

ARE INFANTS AND CHILDREN REALLY MORE VULNERABLE THAN ADULTS TO THE POTENTIAL ADVERSE EFFECTS OF PESTICIDES?

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Protecting the Children

The Food Quality Protection Act (FQPA) of 1996, undoubtedly the most significant piece of U.S. pesticide legislation in recent years, requires EPA to apply an additional 10× uncertainty factor (UF) to the Reference Dose (RfD) “to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children.” Passage of the FQPA was the first of several U.S. legislative / regulatory initiatives that had its origins in a report *Pesticides in the Diets of Infants and Children* published in 1993 by the U.S. National Research Council (National Academy of sciences). In 1997, President Clinton signed an *Executive Order to Reduce Environmental Health and Safety Risks to Children*, the EPA established a new Office of Children’s Health and a new Children’s Health Protection Advisory Committee was established to identify issues of particular concern and procedures for managing them. And, most recently, final approval of EPA’s new proposed *Guidelines for Carcinogen Risk Assessment* is being delayed because of concerns they do not adequately address the issue of child sensitivity.

All of these activities, as typified by EPA’s 1996 *National Agenda to Protect Children’s Health from Environmental Health*, are based on the premise that children are particularly vulnerable to risks from chemicals in the environment and that there is an urgent need to provide them with extra protection. This view has created a new rallying point for environmental groups, a new mission for many aggressive regulators and vote-seeking politicians and yet another alarmist issue that is not justified by the scientific evidence available. But who can argue against providing proper protection for infants and children?

The following provides a brief overview of some of the scientific evidence concerning the question of whether or not children are likely to be more vulnerable than adults to pesticides and other chemicals.

Age-Related Differences in Risk

Since human risk is a function of the hazard of and exposure to a chemical, the major factors that will cause infants and children to be more vulnerable than adults are those that lead to higher infant exposure or greater susceptibility.

Exposure factors

There is no question that there are both qualitative and quantitative differences in the exposure of children and adults to pesticides. The dietary/nutritional needs of infants

are clearly different from those of adults. Not only do children eat more food per unit of body weight than adults, but the nature of their food is different. The heavy reliance of infants on a single food item (milk or formula) and the relatively high child consumption of fruit and vegetable products may cause them to have a relatively high exposure to pesticide residues in these products. Children also typically drink more water than adults. In addition to ingesting normal items of food and drink, children also have a greater opportunity of exploratory ingestion of unusual materials such as soil and dust. Other exposure differences result from the fact that children spend more time in crawling behavior where they come into dermal or other contact with residential pesticide residues on carpets, lawns, etc.

Most people would agree that there are situations in which child exposures to pesticides per unit of bodyweight are higher than those of adults. It should be recognized, however, that such differences are typically no more than 3- to 5-fold, and can readily be accommodated by modern stochastic exposure/risk assessment techniques that express exposure in terms of distributions of food intake and levels of pesticide residues.

Factors causing differential sensitivity

The intensity and/or duration of a toxicological response depends on the ability of a chemical to reach a given target at a critical concentration and the sensitivity of the target to respond. Consequently, age-related differences in susceptibility may occur through:

- age-related differences in pharmacokinetic parameters that determine the ability of a chemical to reach its target at a critical concentration
- age-related differences in the response of the target

Most of the information on possible age-related differences in human susceptibility to chemicals comes from the results of studies with a variety of laboratory animals. While some of this information is valuable, much of it must be interpreted with care. There are large species differences with respect to the overall level of structural and functional development at birth. In humans, the state of development of most organs and systems at birth is quite advanced. In contrast, newborn rats are extremely immature and correspond approximately to a mid-term human fetus. Consequently, the assumption that a toxicological response observed in neonatal rats has any relevance to effects likely

to occur in human infants must be carefully evaluated. In fact, there is a general paucity of animal data that relate directly to predictions of age-related differences in toxicity in humans.

Pharmacokinetic factors

Age-related differences in absorption, distribution, metabolism and excretion can certainly affect the amount and form (e.g., an active metabolite) of a pesticide reaching a target site and could impact the toxic response.

