

# The Current State of Knowledge About the Effects, Risks, and Science of Children's Environmental Exposures

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ABBREVIATIONS. NOAEL, no-adverse-effect level; MOA, mechanism of action; FDA, Food and Drug Administration; CPF, chlorpyrifos; PAH, polycyclic aromatic hydrocarbon; 2,4-D, 2,4-dichlorophenoxyacetic acid; IPM, integrated pest management.

In the preface<sup>1</sup> to this supplement, we pointed out that pediatricians and other clinicians have made major contributions to the discovery of environmental toxicants. Many acute illnesses that are caused by high exposures to some toxicants are clinically diagnosable or at least are commonly in the differential diagnosis, eg, organophosphate poisoning, infant botulism, acute lead encephalopathy, carbon monoxide poisoning, acrodynia, hypervitaminosis A and some cases of aplastic anemia, convulsions, asthma, respiratory distress, methemoglobinemia, Reyes syndrome, kernicterus, and many of the recognizable syndromes that result from exposures to teratogenic drugs and chemicals. In contrast to the obvious effects of high exposures to environmental toxicants, there is less information and less certainty concerning the magnitude of the contribution of many low exposures of environmental toxicants to morbidity, mortality, and subtle alterations in children as well as adults or how the effects of these exposures vary with age or chronicity of exposure.

We also informed the readership that we were going to address the issue of environmental toxicology from both a clinical and a toxicologic viewpoint. Very low exposures to environmental toxicants may lead to diseases that resemble many common illnesses that have other causes, or they may lead to decrements in functioning that are subtle or nonspecific. It is an almost insurmountable task for individual practitioners to conclude a cause-and-effect relationship from low exposures to environmental toxicants among patients in the physician's patient population. Only well-planned, sophisticated epidemiologic and animal studies can answer the questions that pertain to the toxicity of low-level exposures to environmental toxicants, given that not all

individuals will be affected equally, if at all, at any particular level of exposure.

Many of the previous multi-authored compendia that have been published by groups of scientists have been unified in their conclusions that environmental toxicants are a very serious problem and that children are uniformly more vulnerable to these toxicants. Other publications have taken the opposite viewpoint, namely, that environmental toxicants are not a major problem and that children are not uniformly more sensitive or vulnerable. In the present publication, there are 30 articles, many with multiple authors. These authors were selected because they have an interest in this subject and have expertise in this subject, not because they have expressed a particular viewpoint. In fact, there is disagreement about many of the issues discussed in this supplement. There is no uniformity of opinion regarding the magnitude of impact that environmental toxicants have on the health of adults and children. This is attributable to many reasons, including a lack of definitive information on population exposure, no-adverse-effect level (NOAEL), toxicokinetics, toxicodynamics, and mechanism of action (MOA) of many environmental toxicants, despite the profound importance of such information to the health and future functioning of our nation's children.

## RECENT PUBLICATIONS

During the past year and one half since we initiated the preparation of this supplement to *Pediatrics*, we collected >300 new publications that deal with environmental medicine and specific environmental toxicants, including 2 books and another supplement to *Pediatrics* that deals with the subject of environmental health in children.<sup>2-4</sup> We cannot review all of the articles; however, we can comment on a number that will demonstrate that the uncertainty about risks and the need for additional high-quality research has not changed in the past year and one half.

### Books

The book edited by Juberg,<sup>2</sup> entitled *Are Children More Vulnerable to Environmental Chemicals? Scientific and Regulatory Issues in Perspective*, was published by the American Council on Science and Health, an organization that is supported by donations from industry, private citizens, and grants. The American Council on Science and Health is interested in proper nutrition and the risks of chemicals in the environment, alcohol, smoking, and many other environ-

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mental issues. The question asked by the authors in this book is, "Are children uniquely susceptible and at an increased risk of suffering health effects from various exposures, particularly those involving environmental chemicals?" The answer to this question provided by the authors is, "It depends." The authors' conclusion is that toxicology, exposure analysis, environmental health, pediatrics, and risk analysis teach us that "children may be more, less, or equally susceptible to environmental hazards" in comparison with adults. The authors also noted, "We have learned, through experience, of several examples where children are uniquely susceptible to specific hazards, and we have taken action to reduce child exposure. It is the position of the authors that the majority of chemicals in our environment that are detected at very low levels are probably not a risk for either children or adults." Dr C. Everett Koop wrote the preface to this book,<sup>2</sup> stating, "If indeed children are at risk and are particularly vulnerable to trace levels of environmental chemicals, then we should promote highly restrictive regulatory policies even if they are costly. If, however the science leads us to the conclusion that children are not more vulnerable than adults, then the justification for such expenditures evaporates."

