Risk Assessment and Child Health

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ABSTRACT. **Risk assessment, an approach for organizing information about hazards to health, safety, and the environment, provides a framework for gauging the threat to child health from environmental pollutants. A qualitative risk assessment has 4 components: hazard identification, dose–response assessment, exposure assessment, and risk characterization. In a risk assessment, consideration can be given to a population group that potentially has increased susceptibility, whether arising from having a high level of exposure or from increased susceptibility to the agent of concern on a biological basis. Children have been proposed as being at increased risk from some environmental agents, and there has long been concern and debate that the current approach of determining acceptable exposure levels or intake for a person may not yield safe intake limits for infants and children, who may be placed at greater risk than adults because of exposure patterns and inherent susceptibility. The persistence of debate on this critical public health issue reflects, in part, the difficulty of developing sufficiently sensitive and validated animal bioassays for critical outcomes. Epidemiologic studies can play only a limited role, given the complexity of establishing cohorts and tracking exposures from conception forward to assess risks across the lifespan. Meeting society's call for healthy environments for children poses an extraordinary challenge to researchers and to the policy makers who seek to develop evidence-based policies to protect children.** *Pediatrics* **2004;113:952–956;** ***risk assessment, dose-response, exposure, environmental pollutants, children's health.***

ABBREVIATIONS. FQPA, Food Quality Protection Act; EPA, Environmental Protection Agency; NOAEL, no observed adverse effect level; RfD, reference dose.

Risk assessment, an approach for organizing information about hazards to health, safety, and the environment, provides a framework for gauging the threat to child health from environmental pollutants. A risk assessment, when properly conducted, provides an indication of the magnitude of the threat and of the certainty of this estimate. Risk assessment is widely applied, and its use is mandated by some statutes in the United States, including the Federal Insecticide, Fungicide, and Rodenticide Act and the Food Quality Protection Act (FQPA) of 1996, an amendment to the Food, Drug, and Cosmetic Act.[1]

As proposed by the 1983 National Research Council committee on risk assessment,[2] a quantitative risk assessment has 4 elements (Table 1). Judgment as to the presence of a hazard—the hazard identification component—is based on comprehensive review and evaluation of the evidence, with use of criteria for causality of association or similar forms of expert judgment that evaluate "weight of evidence." The hazard identification component draws on the full range of evidence, including human studies, animal studies, and other toxicologic data. If the agent is found not to be a hazard, then a quantitative risk estimate generally would not be made.

A full quantitative risk assessment moves from hazard identification to risk characterization, jointly using data on exposure along with the exposure–risk relationship to estimate the range of risk posed by the agent and the sources and the degree of uncertainty associated with the risk estimate. Uncertainty refers to what is not known, and assumptions are needed to bridge the gaps in scientific knowledge corresponding to uncertainties. Assumptions made in characterizing the hazards that contribute to uncertainty should be transparent and justified. The consequences of alternative assumptions should be explored in sensitivity analyses that vary key assumptions to examine their impact on estimates. For characterizing risk to a population from an environmental agent, information is needed on the distribution of exposure to the agent (exposure assessment) and on the risk associated with various levels of exposure (dose–response assessment). The distribution of exposure may be characterized directly using the methods of human exposure assessment (eg, placing monitors on people) or estimated indirectly using an exposure or computer-based model that links sources of exposure to the pathways that lead to contact of people with the contaminated material. Exposure may occur through the media of water, air, and food or through physical contact, as in the example of radiation. In estimating risk, indicators of typical exposure, the mean or median values, may be of interest, but exposures at the upper end of the range may be particularly relevant to risk management, as those individuals in the upper tail of exposure may have unacceptable but avoidable risks. Figure 1, for example, shows the distribution of radon concentrations in US homes; the pattern of exposure to radon in homes has this type of shape. The distribution indicates that all people have some exposure at home, that the typical or average exposure is low,

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TABLE 1. Four Steps of Risk Assessment

Hazard identification	A review of the relevant biological and chemical information bearing on whether an agent may pose a carcinogenic hazard and whether toxic effects in one setting will occur in other settings.
Dose–response	The process of quantifying a dosage and evaluating its relationship to the incidence of adverse health effects response.
Exposure assessment	The determination or estimation (qualitative or quantitative) of the magnitude, duration, and route of exposure.
Risk characterization	An integration and summary of hazard identification, dose–response assessment, and exposure assessment presented with assumptions and uncertainties. This final step provides an estimate of the risk to public health and a framework to define the significance of the risk.

