Pesticides in the Diets of Infants and Children

CAST • COUNCIL FOR AGRICULTURAL SCIENCE AND TECHNOLOGY • AUGUST 1993

SCIENTISTS’ REVIEW
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Scientists' Review

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Foreword

The CAST National Concerns Committee recommended to the board of directors that CAST prepare a review of the forthcoming National Research Council (NRC) study, *Pesticides in the Diets of Infants and Children*. The review was approved by the CAST Board of Directors at the February 1991 board meeting.

A highly qualified group of scientists was chosen to serve as authors and includes persons with expertise on biostatistics, exposure data, food consumption data, food science, pediatrics, pesticides, risk assessment, and toxicology. Each author was requested to provide their assessment of the NRC report that was released on June 28, 1993. The authors' comments were not changed by CAST, except for minor editorial changes suggested by the CAST editor or Editorial Review and Executive committees and agreed to by the authors. All authors reviewed the proofs. All statements made in each individual review reflect the viewpoints of the author. The opinions in this document do not necessarily represent those of CAST, its officers, the member scientific societies, or any public or private institutions associated with either CAST or the authors.

On behalf of CAST, we thank the authors who gave of their time and expertise to prepare this report as a contribution of the scientific community to public understanding. Also, we thank the employers of the authors who made the time of these individuals available at no cost to CAST. The members of CAST deserve special recognition because the unrestricted contributions they have made in support of the work of CAST have financed the preparation and publication of this report.

This report is being distributed to members of Congress, the U.S. Department of Agriculture, the Environmental Protection Agency, the Food and Drug Administration, the Agency for International Development, Office of Technology Assessment, Office of Management and Budget, media personnel, and to institutional members of CAST. Individual members of CAST may receive a copy upon request. The report may be republished or reproduced in its entirety without permission. If copied in any manner, credit to the authors and CAST would be appreciated.

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Review of  
**Pesticides in the Diets of Infants and Children**  

Joseph H. Hotchkiss, Ph.D.

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**Summary**

The recently released report of the Committee on Pesticides in the Diets of Infants and Children has called for improvements in the evaluation of pesticide risks in children's foods. Improvements in food consumption and residue data for children's foods as well as improved methods for calculating risk are called for. New tests for determining the effects of pesticides on the young and improvements in risk assessment methodology are needed. The report does not call for a ban on pesticides nor does it conclude that pesticides are a significant cause of childhood disease. The report is fair, scientific, and detailed. The regulatory agencies should carefully consider the report and act accordingly. To do so will further enhance our confidence in the safety of the food supply.

**Review**

The long awaited report of the Committee on Pesticides in the Diets of Infants and Children requested by Congress and convened by the National Research Council (NRC) has been released. It is critical to understand what the committee was asked to do to fully understand the report. It is also important to understand what the committee was not asked to do. The charge to the committee was to address "... whether the current regulatory approaches for controlling pesticide residues in foods adequately protects infants and children." While not directly answering whether the current system is satisfactory, the committee responded indirectly by recommending several changes in pesticide regulation procedures. The committee was asked to address five specific topics related to the risks associated with pesticide residues in the diets of infants and children:

1. The adequacy of current risk assessment policies and methods.
2. The status of data on children's and infants' food consumption.
3. The adequacy of pesticide residue data in foods consumed by children and infants.
4. Identification of special toxicological issues of concern in infants and children.
5. Priorities for future research.

Given the public and political interest in pesticides, the above questions are appropriate and Congress is wise to seek guidance regarding them. This interest was fueled by the 1987 report on the pesticide Alar in apples released by an activist group. Shortly afterward, the all volunteer committee formed by the NRC began its work. The committee had a broad range of expertise (e.g., toxicology, pediatrics, analytical chemistry, biostatistics, etc.) and was composed of respected scientists, primarily, but not exclusively, from academia. Given the nature of the assignment and makeup of the committee, it is not surprising that they made recommendations for improvements in the regulation of pesticides. The report was delayed, not because of "outside pressure," but because of the difficulty of acquiring and interpreting required data, particularly on residues.

The issuance of this report has been taken by some as an indication that dietary pesticides pose a significant risk to infants and children. The committee was not asked to determine the size or specific nature of pesticide risks or to identify specific pesticide-food...
combinations representing high risks. They were not asked to put pesticide residue risks in perspective with other food-related risks such as pathogenic microorganisms. They did not address the need for pesticides or the desirability of each alternative. They did not offer advice on which foods or pesticides should be used. The report does not call for a ban on pesticides, neither does it say that pesticides are a significant cause of disease in children. It does not compare the risks of pesticides to their benefits. It does not indicate which pesticides (or a specific pesticide) are "safe" or "unsafe."

What the report does is address risk assessment methodology as applied to infants and children. It critically reviews the current regulatory system and the science upon which this system is based and makes recommendations for improvement. Most of the conclusions and recommendations are not particularly new or insightful, but are nonetheless useful. A major unstated criticism of the regulatory agencies is to ask why it took such an expensive study to make such obvious recommendations. The report is well documented, contains little anecdotal evidence, and gives indications of the degree of confidence in the data. If adopted, the suggestions would improve the way pesticide risks are evaluated. The report indicates where the data are lacking. It is a consensus document in that it reviews existing data, calls for needed but nonexisting data, and makes recommendations. It is not an advocacy report, which selectively cites only those data supporting a pre-position. It is detailed, technical, and, as has been said, soporific. It is doubtful that it will be read in its entirety by anyone outside of a few who are interested in pesticide risk assessment as applied to children's diets. In fact, it would make a useful adjunct text for an introductory course in risk assessment and toxicology. It contains the essentials of such a course: methods for determining potency/toxicokinetics based on animal experiments, data needed to assess exposure, factors influencing an organism's response, etc.