Development of the *stratum corneum*, the critical outer epidermal barrier to dermal penetration is incomplete until just after birth so that premature infants are probably more at risk than adults to dermal exposure to chemicals. At birth, the histological characteristics of human skin are essentially the same as in adults although the skin of infants is less keratinized (softer) allowing dermal penetration of many chemicals to occur more rapidly. While there are several physiological differences between the gastrointestinal system of infants and adults (infants have higher pH, longer gastric emptying time, etc.) no generalizations can be made regarding age-related differences in the absorption of ingested materials.

Similar conclusions are reached with respect to distribution of a chemical throughout the tissues after absorption. As the membrane barrier that selectively controls the passage of chemicals from the blood to central nervous system, the blood-brain barrier has received a great deal of attention. There is now general agreement that, although the blood-brain barrier is incomplete during early fetal and prenatal development, barrier function rapidly increases during the neonatal period and in humans is essentially complete within a few months after birth.

Since the toxicological effects of many chemicals are often determined by their metabolism, age-related changes in biotransformation are a potentially important factor in differences in toxicity. Many of the enzymes involved in both Phase I (cytochrome P-450, glutathione S-transferase, esterases) and Phase II (conjugating enzymes) metabolism remain at low levels during prenatal and neonatal development. They do, however, attain adult levels fairly rapidly postnatally, the process occurring fastest in those species (e.g., 6–12 months in humans) that are more fully developed at birth.

It is difficult to make generalizations about the impact of age-related differences in metabolism on child sensitivity. The enzymes involved in the biotransformation of xenobiotics are many and complex and may reduce (detoxify) or increase (activate) the toxicity of any given chemical. The absence in infants of an enzyme capable of detoxifying chemical X might signal a potential problem while it might prove advantageous in relation to the toxicity of Y that is activated by the same enzyme. With the possible exception of early neonates, it is unlikely that human infants are at significantly greater risk than adults as a consequence of differences in pharmacokinetic factors. Furthermore, any differences in toxicity that do occur in neonates are unlikely to be large and will become increasingly less obvious during the first year of life as many of the biochemical and physiologic systems develop.

Target sensitivity

In considering age-related differences in toxicity, it has become “common wisdom” that infants and children must be more susceptible to chemicals than adults because their organ systems are structurally and functionally immature and represent inherently more sensitive, if not unique, targets. While there are undoubtedly cases examples where this is true, the general applicability of the assumption should not be accepted without careful examination.

An enormous number of structural and functional changes occur throughout prenatal and postnatal development and it is possible that specific targets may be more or less vulnerable to some chemicals during specific stages of development. Unfortunately, knowledge of these changes *per se* is of little value in enabling us to predict targets likely to be particularly sensitive to chemicals and most examples are uncovered by experimentation. The results are mixed.

Immature animals (including humans), for example are more sensitive than adults to the toxic effects of lead in the brain (encephalopathy) and are generally more sensitive to the effects of other heavy metals (e.g., mercury). This is not always the case, however. The CNS in immature 10-day-old rats is two-fold less sensitive to DDT than that in 60-day-old, a fact confirmed by the greater tolerance of preweaning rats to DDT, chlordane, heptachlor and dieldrin. The delayed neurotoxic effects of tri-*o*-cresyl phosphate (TOCP) are less obvious in young chicks, cats and children than in adults suggesting that young animals are more resistant to the axonal degeneration (demyelination) caused by this material.

Recently, much attention has been focused on age-related differences in the anticholinergic effects of organophosphorus (OP) and carbamate pesticides. Reports have been published that neonatal rats are more sensitive than adults with respect to inhibition of brain cholinesterase and several neurobehavioral indices following exposure to OP insecticides. The problem with many of these studies is that they typically involve direct injection of neonatal rats with high doses of OPs that overwhelm physiological defense systems. The results have little, if any, relevance to effects that might be anticipated in humans following trace level oral or dermal exposures to pesticide residues in the real world. Other studies have shown that ChE in neonatal animals differs very little from that in adults with respect to its sensitivity to inhibition by OPs. In fact, fetal brain ChE seems to be protected against inhibition and neonatal brain ChE recovers spontaneously faster than that from adults.

