Pesticides—The NAS Report: How Can the Recommendations Be Implemented?

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— Environ Health Perspect 103(Suppl 6):159–162 (1995)

Key words: infants and children, pesticides, risk assessment, dietary exposure, toxicity testing, residues in food, food consumption

The potential exists for exposure to pesticides from a number of sources, including the diet. Approval of the use of pesticides is regulated under the Federal Insecticide Fungicide and Rodenticide Act, administered primarily by the U.S. Environmental Protection Agency (U.S. EPA). In 1988, Congress asked the National Academy of Sciences to evaluate the U.S. EPA’s existing risk assessment practices to determine whether the agency adequately considered the potential for risk to infants and children. The Academy’s 1993 report, Pesticides in the Diets of Infants and Children, supported the need for improved data and methods for estimating exposure and hazard when setting tolerances on food to better safeguard the health of infants and children. This article presents the federal government’s analysis of the Academy recommendations and describes work completed, underway, and proposed that will lead to improvements in the risk assessment process.

The National Academy of Sciences (NAS) report Pesticides in the Diets of Infants and Children was released in June, 1993 (1). The report focused primarily upon exposure to pesticides in the diets of infants and children. The federal government views the report as an opportunity to improve all aspects of human health risk assessment. The scientific effort that constitutes followup to this report emphasizes the improved characterization of potential hazard, exposure and risk to the young from the use of pesticides. It is, however, also applicable to other age groups, other exposure scenarios, and other environmental agents as well.

It should be emphasized that this effort is not just that of the U.S. Environmental Protection Agency (U.S. EPA). The U.S. EPA is in partnership with the U.S. Dept. of Agriculture (USDA) and the U.S. Food and Drug Administration (FDA), the other two agencies with regulatory responsibilities for pesticides. In addition, there is participation by technical experts from other Federal agencies such as the National Institute for Environmental Health Sciences, the National Center for Health Statistics, and the Census Bureau—and from state governments. We expect that as work goes forward there will be many opportunities for participation in the development of and review and comment on improvements in risk assessment methodologies.

U.S. EPA Administrator Browner, USDA Deputy Secretary Rominger, and FDA Commissioner Kessler testified before Congress in September 1994 to the Administration’s commitment in providing the resources necessary to improve our understanding of the potential for risk to the young from exposure to pesticides. In addition, other major commitments such as the use reduction initiative and the increase in support for the development of alternative agricultural practices, will accelerate the mitigation of any risk that may currently exist.

U.S. EPA, USDA, and FDA have rigorously examined all of the recommendations in the report and have concluded that it is appropriate to implement all of them in some way, predicated upon acquisition of funding in some cases. To the extent possible, the work is being integrated into already existing or planned initiatives, so as to minimize startup time and maximize the use of scarce resources. Participation of all sectors of the scientific community is necessary to improve the government’s capabilities to carry out high quality human health risk assessments. Another important point is that the federal government does not intend to bear the cost of this work alone. Rather, the U.S. EPA will use its regulatory authority, particularly the data call-in capabilities under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), to require the development of some of the information to be used in future risk assessments.

The Health Effects Division of the Office of Pesticide Programs at the U.S. EPA is serving as the lead for developing the implementation plan and monitoring its progress. When the report was first issued, four workgroups consisting of technical experts were quickly formed. The workgroups were charged with a) characterizing the recommendations in their respective areas; b) determining whether the recommendations had, in fact, already been or should be put into practice; and, c) if so, determining what work was being done on the issues and, by whom; and d) framing the strategy for follow-up. These tasks were completed in about a month.

The four workgroups addressed each of the major elements of the report, which contained the key recommendations: toxicology, food consumption, residue data, and risk assessment. While each workgroup addressed its topics separately, each was mindful of the interrelationships that exist among the elements of risk assessment. Thus, each recommendation was covered by at least one group, and when there was overlap, the groups worked together to ensure that the responses were consistent.

Following is a description of the actions taken, underway, and/or planned to address the report’s recommendations.
Toxicology Testing
The NAS committee concluded that the U.S. EPA’s current and proposed pesticide toxicology testing guidelines were not adequate to assess a) toxicity to newborn and preadolescent animals, b) metabolism in animals in these age groups, and c) exposure during early developmental stages. To remedy these deficiencies, they proposed that studies be conducted that compare toxicity and metabolism in adult and immature animals for representative pesticide chemicals/classes.