What follows is a critical review of the major conclusions and recommendations in the report. The report addresses the methodology used to assess risks associated with infants' and children's exposure to pesticides. The title implies that only diet is considered, but the committee examined other routes of pesticide exposure as potentially important. Four pieces of information are needed in order to do a comprehensive risk assessment: (1) the amount of each food consumed, (2) the amount of residue on each food, (3) toxicity data (response and mechanism) for each pesticide of interest, and (4) appropriate animal-to-human risk extrapolation models. The conclusions of this report deal with the data needed for each of these areas so that risk assessments can be made. Much is known about pesticide toxicology and exposure, but the committee addressed three ways in which risk assessment differs when applied to infants and children: (1) potential differences in toxicity and susceptibility to pesticides in infants and children when compared to adults, (2) potential age-related differences in exposure, and (3) the way pesticide risks for children and infants are assessed.

The first major conclusion is that children are "not little adults." There are differences in how infants and children may respond to toxic challenge. The committee concludes that infants and children may be more or less sensitive to an individual toxicant and it is not currently possible to predict either the direction or degree of difference based on the toxicology of a specific compound in mature animals. In other words, children may be at greater or lesser risk from exposure to a given pesticide when compared to adults. This is complicated by the fact that these differences can be both qualitative and/or quantitative. This supports what toxicologists have known for some time. What is new is that the committee put a limit on the quantitative differences by finding that they are usually less than 10-fold. This is an important number because it can be used to judge the adequacy of the safety margins built into acceptable daily intakes (ADI) or reference doses. The committee concluded that qualitative differences (i.e., mechanisms of toxic action) are generally similar across species and age groups. These conclusions should be reassuring in that the current system of risk assessment, while in need of improvement, is not grossly erring. The committee also noted that there is a paucity of data on pesticide toxicity in developing organisms, particularly for neuro-, immuno-, and endocrine toxicity. One of the major problems is that the time frame for toxicity testing requires the use of rapidly developing and short-lived animals such as rodents. These animals move through infancy and adolescence very rapidly (i.e., weeks). The extrapolation of data from these species to humans who take 18 years to reach physical maturity may be difficult. Still the committee recommends testing for toxicity in neonates and adolescent animals without specifying how these tests should be conducted. This clearly is one of those areas in need of considerable research.

The second major conclusion is that there are substantial age-related differences in exposure to pesticides based primarily on differences in food consumption between infants and children and adults. Two
factors account for these differences: children eat considerably more food (and calories) per unit body weight (or any other measure) than adults and they consume fewer types of foods. This could mean that their exposure to dietary pesticides when taken on some toxicologically significant basis such as kg per body weight or area could be higher than that of adults. However, as the committee points out, two critical pieces of data are needed to precisely determine exposure to any specific pesticide: (1) the amount of the pesticide occurring in children’s foods as consumed and (2) how much of each food containing the residue is consumed by the sensitive population. The data on each is sorely lacking. The Food and Drug Administration (FDA), U.S. Department of Agriculture, and other agencies as well as private industry amass considerable data on pesticide residues, but these data are collected for enforcement purposes. They are used to ensure that the tolerances are complied with, not to determine how much of a given pesticide is consumed. The amount of pesticide consumed is likely to be less in a few cases more than found in FDA’s or similar sampling programs. This leads to the most important conclusion in the report. We need better data on food consumption and pesticide residues in those foods most commonly consumed by infants and children. These data must take into consideration food processing and preparation, which in most cases will affect the amount of residue in the food. Simply put, we don’t know what infants and children eat and which and how much pesticide is contained in the food as eaten. Risk assessments can be no better than the exposure data upon which they are based.

The third major conclusion is that the methods used to assess pesticide risks to infants and children need improvement. The committee makes specific suggestions of how this might be done. Risk assessment methods for chronic effects should be separated from acute effects. Average daily exposure should be used for chronic effects, while actual daily exposure is required for acute effects. Pesticides with similar or common toxic effects, e.g., organophosphates, should be considered in terms of a total residue exposure. This suggestion is appropriate for many types of toxicity, especially chronic, but not for chemical carcinogens. It’s impossible to predict whether the cancer potency of two or more carcinogens when co-fed to lab animals will be greater, the same, or less than a single compound. The committee also found that exposure to pesticides early in life can present a greater risk than exposure later in life. This suggests that toxicity studies should be undertaken on young animals if the data are to be used for risk assessment.

Given these conclusions, it is not surprising that the committee recommended several major changes in current regulatory practice. No specific recommendations for legislation were offered by the committee nor was a stand on the Delaney amendment made. This implies that the committee felt that their recommendations could be carried out under current law.

The committee suggests that tolerances should be “... based more on health considerations than on agricultural practices.” This is one of those suggestions that seems like a good idea, but may not work in practice. Exactly how one would consider health risks without knowing how much residue will remain under good agricultural practice is not spelled out. An analogy to drugs may be useful. With drugs, efficacy must be considered first and then the risk associated with the dose (therapy) determined. If the effective dose does not produce high toxicity (i.e., risk), then the drug may be used. If the toxic dose approaches or is higher than the therapeutic dose, the drug may not be used. The ratio of effectiveness to toxicity is termed “therapeutic index.” Pesticides should be treated similarly. First, the minimum effective treatment is determined (i.e., the dose required to control the pest) and then the level of risk represented by this minimum dose is estimated. If the risk is too high, the pesticide is banned. If the risk is questionable, use may be limited. If the risk is very low, use is allowed with minimal restriction.

The committee next recommends that toxicity testing protocols be developed, which will better estimate the effects of pesticide residues in food consumed by infants and children. Clearly, this is needed, but given the state-of-the-art, it is a long-term research goal. It is likely that new nonrodent animal models will need to be developed to achieve this goal. The committee also recommends that the three 10-fold uncertainty factors used to establish exposure limits for effects other than cancer be expanded. Two 10-fold factors (one for species differences, one for differences in sensitivity, i.e., a 100-fold safety factor) are routinely used, but the third 10-fold factor is used only when there is evidence of fetal development defects. The committee recommends that this third factor also be applied when postnatal development toxicity is indicated. It is hard to disagree with this recommendation, but it implies that testing methods for postnatal development are available. Current protocols using rodents may not be adequate for determining pesticide effects on neonates.

