require multidisciplinary solutions. A second corollary is that there needs to be incentives in the policymaking and legislative process for cooperation among and across agencies. This is a weakness of the existing system, which does not always encourage cross-agency coordination.

The second recommended role for the federal government was as the agent for the communication of accurate public health information, so that parents and caregivers can take appropriate preventive actions to lower risks to children. It is equally important that low probability risks should not supplant high probability risks in the minds of parents and caregivers. The third area where the federal government has a role to play is in promoting and coordinating the funding of research. Research activities, Ms. Tirey asserted, ought to be focused on two kinds of questions. One is better ways to assess potential hazards and risks. This means both improved exposure assessment and improved animal models and other toxicological tools for understanding potential interaction between chemicals and humans. As a participant in some of the discussions regarding EPA's children's health testing initiative, she questioned whether the agency was taking the right approach to the issue. Instead of starting with a list of chemicals and deciding whether children are exposed to any of them, she asked if a better starting point was to try to understand what children are exposed to in their environment. The second area of focus for research is traditional public

[406]<http://www.epa.gov/chemrtk/childhlt.htm>

health surveillance tools, including registries and longitudinal cohort studies. Such work needs to take a disease-based approach, trying to understand which factors impact the health outcomes from a disease perspective. The final area where the federal government can play a large role is to provide incentives for collaborative efforts among government, academic, industry and other stakeholder interests. It is only through collaborations, she said, that we are likely to come up with consensus answers that will lead to real actions in interventions.

**Mr. O'Hara** offered a perspective informed by his four-year tenure at the Food and Drug Administration. He made three points regarding the day's presentations. First, he noted that while there was a general call for more research and better data, there was disagreement over what should flow out of that call. One possible outcome is information to educate individuals and families so that they may make their own decisions about how to manage potential risks. Another possible outcome is regulation, which may be needed because marketplace incentives do not operate to prevent risks. He illustrated his second point by reference to the Food Quality Protection Act (FQPA) and pesticides.[407] The FQPA, in effect, put in place a public health standard for pesticides: "reasonable certainty of no harm."[408] From an FDA point of view, the traditional risk-benefit analysis for a food additive takes the position that the risk is borne by the consumer, and the benefit accrues to the producer. However, Mr. O'Hara thought an underlying theme in some of the seminar presentations was that the consumer may experience both the risks and benefits. When risk-benefit analyses are performed on environmental health issues, Mr. O'Hara believes it is necessary to be clear about where the risks lie, and where the benefits accrue.

Mr. O'Hara's last point concerned the need to reintegrate public health and environmental regulation and protection. As Dr. Jackson said in his presentation, environmental health was put on the agenda by EPA in full partnership with the public health service agencies of the government. This was an important and meaningful advance in dealing with the issue, he stated, because people's, and specifically children's, safety is not the province of just one agency or one set of expertise. Mr. O'Hara noted that tobacco is a good example of this, with FDA's finding that tobacco was a pediatric health problem driving its rulemaking, while EPA and other agencies were dealing with tobacco as an environmental health issue under the aegis of Executive Order 13058 ("Protecting Federal Employees and the Public from Exposure to Tobacco Smoke in Federal Buildings," August 13, 1997).[409] Mr. O'Hara implied that these approaches are complementary, not mutually exclusive, and both are components of the drive toward the larger goal of having a healthy society.

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[407]The Food Quality Protection Act of 1996 was enacted as Public Law 104-170. A summary of the FQPA is provided by CRS Report 96-759, *Pesticide Legislation: Food Quality Protection Act of 1996 (P.L. 104-170).* A brief report on implementation status also is available as CRS Report RS20043, *Pesticide Residue Regulation: Analysis of Food Quality Protection Act Implementation.*

[408]In the FQPA, Congress defined a "safe" pesticide residue level as one that ensures "a reasonable certainty of no harm" from exposure to all similarly acting chemicals, considering all routes of exposure.

[409]62 *Federal Register* 43451, August 13, 1997.

**General Discussion**

**Dr. Wilson** offered an alternative perspective on Ms. Florini's assertion that the use of "conservative default" assumptions was a way to encourage data generation. His experience with FDA's food additive regulations was the opposite. The conservative defaults in place for this regulation create the incentive for industry to do a specific set of required tests and no others. The development of new information is discouraged, since departing from that norm might uncover a piece of data that could adversely affect the marketability of the product. This is what happened with cyclamates, he stated.

**Rabbi Swartz** had comments for Dr. Thompson and Dr. Wilson. He said that Dr. Thompson had made a mistake regarding the *USA Today* article she cited, but that it was an instructive mistake.[410] His recollection was that the article did not say to limit the amounts of fresh fruits and vegetables fed to children because of pesticide residues. It instead said to switch from certain foods to other foods which are nutritionally equivalent but have lower residues. The mistake was instructive, he explained, because it was the kind of thing that often happens when communicating about public health: People hear the fear and make a decision based on that, and do not hear the uncertainty or the other parts of the communication. Because of this, evaluations of the benefits and costs of actions need to include considerations of both the monetary impact and how behaviors will change based on people's impressions of what they should be doing, he advised. Rabbi Swartz was not aware of any studies that showed that pesticide regulations have actually changed costs in such a way that nutrition has been deleteriously effected.

A second clarification Rabbi Swartz offered to Dr. Thompson involved her mention of EPA's failure on environmental tobacco smoke regulation. He stated that EPA attempted to take action and was prevented by the Congress and the courts — it was therefore not fair to fault it for failing, in his opinion.[411]

**Rabbi Swartz'** comment for Dr. Wilson was that his statement that nearly all statutes protect the entire population was, in his view, a statement of faith and not a statement of science. There were serious cautionary examples, where, in fact, present standards do not protect children, according to Rabbi Swartz.

**Dr. Wilson** acknowledged that there were counterexamples to his statement, but in his opinion, these were the exception. According to Dr. Wilson, nearly 2,000 substances had been regulated using the standard safety practices. He cited a circumstance where an additive

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[410]The *USA Today* item is a reproduction of an Associated Press wire story entitled "Study: Pesticides in foods too high for kids" (2/18/99), which in turn references a March 1999 article in *Consumer Reports* entitled "How Safe is our Produce?" The newspaper piece quotes the report's author as saying that the findings do not mean parents should stop giving their children produce but might want to be careful about the amounts and types of fruits and vegetables they serve their children. The *Consumer Reports* article states: "One thing you should *not* do is stop serving fresh produce, which provides a host of vital nutrients." (emphasis in original)

[411]EPA has no regulatory authority over indoor air, therefore, it has taken no regulatory action on secondhand smoke.

approved for use in beer in Canada had been implicated in liver damage in individuals who consumed more than a case a day. With this exception, he was not aware of any circumstance where a food additive or pesticide residue deemed safe for humans when used as intended was subsequently found to cause injury.

**Dr. Thompson** replied to Rabbi Swartz that her recollection was that there was indeed a recommendation that parents limit the amount of fruits and vegetables that their children consumed, but that she would review the article and the study it referenced to make sure. Her other response was that she was not laying blame on EPA for the lack of environmental tobacco smoke regulation but was instead addressing the Congress. She expressed a concern over what she called the paradox of testing — the notion that "untested" means "safe" or "not hazardous." Toxicity testing is done to find effects, not to not find effects. This necessarily means that tests are run at a level where effects are likely to be found. The things that are not dealt with well, according to Dr. Thompson, are the uncertainty about the chemicals that are untested, and how the new information is treated when test results are in. It is important to factor in the uncertainty when taking actions and making decisions, even if conservative defaults are being used, she stated. If conservative defaults are treated as the truth, then there really is no incentive for research, in her opinion.