Concern has recently been voiced that EPA's new guidelines for cancer risk assessment do not provide adequate protection for children. The basis for this concern is not clear but seems to be more emotional than scientific. In fact, childhood cancer in the U.S. is relatively rare (about 8,700 new cases per year in young people under 15 years of age) and most cases have specific gene-mediated familial causes. While the contribution of environmental chemicals to childhood cancer is unknown it must be small, and the risk associated with exposure to pesticides vanishingly small. Although infants are undoubtedly more sensitive than adults to the potential mutagenic effects of genotoxic

chemicals and ionizing radiation, there is no scientific evidence to suggest they are generally more sensitive to materials acting through various non-genotoxic mechanisms. Nonetheless, there continues to be discussion about the possible need to provide additional margins of safety for children irrespective of the possible modes of action involved.

Testing for child sensitivity

Perhaps the most difficult problem with respect to evaluating the potential adverse effects of chemicals on children is how to design studies that will identify and measure such effects. For obvious reasons, tests involving human children will never be conducted. Consequently, it is important to identify an animal model (species/age) and design protocols (route, level and duration of exposure) most appropriate for assessing effects on *human* infants and children. Since there is no obvious animal model available for this purpose, we are constantly in the difficult position of trying to assess the relevance to human children of the results of a pot pourri of studies conducted under unrealistic exposure conditions with neonatal rodents or other laboratory animals. While it must be emphasized that there is no evidence that children are any more sensitive than adults to the potential adverse effects of pesticides, it is important that study protocols be carefully reviewed to determine whether they will provide information relevant to children. Unfortunately, toxicologists are constantly being placed in the impossible position of attempting to prove that a certain effect will not occur.

In some cases, it may be possible to modify protocols to include young animals or exposures during some particular stage of development. For many years, for example, there has been discussion about the routine inclusion of perinatal and even fetal exposures in chronic bioassays for cancer and, indeed, several such studies have been conducted. To date, there is no evidence that inclusion of perinatal exposures serves to identify carcinogens that would not be found using standard bioassay procedures. It seems unlikely that the benefits of such studies justify the additional costs they involve. The other possibility is to design completely new studies of more direct relevance to young animals. Several such studies (*e.g.*, pre- and postnatal developmental neurotoxicity) are currently being considered for addition to pesticide testing requirements by the U.S. EPA although there still remains controversy about the protocols to be used and the relevance to humans of several of the toxicological endpoints employed. It should be clearly recognized

that the development of tests that provide direct information on child sensitivity to pesticides and other chemicals is a difficult challenge that will always be associated with a good deal of uncertainty. On the other hand, the question of differential child sensitivity is a problem encountered routinely in the field of medicine where drugs tested primarily on adults are administered to infants and children. In general, this is an area that is not unduly problematic.

Conclusion

There is a broad consensus of scientific opinion (based, in part, on evidence from therapeutic medicine) that any difference in child vs. adult sensitivity is unlikely to be any greater than 10 \times . This is consistent with the 10 \times uncertainty factor currently incorporated into regulatory benchmarks such as the Reference Dose to account for inter-individual variation within the human population. Consequently, among scientists familiar with the area, there is widespread belief that uncertainty factors currently employed provide a satisfactory safety net for the majority of pesticides on the market.

Despite the absence of a compelling scientific basis, the issue of child sensitivity to pesticides and the "urgent need" to provide them with extra protection has become the order of the day for regulators on both sides of the Atlantic and a powerful weapon in the arsenal of the anti-pesticide movement. It is, of course, extremely difficult, particularly for individuals associated with the agrochemical industry, to develop any kind of argument as to why extra child protection in the form of an additional safety factor is not necessary. Furthermore, from the viewpoint of a national regulatory agency, policy must always be dictated by prudence. As a result, it is likely that the development of more stringent pesticide regulation for added child protection will continue. But if the emotive aspects of the issue can be stripped away and the hazard and exposure data carefully and objectively evaluated, there is little, if any, evidence that under current regulatory procedures, children are any more "at risk" than adults to the potential adverse effects of pesticides.

Further reading

- Renwick, A. G.; Dorne, J. L.; Walton, K. (2000) An analysis of the need for an additional uncertainty factor for infants and children *Regulatory Toxicology Pharmacology* **31**, 286–296.
- Scheuplein, R. (2000) Pesticides and infant risk. Is there a need for an additional safety margin *Regulatory Toxicology Pharmacology* **31**, 267–279.

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