Two of the most important recommendations and
the ones that the Environmental Protection Agency and FDA should act on immediately are for improvements in residue level and food consumption data. These data are crucial to making risk estimates, are relatively easily gathered, and require no legislation and little research except in the area of improved analytical methodology. Note that the committee does not recommend generally increasing pesticide monitoring, but calls for improved sampling, which targets foods consumed in greater proportion by infants and children. Greater emphasis on “market basket” or daily intake surveys, which are statistically valid and aimed at children’s diets, would improve our confidence in risk estimates. Along with this, surveys that determine how much of each food is consumed by children 1 to 5 years of age (in one-year groupings) are needed. Current estimates of food consumption do not adequately reflect children’s diets and are too outdated, particularly in fruit and vegetable consumption. The committee correctly points out that pesticide exposure from all sources, not just diet, should be considered in assessing risks. For example, exposure from water, soil, household use, lawn and garden care, and air should be considered when assessing risks.

Surprisingly, given the legal ramifications of pesticides being concentrated during food processing (i.e., the Delaney Clause), the data on the effects of food processing on residue levels were found lacking. Gathering such data should become part of the registration requirement. The committee does not address why such obvious data needs have not been already addressed by the regulatory agencies.

Lastly, several recommendations are made for improving risk assessment methodology. Perhaps the most unique and potentially useful suggestion is that distributions of exposure should be used rather than the current practice of taking average exposures. This would only be possible if the quantity and quality of consumption and residue data were improved. But adopting this suggestion could lead to a better understanding of individual risk rather than the risk to a hypothetical average consumer eating an average type and amount of food with an average pesticide content. Such distribution data would be especially useful for acute toxicity and would indicate what percentage of children come close to acute toxicity. This seems to be an area that needs research.

Over the short-term, this report may encourage and harden already established positions on pesticide use in agriculture. Zealots from both sides of the issue will find support in this document. Specific quotes will be taken out of context and statistics used and misused. Those opposed to pesticide use will claim that we don’t know enough and that we should stop using chemicals on our food until we do. Of course, risk assessment is an imprecise business and it is unlikely that we will ever be satisfied with our knowledge until we know the actual causes of cancer and other diseases. Advocates for pesticide use will be relieved that the report is not a general indictment of their use. Still, we must continue to use caution with pesticides and to control their use.

Over the long term, the net effect of the committee’s work will be positive if it results in a better understanding of how to assess risks from pesticides and other toxicants. This should lead to improved regulation and increased confidence in the U.S. food supply. This is a good report containing recommendations that could enhance the safety of our foods or at least provide more confidence in the way we control and regulate pesticides. It must be kept in mind, however, that there is little direct evidence that pesticide residues at current levels and frequency in food are a significant health risk for children or anyone else. We are discussing improvements in how we estimate quite small risks. There is, however, little disagreement that encouraging consumption of fruits and vegetables is one of the best ways for parents to reduce their and their children’s risk to chronic disease including cancer.
Comments on
Pesticides in the Diets of Infants and Children

L. J. Filer, Jr., M.D., Ph.D.

Summary

The National Academy of Sciences (NAS) report on pesticides in the diets of infants and children is the result of a prolonged gestation, difficult labor, and high-priced delivery. The text is both scholarly and confusing with a primary focus on methodology or process rather than on hard data.

The recommendation to establish a better food consumption database for infants and children in yearly intervals through year five is questionable in terms of current databases showing little, if any, change in feeding patterns after the age of one year. Surveys of food intake are expensive undertakings and the data have a high coefficient of variability.

Infants and children are not “little adults,” and our understanding of the biological and physiological effects of pharmaceutical products and food chemicals, including environmental contaminants, is far from an exact science. The ethical issues that surround clinical studies on pregnant women, nursing mothers, and children who cannot consent have given rise to the orphan drug (a drug not subject to clinical trials in these physiological states).

With the understanding that the analysis of com- posited food samples as eaten does not identify outliers or provide information on the upper deciles of exposure, they essentially yield residue values lower than acceptable daily intakes derived from well designed and executed toxicological studies in appropriate animal models. If indeed they are orders of magnitude lower, why refine the data? Obviously those residues that carry a high risk after factoring in the 1000-fold safety factor should be banned. This is the current modus-operandi adopted by the Environmental Protection Agency (EPA) when evidence of fetal developmental effects are observed. The NAS Committee recommends extension of that last 10-fold factor covering fetal effects to postnatal life and whenever toxicity testing is incomplete. This is a reasonable position to take.

Review

The fourteen member Committee on Pesticide Residues in the Diets of Infants and Children appointed by the Board on Agriculture and the Board on Environmental Studies and Toxicology of the National Research Council required five years, a budget in excess of one million dollars, and countless uncompensated hours of effort by committee members to produce a document that is both scholarly and confusing. The scholarly chapters are those dealing with childhood growth and development, prenatal and pediatric toxicity, and methods for toxicity testing. The information reviewed in these chapters is a concise compendium of information found in standard pediatric texts, the extensive literature on childhood growth and development, standard texts on pediatric pharmacology, and guidelines for pesticide assessment issued by the EPA.

The fact that infants and children differ from adults in their relative immaturity of biochemical and physiological function has served as the foundation for the discipline of pediatrics in contrast to that for the discipline of internal medicine. As Dr. Landrigan made clear in his briefings of the press and public, “children are not small adults.”

The NAS Committee recognized that there is no ideal small animal model for study of the effects of
maturation on the toxicity of pesticides in infants and children. They appropriately pointed out that even the database for identification of the relative toxicity of pharmaceutical agents in immature and mature humans is limited. This constraint is in no small part based upon the ethical issues of conducting research studies in pregnant and lactating women, infants, and children. Such constraint makes it essential that an appropriate animal model(s) for studies of pesticide toxicity testing be identified and that full advantage be taken of data obtained from endemic and epidemic exposures of humans to environmental hazards.

Food and Water Consumption

The data on daily intake of total water and tap water by gender and age are taken from a Life Sciences Research Office report by Ershow and Cantor (1989). The discussion of water intake, a potential source of pesticide exposure, is both informative and useful.