Inherent in Dr Koop's conclusion is that we need accurate scientific studies to determine whether there is a cause-and-effect relationship between trace amounts of chemicals and deleterious effects. We agree with that concept. The important question is whether trace amounts of specific chemicals provide exposures that are above the NOAEL for children and whether the NOAEL is different for children than it is for adults. Each potential toxicant has to be studied to determine its NOAEL; this is essential both for prudent public policy and for the health of children.

The second book was written by Donald T. Wigle and is titled *Child Health and the Environment*.<sup>3</sup> Dr Wigle is an epidemiologist and physician and an affiliate scientist at the Institute of Population Health in Ottawa, Ontario, Canada. The book is a single-authored text with an extensive bibliography. He performed a risk analysis for a very large number of environmental toxicants. In the preface, Dr Wigle states, "Children differ profoundly from adults with respect to physiology, metabolism, growth, development, and behavior. By interfering with child growth and development during critical time periods, environmental hazards may cause structural and functional deficits and lifelong disability."

This is an important statement and could be misinterpreted to indicate that the main issue is that children are universally more vulnerable to all environmental toxicants at lower exposures than are adults. Dr Wigle explained that even if children and adults had the same NOAEL for toxicity for a particular toxicant, the effect on the embryo, child, and adolescent could be more serious because a developing organism is still in the formative stages of development.

In many places in the text, Wigle discusses the "Precautionary Principle." He says, "Modern use of

the precautionary principle in environmental health can be traced to the 1992 United Nations Conference on Environment and Development that promulgated the Rio Declaration. Under the precautionary principle, lack of full scientific certainty does not justify postponement of cost-effective measures to prevent significant potential public health risks. This book documents several historic examples of environment-related child health disasters resulting from failure to apply the precautionary principle."

The precautionary principle is a profoundly important concept that is not always operationalized to all parties' satisfaction. One example that Wigle used to illustrate where the precautionary principle should have been invoked is lead poisoning, and we agree. Even today, primary prevention of this ubiquitous toxin still remains inadequate despite mounting evidence of debilitating effects at very low levels. The opposite extreme, however, occurs when actions are taken in the name of the precautionary principle that are not based on scientific information. Politics, public pressure, inadvertent misinterpretation of the data, and fear of birth defects and cancer all are reasons for unfortunate actions that are based on the fear of environmental toxicants. The banning of Alar and cyclamates, the destruction of the New Jersey cranberry crop, the box warning for progestin-containing drugs for birth defects initiated by the Food and Drug Administration (FDA) in 1977, and many other actions demonstrate that invoking the precautionary principle is a very complicated issue that can be beneficial or detrimental to public health and the economic best interests of the nation.

Wigle says, "Children's environmental health is increasingly recognized as a global health issue of great importance." With respect to lead poisoning, bacterially contaminated water supplies, injuries, environmental tobacco smoke, sunburns, and the need to monitor and study the effects of children's exposure to many other potential toxicants and then act to protect children as the data suggests, he is correct, but if he is including low-population exposures from mercury, arsenic, manganese, cadmium, polychlorinated biphenyls, dioxin, phthalates, acrylamide, pesticides, endocrine disrupters, bisphenol, low-frequency electromagnetic fields, microwave electromagnetic field frequencies, and nuclear power plants, then his concerns are not justified by our current state of knowledge, as we do not have sufficient evidence of negative effects at levels commonly experienced. The important message in and from this book, as is true of this supplement, is that we need more epidemiologic, toxicologic, teratologic, and MOA research if proper assessment of the risk of these environmental toxicants is to be determined.

The third publication is a supplement to *Pediatrics* published in July 2003 titled "A Partnership to Establish an Environmental Safety Net for Children."<sup>4</sup> This monograph contains a number of articles selected from a workshop that was held in March 2001. The purpose of the workshop and publication was to educate pediatricians about how to diagnose and treat environmentally caused diseases. The workshop occurred 3 years ago, and it would be very

useful to have a progress report on whether their goal of training pediatricians to be able to diagnose and treat environmentally caused diseases has been achieved.

There is an excellent article in this monograph by Linet et al<sup>5</sup> from the Epidemiology section of the National Cancer Institute. In summary tables listing the known cause of some childhood cancers, there are no environmental chemical toxicants listed. The authors conclude, "Epidemiologic studies of pediatric cancers have evaluated a relatively large number of postulated risk factors. Little is known about the cause of childhood cancers, particularly the rare forms of these cancers. Familial and genetic factors seem to occur in no more than 5% to 15% of different categories of childhood cancer. Known environmental exposures and exogenous factors explain <5% to 10% of the occurrence of childhood cancer (radiation therapy second tumors, chemotherapeutic and immunosuppressive drugs, solar radiation and malignant melanoma, Epstein-Barr virus infection). Although the burgeoning literature from these and other recent investigations has offered some new insights, the cause of most childhood cancers remains unexplained."<sup>5</sup>