**Ms. Florini** expressed the opinion that Dr. Wilson was confusing an absence of evidence with evidence of absence. The fact that he was unaware of cases where a pesticide or FDA approval had led to harm did not necessarily mean that there were not any. Indeed, the fundamental problem is that we do not know whether or how many cases there are where standards are set at a level where harm might result to portions of the populace. Addressing Dr. Thompson, she agreed with the idea that no new information on chemicals would be developed, if defaults were set in a way that does not allow them to be displaced by better information. The point she was trying to make is that if you do not do something in the first place, you also are not going to trigger the generation of additional information, because it costs money to do so.

**Dr. Chilton** indicated that experience teaches that the most unsafe forms of pesticides disappear from the market on their own, because no one wants products that cause harm. If industry can identify a better and safer product and produce it at the right price, it is going to be purchased, according to Dr. Chilton. The problem, as he sees it, is that FQPA is driving products to standards so restrictive that it's possible some of them will disappear from the market, leaving a gap in cost-effective crop protection. This is a form of regulating to encourage development of improved or new products called technology forcing. While it does work sometimes, at other times there is insufficient profit in a potential new technology to justify its development. In these cases, technology forcing may simply eliminate U.S. domestic suppliers and create demand for imports, Dr. Chilton claimed. Since the import market is far more difficult to monitor, the end result can thus be less safe rather than more safe products, he argued.[412]

[412]Imported foods are subject to the same pesticide residue standards as domestically produced foods, but monitoring of residue levels on imports may be more challenging than monitoring crops in fields.

**Dr. Goldman** cited chlordane as a counterexample to Dr. Chilton's assertion. This insecticide was harmful to humans, she argued, but was not taken off the market until the government acted to ban its use. She agreed with Dr. Cameron that you cannot make a decision without understanding what the impacts of that decision are going to be. However, she expressed concern over the CBA modeling process — in particular, the assigning of monetary values and discount rates to future lives and to human characteristics like IQ, good health, or lung function.

**Dr. Jackson** cited several examples of dire predictions about the impact of regulating or banning pesticides on various crops that did not come to pass. The production industry, he said, has warned that the sky would fall if a product was banned so often that the public health community has become very skeptical of such pronouncements. Another point regarded the rapid toxic screening tools that are now being perfected. The ability to quickly, easily and cheaply measure a large number of chemicals in a small tissue sample will allow the development of body burden profiles for the population and monitoring of hot spots. This will bring scientific information to the decision-making process that has never been available before.

**Dr. Mattison** had both a comment and a question. He noted that data systems are generally not in place for getting feedback on the effect that regulations have on the public health outcomes they were meant to address. Given that this is the case, he asked what data-gathering structures might be implemented that would create "win-win" situations; that is, reward industry, consumers, public health entities, and the other interested parties involved in the regulatory process.

**Dr. Cameron** had a follow-up to Dr. Goldman's remark about discounting. She mentioned an unpublished study by Shane Frederick that was part of his dissertation at Carnegie-Mellon University. This study examined people's preferences for preventing a given number of deaths immediately versus a greater number at some point later in time. The results suggested that people did discount future lives; that is, they did not value them as highly as present-day lives. But Frederick's survey revealed that this lesser value stems from an underlying belief that some future technological advance will come along to save these future lives. But, Dr. Cameron cautioned that we really do not know much yet about how individual people discount. We do know that individuals vary widely in how they discount future benefits, according to Dr. Cameron. So, she agreed that decisions should not be made on the basis of one single arbitrary discount rate, because any such rate is bound to be wrong. Instead, the time profile over which costs and benefits accrue should be described, separately and in detail, and the sensitivity of the overall assessment to the use of different arbitrary discount rates should be demonstrated.

**Dr. Reigart** related that two tenets of the American Academy of Pediatrics (AAP) are that regulatory standards ought to be health-based, based on the "reasonable certainty of no harm" standard, and that pediatricians and families they care for have a right to expect that food, water, and air are safe for children. While serving as chair of AAP's environmental health committee, two things happened that emphasized those tenets for him. One was a statement the committee developed on the risks of ambient air pollution to children. Because ozone exposure can have adverse health effects, and high levels are present in some parts of

the country, the committee had to advise pediatricians to counsel families in those areas to keep their children indoors in the middle of the day and not allow them to exercise. As a pediatrician, he feels that they ought to be able to say that children can go out and play in a safe environment at any time of day. A second thing that happened was the publication of the National Academy of Sciences report entitled *Pesticides in the Diets of Infants and Children*, which said, according to Dr. Reigart, that perhaps our regulation of pesticides in the diets of children was not sufficient to take care of that vulnerable population. The report compelled him to ask for better regulation of pesticides.

**Ms. Tirey** addressed Dr. Mattison's question concerning means to create win-win situations. This question, she said, highlighted one of the conundrums faced by all those concerned about health and safety regulations for chemicals. As noted by other speakers, toxicity testing is set up to show an effect, because you must test up to the level that produces an effect. When there is a focus on particular chemicals, those chemicals then become part of lists that then become replicated in various programs within the regulatory agencies. This creates a "tyranny of the list" where people, for a variety of reasons, substitute away from those products that are on the list to things that are not on the list, without any appreciation of whether those non-listed substances have the same risks or not. If a way could be found to deal with this conundrum, it would help to answer the question that Dr. Mattison posed.

**Dr. Bailar** noted that when the scientific evidence is really conclusive, things do happen and they happen quickly. Two examples of this are TRIS (a flame-retardant that was used in children's sleepwear), which was immediately withdrawn from use when adverse exposure effects were identified in the late 1970's, and vinyl chloride (a chemical with primarily industrial exposures), which was regulated soon after it was identified as a carcinogen. The problem with many of the exposures addressed in the seminar is that the evidence for adverse health effects is not abundantly clear.

**Dr. Chilton** offered that it would be helpful to survey the population, parents in particular, to ask their beliefs about the relative risks of various kinds of hazards to children. He believed such a survey would find that small risks had been over-emphasized and distorted their perceptions about which problems were most important.

**Ms. Florini** rejoined that this would not be useful because it was based on a false dichotomy; parents' concerns over environmental chemicals do not affect their decisions about, for example, putting bicycle helmets on their children, she argued.

**Dr. O'Hara** pointed to increases in children's consumption of fruits and juices over the past twenty years as an example that illustrated that adverse information about chemical exposures was not deterring parents from making good nutritional choices.

**Dr. Schierow** added that studies show large gaps between people's opinions and behaviors. She asked that authors consider the following questions in the final versions of the papers to be prepared after the seminar:

1. Why are accidents — which encompass a wide range of risks from drownings to pesticide poisonings — treated as single category when, for example, cancers — another broad category — are each treated separately? Doesn't that unfairly reduce the apparent risk of the more specific hazards relative to the risk of the general category of hazards? In comparing relative risks, should we look at each cause of mortality or morbidity (or each risk-reducing option) separately?

2. Why might one want to, or not want to, grant a relatively greater role for the federal government in the regulation of environmental risks to children such as air pollution or pesticide residues on food than in regulating risks of injuries due to bicycles or slippery bathtubs?

3. Given the general agreement about the need for exposure information, why do we not have more data?

And with that, the seminar was brought to a close.