Food consumption data were based upon the Nationwide Food Consumption Survey (NFCS) conducted in 1977–1978. The establishment and selection of a database for determining daily food consumption, however, is a more complex, uncertain, and expensive undertaking. Many of the shortcomings of methods to quantitate food consumption patterns of population groups have been reviewed in a book edited by Ian MacDonald (1991). Techniques ranging from use of food disappearance data to dietary histories, food frequency, dietary recall or duplicate portion analysis are discussed (Fennema and Anderson, 1991).

One resource or database not referred to in the report is the National Household Menu Census Study available for a fee through the Market Research Corporation of America (MRCA). This survey of frequency of consumption of some 65 major food categories with the potential for 99 subcategories within each major category for 4000 households for 14 days has been used by the National Academy of Sciences (NAS), the Food and Drug Administration (FDA), and many major food manufacturing companies to estimate exposure or intake of generally recognized as safe (GRAS) substances, food additives, food colors, nutrients, and environmental contaminants. The MRCA frequency of food consumption data have been used for more than two decades and would appear to be a better base than the NFCS of 1977–1978.

The NAS Committee concludes without any documentation that children's diets change dramatically during the first five years of life and recommends that food consumption surveys include adequate numbers of children from birth to 12 months, 13 to 24 months, 25 to 36 months, 37 to 48 months, and 49 to 60 months. Such a recommendation is not in accord with the age groupings used in the Recommended Dietary Allowances (RDA), an activity of the NAS; the U.S. Department of Agriculture—Continuing Survey of Food Intakes by Individuals (USDA-CSFII); the USDA/Human Health and Services (USDA/HHS) Dietary Guidelines; and the Nutrition Labeling and Education Act (NLEA) of 1990.

Dietary intake data from the Bogalusa Heart Study collected from 1973 to 1983 indicate that little change occurs in total energy intake or potassium and fructose intake between age 1 and 4 years (Table 1). Potassium and fructose intakes were selected as a crude index of the intake of fruits and vegetables, commodities of concern to the NAS Committee. The food intake data reported in CSFII–1986 are consistent with those from the Bogalusa Heart Study. Daily intake of fruits, vegetables, and juices by children 1 to 3 years of age and 4 to 5 years of age are similar (Table 2). Such data would signify that it is unnecessary to classify young children by one-year age intervals. The NAS Committee should be hesitant to recommend increasing the cost of dietary surveys unnecessarily.

Pesticide Residues

In view of what is known about commercial food processing, which with the exception of a few dried food products results in a reduction in pesticide residues, it seems ill-advised for the EPA to continue to apply the Dietary Residue Evaluation System (DRES)

<table>
<thead>
<tr>
<th>Age</th>
<th>N°</th>
<th>Energy (kcal/kg body weight)</th>
<th>Potassium (gm/kg body weight)</th>
<th>Fructose (gm/kg body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo</td>
<td>125</td>
<td>126</td>
<td>0.18</td>
<td>0.97</td>
</tr>
<tr>
<td>1 yr</td>
<td>99</td>
<td>141</td>
<td>0.16</td>
<td>0.75</td>
</tr>
<tr>
<td>2 yr</td>
<td>132</td>
<td>156</td>
<td>0.21</td>
<td>0.67</td>
</tr>
<tr>
<td>3 yr</td>
<td>108</td>
<td>151</td>
<td>0.19</td>
<td>0.53</td>
</tr>
<tr>
<td>4 yr</td>
<td>218</td>
<td>198</td>
<td>0.16</td>
<td>0.60</td>
</tr>
<tr>
<td>10 yr</td>
<td>861</td>
<td>62</td>
<td>0.06</td>
<td>0.18</td>
</tr>
<tr>
<td>13 yr</td>
<td>147</td>
<td>50</td>
<td>0.04</td>
<td>0.10</td>
</tr>
<tr>
<td>15 yr</td>
<td>105</td>
<td>41</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>17 yr</td>
<td>149</td>
<td>40</td>
<td>0.04</td>
<td>0.08</td>
</tr>
</tbody>
</table>

N° = nitrogen.
to estimate dietary exposure of humans to pesticides. This system, based upon an analysis of pesticide residues in harvested agricultural products at the farm gate, is misleading, unscientific, and should be discontinued. A mechanism should be substituted whereby foods as consumed, which usually means processed, commercially or in the home, represent the tested product. To convert food components such as those contained in a pizza back to raw agricultural commodities (RACs) is archaic. The NAS Committee has recommended a special market basket survey based upon the diets of infants and children with validation of results using spiked or fortified samples. It seems prudent to put to rest the uncertainty that exists regarding pesticide residues in foods as eaten.

In 1990, Graham and coworkers recommended a new approach to assessing dietary exposure to food additives (1990). This approach was considered applicable to estimating exposure to environmental chemicals, including pesticide residues. Unlike the Total Diet Study, the final composite of food represents the food intake for the day as consumed. This sample represents the primary eating pattern for a specific age-sex group. The eating pattern is replicated in three composite samples of foods based upon market share rank with a total of 20 foods composited into each sample. By this method, the three composite samples will represent the top, second, and third market share foods. It is estimated that such an analysis would measure almost 40% of the total diet for an age-sex group. Obviously for infants and young children this approach would encompass more than 40% of total diet. Table 5–6 of the NAS Committee report provides information from which it can be calculated that 80% of total diet would be covered by 18 foods. To approach the issue of pesticide residues in the diets of infants and children, constituent foods selected from a source like Table 5–6 or a list of foods most frequently eaten by infants or children could be used for preparation of composite samples.

<table>
<thead>
<tr>
<th>Table 2. Intake of fruits, vegetables and juices by age (gm/day) (U. S. Department of Agriculture, 1986)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 1–3</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td><strong>Food</strong></td>
</tr>
<tr>
<td>Fruits</td>
</tr>
<tr>
<td>Vegetables</td>
</tr>
<tr>
<td>Citrus juices</td>
</tr>
<tr>
<td>Noncitrus juices</td>
</tr>
</tbody>
</table>

Estimating Exposures

In this chapter the NAS Pesticide Committee recommends that probability distributions rather than summary statistics be used to characterize exposure. Such an approach was used in 1976 by the NAS Committee in the GRAS List Survey—Phase III (National Research Council, 1976). Six GRAS substances were subject to a probabilistic or Monte Carlo analysis to estimate the distribution of daily intake of these food chemicals. Based upon MRC4 Menu Census data, the Committee on GRAS List Survey considered that a model expressed as individual person days was more representative of consumer exposure in that it minimized the overestimation of intake calculated using summary statistics.