#### **An Example of Environmental Exposure Information in the Popular Press**

An article entitled "Are Cell Phones Safe?" appeared in the January 2003 issue of *Consumer Reports*.<sup>6</sup> The article stated that the FDA and the Federal Communications Commission concluded, "The available scientific evidence does not show that any health problems are associated with the use of cellular phones." Actually, the FDA and the Federal Communications Commission used 2 extensive reports and studies published by the Oak Ridge Associated Universities and the Institute of Medicine of the National Academy of Sciences. At the end of the discussion, the article in *Consumer Reports* mentions that "a Finnish team reported that when human cells were exposed to cell phone radiation in lab studies for one hour, protein changes occurred." The reference to this in vitro study leaves the reader with the idea that cell phones may be a hazard. One cannot determine human risks from cell culture experiments, especially when the epidemiology and animal studies do not indicate that there is an increased risk. Human risks are determined from studying humans in epidemiologic studies and to a lesser extent from studying exposed animals. If the human and animal studies are positive, then the cell culture studies may assist in determining the MOA but not the risk. A nonscientific publication such as *Consumer Reports* may be excused for erroneous interpretation of environmental risks from in vitro studies; however, there have been other recent reports in the scientific literature that continue to argue that in vitro studies can be used for determining the human risks of environmental chemicals.<sup>7-11</sup> The scientists who persist in attempting to determine human risks from in vitro studies succeed only in misdirecting scarce resources that should be spent on human and in vivo animal studies.

#### **Two Examples of Recent Publications of In Vivo Animal Studies**

In the past 2 years, many in vivo animal studies that used exemplary methods have been published. Two particular studies demonstrate the importance, differences, and usefulness of animal studies, as well as the difficulties inherent in drawing inferences from animal studies to describe human risk. The first publication is by Dam et al,<sup>12</sup> entitled "Transcriptional Biomarkers Distinguish Between Vulnerable Periods for Developmental Neurotoxicity of Chlorpyrifos: Implications for Toxicogenomics." The authors studied chlorpyrifos (CPF), an organophosphate insecticide that has had its domestic use curtailed in the United States because of concerns about the chemical's neurotoxicity. These MOA studies involved molecular biological techniques for studying CPF's effect on gene expression. One or 2 doses of CPF were injected subcutaneously into newborn animals on postnatal days 1 to 4 or 11 to 14. No serum blood levels were determined. Studies of the forebrain revealed a significant elevation in 1 protein that persisted for 5 days after cessation of the exposure regimen. Although the investigators studied the effects of CPF in an in vivo animal model, the results are of little use in determining the human risks of CPF for the following reasons:

1. CPF exposure in the human population does not occur via subcutaneous injection. The population exposure occurs from contamination of pesticides in food and water by ingestion or skin absorption.
2. There was no determination of the serum concentration of CPF in the animal model for the 2 exposures that were used.
3. There was no discussion of the levels of CPF that have occurred in human populations and what the range has been.
4. No threshold or NOAEL was determined.
5. The authors performed toxicogenomics without toxicokinetics.

Therefore, this was an interesting molecular biology study with little applicability to the problem of human risk assessment.

Now let us examine a study that would be considered to be a modern, up-to-date, in vivo animal toxicology study published by Tyl et al,<sup>13</sup> entitled "Three-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague Dawley Rats." This is, practically speaking, almost a perfect study for the following reasons:

1. The bisphenol was placed in the diet ad libitum.
2. There were 7 exposure groups.
3. The exposures were listed in parts per million and milligrams per kilogram.
4. The range of exposures used was very large, 0.001 to 500 mg/kg, or a 500 000-fold range.
5. Mating; fertility; gestational indices; ovarian primordial follicle counts; estrous cyclicity; precoital interval; gestational length; offspring sex ratios; postnatal survival; nipple/areolae retention in preweanling males; epididymal sperm number, motility, and morphology; daily sperm produc-

- tion; and efficiency of daily sperm production were not affected at any exposure. There were some effects observed in the 500-mg/kg group.
6. The adult NOAEL for adult animals was at 5 mg/kg/d, and the reproductive NOAEL was at 50 mg/kg/d.

There was total body and some organ reduction in weight at the higher exposures.

To perform a risk analysis for bisphenol in the human population, you need 2 more pieces of information that are not present in the Tyl et al publication,<sup>13</sup> but this missing information is present in other publications. Yamada et al<sup>14</sup> studied maternal serum and amniotic fluid bisphenol concentrations in the early second trimester. The investigators were able to obtain bisphenol exposure data in the mother and the amniotic fluid. The average concentration of bisphenol was 0.32 ng/ml serum, with a range of 0.0 to 1.6 ng/ml. It seems that these levels are far below the threshold exposure determined in the Tyl et al<sup>13</sup> study, but you cannot be certain because we do not have the same pharmacokinetic data in the rat that Yamada et al<sup>14</sup> reported in the human, so we do not know the serum concentration of bisphenol in the rat at the threshold exposure. Furthermore, we do not know whether the metabolism and effects of bisphenol are similar in the human and the rat. You can see how difficult risk analysis can be if the investigator wishes to base the risk analysis and conclusion on the most accurate and complete set of data.

