Age-specific Carcinogenesis: Environmental Exposure and Susceptibility

Richard D. Thomas

International Center for Environment and Health, Arlington, Virginia

Environmental exposures in children may occur through many routes, including diet, air, and the ingestion of various nonfood items such as medications and household materials. This article focuses on dietary exposure, but it does highlight the importance of considering other routes of exposure when assessing exposure in children. It presents many of the findings in the two recent reports, Pesticides in the Diets of Infants and Children and Science and Judgment in Risk Assessment of the National Academy of Sciences (NAS)/National Research Council (NRC). Diet is an important source of exposure for children to potential carcinogens. The trace quantities of chemicals present on or in foodstuffs are termed residues. In addition, there are substances that children may be exposed to in air and water that should be considered in a total exposure analysis. To minimize exposure of the general population to chemical residues in food, water, and air, the U.S. government has instituted regulatory controls. These are intended to limit exposures while ensuring an abundant and nutritious food supply, and safe drinking water and air. The legislative framework for these controls was established by Congress through various local and state laws and such federal laws as the Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Federal Food, Drug, and Cosmetic Act (FDCA), the Safe Drinking Water Act (SDWA), and the Clean Air Act (CAA).

Several different "acceptable concentrations" are established for chemicals in the environment. For example in the case of pesticides, tolerances constitute the single most important mechanism by which the U.S. Environmental Protection Agency (U.S. EPA) limits levels of pesticide residues in foods. A tolerance is defined as the legal limit of a pesticide residue allowed in or on a raw agricultural commodity and, in appropriate cases, on processed foods. A tolerance must be established for any pesticide used on any food crop. Tolerances are not based primarily on health considerations and have in the past not addressed the unique characteristics of infants and children. 

The exposure of infants and children and their susceptibility to harm from ingesting pesticide residues differs from that of adults. Since the current regulatory system does not specifically consider infants and children, it does not examine the wide range of pesticide exposure patterns that appear to exist within the U.S. population. It looks only at the average exposure of the entire population. As a consequence, variations in dietary exposure to pesticides and health risks related to age and such other factors as geographic region and ethnicity are not addressed in current regulatory practice. In addition, humans vary substantially in their inherent susceptibility to carcinogenesis. If each stage in carcinogenesis is examined (e.g., carcinogen uptake and metabolism, DNA damage, DNA repair and misrepair, cell proliferation, tumor progression, and metastasis), there may be substantial variability between humans. Furthermore, some individuals may have determinants (e.g., germ-line mutations in tumor-suppressor genes) that substantially enhance their susceptibility to cancer-causing chemicals.

Concern about the potential vulnerability of infants and children to dietary pesticides led the U.S. Congress in 1988 to request that the National Academy of Sciences (NAS)/National Research Council (NRC) examine this issue.

Age-related Variation in Susceptibility and Toxicity

A fundamental maxim of pediatric medicine is that children are not "little adults." Profound differences exist between children and adults. Infants and children are growing and developing (14–22). Their metabolic rates are more rapid than those...
of adults (23–32). There are differences in their abilities to activate, detoxify, and excrete xenobiotic compounds. All these differences can affect the toxicity of pesticides or other chemical substances in infants and children, and for these reasons the toxicity of pesticides is frequently different in children than in adults (31–35). Children may be more sensitive or less sensitive than adults, depending on the pesticide to which they are exposed. Moreover, because these processes can change rapidly and can counteract one another, there is no simple way to predict the kinetics and sensitivity to chemical compounds in infants and children from data derived entirely from adult humans or from toxicity testing in adult or adolescent animals (1).

The NRC found both qualitative and quantitative differences in toxicity of pesticides and other chemicals between children and adults. Qualitative differences in toxicity are the consequence of exposures during special windows of vulnerability—brief periods early in development when exposure to a toxicant can permanently alter the structure or function of an organ system (14,36,37). Classic examples include chloramphenicol exposure of newborns and vascular collapse (gray baby syndrome (26)), tetracycline and dysplasia of the dental enamel, and lead and altered neurologic development (28).