## Conclusion

It appears that concerns about children's exposure to chemicals in the environment are based, at least in part, on scientific observation and data regarding toxic chemicals and adverse effects of exposure to them in the environment. However, data are very limited and do not permit generalizations about the universe of chemical ontaminants. Scientists generally agree that children's environmental health risks from chemicals differ from those of adults; depending on the chemical, children's risks may be much greater or much smaller than those of adults. A greater health risk to children has been found for environmental exposure to lead, and research demonstrates a potentially greater toxicity to children (because they are continuing to develop), if they are exposed to high enough levels of other pollutants like PCBs and mercury. Thus, the science indicates that there might be increased environmental health risks to children from chemical contaminants, but the extent and significance of the risks are unknown and debatable.

Policy analysts representing a broad spectrum of political philosophies support additional federal funding for toxicological and risk assessment research and for monitoring of environmental contamination and human exposure, in order to improve assessments of children's environmental health risks. But, beyond research, policy preferences diverge, despite shared knowledge of available scientific evidence. Some policy experts would enhance protection of children by attempting to minimize chemical exposure through federal pollution prevention incentives or regulations. Others would avoid actions with effects on the private sector, until additional data had been gathered and competing priorities had been analyzed, allowing resources to be targeted to where they would have the best chance of saving lives or improving quality of life.

The policy debate is driven largely by differences in how people balance diverse concerns about the magnitude of perceived risks, the scientific uncertainty of risk estimates, and a desire to protect children or to avoid errors of over or under responding to control the risk. It is personal and societal values that determine when or whether individuals judge that federal action is justified.

Also underlying the debate are shifting definitions of "environment" and "risk." Whether environmental risks are significant depends on how one defines "environmental" and "risk" and with what other risks environmental risks are compared. For example, ambient air and water pollution may pose a relatively small mortality risk to children, as compared to the risk of a fatal automobile accident. On the other hand, pesticides or pollens in schools or homes might pose a significant asthma risk to a large number of children.

Finally, there are disagreements about the need for federal, as opposed to state or local, regulatory action. These may be complicated by a U.S. tradition of maintaining local public health programs, while supporting state or federal environmental protection programs.

Such diverse views often are a component of debates about environmental policies. The debate about children's environmental health, however, appears more tempered by the

shared goal of experts, policy makers, and stakeholders to preserve and enhance children's health.

# APPENDIX A

# SEMINAR PROGRAM

**Children's Environmental Health:**
**What Role for the Federal Government?**
**May 22, 2000**
Congressional Research Service
Library of Congress
Mumford Room, 6th Floor, Madison Building

**Agenda**

8:30 - 9:00 Morning coffee

**MORNING SESSION: ENVIRONMENTAL HEALTH RISKS TO CHILDREN**

9:00 - 9:10 **Introduction:** Linda-Jo Schierow, Ph.D., Specialist in Environmental Policy, Congressional Research Service

**Topic One**

How do children's environmental health risks differ from those of adults? Are children always more sensitive, vulnerable, or exposed than adults? What scientific evidence exists to support these claims/conclusions? How do environmental health risks compare to other health risks for children?

9:10 - 9:30 **Paper Presentation:** Ruth Etzel, M.D., Ph.D., Director, Division of Epidemiology and Biostatistics, Food Safety Inspection Service, U.S. Department of Agriculture

9:30 - 9:45 **Discussion:**

Philip Guzelian, M.D., Professor of Medicine, University of Colorado Health Sciences Center

William H. Farland, Ph.D., Director, National Center for Environmental Assessment, U.S. Environmental Protection Agency (EPA)

James Lamb, Ph.D., D.A.B.T., J.D., Vice President, Blasland, Bouck & Lee, Inc.

J. Routt Reigart, II, M.D., Professor of Pediatrics and Director, General Pediatrics, Medical University of South Carolina; Chair of EPA's Children's Health Protection Advisory Committee (CHPAC)

9:45 - 10:00 Questions and open discussion moderated by CRS

**Topic Two**

Which environmental pollutants may pose a special health risk to children and what level of evidence exists? (Case studies of lead, mercury, and PCBs)

10:00 - 10:20 **Paper Presentation:** Lynn R. Goldman, M.D., Adjunct Professor, Johns Hopkins School of Hygiene and Public Health; former EPA Assistant Administrator for Prevention, Pesticides, and Toxic Substances

10:20 - 10:35 **Discussion:**

John A. (Jack) Moore, D.V.M., Principal Investigator, Center for Evaluating Risks to Human Reproduction Center, National Toxicology Program; former EPA Assistant Administrator for Prevention, Pesticides, and Toxic Substances

Deborah C. Rice, Ph.D., Risk Assessor, National Center for Environmental Assessment, EPA

Michael D. Shelby, Ph.D., Chief, Laboratory of Toxicology, National Institutes of Environmental Health Sciences (NIEHS)

J. Routt Reigart, II, M.D., Professor of Pediatrics, Medical University of South Carolina; Chair of EPA's Children's Health Protection Advisory Committee (CHPAC)

10:35 - 10:45 Questions and open discussion moderated by CRS

10:45 - 11:00 **BREAK**

**Topic Three**

Do environmental exposures to pollutants increase the rates of adverse health outcomes? (Case study: birth defects)

11:00 - 11:20 **Paper Presentation:** Donald R. Mattison, M.D., M.Sc., Medical Director, March of Dimes

11:20 - 11:35 **Discussion:**

Carole Kimmel, Ph.D., Senior Scientist, National Center for Environmental Assessment, EPA

Michael D. Shelby, Ph.D., Chief, Laboratory of Toxicology, NIEHS

Jonathan M. Samet, M.D., M.S., Professor and Chair, Department of Epidemiology, Johns Hopkins School of Public Health

11:35 - 11:45 Questions and open discussion moderated by CRS

**Topic Four**

Based on available scientific evidence about environmental health risks to children, what can we conclude? To what extent do we have consensus? To resolve the areas of disagreement, what types of research would be most helpful? (Case study: Childhood brain cancer and pesticide exposure)

11:45 - 12:05 **Paper Presentation:** Andrew F. Olshan, Ph.D., University of North Carolina

12:05 - 12:20 **Discussion:**

Christopher J. Portier, Ph.D., Chief, Laboratory of Computational Biology and Risk Analysis, and Associate Director, National Toxicology Program, NIEHS

John Bailar, M.D., Ph.D., Professor, University of Chicago; retired PHS officer, formerly at the National Cancer Institute

William H. Farland, Ph.D., Director, National Center for Environmental Assessment, EPA

Bernard A. Schwetz, D.V.M., Ph.D, Senior Advisor for Science, Food and Drug Administration, and Acting Deputy Commissioner, Food and Drug Administration (Unexpectedly unable to attend.)

Philip J. Landrigan, M.D., M.Sc., Professor and Chair, Department of Community and Preventive Medicine, Mt. Sinai School of Medicine (Unexpectedly unable to attend.)

12:20 - 12:30 Questions and open discussion moderated by CRS

12:30 - 1:30 **LUNCH:** Montpelier Room, 6th Floor, Madison Building

**AFTERNOON SESSION: FEDERAL ACTIVITIES TO ADDRESS CHILDREN'S ENVIRONMENTAL RISKS**

1:30 - 1:40 **Recapitulation and preview:** C. Stephen Redhead, M.Sc., Specialist in Public and Environmental Health, Congressional Research Service

**Topic Five**

What, if any, is the appropriate role of the federal government (as opposed to state or local government) in managing children's environmental health risks, given the state of the science?