Combining studies of Tyl et al<sup>13</sup> and Yamada et al<sup>14</sup> may seem to be a rare occurrence in the field of risk analysis. Fortunately, it is occurring more often.<sup>15</sup>

#### RECENT STUDIES CONCERNING THE RISKS OF ENVIRONMENTAL EXPOSURES TO PESTICIDES

As noted in several places in this supplement, "pesticides" includes a diverse group of chemical agents that include insecticides, rodenticides, nematocides, fungicides, and herbicides. We previously mentioned that in the past one and one half years, while this supplement was being prepared, numerous articles concerning environmental toxicants have been published. There have been no dramatic discoveries in risk analysis or definitive conclusions about any particular toxicant. Certainly there still exists the same concern and anxiety about the effects of toxicants and the polarization by those who have concluded that the risks have been exaggerated and those who have concluded that environmental chemicals are a major cause of disease and death. That polarization still exists. A review of the articles published in 2002 and 2003 dealing with the effects of environmental exposure to pesticides, herbicides, etc reflects the state of our knowledge, the controversial conclusions, and the questions that have to be answered. Some of these articles are excellent, and some are not, but all of the articles are recent publications. If a pediatrician or any other clinician read these articles, then how would the information assist them in determining whether environmental exposures to pesticides represent a risk to their patients?

Please see the excellent article by Weiss et al in this supplement that summarizes the wide range of agents subsumed under the category of "pesticides" and the very small percentage of all pesticides used that actually are used in homes and gardens.

Perera et al<sup>16</sup> reported the association of exposures to polycyclic aromatic hydrocarbons (PAHs) with a decrease in birth weight and head circumference and for exposures to CPF, a decrease in birth weight and length in a low socioeconomic population of African American and Dominican women. The investigators concluded that "this study provides evidence that environmental pollutants at levels currently encountered in New York City adversely affect fetal development." There were 263 total pregnant subjects, 116 African Americans and 146 Dominicans. In these 3 categories, the birth weight was 3382 g, 3299 g, and 3348 g; the birth length was 50.9 cm, 50.8 cm, and 50.1 cm; and the head circumference was 34.1 cm, 33.8 cm, and 34.3 cm. The air levels of PAHs in these 3 categories of patients were 3.7 ng/m<sup>3</sup>, 3.5 ng/m<sup>3</sup>, and 3.9 ng/m<sup>3</sup>. The serum levels of CPF in the 3 categories of patients were 7.5 ng/g, 8 ng/g, and 7.1 ng/g. With these very low levels of PAHs and CPF, should one conclude that the differences have a causal relationship to the differences in physical parameters? The authors pointed out that parenteral administration of CPF at higher doses can reduce the number of brain cells and result in neurobehavioral effects in experimental animals. Pediatricians who read this publication would not be impressed with the differences in birth weight, head circumference, and birth length in this small group of patients and certainly would not infer that the differences in head circumference in these children indicated that there was a reduction in brain cells or a risk of neurobehavioral disorders in the children with the smaller physical parameters.

Thiruchelvam et al<sup>17</sup> exposed mice in the early postnatal period to the herbicide paraquat and the fungicide maneb. Paraquat was administered subcutaneously at 0.3 mg/kg and maneb was administered subcutaneously at 1 mg/kg on postnatal days 5 to 19. At 6 weeks of age, there was a 20% reduction in activity, which declined to 40% by 6 months of age. A subset of mice were challenged as adults with large doses of paraquat and maneb, and the challenged mice had the greatest reduction in motor activity. These treatments reduced the number of dopaminergic neurons, and the investigators concluded that exposure to pesticides in the mouse neonatal period contributed to increased susceptibility to the toxic effects of pesticide exposure in the adult. The authors believed that their model represents a potential Parkinson's phenotype. However, there are some problems with this study if one is interested in using the data for risk assessment:

1. In the real-life situation, these 2 chemicals are not applied for their agricultural purposes at the same time of the year, so there would never be a time when humans would be exposed to both of these agents simultaneously.

2. The chemicals were administered parentally, which is not the way humans would be exposed.
3. There was not a pharmacokinetic component to these studies, which is important to note, because the method of administration is not the way human populations would be exposed.
4. No attempt to determine a threshold or NOAEL exposure was included in the report.