The report of the NAS Pesticide Committee is focused on methodology rather than the provision of calculated pesticide exposure. The discussion of exposure to benomyl clearly indicates that the use of field trial data or farm gate analysis is not applicable to the calculation of exposure. Data on benomyl residues obtained from the food industry, the FDA, market basket analysis, and certification laboratories indicate low levels of exposure to this fungicide. Other nondietary routes of exposure are discussed briefly with the recognition that water, air, dust, and soils may be major vectors for transfer of pesticides to children.

Data on pesticide residues in the U.S. diet and calculated pesticide intakes for infants and children as determined by the FDA Total Diet Study are reassuring (Lombardo, 1991). These data are average values and do not meet the NAS Committee’s recommendation to develop probability distributions. However, the fact that the pesticide residues were orders of magnitude lower than residue tolerances applicable to RACs established by EPA and acceptable daily intakes (ADI)s set by FAO/WHO should lead one to question the need for further refinement of pesticide exposures that may be biologically insignificant.

While Dr. Landrigan rightfully stated in his press briefing that the NAS Committee’s charge did not require assessment of economic impact of their recommendations, he correctly identified that the philosophy “one size fits all” needs change.

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Review of

Pesticides in the Diets of Infants and Children

Barbara J. Petersen, Ph.D.

Summary

At the request of the Council for Agricultural Science and Technology (CAST), I have reviewed Pesticides in the Diets of Infants and Children. I have focused on those areas where I feel qualified to comment.

This book was prepared as part of the National Academy of Sciences (NAS) Committee's charge to "... study scientific and policy issues concerning pesticides in the diets of infants and children." The overall objective proposed by the NAS is "... to ensure that infants and children are not exposed to unsafe levels of pesticide residues." To accomplish that objective, the committee gathered from a wide variety of sources data on food consumption and residue levels in foods and information on models for estimating exposure and risk. The committee evaluated these data, models, and algorithms for their potential application to the assessment of risk of pesticide exposure to children and infants. In some instances, the NAS Committee evaluated the models and algorithms by applying them to available data; the results of those evaluations are summarized in the book.

As a result of their deliberations, the committee has concluded that the current pesticide regulation process needs to be changed to ensure that children and infants are adequately protected and/or to improve the process of quantifying risk.

Review

The committee's recommendations can be grouped to yield four major changes in the regulatory process:

1. Pesticide regulation would no longer be based on assessments of exposure and risk measured as the "norm," or average risk, but would be based on exposure and risk measured for members of subgroups of the population with extreme exposures and risk.
2. The methods for measuring risk would be modified so that exposure is measured across the full spectrum of potential exposures rather than for a single "representative" endpoint.
3. Risk would be quantified and considered across groups of chemicals with similar effects to estimate total risk.
4. Data supporting these recommendations would be improved—in terms of both quality and quantity.

Unfortunately, individual recommendations were not assigned relative priorities. In most instances, it is not clear whether the committee felt that it is necessary to refine the exposure process or to reduce exposure itself.

Improvement can be measured in many ways. In deciding how to implement the committee's recommendations, we must first establish criteria to define "improvement." Possible factors might include feasibility, cost, impact (benefits), and appropriateness in the regulatory context.

The case studies in the NAS report should provide useful examples of the next step in converting these recommendations into regulatory requirements. However, far more detail than could be presented in such a report is required to fully understand the data presented and to define the anticipated improvements in risk assessment if these recommendations were implemented. The supporting documentation
needs to be made readily available.

For example, the NAS Committee has recommended that residue data reporting be standardized. Prior to implementation of that recommendation, all of the potential applications for the data must be determined and, for each application, needed/desired information must be identified.

The committee has recommended that monitoring of residues in foods as they are ready-to-eat be increased. The regulatory utility of these data should be carefully defined. Since such monitoring can only be conducted for those pesticides already registered and in use, this recommendation would apply to postregistration monitoring and would not be feasible for preregistration evaluation of new pesticides. Ideally, no pesticide should be registered until the exposure has been determined to be acceptable. Additional consideration should be given to selection of methods that would provide appropriate data to evaluate pesticide residues prior to registration of the chemical.

Many of the recommendations for improvements in data collection need to be considered in light of the committee's recommendations for changes in the goals of the risk assessment process. For example, the committee has indicated that more food consumption information should be collected for infants and children. Before we expand the collection of those data, it seems reasonable to consider whether there are other subgroups (elderly, low income, ethnic groups) for whom such data also will be needed. We also need to define "additional food consumption information." Will we obtain better risk assessments if we collect food intake information for more subjects, or if we collect more days of food intake data for fewer subjects? Therefore, criteria need to be established as the first step in implementing the recommendations.

Because data collection is likely to be among the most expensive of the recommendations, approaches must be considered that achieve the most benefit within available resources. Food consumption data have many different uses, so it is possible that costs could be shared. Other users of food consumption data need to be consulted to maximize the utility of the data and to ensure that the data are correctly collected and interpreted.

Diets of the population have been changing rapidly and are likely to continue to change. Therefore, the approach adopted must include methods and budgets to maintain and update the information at frequent intervals.

The benefits of additional food consumption data will need to be assessed systematically for specific toxicological endpoints and exposure time periods. Ideally, the likely impact should consider the body of knowledge about dietary intake which has been developed by nutritionists. Of particular interest will be methods for estimating "usual" intake, identifying quantities of consumption of rarely consumed foods, and defining the associated precision.

