NEW APPROACHES FOR ASSESSING THE ETIOLOGY AND RISKS OF DEVELOPMENTAL ABNORMALITIES FROM CHEMICAL EXPOSURE

LYNN R. GOLDMAN
Assistant Administrator, Office of Prevention, Pesticides, and Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C.

Abstract — Developmental toxicants, insidious in modes of action and effects, strike the very origin of our lives: the developing embryo, fetus, neonate, and child; they cause spontaneous abortions, stillbirths, malformations, early postnatal mortality, reduced birth weight, mental retardation, sensory loss as well as other functional or physical changes, including subclinical effects having far reaching social and economic impacts. The large majority of developmental defects have unknown etiologies. With this uncertainty, EPA and the scientific community worldwide give high priority to finding new approaches for assessing etiology and risks of developmental effects. The United Nations Conference on Environment and Development (UNCED) and Agenda 21 mobilized the international community to focus on risks posed by chemicals in the environment, including developmental risks. The international harmonization of test and risk assessment guidelines for developmental effects are priorities. Lead, persistent organic pollutants (POPs), endocrine disruptors, and the improvement of quantitative risk assessment methodologies, particularly for children, are priorities. EPA reinvented its research agenda to assure wide involvement of the National Science Foundation, other federal agencies, and national experts in research to address the U.S.'s public health and environmental priorities. © 1997 Elsevier Science Inc.

Key Words: developmental abnormalities; chemical exposure.

INTRODUCTION

It is appropriate that we meet this December to examine new approaches for assessing the etiology and risk of developmental effects from chemical exposure. Twenty-five years ago this month, a Republican President and Democratic majority in the Congress founded the Environmental Protection Agency (EPA). Over the past quarter century we have accomplished much to protect the public health and the environment, thanks to dedicated people, strong environmental laws, and an evolving science base for sound decision making. Together, we have made strong progress. For example:

- Today we use safer chemicals than we did in 1970, and in safer ways. The most highly toxic and persistent pesticides threatening human health, nontarget species, and ecosystems have been either banned or severely restricted (1). Pollution Prevention, including source reduction, is now a core strategy for the EPA and for producers and users of pesticides and other chemicals (2).

- The air is cleaner. Severe smog episodes of the 70s are largely a relic. Since 1984, emissions of the toxic metal lead have decreased 75% and concentrations in urban areas decreased 86% (3). Between 1976 and 1991, average blood lead levels in children have decreased from 0.62 to 0.14 μmol/L (4). Toxic emissions from the chemical industry have been cut 49% and from all industries cut 43% since 1988 (5). Fifty million more Americans in 55 cities are breathing cleaner air today than in 1990—air that meets public health standards (6).

- Rivers, streams, and lakes are cleaner than they were in 1970. The National Pollutant Discharge Elimination System permits have been effective in reducing point discharges of pollutants into the nation's waters (7). The municipal wastewater treatment standard has been met across the U.S. by most municipalities (8). Voluntary partnerships between EPA and the states are reducing pesticides in groundwater (9).

- The rate of Superfund site cleanups has increased with more cleanups in the past 3 years than in the previous 12 (10). Brownfields redevelopments are successfully reclaiming once polluted hazardous waste sites for safe, productive uses for business and municipalities (11).

- Waste disposal is handled more responsibly than in 1970. We now have safeguards to ensure that solid waste and toxic wastes are handled in ways that reduce risks to health and the environment and avoid costly waste cleanups. At home, school, and work, the principles of pollution prevention—reduce, reuse, or recycle—have taken hold firmly in less than a decade.

The Clinton Administration is committed to the...
principle of sustainable development, to assure that the legacy of a clean and supportive environment passes from generation to generation. Sustainable development means that we meet the needs of the present without compromising the ability of future generations to meet their own needs (12). To carry out this obligation to ourselves and future generations, we must continue the progress we have made in developing our science base, especially in developmental toxicology.

**DEVELOPMENTAL TOXICANTS: NEED FOR NEW APPROACHES?**

Over the past day and a half of the symposium, we have been privileged to hear many excellent presentations highlighting the importance of improving methods to identify and assess health and environmental risks associated with developmental toxicants. Insidious in modes of action and effects, developmental toxicants strike at the very origin of our lives: the developing embryo, fetus, neonate, and child. Many developmental abnormalities are of concern: spontaneous abortions, stillbirths, malformations, early postnatal mortality, reduced birth weight, mental retardation, sensory loss plus other adverse functional, or physical changes. These abnormalities and their possible associations with chemicals in the environment must be investigated to assure that we are not poisoning ourselves, other species, and the planet.