Source: National Research Council.[2]

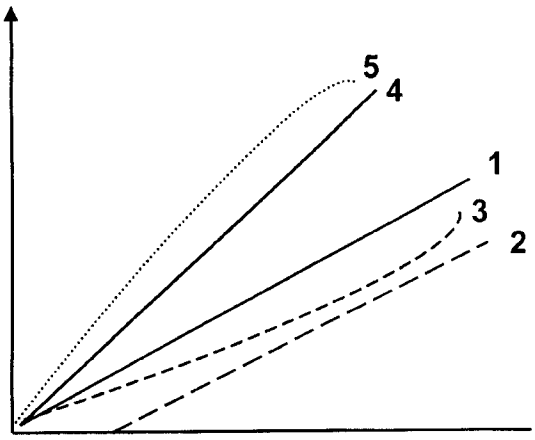

Fig 2. Examples of dose–response models used for carcinogens: 1, linear nonthreshold model; 2, linear threshold model; 3, sublinear threshold model; 4, linear nonthreshold model (steeper slope than 1 indicates greater susceptibility); and 5, supralinear nonthreshold model. Adapted from Samet and Burke.[3]

and that some homes produce exposures that are high and in a range that is considered unacceptable.[3]

The exposure–response relationship describes how risk varies in relation to exposure (or dose), as seen in Fig 2.[3] Exposure reflects contact with the pollutant and generally has units of concentration multiplied by time, whereas dose refers to the material actually entering the body. Dose can be further specified as the biologically relevant dose: that is, the material actually reaching the target site in the body. For airborne lead, for example, exposure would be estimated as the product of the atmospheric concentration with the duration of exposure, whereas dose would be the amount inhaled and then absorbed into the body. Blood lead or bone lead are biomarkers for the dose of lead. Generally, because of the kinds of information available, risk assessments use exposure–response rather than dose–response relationships.

The shape of the exposure–response relationship reflects the biological process of injury by the environmental agent (Fig 2). Key features of the relationship include the presence or absence of a threshold (curve 2 shows a threshold) and the pattern of increase of risk with exposure, and particularly whether the pattern seems linear or nonlinear. Curves 1 and 4 both show linear nonthreshold relationships; the steeper slope of curve 4 suggests greater susceptibility, as might be anticipated for exposures of children to some agents. Characterization of the exposure–response relationship is based in all lines of available evidence, including knowledge of mechanisms of injury and structure–activity relationships, animal bioassays, and human epidemiologic studies. For most agents, human data are limited and animal experiments are the principal basis for describing the exposure–response relationship. Reliance on animal bioassay data brings the obvious uncertainty of extrapolation from various animal species to humans. Moreover, only rarely are animal studies conducted in the range of human exposures; therefore, most often, knowledge of modes of action is used to infer the shape of dose–response relationships for humans. For cancer, animal data are generally analyzed with the assumption of a linear relationship between exposure and risk.

The recent assessment of the risks of indoor radon by the Biological Effects of Ionizing Radiation Committee VI of the National Research Council is illustrative of a comprehensive risk assessment.[4] This risk assessment begins by reviewing the experimental evidence relevant to respiratory carcinogenesis by radon and its radioactive progeny, finding that

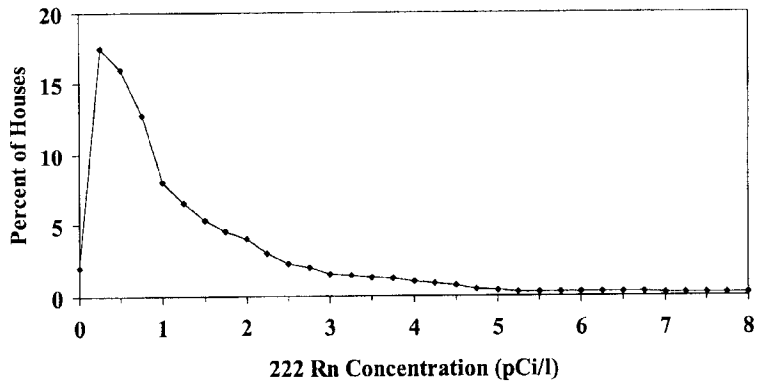

Fig 1. Distribution of radon levels in US homes.[3]

knowledge of the mechanism of injury to DNA by α particles suggests a linear nonthreshold relationship. For the United States, information on exposure to radon in indoor environments was obtained through a national survey of indoor radon concentrations. The exposure–response relationship was characterized by comprehensive statistical analysis of data from 11 cohort studies of underground radon-exposed miners. This analysis led to several statistical models that describe how the risk of lung cancer associated with radon exposure varies with exposure, the rate at which exposure is received, and the time since the exposure took place. By combining the exposure information with the epidemiologically derived exposure–response models, the committee could estimate the annual burden of lung cancer deaths in the United States from indoor radon, a number estimated as ranging from 15 400 to 21 800. On the basis of the limited epidemiologic data available from underground tin miners in China, who previously often began mining as children, and a finding that the excess cancer risk from radon declines over time, the committee concluded that childhood radon exposure did not increase risk more than exposure at older ages. The report sets out each of the assumptions made in deriving these numbers, along with a quantitative estimate of the uncertainty associated with key parameters.