These experiments offer no opportunity to attempt a risk assessment for neurologic injury in the human. However, it does provide investigators with a model to study neurologic damage with some specificity.

Cavieres et al<sup>18</sup> exposed mice in the preimplantation and organogenetic periods to a commercial mixture of 2,4-dichlorophenoxyacetic acid (2,4-D), mecoprop, and dicamba that was placed in the drinking water. The range of exposure was very large. The lowest exposure for 2,4-D, mecoprop, and dicamba was 0.01 mg/kg, 0.004 mg/kg, and 0.0009 mg/kg, respectively. The highest exposure for 2,4-D, mecoprop, and dicamba was 100 mg/kg, 40.39 mg/kg, and 9.166 mg/kg, respectively. There is a 10 000-fold increase from the lowest to the highest exposure, yet there was no effect on term fetal weight or term crown rump length. There was a reduction in litter size, but it occurred in only the very lowest exposure. How could an exposure of 1/10 000th of the highest dose reduce the litter size when the highest exposure had no effect?

Shaw et al<sup>19</sup> performed a case-control study of 1034 women who had occupational exposures to chemicals, insecticides, propellants, dyes, and pigments. These women had delivered children with cleft lip, cleft lip and palate, conotruncal heart defects, and limb deficiencies. The authors concluded that chemical occupational exposures did not contribute substantially to the occurrence of these anomalies in the California population. There were no pharmacokinetics in this study, and only a portion of the pregnant women were exposed to insecticides.

Qiao et al<sup>20</sup> administered CPF subcutaneously to pregnant and neonatal rats. The exposure during pregnancy occurred on days 9 to 12 or 17 to 19. The investigators had previously demonstrated clear-cut damage and cell loss when subcutaneous exposure occurred postnatally. Administration of CPF to the developing embryo or fetus was less damaging to the fetus than exposure during the neonatal period. Subcutaneous administration of CPF at 5 mg/kg seemed to have no fetotoxic effects. The investigators concluded that the fetal brain had lower vulnerability than the neonatal brain to CPF. This is an unusual finding, namely, that the fetus is less susceptible to a toxicant than the neonate. It is difficult to apply these results to the human, because the exposures that were used were very high and were administered subcutaneously. For many of the fetotoxic effects, the threshold was >5 mg/kg subcutaneously. The exposure that resulted in some effects is many times the environmental exposure.

James<sup>21</sup> reported an association of transposition of the great vessels with maternal exposures to herbicides and rodenticides. Most teratogens produce a

constellation of malformations, not an isolated defect such as transposition, which is also usually associated with large fetuses. When you conclude a causal association with this kind of specificity for a malformation, one would expect that an animal model would be able to be developed readily.

Wijngaarden et al<sup>22</sup> examined the risk of childhood brain cancer in relation to parental exposure to classes of pesticides among 154 children who received a diagnosis of astrocytoma and 158 children who received a diagnosis of primitive neuroectodermal tumors. Control subjects were selected by random-digit dialing. The parents' work history was evaluated with regard to all 4 classes of pesticides. Most risk estimates were around unity. "Overall, it seems unlikely that parental exposure to pesticides plays an important role in the etiology of childhood brain cancer."

Garry et al<sup>23</sup> studied 695 farm families with 1532 children and evaluated the incidence of birth defects, the season of conception, and the gender ratio of the children. The children in the previous study by these investigators included male pesticide applicators. The documentation of the presence of birth defects came from the parents. The incidence of birth defects was 31.3 per 1000 births, which is the incidence reported by the Centers for Disease Control and Prevention as the average for the country. The investigators indicated that the incidence of birth defects in those pregnancies conceived in the spring at the time of pesticide spraying was twice as great (7.6%). This study is not biologically plausible, because the increase in birth defects would have to be genetically induced in the father who was exposed. Parents who were treated with mutagenic cancer chemotherapeutic drugs and the radiation survivors of the atomic bomb in Japan did not have an increase in offspring with birth defects. Therefore, it is very unlikely that pesticides, which do not have mutagenic potential comparable to cancer chemotherapeutic drugs or radiation, could significantly increase the incidence of genetic disease.

Sheets<sup>24</sup> studied the age-dependent differences in susceptibility to the toxicity of organophosphorus and pyrethroid insecticides. The published literature concerning high-dose acute poisoning of animals with organophosphorus insecticides indicates that neonatal rat pups have a lower median lethal dose than adult rats. This was also true for the pyrethroid insecticides. The question raised by the author was whether this increased susceptibility in the neonate persisted at low exposures that would be present in the environment and food supply. The question was posed to determine whether regulatory guidelines established to protect the public from environmental insecticide exposure had to consider the increased susceptibility of the neonate that was manifested at the high-dose toxic exposures. Multigenerational studies involving rats exposed to the organophosphorus insecticides coumaphos, fenimiphos, trichlorfon, oxydemeton-methyl, and tribufos at various concentrations in parts per million were done. Cholinesterase was determined in tissue and plasma. A similar multigenerational study was performed in

rats that were exposed to the pyrethroids cismethrin, permethrin, deltamethrin, and cypermethrin. The results indicated that at a number of low environmental dietary exposures to organophosphorus insecticides, the suppression of cholinesterase was greater in adult rats than in the neonatal and young pups. So the neonates were less sensitive than the adults. There was no difference in the sensitivity to the pyrethroids in the neonatal pups as compared with the adult rats. These studies undermine any generalization suggesting that the neonate is more sensitive and more vulnerable to environmental toxicants.