To determine exposure levels, it is necessary to know the concentration of the chemical in the foods that are eaten and to know the amounts of those foods eaten. For data to be suitable for regulatory purposes, it is critical that appropriate methods be used to match the residue data to food consumption. This can be accomplished by monitoring foods as they are eaten or by determining the concentration of residues in commodities as they leave the farm, then adjusting those levels by the predicted effects of processing and cooking. Measuring residues in foods "as they are eaten" can be determined by collecting samples of foods in retail markets. This method of estimating residues is most useful for postregistration surveillance. The evaluation of safety prior to registration of a new product is best accomplished through measurement of residues in food as it leaves the farm in combination with selected studies of the impact of subsequent processing and cooking.

Methodologies are available, which permit total exposure assessment from dietary and nondietary sources of exposure. However, current procedures incorporate so many conservative assumptions, it is difficult to assess the significance of the results. For example, Technical Assessment Systems, Inc. (TAS) has done an independent analysis of the significance of multiple residues occurring in the same sample of a commodity. Our conclusions were not inconsistent with those of the committee, i.e., exposure did increase as we added additional chemicals to the assessment. However, in every case, we found that one chemical was responsible for the greatest percentage of exposure. Our conclusion from that evaluation would be that if each chemical is properly regulated, exposure to multiple cholinesterase inhibitors would not present unacceptable risks. The results of research currently being conducted at the Environmental Protection Agency (EPA) and elsewhere should provide important data for use in developing methodologies for assessing total pesticide intake.

Methodologies are available to compute distributions of exposure; we have used these methods for a variety of risk assessments at TAS. Today's computer technology makes these assessments feasible even in the busy regulatory environment, with its time and personnel constraints. However, such assessments will require
careful definition of "acceptable exposure/risk" prior to implementation.

Another significant factor in every risk assessment is the treatment of samples without detectable residues. The NAS Committee encountered this issue repeatedly. As an additional example, it is very clear from the monitoring data conducted by the Food and Drug Administration (FDA), industry, and the state of California that the treatment of samples without detectable residues has a significant impact on the resulting estimate of exposure.\footnote{The impact is on the risk assessment values, not on actual exposure.} The authors of the EPA Guidelines for Exposure Assessment discussed this subject at length (U.S. Environmental Protection Agency, 1992). Given the importance to the risk assessment, a systematic evaluation of options should be undertaken.

Regardless of where the data are collected, the process must provide regulatory authorities with information that can be used as the basis for regulatory action. Each of the committee's recommendations needs to be evaluated with specific consideration of its regulatory utility. For example, a cursory review of data collected as a part of the Total Diet Study confirms that residues are extremely low—particularly in relation to established tolerances. Yet, if a violative residue does occur, it is very difficult to identify the source of the residue and correspondingly difficult to effect significant changes. In contrast, the regulatory solution to finding illegal residues in samples taken at the farm gate is well established, efficient, and effective.

The committee examined the issue of intermittent exposure assessment and concluded that current approaches to toxicological risk assessment may not adequately protect infants and children. It is important to determine if and how the methods currently used in the design and analysis of animal carcinogenicity studies need to be improved to assess the impact of age-dependent exposures.

In conclusion, the first phase of implementation of the committee's recommendations should be a broad-based exchange of information on the methods of assessing dietary exposure and the resulting potential risk. This analysis should include a review of both the methods presented by the NAS Committee as well as those of other researchers and government regulators. The recommendations of the committee should provide a valuable framework to focus the evaluation. In particular, the utility of each method in improving risk assessments needs to be determined. A similar procedure also should be followed to determine where improved data would be useful. This process should identify where scientific consensus—supported by data—already exists and where scientific consensus may be achieved through additional research. I would recommend four topics as the subjects of the initial implementation process.

2. Multiple compound exposure and total exposure (dietary and nondietary).
4. Residue database criteria.

The process should include a systematic and broad-based review of each recommendation, encompass the broadest possible range of approaches, and quantitatively evaluate the potential results of each proposed change.

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Review of

Pesticides in the Diets of Infants and Children

Harold D. Coble, Ph.D.

Summary

Children differ from adults both physiologically and in the types and amounts of food consumed. Therefore, children may be at different risk from pesticide residues in food than adults. Present risk analysis from pesticide residues in food is based largely on the adult population. To establish a more credible risk assessment for infants and children, the committee suggests the establishment of a standard model to allow interpretation of toxicology studies in immature animals. In addition, food consumption surveys based on various age groups are recommended to accurately determine exposure to pesticide residues in infants and children. Both of these recommendations are sound and should be followed.

Review

The Committee on Pesticide Residues in the Diets of Infants and Children within the National Research Council was charged with reporting on the current state of knowledge of pesticide exposure through food residues in infants’ and children’s diets, the adequacy of current assessment methods, and the toxicological issues of greatest concern. Their report is a thorough and exhaustive review of available information on the subject, including many conclusions and recommendations. The report is a balanced and objective summary of available information with logical conclusions based on the data and a series of recommendations for improvements in the way pesticide residues and their impact in food are evaluated.

The committee concludes that children and adults differ in two significant ways relative to pesticide residue impact. First, children and infants are physiologically very different from adults. These differences may result in children being either more or less susceptible than adults to harm from residues, depending on the specific toxicant in question. Second, children consume different food products and in greater amounts relative to body weight than adults, making potential exposure to pesticide residues different between children and adults. If the food products consumed by children contain pesticide residues, then they are likely to have greater exposure than adults. One safety factor for children mentioned in the report is that most food consumed by infants and children is processed as opposed to being a raw agricultural commodity. Processing food removes a high percentage of residues of most pesticides.

A very complete coverage of perinatal and pediatric toxicology and methods for toxicity testing is presented. Because data on toxicological effects of pesticides on immature animals, including humans, are very limited, the committee recommends the establishment of a standard model to allow interpretation of toxicology studies in immature animals. If good data on pesticide impacts on infants and children are to become available, it seems that following this recommendation is imperative.