1:40 - 4:20 **Paper Presentations:**

1:40 - 1:55 Kenneth W. Chilton, Ph.D., Senior Scholar, Center for the Study of American Business, Washington University in St. Louis

1:55 - 2:10 Rabbi Daniel Swartz, Executive Director, Children's Environmental Health Network

2:10 - 2:25 Kimberly M. Thompson, Sc.D., Assistant Professor, Harvard School of Public Health

2:25 - 2:40 Richard J. Jackson, M.D., M.P.H., Director, National Center for Environmental Health, Centers for Disease Control and Prevention

2:40 - 3:00 **BREAK**

3:00 - 3:30 **Discussion:**

Trudy Ann Cameron, Ph.D., Professor, Department of Economics, University of California at Los Angeles

James D. Wilson, Ph.D., Senior Fellow, Resources for the Future

Karen L. Florini, Senior Attorney, Environmental Defense

Sandra L. Tirey, Assistant Vice President for Regulatory Affairs, Chemical Manufacturers Association

Jim O'Hara, M.A., Executive Director of Health-Track, a project supported by The Pew Charitable Trusts through a grant to Georgetown University

3:30 - 4:20 Questions and open discussion moderated by CRS

4:20 - 4:30 **Wrap up:** C. Stephen Redhead, M.Sc., Specialist in Public and Environmental Health, Congressional Research Service

4:30 - 4:40 **Closing words:** Kenneth Olden, Ph.D., Director of NIEHS and the National Toxicology Program (Unexpectedly unable to attend.)

# APPENDIX B

## BIOGRAPHICAL SUMMARIES

## BIOGRAPHICAL SUMMARIES
## PROVIDED BY AUTHORS AND DISCUSSANTS*

(In the order of presentation)

### Ruth A. Etzel, M.D., Ph.D.

Ruth Etzel graduated with a B.A. summa cum laude in biology from the University of Minnesota in 1976 and with an M.D. from the University of Wisconsin in 1980. After completing a three-year residency in Pediatrics at the University of North Carolina in Chapel Hill, she was awarded a two-year fellowship from the Robert Wood Johnson Clinical Scholars Program. She received her Ph.D. in epidemiology from the University of North Carolina School of Public Health in 1985.

Dr. Etzel worked for 12 years at the CDC where she developed and directed the Air Pollution and Respiratory Health Branch. She is currently Director of the Division of Epidemiology and Risk Assessment at the Food Safety and Inspection Service in Washington, D.C.

Dr. Etzel is Board-certified in two specialties, Pediatrics and Preventive Medicine. She is the Vice Chair for Public Health and Preventive Medicine on the American Board of Preventive Medicine. She is the immediate past chair of the American Academy of Pediatrics Committee on Environmental Health. For 15 years, her research has focused on the effects of indoor and outdoor air pollutants on children's health. She has received numerous research awards, including the prestigious Arthur S. Flemming Award, presented each year to ten rising stars in Federal service, and the United States Public Health Service Professional Association's Clinical Society Open Award for her research linking life-threatening lung bleeding in infants with exposure to molds in the indoor air. She is a member of the Institute of Medicine Roundtable on Environmental Health Sciences, Research and Medicine and the Editor of the American Academy of Pediatrics *Handbook of Pediatric Environmental Health.*

* Edited for consistency in format.

CRS-200

**Philip S. Guzelian, M.D.**

Philip S. Guzelian is a Professor of Medicine at University of Colorado Health Sciences Center, Denver, Colorado. He is Chief of the Section of Medical Toxicology. For the 17 years before moving to Colorado, Dr. Guzelian was Professor of Medicine in the Departments of Internal Medicine, Pathology, and Pharmacology & Toxicology at the Medical College of Virginia/Virginia Commonwealth University in Richmond, Virginia. He received his M.D. degree from the University of Wisconsin at Madison in 1967, interned at the Cleveland Metropolitan General Hospital in Cleveland, Ohio, 1967 to 1968. He was a Clinical Associate at the National Institute of Child Health and Human Development, National Institutes of Health, Baltimore, Maryland, from 1968 to 1970, and a resident in Internal Medicine at the University of Wisconsin, Madison, from 1970 to 1971. Dr. Guzelian is board-certified in Internal Medicine. He has been elected to membership in the American Society of Biochemistry and Molecular Biology, the Association of American Physicians, the Society of Toxicology, and the Academy of Toxicologic Sciences. He has served on the editorial boards of numerous scientific journals. His current research involves molecular mechanisms by which the liver responds to the presence of foreign substances. He has authored or co-authored over 150 abstracts, peer-reviewed articles, and book chapters in the area of toxicology with a major emphasis on the effects of chemicals on the liver. His experience with public health issues on toxicology include service as a member of the National Academy of Sciences Committee on Toxicology, the Threshold Limit Value (TLV) Committee of the American Conference of Governmental Industrial Hygienists, Inc., and the Scientific Review Council of the National Institute of Environmental Health Sciences. Because of his training, both in medicine and in basic science and toxicology, he received the 1984-1989 Burroughs Wellcome Toxicology Scholar Award given through the Society of Toxicology.

CRS-201

**William H. Farland, Ph.D.**

Dr. Farland is the Director of the U.S. Environmental Protection Agency's (EPA) National Center for Environmental Assessment (NCEA), a major component of EPA's Office of Research and Development (ORD). NCEA has primary responsibility for the conduct of chemical-specific risk assessments in support of EPA regulatory programs, the development of Agency-wide guidance on risk assessment, and the conduct of research to improve risk assessment. NCEA was established in May 1995. Prior to his appointment as Center Director, Dr. Farland was Director, Office of Health and Environmental Assessment. He had served in this position since 1988. Prior to his selection as Office Director, Dr. Farland served as the Director, Carcinogen Assessment Group and Acting Director, Reproductive Effects Assessment Group. Dr. Farland began his EPA career in 1979 as a Health Scientist in the EPA's Office of Toxic Substances. Dr. Farland's career has been characterized by a commitment to the development of national and international approaches to the testing and assessment of the fate and effects of environmental agents. He currently leads the Agency's multi-year effort to reassess dioxin and related compounds and is also the ORD executive lead for children's health research.

Dr. Farland holds a Ph.D. (1976) from the University of California in Los Angeles in cell biology and biochemistry, a M.A. (1972) in zoology from the same institution and a B.S. (1970) from Loyola University, Los Angeles. He was awarded an Individual National Research Service Award from the National Cancer Institute to pursue postdoctoral training in DNA damage and repair at the University of California, Irvine and at Brookhaven National Laboratory.

Dr. Farland serves on a number of committees and advisory boards. Within the Federal government, he is a member of the National Toxicology Program's Executive Committee, EPA Liaison to the Public Health Service Environmental Health Policy Committee, past Executive Secretary of the Federal Coordinating Council on Science Engineering and Technology 's Ad Hoc Working Group on Risk Assessment and co-chair of the Committee on Life Sciences and Health's Subcommittee on Risk Assessment. He also currently serves on the Office of Science and Technology's Committee on Environment and Natural Resources' Risk Assessment Subcommittee. Dr. Farland served as co-chair of the Federal Liaison Group to the National Academy of Sciences Committee on Risk Assessment Methods.