Quantitative differences in toxicity between children and adults are due in part to age-related differences in absorption, metabolism, detoxification, and excretion of xenobiotic compounds, that is, to differences in both pharmacokinetic and pharmacodynamic processes. Differences in size, immaturity of biochemical and physiological functions in major body systems, and variation in body composition (water, fat, protein, and mineral content) can all influence the extent of toxicity (19,20,38). Because newborns are the group most different anatomically and physiologically from adults, they may exhibit the most pronounced quantitative differences in sensitivity to chemicals (3,39,40).

The NRC concluded that the mechanism of action of a toxicant—how it causes harm—is generally similar in most species and across age and developmental stages within species (9). For example, if a substance is cytotoxic in adults, it is usually also cytotoxic in immature individuals.

Lack of data on chemical toxicity in developing organisms was a recurrent problem encountered by the NRC. In particular, little work has been done to identify effects that develop after a long latent period or to investigate the effects of chemical exposure on chronic neurotoxic, immunotoxic, or endocrine responses in infants and children. We therefore had to rely mostly on incomplete information derived from studies in mature animals.

The NRC reviewed current U.S. EPA requirements for toxicity testing by chemical manufacturers, as well as testing modifications proposed by the agency. In general, we found that current and past studies conducted by chemical manufacturers are designed primarily to assess toxicity in sexually mature animals. Only a minority of testing protocols have supported extrapolation to infant and adolescent animals. Current testing protocols do not, for the most part, adequately address the toxicity and metabolism of chemicals in neonates and adolescent animals or the effects of exposure during early developmental stages and their sequelae in later life.

**Age-related Differences in Exposure**

Estimation of the exposures of infants and children to chemical residues requires information on dietary composition, residue concentrations in and on the food and water consumed, and other routes of exposure. The NRC found that infants and children differ both qualitatively and quantitatively from adults in their exposure to chemical residues in foods (1). Children consume more calories of food per unit of body weight than do adults. But at the same time, infants and children consume far fewer types of foods than do adults. Thus, infants and young children may consume much more of certain foods, especially processed foods, than do adults. And water consumption, both as drinking water and as a food component, is very different between children and adults. Differences in exposure were generally a more important source of differences in risk than were age-related differences in toxicologic vulnerability. It should be noted that infants and young children consume large quantities of processed foods, such as fruit juices, baby food, milk, and infant formula. The younger the child, the less diverse are the foods that are consumed.

The high levels of consumption within a particular age group are especially relevant when considering foods that might contain residues capable of causing acute toxic effects. Also, geographic, ethnic, and other differences may be overlooked. To overcome the problems inherent in the current reliance on “average” exposures, we used the technique of statistical convolution (i.e., combining various databases) to merge distributions of food consumption with distributions of residue concentrations. This approach permits examination of the full range of pesticide exposures in the pediatric population of the United States.

**New Approaches to Risk Assessment for Infants and Children**

To properly characterize risk to infants and children from pesticide residues in the diet, information is required on food consumption patterns of infants and children, concentrations of pesticide residues in foods consumed by infants and children, and toxic effects of pesticides, especially effects that may be unique to infants and children. If suitable data on these three items are available, risk assessment methods based on the technique of statistical convolution can be used to estimate the likelihood that infants and children who experience specific exposure patterns may be at risk. To characterize potential risks to infants and children in this fashion, we utilized data on distributions of pesticide exposure that, in turn, were based on distributions of food consumption merged with data on the distribution of pesticide residue concentrations. The NRC found that age-related differences in exposure patterns for 1- to 5-year-old children were most accurately illuminated by using 1-year age groupings of data on children’s food consumption (1).

Exposure estimates should be constructed differently depending on whether acute or chronic effects are of concern. Average daily ingestion of pesticide residues is an appropriate measure of exposure for assessing the risk of chronic toxicity. However, actual individual daily ingestion is more appropriate for assessing acute toxicity. Because chronic toxicity is often related to long-term average exposure, the average daily dietary exposure to pesticide residues may be used as the basis for risk assessment when the potential for delayed, irreversible chronic toxic effects exists. Because acute toxicity is more often mediated by peak exposures occurring within a short period (e.g., over the course of a day or even during a single eating occasion), individual daily intakes are of interest. Examining the distribution of individual daily intakes within the population of interest reflects day-to-day variation...
in pesticide ingestion both for specific individuals and among individuals.