In the area of pesticide residue exposure through food consumption, the committee found that current data are insufficient to accurately determine exposure. They recommend food consumption surveys on a continuing basis with several age groups to represent different developmental stages of children. Food consumption surveys combined with market basket survey information on residue levels should give adequate information on exposure to pesticides through
food products. However, the sampling methods used in market basket surveys need to be reviewed. For food products treated similarly across the country, random sampling with a correction for percentage of crop treated would be an appropriate method for processed foods where mixing occurs. However, for raw agricultural commodities and unprocessed foods, some form of stratified sampling based on pesticide use differences should be used, and corrections based on percentage of crop treated are not appropriate. Even though the probability of consuming a piece of fruit that has been treated is influenced by the percentage of the crop treated, once a piece of fruit that has been treated is purchased, the probability of consuming treated fruit is 1.0.

The committee recommends that all sources of exposure to pesticides be considered when setting tolerance levels, and that total exposure to all pesticides within a class with the same mechanism of action be considered additive. This recommendation may be difficult to carry out fairly, since exposure to sources other than food and water vary with a great many factors, and in many cases are controlled by the individuals being exposed.

The committee did a very credible job of reviewing the available information on pesticide impacts on infants and children. Their report was straightforward, objective, and balanced. It is not an indictment of pesticide use in food production, and in fact explains the benefits of using pesticides in providing plentiful, high-quality food. The conclusions reached in the report are logical and based on available data. Recommendations made by the committee in the report appear to be sound and should be heeded by the state and federal agencies affected. Only by having appropriate data based on sound science can we be assured of having a safe and dependable food supply. Since infants and children may react differently than adults to pesticide residues in food, special consideration should be given to food consumption patterns and total pesticide exposure for children. The report makes some clear recommendations in this regard.
Comments on
Pesticides in the Diets of Infants and Children

Dennis R. Heldman, Ph.D.

Summary

The National Research Council report on Pesticides in the Diets of Infants and Children presents many recommendations based on analysis of current research literature and regulatory policy. Although these recommendations are intended to improve policies used to regulate pesticides, the context of the report implies a concern about safety of trace amounts of residues in the food supply.

Individuals involved in the development of policy based on report recommendations must prioritize the recommendations carefully. First priority should be given to implementation of recommendations with direct impact on regulation of pesticides. This should occur after evaluating the cost of collecting the information needed. Recommendations with direct food safety implications require even greater feasibility analysis. The analysis requires evidence that safety of the food supply would be improved as a result of implementation.

Review

The release of the National Research Council (NRC) report, Pesticides in the Diets of Infants and Children, on June 28, 1993 represents another in a series of events that focuses on pesticide residues in the food supply in the United States. As indicated in the opening paragraph of the preface of the report, “... the U.S. Congress requested that the National Academy of Sciences establish a committee within the National Research Council to study scientific and policy issues concerning pesticides in the diets of infants and children.” This request was made in 1988, shortly after the publication in 1987 of an NRC report, Regulating Pesticides in Foods: The Delaney Paradox. It is important to recognize that the request for both of these reports is the result of concerns with policies for regulation of pesticide use. Because food safety was not a concern, the detailed scientific recommendations made throughout the report must be evaluated with these factors in mind. It follows that the recommendations are likely to be utilized to support changes in policy and in a shorter time period than required to assemble the technical information identified in the recommendations.

Many readers may view the content of this report as an additional indicator of an increasing crisis associated with food safety. Food safety is generally divided into two categories: (1) safety concerns with microbiological origin or (2) safety concerns due to chemical residues. Well-designed studies and documented reports from the Centers for Disease Control, as well as other reports, confirm that food safety concerns are most often traced to a microbiological origin. Although scientists, regulators, and legislators attempt to maintain focus on the high-priority concerns, reports on pesticide residues in the diet of infants and children tend to confuse the issue.

The authors of the report on pesticide residues in the diets of infants and children should be commended for their detailed scientific analysis and the excellent set of technical recommendations presented in the report. The committee assembled to conduct the analysis was asked to respond to three issues: (1) the magnitude of exposure to pesticide residues in the diets of infants and children, (2) the adequacy of current risk assessment methods and policies, and (3) toxicological issues of greatest concern when considering potential sensitivities of infants and children.
The recommendations in the report respond to these questions in a very convincing and well-documented manner. The new challenge confronting policymakers is to respond to the report's recommendations. The following observations are obvious:

1. Responding to the recommendations of the report would require significant investment of financial resources and would require several years before the desired information is available.
2. The report recommends changes in policy needed to ensure safety of food until additional information is assembled.
3. Any changes in policy for regulating pesticides are likely to eliminate the use of some current pesticides and to encourage an overall reduction in pesticide use.
4. Eliminating the use of current pesticides and the overall reduction in pesticide use is likely to reduce the availability of certain foods that are essential for the nutrition of consumers.

These observations represent the negative impact of the NRC report, *Pesticides in the Diets of Infants and Children*. There may be well-documented reasons to reduce chemicals in the environment as well as to decrease human exposure to pesticides during application, but these concerns are not addressed in this report. The focus of the report is on the diets of infants and children and tends to suggest the potential of a food safety problem of more than moderate concern.

As indicated, the challenge to policymakers is implementation of the recommendations from the report. Because there is no evidence that the significant investment in research and information gathering as required by the recommendations will improve the safety of food by a detectable amount, any investment must be evaluated carefully by the policymakers. The priority given to investments in response to the recommendations as compared to research on identification of the causes of diet-related diseases requires careful consideration. It is well documented that these diet-related diseases do exist and have existed much longer than use of pesticides in agricultural production. If the goal of this and similar reports were to improve the safety of food, the focus should be on all components of the diet and not on trace residues that are usually undetected in the food supply.

The report, *Pesticides in the Diets of Infants and Children*, is scientifically sound. The committee assembled to serve as authors of this report have conducted a detailed analysis in response to the charge from Congress and responded with well-documented and scientifically sound recommendations. The theme throughout the report is risk assessment and the types of input necessary to improve the output from risk assessment. Because this is the tool utilized by the Environmental Protection Agency (EPA) in evaluating pesticides for registration, the recommendations are clearly designed to assist the EPA in responding to the regulatory charge from Congress. Risk can be defined as follows:

\[
\text{Risk} = \text{Exposure} \times \text{Toxicity}
\]

and

\[
\text{Exposure} = \text{Residue Concentration} \times \text{Consumption}
\]

As might be expected, these topics have become the titles of chapters within the report. Nearly half of the report deals with toxicology and includes specific chapters entitled Special Characteristics of Children, Perinatal and Pediatric Toxicity, Methods for Toxicity Testing, and Estimating the Risks. Additional chapters are Food and Water Consumption, Pesticide Residues, and Estimating Exposures. The significant emphasis on toxicology probably reflects the composition of the committee assembled to write the report.