Several environmental agents are known developmental toxicants for humans (e.g., lead, polychlorinated biphenyls or PCBs, methyl mercury, ionizing radiation, glycol ethers, ethanol); many other agents, based on animal studies, are suspected human developmental toxicants (e.g., pesticides such as DDT, vinclozolin, and dinoseb) (13). This is cause for concern.

Consider, for example, the emotional, intellectual, and financial costs associated with one child poisoned by lead in the home, a child whose promise for the future is delimited from the start because of totally avoidable toxicity to the developing brain. The societal and economic costs of children with birth defects and developmental disabilities are very high and are borne by all. Close to one-half of the children in hospital wards are there because of congenital malformations (14). Approximately 3% of newborn children have one or more significant congenital malformations at birth, and by the end of the first postnatal year, about 3% more are recognized to have serious developmental defects (15). Many more have subclinical effects that cannot be observed for the individual child but, as with lead poisoning, have extensive social and economic impacts (16). With the current state of science, while some of these diseases are attributable to environmental, genetic, and other factors, the causes of most of these diseases are unknown (17). We need to identify the preventable causes, to protect future generations. Given these uncertainties, the EPA gives high priority to the importance of finding new approaches for assessing etiology and risks of developmental effects. Simultaneously, where risks have been identified, we are moving forward to reduce those risks.

**INTERNATIONAL COOPERATION TO REDUCE TOXIC RISKS FROM CHEMICALS**

*International agenda for chemical safety*

The U.S. EPA is not acting in a vacuum. World trade in chemicals and products continues to expand; an estimated 100,000 chemical substances are currently in international commerce (18) and 70,000 in the U.S. (19). Like the U.S., the international community recognizes that substantial use of chemicals is essential to meet social and economic goals worldwide. The international community also recognizes the great need to strengthen countries’ capabilities for assessing and managing risks from chemical exposure, including developmental and reproductive risks.

In 1992 in Rio, the United Nations Conference on Environment and Development (UNCED) brought together most nations of the world to agree upon an agenda for environmental protection and sustainable development for the next decade. In *Agenda 21*, UNCED reports:

Gross chemical contamination, with grave damage to human health, genetic structures and reproductive outcomes, and the environment, has in recent times been continuing within some of the world’s most important industrial areas. Restoration will require major investment and development of new techniques (20).

Chapter 19 of *Agenda 21* set several goals to achieve sound management of chemicals worldwide and identified means of achievement:

Major research efforts should be launched to improve methods for assessment of chemicals, [to] work toward a common framework for risk assessment and to improve procedures for using toxicological and epidemiological data to predict the effects of chemicals on human health and the environment, so as to enable decision makers to adopt adequate policies and measures to reduce risks posed by chemicals (21).

In 1994, the countries came together again to establish the Intergovernmental Forum on Chemical Safety (IFCS). The IFCS is coordinating efforts by all UN nations to meet the ambitious chemical safety targets in *Agenda 21* (22). *Agenda 21* also called for the collaboration on chemical safety between international organizations to cooperate on environmentally sound management of toxic chemicals (23). This was accomplished in 1995, with formation of a coordinating mechanism called the InterOrganisation for Sound Management of Chemicals (IOMC) (24).

The EPA’s goals align with the international goals;
the Agency actively supports the international community in meeting its ambitious plans. Specific areas of work include expanding and accelerating international assessment of chemical risks, harmonization of classification and labeling of chemicals. Information exchange on toxic chemicals and chemical risks, and establishment of risk reduction programs.

International harmonization of guidelines for assessing developmental toxicity

One area of international cooperation that particularly relates to the mission of EPA and the assessment of etiology and risks of developmental toxicants is the harmonization of chemical toxicity testing guidelines. The Organization for Economic Cooperation and Development (OECD) carries out many environmental activities for member countries, including serving as focus for internationally coordinated chemical testing. Overall, the OECD goals are to make chemical testing more systematic, relevant, and cost effective; allow for increased exchange and acceptance of test data between countries; and promote a consistent basis for legislation and regulatory activity for member countries and nonmember countries that choose to adopt the guidelines (25).

The EPA has recently published proposed new test guidelines for developmental and reproductive toxicity, and these revisions are influencing development of harmonized international test guidelines. The EPA proposed test guidelines are titled Health Effects Test Guidelines: Prenatal Developmental Toxicity Study and Reproduction and Fertility Effects (26). The developmental and reproducitivity guidelines were developed in part as a response to recommendations made by the National Research Council’s report, Pesticides in the Diets of Infants and Children (27). The NRC concluded that the EPA’s testing procedures were inadequate for assessing many developmental endpoints of concern for children’s risks.