In addition, William Farland is currently a member of the Scientific Advisory Council of the Risk Sciences and Public Policy Institute, Johns Hopkins University School of Hygiene and Public Health, the Strategic Science Team of the Chemical Manufacturers Association's Board Research Committee, and the Science Advisory Panel on EMF Research at the Electric Power Research Institute. Dr. Farland is also a former Councilor of the Society for Risk Analysis and is an active participant in its annual meetings and the annual risk assessment course. He continues to teach and publish and has been a member of the Editorial Board for *Risk Analysis* since 1987 and for *Environmental Health Perspectives* since 1997.

**James C. Lamb, Ph.D., D.A.B.T., J.D.**

Dr. James Lamb is the Vice President of Blasland, Bouck & Lee, Inc. in Reston, Virginia where he consults with industrial clients on various issues relating to toxicology, risk assessment, and risk communication. He has served the federal government as the Special Assistant to the Assistant Administrator for Pesticides and Toxic Substances at EPA and as the Head of the Fertility and Reproduction Group for the National Toxicology Program. He received his A.B. in Chemistry and Ph.D. in Pathology from the University of North Carolina-Chapel Hill, and a J.D. from the North Carolina Central University School of Law. He is a board-certified toxicologist and past-president of the American Board of Toxicology. Dr. Lamb has served on two NAS Committees: the Committee on Risk Characterization and the Committee on Hormone-Related Toxicants in the Environment. He has published over a hundred scientific papers on risk assessment, endocrine disruption and reproductive and developmental toxicology.

**John Routt Reigart, II, M.D.**

Dr. Reigart is a Professor of Pediatrics, Director of General Pediatrics, and Director of Emergency Pediatrics at the Medical University of South Carolina. He also is the Chairman of the U.S. Environmental Protection Agency's Children's Health Protection Advisory Committee, and Chairman of the Board of Directors of the Children's Environmental Health Network. An expert on lead poisoning of children, Dr. Reigart has advised the Centers for Disease Control, President Bush's Council for Environmental Quality, and The Pew Charitable Trusts, among others. He has numerous peer-reviewed publications and is a peer reviewer for the *Journal of Pediatrics*, the *New England Journal of Medicine*, *Pediatrics*, and several other professional journals.

**Lynn R. Goldman, M.D.**

Lynn Goldman, a pediatrician and an epidemiologist, is a Visiting Scholar at the Johns Hopkins University School of Hygiene and Public Health. In 1993, Dr. Goldman was appointed by the President and confirmed by the Senate to serve as Assistant Administrator for the EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS). In that position, she was responsible for the nation's pesticide, toxic substances and pollution prevention laws. Under her watch, EPA expanded right-to-know under the Toxics Release Inventory and overhauled the nation's pesticides laws. Dr. Goldman made significant progress on the issues of testing of high volume industrial chemicals and identification of chemicals that disrupt endocrine systems. At EPA she was successful in promoting children's health issues and furthering the international agenda for global chemical safety.

Prior to joining the EPA, Dr. Goldman served in several positions at the California Department of Health Services, most recently as head of the Division of Environmental and Occupational Disease Control. She has conducted public health investigations on pesticides, childhood lead poisoning and other environmental hazards. She received a B.S. in Conservation of Natural Resources from the University of California, Berkeley, a Masters of Public Health from the Johns Hopkins University School of Public Health, and an M.D. from the University of California, San Francisco. She completed a pediatric residency at Children's Hospital, Oakland and a preventive medicine residency at the University of California, Berkeley and is board certified in pediatrics.

**John A. Moore, D.V.M.**

John A. (Jack) Moore has had a career that represents a unique blend of experience as a research scientist, manager, regulator, and senior government policy.

He was President and Chief Executive Officer of the Institute for Evaluating Health Risks (IEHR) from 1989-2000. IEHR served government, industry and the public on issues that address the health risk of chemicals. He led the IEHR effort that developed an evaluative process for assessing reproductive and developmental toxicants. The process received favorable national and international recognition and is currently used by the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction.

Upon U.S. Senate confirmation, Dr. Moore was Assistant Administrator of the Office of Pesticides and Toxic Substances at the U.S. Environmental Protection Agency from 1983-1989. He also acted for one year as Deputy Administrator. He is credited with restoring scientific and management credibility to the pesticides program, developing a sound approach to managing the risk of asbestos in our nations' buildings, defining EPA's policies in the developing area of biotechnology and the development of scientific policy for the Agency's use of risk assessment.

Dr. Moore spent fourteen years (1969-1983) at the National Institute for Environmental Health Sciences, NIH. There he rose through positions of increasing responsibility to finally serve in the dual positions of Director, Toxicology Research and Testing, and Deputy Director of the National Toxicology Program (NTP).

He received a Doctor of Veterinary Medicine degree from Michigan State University in 1963; he is also a Certified Diplomate of the American Board of Toxicology. Among his many honors and achievements is recognition by his alma mater as a Distinguished Alumnus and having received the highest federal award of Distinguished Executive in 1986.

Currently, Dr. Moore serves as Principal Investigator of the NTP Center for Evaluating Risks to Human Reproduction, selectively consults on toxicology and policy issues, and continues his fifteen year effort in the US and through the OECD to establish an international toxicology data base for high production volume chemicals.

CRS-206

**Deborah C. Rice, Ph.D.**

Dr. Deborah Rice is currently a risk assessor in the area of neurotoxicology with the National Center for Environmental Assessment at the Environmental Protection Agency. She received the Ph.D. in toxicology from the University of Rochester. Dr. Rice previously was a research scientist in the Toxicology Research Division of Health Canada, where she headed a behavioral toxicology laboratory utilizing a large colony of macaque monkeys. Dr. Rice's research program focused on characterizing nervous system impairment produced by developmental exposure to the major environmental pollutants lead, methylmercury, and PCBs. Robust behavioral impairment was observed as a result of ongoing exposure to lead at blood lead concentrations as low as 10 $\mu$g/dl. Dr. Rice identified impairment in visual, auditory, and somatosensory function as a result of developmental methylmercury exposure; delayed neurotoxicity as a result of early exposure was also documented, as well as an age-exposure interaction in functional decrement in aging monkeys. Dr. Rice identified behavioral deficits in monkeys exposed postnatally to an environmentally-relevant congener mixture of PCBs, and who had blood PCB concentrations typical of environmentally-exposed humans.

Dr. Rice is currently an Associate Editor for the journals *Neurotoxicology*, *Neurotoxicology and Teratology*, and *Environmental Research*. Dr. Rice has authored or co-authored over 100 research articles and book chapters in the areas of neurotoxic effects of specific agents, methodological approaches for neurotoxicology research, and risk assessment.

CRS-207

**Michael D. Shelby, Ph.D.**

Dr. Shelby was named Chief, Laboratory of Toxicology, Environmental Toxicology Program, National Institute of Environmental Health Sciences (NIEHS) in April, 1996. He has been at NIEHS since 1977, serving first in the office of the Associate Director for Genetics, then as head of the Mammalian Mutagenesis Section and later as head of the Reproductive Toxicology Group. Prior to joining NIEHS, he was a research associate at the Biology Division, Oak Ridge National Laboratory. He received his B.S. in biology from Central State College, Edmond, Oklahoma and his Ph.D. from the University of Tennessee, Knoxville. His graduate training was in radiation mutagenesis and DNA repair. Until 1996 his primary responsibilities at NIEHS centered on in vivo chemical mutagenesis studies that covered both somatic cell effects and their utility as short term tests for chemical carcinogens, and germ cell mutagenicity studies and their application to genetic risk estimation.