Barone et al<sup>25</sup> are concerned about the impact of environmental toxicants on the developing nervous system. The literature is reviewed, and there is significant theoretical discussion pertaining to the toxic effects of pesticides. The authors are concerned about the lack of availability of sensitive neurobehavioral tests to study the perturbations of the developing nervous system "to improve detection and reduce uncertainty about the nature of adverse effects following developmental exposure to environmental neurotoxicants."

Crisostimo and Molina<sup>26</sup> evaluated the outcome of pregnancy among farming households of Nueva Ecija (Philippines) with conventional pesticide use versus integrated pest management (IPM). This is a classical ecological study in which exposure is determined by proximity, job description, and pesticide use in 2 farming communities. One community used a system of IPM, which controlled the pests at a level that minimized economic damage, and the other group of farmers applied pesticides beyond spot spraying. The implication was that the exposures were lower in the IPM group. A pesticide was considered to include insecticides, herbicides, fungicides, and rodenticides. The outcome measurements were the incidence of spontaneous abortion, preterm birth, and birth defects. Male and female exposures included exposures in women before and during pregnancy. Both parents had to have been exposed. The results were as follows.

This is not an atypical epidemiologic study, in which the exposure has not been determined toxicokinetically. The pesticides involved include a large number of chemicals, and there is no way to determine whether any of the study population had a significant exposure, ie, exceeded the NOAEL for any of the agents used by the farmers. None of the reproductive outcomes assessed exceed the known background incidence of these reproductive problems. The data are also not consistent. In the low-exposure group (IPM), the preterm birth rate is 3 times greater than in the high-exposure group. Although the authors concluded that pregnant women should avoid using pesticides, they advised the population to continue with the status quo because the reproductive effects are so low. In reality, you cannot draw any conclusion.

It should be pointed out as previously mentioned that insecticide is a very small portion of the pesticides that are used in the United States. Of the 750 million pounds of pesticides applied annually in this

country, household and garden use of insecticides account for <4% of pesticide use.

#### CONTINUED DISCUSSIONS ON THE SENSITIVITY OF CHILDREN

Scheuplein et al<sup>27</sup> and Miller et al<sup>28</sup> published in 2002 analyses of the concept that children are different. Miller et al<sup>28</sup> provided a scholarly analysis of the biochemical and physiologic differences between children and adults as part of a project of the California Environmental Protection Agency. These authors reviewed the literature in an attempt "to determine if there are generic differences between children and adults that may be applicable to risk assessment of certain classes of compounds." The authors provided data that are widely known about the differences between children and adults, but they also pointed out the need for toxicokinetic studies that are vitally necessary to perform adequate risk assessment. Scheuplein et al<sup>27</sup> agreed with Miller et al<sup>28</sup> that neonates are toxicologically immature. However, they indicated that by 6 months of age and in many instances even earlier, "most metabolic systems are reasonably mature, becoming almost completely mature by 1 year of age. In many cases children are less sensitive than adults." Scheuplein et al<sup>27</sup> suggested that although it is true that neonates are clearly more sensitive to high exposures of some environmental toxicants, the literature suggests that this is not a generalization that can be applied to low-level environmental exposures to these same chemicals.

We could continue reviewing the many other recent articles that deal with "pesticides," but the scenario would not change. None these publications permits the pediatrician to conclude that there is or is not a significant risk from environmental exposure to "pesticides." Why is this true?

1. Many of the epidemiology studies include organophosphate and pyrethroid insecticides, other pesticides, herbicides, fungicides, and rodenticides. In fact, without human exposure data, it is difficult to perform an adequate risk analysis. The MOAs of a conglomerate of chemicals may be different. In 1999, the FDA<sup>29</sup> eliminated the class warning on progestational drugs because it is inappropriate to conclude that all chemicals in a functional group have the same risks. The risks of each chemical have to be based on its own epidemiology, animal toxicology studies, and toxicokinetic and toxicodynamic studies. It took 20 years for the FDA to conclude that there is no such entity as generic toxicology, toxicokinetics, or risk assessment. Ecological studies that assume exposures on the basis of proximity or occupation but have no human exposure measurements are unable to conclude that any association that is found is causal. In fact, without toxicokinetic data, it is even difficult to assume that an exposure of significance has taken place.
2. Very few published animal studies are modeled after the bisphenol study published by Tyl et al,<sup>13</sup> in which the toxicant was administered over a

very wide dosage range that included the potential environmental exposure. In the Tyl study, the NOAEL was determined as well as the toxicokinetics. Numerous toxic endpoints were studied. The exposure was continued for 3 generations. Many other parameters were examined that made this study exemplary, yet the risk analysis required information on the toxicokinetics in the human<sup>14</sup> before a reasonable risk analysis could be initiated.