These expanded testing guidelines assay several developmental and reproductive endpoints more thoroughly than earlier guidelines. For example, the new prenatal developmental toxicity guideline calls for late gestation dosing to detect more completely endocrine and neurologic developmental effects. It increases numbers of rabbit fetuses and requires additional evaluations of brain development, sexual development, and immunologic development to enhance sensitivity for capturing developmental effects from prenatal exposure. It requires evaluation of fetal cartilage development. The new 2-generation reproductive toxicity test guideline provides new sperm measures, ovulatory cyclicity data, sexual development, and postmortem evaluations on adults and offspring to assess endocrine and other reproductive effects more completely. More sensitive assays for both male and female reproductive functions are also provided.

In December 1995, OECD decided that the EPA’s Office of Prevention, Pesticides and Toxic Substances proposed revisions to the Prenatal Developmental Toxicity and the Reproduction and Fertility Effects test guidelines should be used as the basis for future revisions to the OECD guidelines for developmental and multi-generation reproductive toxicity testing. The U.S. EPA continues to play a prominent role in the OECD-directed process of review, revision, and harmonization of international toxicity testing guidelines (28).

Risk assessment guidelines

The World Health Organization (WHO), International Program for Chemical Safety (IPCS), and OECD coordinate the international harmonization of risk assessment guidelines. For developmental and reproductive toxicity, efforts are underway in cooperation with the International Federation of Teratology Societies to harmonize terminology used to describe observations, supporting more consistent interpretation of studies. The U.S. experience in developmental toxicity risk assessment is a key factor in the harmonization effort. The EPA’s Guidelines for Developmental Toxicity Risk Assessment, published in December 1991, is the only complete risk assessment guideline for developmental toxicity available in the world today (29). In using the developmental toxicity guidance and in the 1994 National Research Council’s (NRCs) report, Science and Judgment in Risk Assessment (30), the EPA has identified data gaps that have implications for research planning and the preparation of international guidelines.

Lead

Lead is a well-known cause of reproductive and developmental risks, and the EPA has been working to address this problem. The United States’ earlier actions on lead toxicity banned the use of lead in residential paints and phased out the use of leaded gasoline. This has resulted in dramatic lowering of average blood lead levels in U.S. children, yet unacceptable lead exposure rates occur due to lead-based paint in housing stock (31). The EPA is continuing efforts to reduce childhood exposure to lead, including the development of lead hazard information, training for lead removal professionals, a lead disclosure regulation that alerts home buyers to lead hazards, and a national lead hotline (32).

The U.S. is an international leader in trying to combat exposure to lead. The United Nations Council on Sustainable Development in 1994 and the United Nations Environmental Program (UNEP) in 1995 resolved to phase out lead in gasoline (33). The OECD is considering acts to reduce risks from lead in gasoline, products
intended for children, exposures in the work place, point source emissions, and in housing and other consumer products. We are cooperating with many other countries—most notably Russia—to phase out lead in gasoline.

**Persistent organic pollutants (POPs)**

There is increasing international awareness of the global implications of long-range transport of persistent organic pollutants (POPs), especially regarding their effects on aquatic species.

POPs are lipophilic, allowing them to bioconcentrate in the fat of animals. Having a long biologic half-life in fat tissue, they persist and can achieve toxicologically relevant concentrations in animals. Moreover, because they are highly persistent and mobile, they have long-range atmospheric transport and have been found in virtually every region of the world (34).

Experimentally, POPs have been associated with significant adverse effects in a wide range of species and at nearly all trophic levels. Effects observed include immunotoxicity, dermal effects, impairment of reproductive performance, and carcinogenicity. Many POPs, such as DDT and PCBs, are potential environmental endocrine disrupters, affecting reproduction and development via receptor-mediated effects. For example, DDT is a powerful antiandrogen; some PCBs are dioxin-like and may trigger Ah receptor activity and, thus, disrupt cell growth and development (35).

POPs have posed difficult risk management problems on an international scale. For instance, the U.S. and Canada are working together to protect the Great Lakes because the sources of POPs can be from far away. The International Joint Commission has called for the virtual elimination of discharges of POPs into the Great Lakes area to allow the ecosystem to recover and to protect consumers of Great Lakes fish (36).

On a broader scale, these issues have arisen repeatedly in international forums, leading in 1995 to a decision by the UNEP Governing Council to establish an international process for assessing and managing risks from POPs (37). In May 1995, UNEP adopted Decision 18/31 agreeing to an initial list of 12 chemicals for assessment and management worldwide: aldrin/dieldrin, benzo(a)pyrene, chlordane, DDT/DDE/DDD, hexachlorobenzene, alkyl lead, mercury, mirex, octachlorostyrene, PCBs, 2,3,7,8-tetrachlorodibenzo furans, and p-dioxins, and toxaphene. International assessments under development by the IFCS were reviewed by countries in February 1996. UNEP will coordinate processes to develop international agreement to manage the risks.