The Laboratory of Toxicology that he now heads includes research groups that address a broad range of disciplines representing reproductive toxicology, immunotoxicology, neurotoxicology, mammalian mutagenesis, respiratory toxicology, and endocrinology. He served on the EPA Endocrine Disruptor Screening and Testing Advisory Committee and as a member of their Screening and Testing Work Group. He is a Managing Editor of Mutation Research and has served as President of the Environmental Mutagen Society, the Genotoxicity and Environmental Mutagen Society, and the NIEHS Assembly of Scientists.

He established and serves as the NIEHS Project Officer for the NTP Center for the Evaluation of Risks to Human Reproduction.

**Donald R. Mattison, M.D., M.Sc.**

Dr. Donald Mattison was named medical director of the March of Dimes in January 1999. He oversees the medical, public health and scientific basis for the foundation's programs.

Previously, he was dean of the Graduate School of Public Health at the University of Pittsburgh, where he also was professor of Environmental and Occupational Health. In addition, he was professor of Obstetrics, Gynecology and Reproductive Services in the University's School of Medicine.

Dr. Mattison has held numerous academic, clinical and research appointments, including professor of Interdisciplinary Toxicology in the Department of Pharmacology and professor of Obstetrics and Gynecology at the University of Arkansas for Medical Sciences; and chief of the Section on Reproductive Toxicology, Pregnancy Research Branch, at National Institute of Child Health and Human Development. He was a member of the U.S. Public Health Service, where he attained the rank of commander and later served in the reserves.

He currently serves on various national committees related to environmental health, public health and disease prevention, including the Children's Environmental Health Advisory Committee of the U.S. Environmental Protection Agency; Chair of the Board on Health Promotion and Disease Prevention of the Institute of Medicine; and Vice-Chair of the Board on Environmental Studies and Toxicology, of the National Research Council. He also serves on the Science Advisory Board for the National Toxicology Program, National Institute of Environmental Health Sciences and the Science Advisory Board of the National Center for Environmental Health of the Centers for Disease Control and Prevention.

In 1997, he was elected a fellow of the American Association for the Advancement of Science and, in 1999, a fellow of the New York Academy of Medicine. He is the author of numerous scientific journal articles, and co-edited the seminal contribution on *Male Mediated Developmental Toxicology*.

Dr. Mattison earned a BA from Augsburg College in Minnesota, an MS from the Massachusetts Institute of Technology, and an MD from the College of Physicians and Surgeons, Columbia University. He is a diplomate of the American Board of Toxicology and a fellow of the Academy of Toxicological Sciences.

**Carole A. Kimmel, Ph.D.**

Dr. Kimmel is a Senior Scientist in the National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Dr. Kimmel earned her Ph.D. in anatomy and teratology from the University of Cincinnati, and did a postdoctoral fellowship in toxicology at the University of Cincinnati. Dr. Kimmel's research career at Harvard Medical School, the National Institute for Environmental Health Sciences, the National Center for Toxicological Research/FDA, and the EPA has focused on the causes and mechanisms of developmental toxicity, including prenatally-induced birth defects, mortality and growth retardation, as well as longer-term functional (e.g., neurological, cardiovascular) alterations. Dr. Kimmel has led the EPA's efforts in the development of risk assessment guidelines for noncancer health effects, including improved methods for quantitative risk assessment for developmental toxicity. She also has served on the National Research Council's Committee on Toxicology and currently chairs the Reproductive and Developmental Toxicology Subcommittee. She is Past President of both the Teratology Society and the Neurobehavioral Teratology Society, past Councilor of the Society of Toxicology (SOT), and Past-President of the National Capital Area Regional Chapter of SOT. Internationally, Dr. Kimmel has worked with the International Programme on Chemical Safety/WHO and the Organization for Economic Cooperation and Development in their joint project to harmonize risk assessment for reproductive and developmental toxicity. Dr. Kimmel has over 125 publications, including three books and several symposium proceedings. Dr. Kimmel has won numerous awards, including the EPA's Science Achievement Award in Health Sciences twice for her work in developmental toxicity risk assessment and quantitative risk assessment, the FDA Commissioner's Special Citation for her work on pregnancy labeling of drugs, and the Society of Toxicology's Arnold J. Lehman Award for her contributions in risk assessment. Most recently, Dr. Kimmel chaired the Toxicology Working Group of the EPA's 10X Task Force which developed recommendations for toxicology data requirements related to protecting children's health from pesticide exposures. She currently chairs the EPA's Technical Panel to re-examine the Reference Dose (RfD) process, and serves as co-chair of the Developmental Disorders Working Group for the Presidential Task Force on Environmental Health Risks and Safety Risks to Children.

**Jonathan Samet, M.D., M.S.**

Dr. Samet is Professor and Chairman of the Department of Epidemiology of the Johns Hopkins University School of Hygiene and Public Health. Dr. Samet received a Bachelor's degree in chemistry and physics from Harvard College, an M.D. degree from the University of Rochester School of Medicine and Dentistry, and a Master of Science in epidemiology from the Harvard School of Public Health. He is trained as a clinician in the specialty of internal medicine and in the subspecialty of pulmonary diseases. From 1978 through 1994, he was a member of the Department of Medicine at the University of New Mexico School of Medicine where most recently he was Professor and Chief of the Pulmonary and Critical Care Division in the Department of Medicine. At the Johns Hopkins University School of Hygiene and Public Health, he is Co-Director of the Risk Sciences and Public Policy Institute. His research has addressed the effects of inhaled pollutants in the general environment and in the workplace. He has written widely on the health effects of active and passive smoking and served as Consultant Editor and Senior Editor for Reports of the Surgeon General on Smoking and Health. He has served on the Science Advisory Board for the U.S. Environmental Protection Agency and was Chairman of the Biological Effects of Ionizing Radiation Committee VI of the National Research Council. He is presently Chairman of the National Research Council's Committee on Research Priorities for Airborne Particulate matter. He was elected to the Institute of Medicine of the National Academy of Sciences in 1997.

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**Andrew F. Olshan, Ph.D.**

Dr. Olshan is Associate Professor in the Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill. He received his Ph.D. in epidemiology from the University of Washington. He was a postdoctoral fellow in medical genetics at the University of British Columbia from 1987 to 1989 and Assistant Professor in the Department of Clinical Epidemiology and Preventive Medicine, University of Pittsburgh from 1989 to 1991. His major research areas include parental occupational and environmental exposures and the risks of birth defects and cancer in children. He is also involved in the investigation of the interaction of inherited susceptibility factors, environmental exposures and the risk of disease. He has conducted several large national studies of risk factors for childhood cancer. In addition, he has an active research program in the molecular epidemiology of adult head and neck cancer.

**Christopher J. Portier, Ph.D.**

Dr. Portier is Chief of the Laboratory of Computational Biology and Risk Analysis, and Associate Director of the National Toxicology Program at the National Institute for Environmental Health Sciences. He had a doctorate in biostatistics granted by the University of North Carolina at Chapel Hill. His research interests include cancer models, risk assessment, toxicokinetics, and survival analysis. He is author of over 100 peer-reviewed publications. He is a frequent guest researcher at the German Cancer Research Center and the Scientific Coordinator for courses in quantitative risk assessment offered by the International Agency for Research on Cancer. He serves on numerous international and national committees dealing with risk assessment issues. He also is a permanent member of the U.S. EPA Science Advisory Panel (established under the Federal Insecticide, Fungicide, and Rodenticide Act).