#### PROVOCATIVE POSITIONS OR SOLID SCIENCE?

Three publications in the past 2 to 3 years give evidence that even if we are unable to determine the magnitude of the impact of environmental chemicals on disease in children and adults, many scientists have taken a position. Mattsson<sup>30</sup> asked, "Do pesticides reduce our total exposure to food borne toxicants?" The research of Ames<sup>31</sup> is referred to in Mattsson's article, which suggests that natural mutagens and carcinogens exist in fruits, vegetables, and other crops and that the impact of these toxicants are probably much more important than industrial environmental chemicals that have been introduced into the environment. It certainly is a provocative hypothesis, and the concept has some scientific basis. Mattsson suggested that crops that are stressed increase the level of these natural toxicants. Therefore, treatment with agents that prevent infestation, fungus infections, or spoilage might actually protect the population from natural mutagens, eg, mycotoxins, potato blight, other infestations.

The Comprehensive Environmental Response Compensation and Liability Act<sup>32</sup> requires the Agency for Toxic Substances and Disease Registry to publish periodically a list of chemicals of hazardous substances that are found at facilities on the national priorities list of polluted areas. The 2001 list has 254 chemicals. The prioritization is based on the chemical's frequency of occurrence at polluted sites, the chemical's toxicity, and the potential for human exposure. We hope that pediatricians or other clinicians would not rely on this list for information on whether a chemical is a hazard to his or her patients. A very important piece of information is missing in this document: the dose or exposure that is harmful. A compilation of "hazardous" chemical without the population exposure and the NOAEL is meaningless and, even worse, anxiety provoking to clinicians and scientists who are not familiar with the science of toxicology. Probably more pediatric patients are affected by water intoxication in the United States each year than by 97% of the chemicals on this list. Scialli<sup>33</sup> coined the phrase "the tyranny of lists." In his article, he pointed out that lists of chemical toxicants, mutagens, carcinogens, and teratogens are useless unless you provide 1) the risk at various exposures for the agents with deterministic (threshold) effects; 2) the NOAEL; and 3) the range of the population exposure.

#### The Cost of Intervention

Tengs et al<sup>34</sup> listed 500 life-saving interventions and their cost effectiveness. Environmentalists might

think that those authors are trying to provoke the readership, because it seems that their calculations demean the importance of the risks of environmental chemicals. The authors are from 5 prestigious universities and the Harvard School of Public Health, and these calculations are serious business to them. This article<sup>34</sup> addresses the topic of making choices in many areas of society. In the area of the risks of environmental exposures, decisions have to be made with regard to the elimination of environmental risks. Some abatement or preventive programs save lives or prevent disease without costing society anything. Other programs would cost inordinate amounts, but we cannot even begin to consider the cost if we do not have data on the risks of low-level exposures to environmental toxicants. As an example, a recent publication suggested that lead exposures in the 1 to 10  $\mu\text{g}/\text{dL}$  range are associated with a decrease in intellectual ability. If additional work indicates that the effect is in fact causal and the reduction is greater per  $\mu\text{g}/\text{dl}$  in the lower range, then how should we decide whether we have to strengthen lead abatement programs even further, move to primary prevention, or maintain the present level as being satisfactory?

#### Diseases That Are Difficult to Diagnose

We cannot discuss every area that has been presented in this supplement. However, we will mention the controversy concerning the incidence of pervasive neurodevelopmental disorders in children and their cause. A number of publications have debated the changing incidence of these disorders, which includes autism.<sup>35</sup> Hyman et al<sup>35</sup> stated, "There is much concern about whether the prevalence of pervasive developmental disorders, sometimes referred to as autistic spectrum disorders, is increasing." Because neurodevelopmental disorders are not infrequent and involve the organ that defines the human species, these problems can have an immense impact on the child and the family. We know some of the causes of this group of disorders, but there are few biomarkers. Epidemiology relies heavily on making the correct diagnosis, which is not an easy task in pervasive developmental disorders. Without agreement on the diagnosis, it is easy to understand how the apparent prevalence of this group of diseases could change over a period of decades. It is easy to perform epidemiology studies that deal with environmental toxicants and cleft palate, because there is little controversy about the diagnosis, but the epidemiology of diseases without defined biomarkers or agreed-on diagnostic criteria presents very difficult problems to investigators who attempt to determine their cause.