In October 1995, the Decision 18/31 was strengthened when the UNEP Intergovernmental Conference for the Protection of the Marine Environment from Land-
models incorporate underlying biologic processes, pharmacokinetics, and dose–response relationships into a comprehensive model that more accurately predicts risks from animal data to humans and from high doses to low doses (46).

To develop the BBDR model for developmental toxicity risk assessment, the EPA's research program has undertaken multifaceted research initiatives by which to achieve the complex, long-term goal of the BBDR model. Some of the work that is ongoing includes dose–response modeling with investigation of the P53 (tumor suppressor) signaling cascades for abnormal development of the eye and other organ systems, the interrelationships of multiple toxic endpoints, the response–surface model for describing exposure concentration and duration (C × T) relationships, models for age-specific changes in organ size and growth rates, and investigation of stress protein induction as a biomarker for developmental effects. In addition, since the publication of the original EPA Developmental Toxicity Risk Assessment Guideline in 1986, the Agency has continued to work with Benchmark Dose Analysis (BMD) as a replacement for no observed adverse effect level (NOAEL) when sufficient data are available. A technical guidance document for applying the BMD approach is scheduled for completion and distribution this year.

These research projects are done collaboratively via grants and interagency agreements between the EPA, other federal research laboratories, and university laboratories both in the U.S. and abroad. Results are published in peer-reviewed journals. However, the litmus test for continued EPA support of the research is demonstrated advancement of the state-of-art of risk assessment and, of course, continued availability of funds.

**TRI: exposure information and local empowerment**

An important component of assessing risk is determining exposure. One very critical way EPA provides information to the public is through the Toxics Release Inventory (TRI) (47). The TRI not only has empowered communities with information about toxic chemicals in their neighborhoods, but also has informed the work force about potential exposures inside the plants and has alerted companies to opportunities for waste reduction.

The original TRI list was dominated by chemicals that were either acutely toxic to humans or carcinogenic (48). In 1994, the EPA added 286 chemicals to the TRI, nearly doubling the number of chemicals that must be reported (49). Among these new chemicals, 65 have known reproductive and/or developmental effects. (See Table 1: Developmental and Reproductive Toxicants Added to the U.S. Toxics Release Inventory in 1994.)

Many new TRI chemicals are pesticides or pharmaceutical agents (most of the chemicals are subject to a lawsuit filed by the Chemical Manufacturers Association that seeks to remove them from the list) (50). Industry's reporting on these chemicals began in 1995 with first reports available in 1997. In keeping with the EPA's new approaches to environmental protection, this reporting expands the right-to-know data base for developmental and reproductive toxic agents. Public right-to-know about chemical emissions is fundamental to achieving sound, on-the-ground management of chemicals that protects public health and the environment. TRI, therefore, is perhaps the EPA's most important tool for empowering local communities to make appropriate environmental decisions.

**Assessment of risks to children**

The NRC report Pesticides in the Diets of Infants and Children focused attention on risks to infants and children posed by pesticides (51). Profound differences exist between children and adults; infants and children are growing and developing. In October, 1995, Admini-

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<td>Sodium dicamba</td>
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strator Browner announced a new policy requiring the assessment of risk to children for all major EPA decisions (52). The policy recognizes that:

Children are not little adults. Children may be more or less sensitive than adults when confronted with an equivalent level of exposure to an environmental pollutant. In many cases, their responses are substantially different—qualitatively and/or quantitatively— including differences in pharmacokinetics, pharmacodynamics, body composition, and maturity of biochemical and physiological functions; e.g., metabolic rates and pathways.

Therefore, to consider the risks to infants and children consistently and explicitly in regulatory decision making, the policy requires development of a separate assessment of risk to infants and children or state clearly why this is not done.

This policy recognizes children's unique susceptibilities and distinct exposure patterns that must be considered in risk assessment to assure that children are protected. In the report *Pesticides in the Diets of Infants and Children*, the NRC recommended that in assessing risks to children, pesticide exposure should be the "total pesticide exposure," accounting for all sources and pathways of pesticide intakes by children. Moreover, the NRC concluded that differences in exposure between adults and children were more likely to account for differences in risk than were age-related differences in toxicity (53). Consequently, the EPA's research initiatives explore these exposure issues for children to fill data gaps and improve risk assessment's ability to protect children.