The first chapter with specific recommendations is entitled Special Characteristics of Children. Within this chapter, the authors of the report have conducted a detailed analysis on the potential vulnerability of children less than 18 years of age to chemical toxicity. The authors suggest in their conclusions that infants and children are different than adults, with the biochemical and physiological functions of the young body being more sensitive to the toxicity of chemicals. It should be noted that the recommendations will apply to all chemicals including pesticides and that the recommendations for research on toxicology of these chemicals are significant.

The chapter on perinatal and pediatric toxicity includes discussion on the mechanisms of toxicity and the potentially vulnerable organ systems or functional systems in the infant or child. There are numerous recommendations following the discussion in the chapter, with significant emphasis on the need for additional toxicological research leading to a better understanding of the sensitivity of immune, reproductive, and nervous systems. It should be noted that one of the recommendations acknowledges that translation of toxicity data from laboratory animals to humans may be inaccurate. It follows that special considerations are required to interpret these types of toxicological data and to evaluate risks based on tox-
icity data from animals.

An entire chapter is devoted to methods for toxicity testing and contains several pages of recommendations on this subject. Although the emphasis during discussions and recommendations is on testing of pesticides, it is evident that the same testing protocol improvements are required for all chemicals where human exposure occurs. The significant research required to improve methods for toxicity testing will need careful consideration in relation to the recommendations from other chapters.

The chapter on food and water consumption provides an overview of the deficiencies in data available on food consumption and the pattern of food consumption by age groups. The recommendations in this chapter clearly identify the need to improve these types of data and to provide specific guidelines on the types of information that should be assembled. Although the recommendations refer to the need for consumption data on food as consumed, a specific recommendation suggests the need for conversion of product as consumed into consumption of components from raw agricultural commodities. The need for this recommendation is not evident because food consumption data can be assembled on the basis of foods as consumed. The recommendations in this chapter emphasize the need to expand consumption to include water as a part of the consumption pattern. The recommendations are sound and would improve the types of information available for evaluating exposure and risk. It should be acknowledged that these types of information have much broader value and use than in evaluating risks associated with pesticide residues.

The chapter on pesticide residues provides a detailed analysis of the types of residue data available. The committee recommendations include the establishment of a national databank and standard methods for analysis and assembly of pesticide residue data. Although the recommendations represent worthy goals, it is difficult to imagine a sampling protocol that would provide statistically valid information for all pesticide residues and all foods at a cost that would not be prohibitive.

The chapter on estimating exposures contains some of the most significant recommendations of the entire report. The committee concludes that estimation of dietary exposure to pesticides for infants and children requires the combined probability distributions for food consumption and for distribution of residue levels. This approach will provide a probability distribution for individual exposures. The committee's recommendations include probability distributions based on actual data rather than simple summary statistics such as means or percentiles. They also recommend that chronic toxicity risk be differentiated from acute toxic effects. The chapter includes a recommendation that routine application of adjustments for percentage of crop treated not be included in estimating dietary exposure. This may be reasonable if residue levels are established and used only on foods as consumed. The final recommendation is that nondietary sources of exposure to pesticides be considered as a part of the entire risk evaluation. This recommendation should be expanded to include all sources of similar chemicals and recognition that sources other than dietary may be the primary source of exposure to many chemicals.

The final chapter of the report on estimating the risks is a summary of many of the previous recommendations. Many of the recommendations refer to the lack of solid toxicity data for many of the chemicals associated with pesticides. The recommendation on the use of a benchmark dose for risk assessment offers interesting possibilities. Finally, the use of risk distributions rather than point estimates is one of the most important conclusions of the entire report.

In summary, the authors of the report, *Pesticides in the Diets of Infants and Children*, have provided a sound analysis and basis for many recommendations. The challenge to policymakers is to prioritize the recommendations of the report in a manner that will respond to the original concerns. Several of the recommendations have direct impact on the pesticide regulation process and should be given a high priority. Other recommendations are more closely associated with improvement of food safety and should be given a low priority because responding to the recommendations is unlikely to improve the safety of food by any detectable amount.

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Abbreviations

ADI       Acceptable Daily Intake
CAST      Council for Agricultural Science and Technology
DRES      Dietary Residue Evaluation System
EPA       Environmental Protection Agency
FDA       Food and Drug Administration
GRAS      Generally Recognized as Safe
MRCA      Market Research Corporation of America
N         Nitrogen
NAS       National Academy of Sciences
NFCS      Nationwide Food Consumption Survey
NLEA      Nutrition Labeling and Education Act
NRC       National Research Council
RAC       Raw Agricultural Commodity
RDA       Recommended Dietary Allowances
TAS       Technical Assessment Systems, Inc.
USDA–CSFII U.S. Department of Agriculture–Continuing Survey of Food Intakes by Individuals
USDA/HHS  U.S. Department of Agriculture/Human Health and Services
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Food Biotechnology Regulations

Future of Irrigated Agriculture

Future of the Land Grant University System and Agricultural Research

Impact of Pesticides on Water Quality

Implications of Alternative Farming Systems on the Environment

Integrated Animal Waste Management

Naturally Occurring Antimicrobials in Food

Public Land Grazing

Public Perceptions of Agricultural Chemicals

Quality of U.S. Agricultural Products

Relationship of Value-Added Activities on Agricultural Products and the U.S. Trade Balance

Risk/Benefit Assessment of Antibiotics Use in Animals

Risks and Benefits of Selenium in Agriculture

Risks Associated with Foodborne Pathogens

Solid Waste: Challenges and Opportunities in Agriculture

Waste Management and Utilization in Food Production and Processing

Wetlands: Impact and Regulation

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