In an example more directly relevant to practicing pediatricians, the Environmental Protection Agency (EPA)[5] estimated the burden of lower respiratory illness and of asthma exacerbation associated with exposure at home to secondhand smoke. By the early 1990s, when the agency conducted its risk assessment, there was strong evidence linking secondhand smoke to these heath effects (ie, the hazard had been confirmed). The quantitative estimation was made using data on the relative risks for asthma onset and for lower respiratory illness and an estimate of the proportion of women of childbearing age who smoked. The risks were characterized by 8000 to 26 000 new cases of asthma annually for children younger than 18 years and 150 000 to 300 000 new respiratory tract infections annually in children younger than 18 months. The attributable risks were driven by parental smoking.

In a risk assessment, consideration can be given to a population group that potentially has increased susceptibility, whether arising from having a high level of exposure or from increased susceptibility to the agent of concern on a biological basis. Children, for example, may be at increased risk from some environmental agents both because of generally higher dose levels than adults and because of increased vulnerability reflecting immature host defenses and the incomplete development of target organs.[6,7] The incremental risk associated with greater exposure would be captured in the exposure distribution for the subpopulation of interest. An increase in biological susceptibility would be reflected in a steeper exposure–response relationship than in the nonsusceptible or general population (Fig 2).

SETTING SAFE LIMITS OF EXPOSURE

Quantitative risk assessments are performed to assess the magnitude of the risk to population health associated with existing patterns of exposure and the degree to which risk can be reduced by control programs. If a threshold is evident, then a general approach to setting a limit for exposure is to allow exposure up to some point below the threshold that incorporates uncertainty factors that may be appropriate when such assessments involve extrapolations and/or incomplete data.[8,9] If there is no threshold, so that any exposure conveys some risk, then exposure limits are generally set on the basis of acceptability of the residual risks projected after control measures have reduced exposures to the extent possible. Often, in managing risks, other considerations come into play, such as technologic capacity to reduce exposures, and costs and benefits. For radon, for example, the EPA's guideline for indoor radon, 4 picocuries per liter of air, was reached by balancing the risks at this concentration, the costs and feasibility of lowering levels below the guideline, and the lack of precision of measurements of indoor radon at lower levels.

In approaching the setting of safe limits of exposure for many substances, including pesticides, governmental agents follow formulaic approaches for estimating levels of exposure or dose that will not be harmful to the public health. Generally, statutes contain language through which Congress guides agencies in setting such standards. For example, for the major outdoor air pollutants, the Clean Air Act calls for the administrator of the EPA to set standards that provide "an adequate margin of safety." Because human data are available for only a few environmental pollutants, as in the example of radon, the identification of acceptable levels is based in animal bioassay data. Typically, as seen in Fig 3,[10] animal bioassays involve exposures to animals bracketing levels at which responses can be anticipated and at lower levels at which responses are not anticipated. For setting an acceptable level of exposure for the noncancer health effects of specific concern in children, 2 key points are identified in the assay data: 1) the lowest exposure at which an adverse effect is detected, the lowest observed adverse effect level; and 2) the exposure at which no adverse effect is observed, the no observed adverse effect level (NOAEL).

To bridge from these points to an acceptable exposure or intake for a person, the EPA uses reference doses (RfDs) or reference concentrations in setting limits for oral and inhalation exposures to chemicals, respectively. The RfD is calculated with the NOAEL as a starting point, followed by further reductions to take account of sources of uncertainty and variability. One evident source of uncertainty to be addressed is the extrapolation from an animal bioassay to humans, and another is the possible variability of responses across people. These uncertainties are taken into account in setting acceptable intake limits by dividing the NOAEL by factors for each. The range of factors used for this purpose has varied by