Endocrine disrupters

Chemicals such as the synthetic hormone diethylstilbestrol (DES) are known to disrupt development of the reproductive tract in females. Many environmental endocrine disrupters, including pesticides and other toxic substances, are apparently ubiquitous in the environment (54). They have the potential to disrupt male and female reproductive function and development of the reproductive system in offspring by mimicking or altering hormonal action (55). Very low prenatal exposure to dioxin, for example, can cause irreversible effects on sexual differentiation in the fetus (56).

The EPA is conducting studies to understand better how agents affect reproductive function and development. During sexual development there are several critical periods when the reproductive system is uniquely susceptible to chemically induced perturbations. Inappropriate chemical signals during these periods can result in irreversible lesions; similar exposures at other stages may produce no effects. EPA scientists are pursuing the effects of exposure to a variety of persistent environmental contaminants, including PCBs, lindane, methoxychlor, dioxin, vinclozolin, and DDT to provide more reliable and accurate information for risk assessment, studying critical developmental stages, target tissue, sensitive endpoints of altered reproductive development, critical periods of reproductive life and of reproductive cycles, and toxic mechanisms of action.

To broaden the knowledge base of what is known about endocrine disrupters and possible research needs, the EPA sponsored an expert workshop in April 1995. The charge was to identify research gaps and establish priorities for future research activities supporting risk assessment of health and environmental effects of endocrine disrupters (57). In a parallel activity, the EPA Risk Assessment Forum is preparing a report that reviews the current state of the science on endocrine disruption in humans, laboratory testing, and wildlife species (58). The report will serve as an interim assessment until a more extensive exploration of the issue can be completed by the National Academy of Sciences (NAS).

THE EPA'S RESEARCH AGENDA: SCIENCE TO ACHIEVE RESULTS (STAR)

During the past few years, several blue-ribbon independent studies and reports were published on the conduct of both EPA's and other federally supported research; for example, the Carnegie Commission's Report: *Environmental Research and Development, Strengthen the Federal Infrastructure*, and the National Research Council's study: *Research to Protect, Restore, and Manage the Environment: Interim Report of the Committee on Research and Peer Review in EPA* (59). After considering the findings of these and other studies, EPA modified its science and research programs, including the following most noteworthy changes:

- Consolidation of the laboratories in EPA's Office of Research and Development (ORD) into four national research laboratories that align with the risk assessment/risk management paradigm: 1) health and environmental effects, 2) environmental exposure, 3) risk characterization and assessment, and 4) risk management;
- Preparation of an ORD Strategic Plan;
- Inclusion of the best and brightest in the academic community in ORD research by redirection of resources within the ORD budget from contracts and noncompetitive cooperative agreements to competitively awarded grants; and
- Establishment of a graduate fellowship program to encourage graduate students to study and do research in areas related to the environment.

During the past decade, the EPA's R and D program has been funded from $400 to $500 million per year, but with a small proportion going to competitive research
grants. In the redirection of extramural research funds, the EPA’s research initiatives for the last 2 years increased funding for competitively awarded grants, provided for a partnership with the National Science Foundation (NSF) to peer review grant proposals, and cooperated with other federal agencies in funding competitive grants where there were common research interests; i.e., NSF, Department of Energy (DOE), and Office of Naval Research (NSR). The Agency plans to continue this strategy for research, recognizing that it is important to strengthen partnerships with the academic community.

CONCLUSION

This is a time of very rapid generation of knowledge about the risks of developmental and reproductive effects. As these risks are being realized, governments and the international community are responding. As we have seen, EPA has taken several steps to improve its risk assessments and incorporate developmental and reproductive concerns into a robust research and regulatory program.

Increased interest at the international level is shown by the United Nations Fourth World Conference on Women, held in Beijing in September of 1995. (61) An international consensus among women supported increased research and data collection, analysis, and sharing on all issues related to health with a strong emphasis on gender-specific susceptibility to risks from exposure to chemicals in the environment. The Conference Report emphasizes that

...women play an important role in promoting sustainable development through their concern for the quality and sustainability of life for present and future generations. Governments have expressed their commitment to creating a development paradigm that integrates environmental sustainability with gender equality and justice within and between generations as contained in chapter 24 of Agenda 21 (62).

Concern for the quality and sustainability of life for present and future generations, creation of a new economic development paradigm that integrates environmental sustainability with gender equality and justice within and between generations, and the call for research and data sharing all point to the need for a better understanding of reproductive and developmental adverse effects. Calls for better information about these effects were urgent among the conferees. This is the dawn of a time when much new knowledge and research can emerge, so that we can reduce developmental and reproductive risks.

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