Implementing this recommendation requires a research phase to determine if and how changes could/should be incorporated into testing guidelines. Thus, the initial approach is to design a research program that will yield a set of general principles concerning age-related toxicity. Results from these studies could also be used to design and develop testable hypotheses for epidemiologic studies in humans. An interagency group has drafted a multiyear research plan, which was introduced at the Office of Pesticide Program’s Workshop in June 1994. It will be discussed again at a scientific workshop in mid-1995. Implementation of the plan will follow external scientific peer review.

Additional recommendations included specific suggestions for enhancing existing guidelines and for the introduction of new ones. In December 1993, the U.S. EPA held a consultation with its FIFRA Scientific Advisory Panel (SAP) and Science Advisory Board (SAB) on proposed updates to the reproduction and developmental toxicity guidelines and a draft guideline for immunotoxicity screening. The proposals were generally well received. Final versions will be issued by the end of 1995.

The NAS Committee also recommended that the rat chronic carcinogenicity study design be modified to incorporate in utero exposure. The U.S. EPA analysis of three recently completed studies conducted by the National Toxicology Program (NTP), a series of comparative studies from FDA files, and information in the published literature is complete. Preliminary conclusions from that analysis suggest that little additional information is gained when an in utero component is added to the conventional study design.

Another recommendation stated that measurements of thyroid function should be added routinely to the rodent long-term study. While this is relatively easy to do, it is not completely clear what additional value this would have, except in a relatively small number of cases. NTP is adding these parameters to a number of 90-day studies in a pilot program in an attempt to answer this question. A final decision awaits the results of this initiative.

Food and Water Consumption
The second area considered by the NAS committee was whether the food and water consumption assumptions used by the U.S. EPA were appropriate. Chastising the U.S. EPA for not having a better understanding of contemporary food consumption patterns of infants and children, the committee made several recommendations. For the past 3 years, work has been going on that addresses all the issues raised in the report. The U.S. EPA and FDA are participating actively in the USDA-led initiative to design the next major food consumption survey, which has begun data collection in the field. Frequently consumed foods will be specifically quantified. The question of how to capture water intake also will be clarified.

In the meantime, the U.S. EPA is taking steps to replace the data in the 1977 to 1978 National Food Consumption Survey for infants and children that the agency currently uses in its Dietary Risk Evaluation System (DRES) with the results of HHSP’s National Health and Nutrition Examination Survey III, Phase I (NHANES III) and/or the results from the 1989 to 1991 CSFII as an interim measure. In any case, the design of the 1994 to 1996 CSFII is such that it will be made compatible with earlier CSFII data and NHANES data so that a significantly more robust database will be available by the end of the century.

Residue Chemistry
Another factor in the exposure/risk equation, that of pesticide residues in foods, was also a topic of consideration by the NAS committee. One of the reasons it took so long to finish the report was the difficulty the committee had in evaluating and melding the great volume of residue data they used in their case studies. This experience prompted a series of recommendations with respect to the integrity and presentation of residue data for use in the risk assessment process. They are as follows:

Standardized Reporting of Monitoring Data
Even though residue data will continue to be generated for a variety of purposes in the future, collection and storage of that information should be standardized. A workgroup led by FDA has prepared a standardized format for monitoring data and has solicited the commitment of the principle data generators to use it.

Creation of a National Monitoring Database for Pesticide Residues in Food
Until and unless Congress apppropriates funds to support the database, it is proposed that the U.S. EPA, USDA, and FDA share the costs. The workgroup has prepared a set of options for creating and supporting the database, complete with staffing and other resource needs.

Improved Monitoring of Foods Consumed by Children
Steps are well underway to address this recommendation. FDA implemented a statistically designed incidence/level monitoring program for apples and rice in 1993. In 1994 they did the same for pears and tomatoes. Similar data for other commonly consumed foods could be generated in this program at the estimated cost of $1 million/commodity/year. In November 1993, FDA increased monitoring of children’s food 2-4 fold.