#### CONCLUSION

##### General Conclusions

Our concerns about environmental chemicals and physical agents and their potentially differential effect on the fetus and child are clearly justified because, in most cases, we do not have enough infor-

mation not to be concerned. One cannot dismiss the impact of environmental toxicants without adequate information of the population exposure and the NOAEL. This can be obtained only from quality animal toxicology studies and excellent epidemiologic studies with toxicokinetic and toxicodynamic information in the human and animal studies. Therefore it is essential that we initiate the following:

1. Human epidemiology studies: Expand our research programs to perform high-quality animal and human epidemiology studies. Ecological studies that do not measure exposures to the human population are more confusing than helpful in determining human risks. Studying exposures to agent groups, eg, solvents and pesticides, does not permit risk assessment for individual toxicants. The longitudinal National Children's Study now being planned will provide an outstanding opportunity to resolve many of the unanswered and vitally important questions raised throughout this supplement.
2. Programs for reducing the introduction of chemicals into the environment: Everyone would be in agreement that it would be to our benefit not to have any chemicals dispersed into the environment or have any chemical exposures in the workplace or in the home. All chemicals have the potential for developmental toxicity if the exposure is high enough. It would be better if there were not 1 molecule of lead, dichlorodiphenyltrichloroethane, dioxin, methyl mercury, or polychlorinated biphenyls in the environment, but they are there. The question is what are we going to do about this problem now and in the future. That is why we need a very extensive program of monitoring, reducing, and eliminating the delivery of chemicals to our environment and the exposure of our population to these chemicals. Efforts along these lines include developing and using chemicals that are biodegradable and do not remain permanently in the environment. Fungicides and pesticides that are essential for efficient crop production might be able to be replaced by using molecular biological tools to make the fruits and vegetables resistant to fungus infestation and insect infestation so that chemical usage could be reduced. However, chemicals have also provided tremendous benefits to society from both an economic and a health perspective. Therefore, it is not an easy task to balance the economic and health benefits of chemicals and the risks that they may represent if levels exceed the NOAEL. Introducing or banning chemicals that expose the human population is a task that is extremely difficult and needs to be planned carefully on the basis of risks and benefits.

Conclusions that can be drawn from the articles in this supplement are as follows:

1. Children are more sensitive and vulnerable to a number of environmental toxicants; even when the NOAEL is similar in children and adults, the

toxic manifestations include an array of developmental problems that do not occur in adults.

2. With many toxicants, there is not a significant difference between the toxic doses of the toxicants in children and adults, and in some instances, adults may have deleterious effects when children do not. In other words, each stage of development has to be studied for each toxicant at a multitude of exposures.
3. We do not have enough information about 1) the threshold or the NOAEL exposure for numerous environmental toxicants, b) the actual exposure to many environmental toxicants that the population receives, c) how many exposures to toxic agents are far below the NOAEL, and d) how many toxicants are present in the environment above the NOAEL.
4. What approaches can be initiated to reduce environmental toxicant exposures? Reductions in sources of children's lead exposure is the classic example of how investigative evidence can be used to confirm a risk, and social engineering can be used to reduce the exposure and the risk.
5. There exists a need for basic research, animal research, and more sophisticated human epidemiologic studies to determine the risks of various low exposures for the majority of environmental toxicants.
6. Greatest deficiencies exist in our knowledge about the MOA and the actual population exposures to many environmental agents. Epidemiologic studies can demonstrate statistical associations between exposures and effects. It is difficult to interpret statistical associations found in low-exposure, ecological epidemiologic studies when there is no documentation of the actual exposure and when there is no evidence of demonstrable pathologic, biochemical, physiologic, or molecular biological effects. Should we not be interested in determining how lead lowers the IQ in a child with a serum level of 5  $\mu\text{g}/\text{dL}$ ? Knowledge of the MOA could have far-reaching importance, but if there is no demonstrable MOA for lead at this serum level, then it becomes far more difficult to be definitively certain that the association is causal.

We have dedicated this supplement to practicing pediatricians in the hope that the articles will stimulate their interest in reading the literature that deals with environmental toxicology. A better understanding of toxicology will permit physicians to better counsel their patients about the risk or lack of risks of environmental exposures. They will also realize that a few scientists have taken positions that environmental toxicants are a major health problem, and some have denigrated the risks of chemical exposures on the health of children. For individual chemicals, we have examples of serious effects and no effects, but for most chemicals, we do not have adequate data. That is why the bottom line of this supplement is the request for more and better toxicology research.

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## The Current State of Knowledge About the Effects, Risks, and Science of Children's Environmental Exposures

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