CRS-213

**John Bailar, M.D., Ph.D.**

Dr. Bailar is a retired commissioned officer of the U.S. Public Health Service. He worked at the National Cancer Institute in Bethesda for 22 years, and since then he has held academic appointments at Harvard, McGill University, and now at the University of Chicago, where he is a Professor and Chair of the Department of Health Studies. For 6 years, Dr. Bailar was Editor-in-Chief of *The Journal of the National Cancer Institute*. For 11 years he was the statistical consultant for *The New England Journal of Medicine*, and more recently he has been a member of the Editorial Board of that journal. He has an M.D. degree from Yale University and a Ph.D. in statistics from American University. Dr. Bailar was a MacArthur Fellow from 1990 to 1995, and he has been elected to both the Institute of Medicine and the International Statistical Institute. He has published about 250 scientific papers of various kinds, as well as several books. His 40-plus year career has been devoted to the interpretation of statistical evidence in medicine, with special emphasis on cancer.

**Bernard A. Schwetz, D.V.M., Ph.D.**

Dr. Schwetz is the Acting Deputy Commissioner of the Food and Drug Administration (FDA) and the Senior Advisor for Science for the agency. He was Director of FDA's National Center for Toxicological Research in Jefferson, Arkansas, from 1993 to 1999. A diplomate of the American Board of Toxicology, Dr. Schwetz was acting Director of the Environmental Toxicology Program at the National Institutes of Health's National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, NC, before coming to the FDA in 1993. He was also Associate Director of the National Toxicology program there. He had been Chief of the Institute's Systems Toxicity Branch since 1982. Dr. Schwetz currently serves as Adjunct Professor, Department of Pharmacology and Toxicology/Division of Interdisciplinary Toxicology, at the University of Arkansas for Medical Sciences. He was editor, *Fundamental and Applied Toxicology* from 1986-1992, and serves on the Editorial Advisory Board, *Environmental Health Perspectives* and *Critical Reviews in Toxicology*. Dr. Schwetz is an invited member of the Commonwealth of Canada Health Protection Branch Science Advisory Board, an elected member of the National Academy of Sciences Institute of Medicine, a member of the Society of Toxicology (SOT) and the National Capitol Area Chapter, SOT; the American Veterinary Medical Association; National Society of Phi Zeta, Honor Society of Veterinary Medicine; Teratology Society; Behavioral Teratology Society; and the Reproductive Toxicology Specialty Section of the SOT. He is past president of the Reproductive Toxicology Specialty Section of the SOT and of the North Carolina Chapter and the South Central Chapters of the SOT. In addition to numerous other professional awards during his career, Dr. Schwetz received the U.S. Government's 1998 Meritorious Executive Presidential Rank Award.

**Philip J. Landrigan, M.D., M.Sc.**

Dr. Landrigan is the Ethel H. Wise Professor and Chair of the Department of Community and Preventive Medicine and Director of Environmental and Occupational Medicine at the Mount Sinai School of Medicine in New York City. He also holds a Professorship in Pediatrics at Mount Sinai. He directs the Mount Sinai Center for Children's Health and the Environment. Dr. Landrigan is a member of the Institute of Medicine of the National Academy of Sciences. He is Editor-in-Chief of the *American Journal of Industrial Medicine* and previously was Editor of *Environmental Research.* He has chaired committees at the National Academy of Sciences on Environmental Neurotoxicology and on Pesticides in the Diets of Infants and Children. He is Chair of the Asbestos Advisory Board of the State of New York. In New York City, he served on the Mayor's Advisory Committee to Prevent Childhood Lead Paint Poisoning and on the Childhood Immunization Advisory Committee of the New York City Department of Health. He is Chair of the New York State Advisory Council on Lead Poisoning Prevention. From 1995 to 1997 Dr. Landrigan served on the Presidential Advisory Committee on Gulf War Veterans' Illnesses. In 1997 and 1998, Dr. Landrigan served as Senior Advisor on Children's Health to the Administrator of the U.S. Environment Protection Agency. He was responsible at EPA for establishing a new Office of Children's Health Protection.

**Kenneth W. Chilton, Ph.D.**

Kenneth W. Chilton is Distinguished Senior Fellow and Manager of Environmental Research at the Center for the Study of American Business at Washington University in St. Louis, Missouri. He has been with the Center since 1977, serving as director from 1995-1998.

Dr. Chilton has published numerous reports and spoken to a variety of audiences about environmental issues. His recent studies include: "Are Economic Growth and a Sustainable Environment Compatible? Enhancing Environmental Protection While Fostering Economic Growth;" "Questioning the Emphasis on Environmental Contaminants as a Significant Threat to Children's Health;" "EPA's Case for New Ozone and Particulate Standards;" "Who Is 'Responsible' for Garbage?" and "Clean Water's Muddied Future." He is co-editor of *Environmental Protection: Regulating for Results* (Westview Press, 1991).

Dr. Chilton received his B.S. and M.S. in management science from Northwestern University (1967, 1968). He received his M.S., B.A., and Ph.D. in business administration from Washington University (1992, 1994). He and his wife, Linda, have been married for 34 years and have two children, Jennifer Chilton-Kallery, and Thomas, and a grandson, Karl and granddaughter, Maggie.

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**Rabbi Daniel Swartz**

Rabbi Daniel Swartz currently serves as the Executive Director of the Children's Environmental Health Network (CEHN), a national organization devoted to protecting children from environmental health hazards through education, policy and research initiatives. The Network, through active collaboration with groups such as the American Academy of Pediatrics and the American Public Health Association, has played key roles in establishing national policy and research agendas for the protections of children's health and in the establishment of EPA's Office of Children's Health Protection.

He is also the author of numerous nationally-published op-eds and guest editorials on children's health and other environmental issues, and he speaks widely on these subjects. He has published both peer-reviewed and popular science articles on issues ranging from plant ecology to global climate change. He has also published both popular and scholarly studies of religious traditions and environmental values, including *To Till and To Tend: A Guide for Jewish Environmental Study and Action*, and "Jews, Jewish Texts, and Nature: A Brief History," in *This Sacred Earth: Religion, Nature, Environment*, edited by Roger Gottlieb.

Before becoming the director of CEHN, Swartz served as the Associate Director of the National Religious Partnership for the Environment (NRPE), coordinating policy among the Coalition on the Environment and Jewish Life, the Evangelical Environmental Network, the National Council of Churches, and the United States Catholic Conference. In addition to ordination and his MHL, Rabbi Swartz holds degrees from Brown University in Geological Sciences and in Environmental Science. He has received numerous academic honors, including prizes in Scholarship and Scholastic Excellence from the Hebrew Union College-Jewish Institute of Religion, the Senior Prize in Environmental Studies from Brown, and election to both Phi Beta Kappa and Sigma Xi. The most important thing in his life is his marriage to Roya Fahmy Swartz.

**Kimberly M. Thompson, Sc.D.**

Dr. Kimberly M. Thompson is Assistant Professor of Risk Analysis and Decision Science at Harvard University in the School of Public Health. Her research interests and teaching focus on the issue related to developing and applying quantitative methods for risk assessment and risk management, and consideration of the public policy implications associated with including uncertainty and variability in risk characterization. Drawing on a diverse background, she seeks to effectively integrate technological, social, political, legal, and economic issues into risk analyses that inform public policy and improve decision making. She recently initiated a long-term effort to use an analytical approach to address risks to children (http://www.kidsrisk.harvard.edu). This effort will broadly apply comparative risk analysis tools to highlight the value of informed decisions, and it will ultimately lead to the development of appropriate risk models for children. This work builds on Professor Thompson's long-standing interest in the issues related to variability in risk for sensitive sub-populations (notably children) and the potential risk tradeoffs associated with policies designed to protect them. Professor Thompson holds a Doctor of Science degree from Harvard and Bachelor and Master of Science degrees from the Massachusetts Institute of Technology.