Compared to late-in-life exposures, exposures to pesticides early in life can lead to a greater risk of chronic effects that are expressed only after long latency periods have elapsed. Such effects include cancer, neurodevelopmental impairment, and immune dysfunction. The NRC developed new risk assessment methods to examine this issue (1,2).

Although some risk assessment methods take into account changes in exposure with age, these models are not universally applied in practice. The NRC explored the use of newer risk assessment methods that allow for changes in exposure and susceptibility with age (41–47). However, we found that sufficient data are not currently available to permit wide application of these methods.

**Conclusions and Recommendations**

Estimates of expected total exposure to pesticide residues should reflect the unique characteristics of the diets of infants and children and should account for both dietary and nondietary intake of pesticides and other chemical substances. Exposure estimates should recognize that pesticide residues may be present on more than one food commodity consumed by infants and children and that more than one pesticide may be present on one food sample. Finally, determinations of safe levels of exposure should take into consideration the physiologic factors that can place infants and children at greater risk of harm than adults.

**Toxicity Testing**

The NRC believes it is essential to develop toxicity testing procedures that specifically evaluate the vulnerability of infants and children. Testing must be performed during the developmental period in appropriate animal models and the adverse effects that may become evident must be monitored over a lifetime. Of particular importance are tests for neurotoxicity and toxicity to the developing immune and reproductive systems.

**Exposure Assessment**

The available data indicate that infants and children consume much more of certain foods on a body-weight basis than do adults. Because higher exposures can lead to higher risks, it is important to have accurate data on food and water consumption patterns for infants and children. To maximize the utility of pesticide residue data collected by various laboratories, the NRC recommends the use of comparable analytic methods and standardized reporting procedures and the establishment of a computerized database to collate data on pesticide residues generated by different laboratories. More complete information is needed on the effects of food processing on levels of pesticides—both the parent compound and its metabolite—in specific food–chemical combinations potentially present in the diets of infants and children.

**Risk Assessment**

All exposures to pesticides—dietary and nondietary—need to be considered when evaluating the potential risks to infants and children. Nondietary environmental sources of exposure include air, dirt, indoor surfaces, lawns, and pets.

- Estimates of total dietary exposure should be refined to consider intake of multiple pesticides with a common toxic effect. Converting residues for each pesticide with a common mechanism of action to toxicity equivalence factors for one of the compounds would provide one approach to estimating total residue levels in toxicologically equivalent units.
- Consumption of pesticide residues in water is an important potential route of exposure. Risk assessment should include estimates of exposure to pesticides in drinking water and in water as a component of processed foods.

Given adequate data on food consumption and residues, the NRC recommends the use of probability distributions rather than single-point data to characterize the likelihood of exposure to different concentrations of pesticide residues. The distribution of average daily exposure of individuals in the population of interest is most relevant for use in chronic toxicity risk assessment and the distribution of individual daily intakes is recommended for evaluating acute toxicity.

The NRC identified important differences in susceptibility to the toxic effects of pesticides and exposure to pesticides in the diet with age. For carcinogenic effects, the NRC proposed new methods of cancer risk assessment designed to take such differences into account. Preliminary analyses conducted by the NRC suggest that consideration of such differences can lead to lifetime estimates of cancer risk that can be higher or lower than estimates derived with methods based on constant exposure. Currently, most long-term laboratory studies of carcinogenesis and other chronic end points are based on protocols in which the level of exposure is held constant during the course of the study. To facilitate the application of risk assessment methods that allow for changes in exposure and susceptibility with age, it would be desirable to develop bioassay protocols that provide direct information on the relative contribution of exposures at different ages to lifetime risks. Although we do consider it necessary to develop special bioassay protocols for mandatory application in the regulation of pesticides, it would be useful to design special studies to provide information on the relative effects of exposures at different ages on lifetime cancer and other risks with selected chemical carcinogens.

In summary, better data on dietary exposure to chemical residues should be combined with improved information on the potentially harmful effects of chemicals on infants and children. Risk assessment methods that enhance the ability to estimate the magnitude of these effects should be developed, along with appropriate toxicological tests for perinatal and childhood toxicity.

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