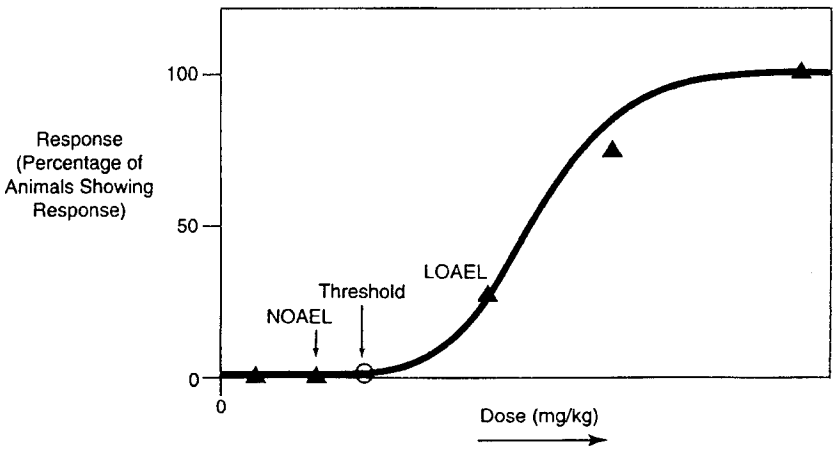

Fig 3. Depiction of a hypothetical dose–response curve. Data points are represented by triangles. The NOAEL is the highest dose that caused no significant effects (over background) in offspring. The lowest-observable adverse effect level is the lowest dose that caused significant effects (over background) in offspring. The threshold is the calculated lowest point on the dose–response curve at which a dose of test agent would elicit changes in offspring; doses below the threshold will not cause deleterious effects in offspring and should be considered safe.[9]

agency and country.[11] Typically, the NOAEL is divided by 100, representing assumption of a 10-fold uncertainty for the species extrapolation and an order of magnitude spread in the variability of responsiveness. This approach is assumed to yield a subthreshold and hence a "safe" exposure or dose.

ENSURING SAFETY FOR CHILDREN

There has long been concern that this approach may not yield safe intake limits for infants and children, who may be at greater risk than adults because of exposure patterns and inherent susceptibility.[1,8] For pesticides in foods, the FQPA places the burden on the administrator of the EPA to determine that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures." To achieve this goal, the FQPA of 1996 requires an additional uncertainty factor of 10 for children in regard to pesticides in foods, unless there are sufficient data to indicate that some other factor will suffice. The FQPA further protects children by requiring the EPA to consider aggregate exposure, that is, the exposure to pesticides from different routes, and cumulative risk, that is, the "cumulative effects of such residues and other substances that have a common mechanism of toxicity."

The additional uncertainty factor of 10 stems from the National Research Council's 1993 report, "Pesticides in the Diets of Infants and Children."[8] The rationale for this factor lies in the many aspects of development that could contribute to vulnerability of the fetus, infants, and children to chemicals.[8,12] In addition, exposures and doses for some agents, eg, lead, may be particularly high for some children, and there could be unanticipated synergism among the various factors, potentially increasing risk for children. Others have argued, on the basis of largely empiric analysis, that this additional factor is not needed.[12–15] Those who are critical of the additional FQPA uncertainty factor cite empirical analyses, showing that current practices do not result in inadequate protection against developmental toxicity and also point to evidence that children are not necessarily and uniformly at greater risk than adults.

This debate cannot be resolved readily with available data, and the proposition that an additional uncertainty factor is not always needed for children does not exclude the need on a case-by-case basis. The persistence of debate on this critical public health issue reflects the difficulty of developing sufficiently sensitive and validated animal bioassays for critical outcomes. Epidemiologic studies can play only a limited role, given the complexity of establishing cohorts and tracking exposures forward from conception and that EPA must make safety decisions for products to which children are not exposed. There are only a few examples of agents for which such studies have been informative (eg, lead, methylmercury), and these examples represent failures of protective approaches.

CONCLUSIONS AND RECOMMENDATIONS

Meeting society's call for healthy environments for children poses an extraordinary challenge to researchers and the policy makers who develop evidence-based policies to protect children. Children have many chemical exposures through food, air, and water, and new chemicals are introduced into the environment at a rapid rate and with little testing. Windows of vulnerability during development raise concern for susceptibility and for risk for irreversible consequences of early exposures, such as impaired neurocognitive functioning and increased cancer risk. Animal bioassays, the mainstay of testing, are inherently limited and of uncertain sensitivity and relevance. They are costly and cannot feasibly be conducted across the full range of outcomes relevant to child health. Myriad differences between fetuses, infants, children, and adults introduce substantial uncertainty in extending findings from one group to another. Assumption of an additional uncertainty factor, as with the FQPA's factor of 10 for children, seems warranted when the evidence is incomplete or uncertain, but the appropriateness of this factor, particularly its assumption for a wide range of exposures and outcomes, is not established.

Several lines of research may prove useful and lead to better-informed strategies for protection of children:

- Additional empirical research, using the animal bioassay data, to assess the degree of protection provided by alternative strategies for use of the evidence in setting RfDs
- Exposure assessment studies to better characterize exposures of children to chemicals during critical periods
- Development of sensitive suites of biomarkers
- Development of surveillance strategies for developmental consequences of environmental chemicals
- Population-based studies to assess the contributions of chemical pollutants to key noncancer health effects, including impaired neurocognitive development

This is an ambitious set of recommendations but offers an agenda that needs to be followed if evidence is to drive our handling of environmental risks to children. Absent this needed evidence, we cannot answer the question posed in the title of this manuscript: whether current risk assessment approaches are sufficiently protective of children.

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