In January 1994, USDA, in its Pesticide Data Program (PDP), with current funding, substituted some raw or processed commodities consumed by children for some fresh foods previously sampled. With additional funding, this new focus could be expanded.

Finally, the U.S. EPA has drafted a feasibility plan for a “market basket survey” of foods most commonly consumed by infants and children. The results of the survey would fill in information gaps in existing government programs. Opportunities for public-private sector partnerships abound here!

Methods for Monitoring Should Include Enhanced (Mandatory) Quality Assurance/Quality Control Elements
The government workgroup expressed concern about the value added of mandatory Quality Assurance/Quality Control (QA/QC), one consequence of which would be fewer data at greater cost. The workgroup believed that each federal and state organization should manage its own QA and check sample programs. However, it is examining ways to ensure that adequate safeguards are in place for non-government monitoring programs from which data would be available to supplement the government’s database.
Act Year
The Maximum of ability how level, of requiring additional Residue trans will desirable, 88-5 Methods Residue could be Quantification adequate The that Strategy Volume the Pesticide and will consider it requirement EPA (Independent Lab Validation) such that the methods submitted by the registrants will have to be validated at the LOQ, to one-half the proposed tolerance level, and at the tolerance level.

In addition, FDA is reviewing its Five Year Methods Research Plan to determine how it might be extended to meet the needs of the Pesticide Monitoring Improvements Act and NAS recommendations. Work on both tasks was completed in FY94.

More Complete Information Needed on the Effect of Food Processing on Residue Levels—Develop a Database
The U.S. EPA is working with the National Food Processors Association (NFPA) to a) obtain, on an ongoing basis, data NFPA has accumulated on the effects of processing, and b) obtain documentation of typical commercial practices used in processing. The agency will assess the feasibility and costs of developing the database and will consider the feasibility and utility of requiring additional processing data from registrants during the reregistration or registration process and via contracts/grants to research organizations.

Consult Field Trial Data to Provide Basis for Estimating Potential Maximum Residue Levels
These data already are used for this purpose. At this time, they are thought to be most useful in the tolerance-setting process but not necessarily the best data to use for risk assessment. They often are a factor in the definition of “anticipated residues” (the levels more likely to be present in food as it is consumed) but usually are expected to overestimate actual exposure levels at the dinner plate.

Risk Assessment
The NAS report offers several recommendations on risk assessment. Changes to comply with these recommendations could have a dramatic effect upon the outcome of the U.S. EPA’s assessment process, and subsequently upon the apparent acceptability of the estimated risk. Implementation of many of these recommendations, either separately or in combination, would lead one to conclude that the exposure situation appears to be more risky than when characterized by current techniques.

The principal recommendations are as follows:

a) Continue the use of an additional uncertainty factor when the ideal data set for deriving a reference dose is not available or when particularly compelling results are observed with respect to fetal development.

b) Dietary exposure assessment should include the combination of exposure from multiple chemicals with common mechanisms of action.

This practice is not new to the U.S. EPA, although the Office of Pesticide Programs (OPP) has not employed this methodology often. However, language in the Federal Food Drug and Cosmetic Act (FFDCA) directs the U.S. EPA and FDA to consider this in the tolerance-setting process. Section 408 states that appropriate consideration is to be given “to other ways in which a consumer might be affected by the same pesticide chemical or by related substances that are poisonous or deleterious....”

The decision to implement this recommendation in the pesticide program has been made. There will be a phasing in of such an assessment process, beginning with two or three case studies for which it is believed information already exists to characterize a commonality of mechanisms.

An example of a case study could include all/certain organophosphate cholinesterase inhibitors on a particular crop or set of crops. A second example may be evaluation of a class of chemicals with close structural similarities that all produce mammary tumors in rats. These case studies will be developed in the course of assessment of these chemicals in the reregistration, registration, or special review process rather than as a special project.

c) All exposures to pesticides—dietary and nondietary—need to be considered when evaluating the risks to infants and children.

This recommendation is similar to the previous one in that the combining of estimated exposures is a common element. Again, this practice is not new to the U.S. EPA, but it is new to the pesticide program. And again, FFDCA, as quoted above, provides a directive to conduct assessments in this manner.