**Richard J. Jackson, M.D., M.P.H.**

One of seven children, Richard Jackson was born and raised in Newark, New Jersey. Two years of contemplation and study in a Jesuit seminary led to his desire to subject ideas to the objective lens of science and to an abiding appreciation for the beauty and fragility of the physical world. Dr. Jackson received his baccalaureate degree in biology from St. Peter's College in Jersey City; a Master of Medical Sciences degree from Rutgers Medical School in New Brunswick; his M.D. from the University of California, San Francisco; and his M.P.H. in epidemiology from the University of California at Berkeley.

As a pediatrician and an advocate for children and the environment, Dr. Jackson has pressed for a strong public health presence in all decisions involving the environment. His work at the California Department of Health Services, particularly in protecting children as well as adults from unhealthy exposures to pesticides, solidified his conviction that public health must "be at the table" when decisions are made about the environment. Further, he argues for an expanded intellectual base that would contain substantial information about children's environmental health and safety issues.

Dr. Jackson is a founding board member of the Alliance to End Childhood Lead Poisoning and the Children's Environmental Health Network. In 1994, he began his tenure as Director of CDC's National Center for Environmental Health. He has worked to make certain that public health concerns figure prominently in decisions made by other federal agencies and national and international policymakers. He serves on the Environmental Health Policy Committee of the Department of Health and Human Services , advises the Department of Defense on epidemiologic issues, and serves on two U.S.-Russia health-policy committees concerned with radiation and overall environmental health.

In addition, Dr. Jackson serves on the editorial boards of two peer-reviewed medical journals and has published more than 30 refereed papers and several book chapters. He has testified before United States Congressional committees on a variety of issues, including pesticides in the diets of infants and children, Gulf War Syndrome, and environmental hazards to children; and he has lectured on environmental health issues at universities, institutes, and conferences throughout the world. He and his wife, Joan Guilford, continue learning frontline pediatrics from their three teenage sons.

**Trudy Ann Cameron, Ph.D.**

Trudy Ann Cameron (Ph.D. Economics, 1982, Princeton University) is Professor of Economics at UCLA and was also a founding faculty member of the Department of Policy Studies in the School of Public Policy and Social Research at UCLA. Her main research interests center around the econometrics of valuation for non-market goods, and focus primarily on quantifying the benefits associated with environmental goods. She is a past vice-president of the Association of Environmental and Resource Economists, and a past associate editor of the organization's *Journal of Environmental Economics and Management*. She has also served as an associate editor for the *American Journal of Agricultural Economics*, which also carries a significant number of papers in environmental and resource economics. In addition to her service on the Economics and Assessment Work Group of the Children's Health Protection Advisory Committee, Dr. Cameron is concluding her third term on the Environmental Economics Advisory Committee of the EPA's Science Advisory Board, and has just begun to serve on the EPA's Advisory Council for Clear Air Compliance Analysis. She teaches environment and resource economics, as well as quantitative methods courses, at both the graduate and undergraduate levels, in addition to regular sections of microeconomics principles. She is married to Gregory M. Williams, Professor of Chemistry at the California State University at Fullerton. They have two daughters, aged ten and three.

**James D. Wilson, Ph.D.**

James D. Wilson is Senior Fellow and leader of the risk analysis program in the Center for Risk Management at Resources for the Future (RFF). An organic chemist by training, he spent twenty-nine years with the Monsanto Company, in research, research management and then health and environmental policy. His research has focused on structure-activity relationships, including environmental chemistry broadly, "dioxin" and related chemicals, relation of chemical structure to physical and physiological properties, the use of science in decision making, and the influence of organizational structure on decision making. His current research at RFF concerns the development and use of standardized risk assessment practices, particularly default options. His tenure at Monsanto included managing the interface between one business unit and product regulatory agencies. He was President of the Society for Risk Analysis in 1993 and was named a Fellow of the Society in that year. He was born and raised in The Dalles, OR, and holds an A.B. from Harvard and a Ph.D. (organic chemistry) from the University of Washington.

**Karen L. Florini**

Karen Florini is a Senior Attorney with the Environmental Health Program in Washington, D.C. office of Environmental Defense (formerly Environmental Defense Fund), where she specializes in environmental information issues, toxic chemicals, and related topics. Founded in 1967, Environmental Defense is a leading national nonprofit environmental advocacy group with more than 300,000 members and offices in seven locations around the United States.

Ms. Florini is frequently invited to testify before Congress and asked to provide technical and policy information to congressional staff. She also conducts litigation, participates in the federal regulatory process, and prepares public education materials. She is a member of the project team for Environmental Defense's widely praised "Scorecard" Internet public information service (www.scorecard.org), which provides information on a variety of environmental issues including toxic chemicals and hazardous air pollutants.

Prior to joining Environmental Defense in 1987, Ms. Florini served for three years as an attorney in the U.S. Department of Justice's Land and Natural Resources Division. After graduating from Harvard Law School in 1983, Ms. Florini clerked for Judge John Fullam of the U.S. District Court in Philadelphia. During law school, she was Editor-in-Chief of the Harvard Environmental Law Review. She received her undergraduate degree with High Honors from Oberlin College in 1979, with a double major in biology and environmental policy.

**Sandra L. Tirey**

Sandra L. Tirey, M.S., is co-leader of the American Chemistry Council's Public Health Team and Assistant Vice President for Regulatory & Technical Affairs. tHE American Chemistry Council (ACC, formerly the Chemical Manufacturers' Association) represents companies engaged in the business of chemistry. The Public Health Team seeks to integrate science and advocacy to promote a public understanding and scientific debate of public health issues affecting the chemical industry, particularly issues related to allegations of chemical effects on the endocrine system and children's health.

Ms. Tirey holds an M.S. in Environmental Sciences from the School of Public Health of the University of Texas Health Science Center at Houston and a B.A. from Rice University. Prior to joining CMA in 1987, Ms. Tirey served as research coordinator for Consultants in Epidemiology and Occupational Health Inc., and before that she was on the industrial hygiene staff for Tenneco, Inc., and served as an industrial hygiene intern at Shell Oil Company's Deer Park Facility.

**Jim O'Hara, M.A.**

Jim O'Hara is Executive Director of Health-Track, a project supported by The Pew Charitable Trusts through a grant to Georgetown University, working to build support for a comprehensive national approach to tracking and monitoring the links between the environment and health, with the ultimate goal of preventing chronic disease.

Mr. O'Hara was formerly Deputy Assistant Secretary for Health at the U.S. Department of Health and Human Services. In that position, he was responsible for the formulation of federal public health policy in a number of areas, such as tobacco control and food safety, and was a senior advisor to the Assistant Secretary for Health/Surgeon General, Dr. David Satcher, and the Secretary, Dr. Donna E. Shalala. Prior to that Mr. O'Hara was associate commissioner for public affairs at the Food and Drug Administration (FDA). At FDA, he was responsible for developing and implementing the strategic communications plans for initiatives such as blood safety, tobacco control, food safety and food labeling; in addition, he was a contributor to the Administration's article in *The Journal of the American Medical Association* on the improvement of drug approval times in the United States.

A veteran reporter with more than 17 years of experience, Mr. O'Hara was a Knight Fellow at Stanford University. He received his MA from the University of Chicago.

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