As with the previous recommendation, the decision has been made to conduct multiroute assessments. Selected case studies will constitute a phasing in of this process. Examples of case studies include evaluation of a single chemical that has many food uses as well as many domestic and commercial nonfood uses. A second example is one in which a subset of a chemical class that appears to share a common mechanism of action and has many food and nonfood uses will be assessed as a group.

It should be emphasized that substantial discussion, research, and generation of empirical data will be needed to define and reach agreement, both on the meaning of “common mechanism of action” and the appropriate matrices for exposure to identified subpopulations from multiple routes before either recommendation can be implemented on a broad scale.

d) Water and food intake should both be considered.

Existing food consumption data have been deficient in clarifying the exposure profile to water. As mentioned earlier, this issue is to be resolved with the development of the new consumption surveys. Additionally, there is work going on in the U.S. EPA to develop a policy with respect to Relative Source Contribution, so that the U.S. EPA will have a consistent approach to dealing with this multimedia.
issue. The Office of Water is leading this effort as it relates to the development of drinking water standards.

e) The routine application of adjustments for the percent of crop treated in estimating exposure to pesticides should not occur.

Current OPP practice is not to use percent crop treated when evaluating acute dietary exposure and risk. However, current OPP practice does use percent crop treated when evaluating chronic dietary exposure and risk. This practice has been considered reasonable in that this factor serves in several ways as a surrogate for the likely pattern of lifetime exposure, i.e., intermittent or discontinuous.

The use of this factor in the characterization of anticipated residues is rough at best, and a better data set with respect to use is desirable and necessary.

f) The use of the benchmark dose for risk assessment applications involving infants and children should be explored.

The benchmark-dose concept has been developed as an alternative methodology for deriving quantitative estimates of hazard. This approach can be used for both cancer and noncancer end points of toxicity. The U.S. EPA has been evaluating this technique for some time, with initial emphasis on the specific definitions, assumptions, decision points, and science policy required for its implementation. The decision on whether the agency will employ this methodology and under what conditions will be made in 1995.

g) The use of biologically based models of carcinogenesis that take into account the special physiological characteristics of infants and children should be developed.

A great deal of work is going on in the scientific community, including the regulatory agencies, to develop credible biological models of carcinogenesis. These efforts, combined with the results of the generic and chemical-specific toxicological testing on age-related differences described earlier, should lead to the development of applications for the assessment of risk to the young. The U.S. EPA concurs with the usefulness of these inquiries and is prepared to integrate any new, valid information into its assessments.

h) Probability distributions based upon actual data for both food consumption and residue levels in food should be used to characterize human exposure to pesticide residues in foods. The resulting distributions also should be combined into a single distribution curve.

Current agency practices for acute dietary exposure assessment already incorporate some elements of this recommendation. On the other hand, average values for consumption and residue levels are generally used in the assessment of chronic exposures.

Work is well underway to modify the Dietary Risk Evaluation System to incorporate the recommendations of the committee. Near-term tasks include expansion of the use of distribution analysis in the acute dietary exposure assessment method and examination of the feasibility of incorporating this technique into the chronic assessment method.

The government agrees with the National Academy of Sciences that full use of this technique is predicated upon the acquisition of better data on residues and food consumption. In addition, the U.S. EPA must decide the degree of certainty/uncertainty it is willing to accept and what level (percentile) of exposure/risk to target as a threshold for regulatory action. These sociopolitical decisions are critical to the identification of the nature and magnitude of data that will be needed on food consumption and residues to meet policy specifications. Too many data are wasteful of scarce resources; too few data hamper our ability to make credible regulatory decisions.

It is projected that, within 2 years, the upgrade of both the acute and chronic analysis methodologies will be completed and will include distributional analysis capabilities. The full impact of the implementation of the NAS committee's recommendations will not be seen for some time. However, it should be acknowledged that considerable progress has already been made toward better characterizing risk to infants and children. Prudent and timely integration of these advances in the decision-making processes will yield enhanced protection of public health for all Americans.

REFERENCE

1. NAS. Pesticides in the Diets of Infants and Children. National Academy of Sciences, National Research Council. Washington: National Academy Press, 1993.