

## Comments on "Children's Health, Susceptibility, and Regulatory Approaches to Reducing Risk from Chemical Carcinogens"

In their recent commentary, "Children's Health, Susceptibility, and Regulatory Approaches to Reducing Risk from Chemical Carcinogens," Charnley and Putzrath (1) noted the seminal importance of the National Academy of Sciences (NAS) report *Pesticides in the Diets of Infants and Children* (2) in having catalyzed current concern about risks to children's health from environmental chemicals. As members of the NAS committee who wrote that report, we thank Charnley and Putzrath (1) for their acknowledgment. We are concerned, however, that their suggestion that child-protective safety factors be subjected to cost-benefit analysis would undercut a major recommendation of the NAS committee as well as a central provision of the Food Quality Protection Act (FQPA) (3). Specifically, the FQPA, motivated in part by our committee's report, calls for the application in risk assessment of an additional margin of safety to protect children's health in two circumstances: *a*) in the absence of data demonstrating assurance of safety, and *b*) in the presence of data showing children to be at greater risk to a particular chemical than adults.

Child-protective safety factors would not be a necessary default in risk assessment if good data were available on children's exposure and sensitivity to each of the many chemicals that they encounter. That, however, is not the case. Quantitative data on the exposures of fetuses, infants, and children to most chemicals are limited, as are data on the toxicity of most chemicals. A recent analysis by the U.S. Environmental Protection Agency (4) indicates that even minimal toxicologic data exist for only 43% of the 15,000 chemicals produced each year in quantities of over 10,000 pounds; data on developmental toxicity, the sort of data that would permit direct comparison of child versus adult sensitivities, are available for only about 20% of these high-production volume chemicals.

To address these large gaps in data, the NAS Committee on Pesticides in the Diets of Infants and Children (2) recommended that "there should be a presumption of greater toxicity to infants and children." The committee suggested that

an uncertainty factor up to ten-fold ... be considered ... when data from toxicity testing relative to children are incomplete.

The committee coupled this recommendation with a call for expanded research that would enhance the "current limited database on

relative sensitivity." It was the NAS committee's clear intent that the presumption of greater toxicity and the imposition of an additional safety factor would catalyze expansion of the database on developmental toxicology.

Charnley and Putzrath (1) questioned the wisdom of incorporating child-protective safety factors in risk assessment. They asked whether the cost is worth the benefit. The principal basis for their question lies in a comparison they presented of the relative sensitivities of children and adults to a series of carcinogenic chemicals. Drawing upon the work of our NAS committee, they found that adult animals are more susceptible to 53% of carcinogens, that young animals are more susceptible to 37%, and that there is no age-related difference in 10%.

We agree with those findings because they come mainly from our report (2). However, Charnley and Putzrath (1) presented their argument in a vacuum, and they manifested little apparent cognizance of the enormous voids in knowledge that surround it. The limitations in their analysis are threefold.

First, Charnley and Putzrath (1) mentioned only in passing the great differences in exposure that exist between adults and children. The NAS committee found, however, that differences in exposure are often orders of magnitude greater than differences in susceptibility. We noted in our report that children drink more water, eat more food, and breathe more air per pound of body weight than adults and thus are disproportionately exposed to any toxic chemicals contained in those media (2). Additionally, children's behavior—their play close to the ground and their oral exploratory activity—increases further their opportunities for intake of chemicals. Because children's risk of injury from toxic chemicals is determined by both exposure and susceptibility, we have difficulty in seeing how Charnley and Putzrath (1) can draw major conclusions about children's risks without considering both of these factors.

Lack of toxicologic data is a second important limitation underlying the analysis of Charnley and Putzrath (1). Their tables on relative sensitivity to chemical carcinogens, the tables that provide the central foundation of their analysis, are based on only about 30 chemicals. These chemicals represent fewer than 0.2% of the 15,000 high-production volume chemicals in commerce. There is no way to know whether these findings pertain to the broader chemical universe or whether they are representative of that universe. And in the absence of toxicologic testing data, there is no way to know which are the chemicals to which children are especially sensitive.

A third limitation of Charnley and Putzrath's analysis (1) is that it considers only

cancer. Cancer, while clearly a health outcome of great concern, may turn out not to be the outcome with greatest age-related differences in risk. It is conceivable that differences in susceptibility to neurotoxins or to reproductive toxins could vary much more sharply across age groups than differences in susceptibility to carcinogens.

In summary, by arguing that a child-protective safety factor should not be added to risk assessment unless it can be directly shown to confer benefit, Charnley and Putzrath (1) assume that children are no more sensitive to chemicals than adults and that the consequences of toxicity are no greater. Charnley and Putzrath thus offer an analysis whose conclusions and recommendations are diametrically at odds with those of the NAS Committee on Pesticides in the Diets of Infants and Children. Their risk assessment strategy, if adopted, would remove the stimulus to expanded toxicologic testing that was recommended by the NAS committee and that is embodied in the FQPA. It would result in perpetuation of the current unhappy situation in which the overwhelming majority of the chemicals to which children are at risk of exposure have never been tested for their developmental toxicity.

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### HealthRisk Strategies Response

We appreciate the comments of Landrigan et al. and find that few of them are inconsistent with the conclusions presented in our paper (1). Indeed, many of their comments are mentioned in our paper. Nowhere in our paper, however, do we argue that child-protective safety factors should be subject to cost-benefit analysis, nor do we suggest "that a child-protective safety factor should not be added to risk assessment unless it can be directly shown to confer benefit," as Landrigan et al. state. Curiously, Landrigan et al. fail to acknowledge or to address the conclusions in our paper, which focus on dose-response assessment (the subject of our paper); they prefer instead to reiterate yet again the conclusions of their 1993 NAS report (2), with which we are certainly familiar.

For example, we agree with Landrigan et al.'s comment that children's exposures differ from those of adults. We acknowledge that difference in our paper (1) by pointing out that it can be accounted for as part of exposure assessment, but we also noted that for the purpose of our paper, we chose to focus on biological susceptibility, an aspect of children's risk that is the subject of much current research, including that of Landrigan et al. We also agree that cancer is not the only end point of interest, as we pointed out in our paper when we acknowledged that the age-dependence of other outcomes, such as neurotoxicity, is poorly characterized. We certainly agree that the paucity of toxicologic data for most environmental chemicals is a serious limitation. It is precisely that limitation that underlies the conclusions of our paper.

As we stated in our paper (1), our goal was to articulate some of the questions that must be addressed in the context of dose-response assessment to determine whether an extra 10× uncertainty factor is appropriate, necessary, or adequate to protect children from chemical carcinogens or other environmental chemicals. The NAS report (2) recommends that

an uncertainty factor up to the 10-fold uncertainty factor traditionally used by EPA [the U.S. Environmental Protection Agency] and FDA [Food and Drug Administration] for fetal developmental toxicity should also be considered when there is evidence of postnatal developmental toxicity and when data from toxicity testing relative to children are incomplete.

Our paper thus articulated some of the questions the U.S. EPA might pose when considering the need to apply such an uncertainty factor and, as such, is quite consistent with the recommendations of the NAS report.

In our paper (1), we discussed, for example, the fact that age-related differences in susceptibility seen at high doses in laboratory experiments may not hold true at low doses. As a consequence, whether the use of uncertainty factors will be sufficiently (or overly) protective depends on the dose at which the measurement is made compared to the exposure of interest. We pointed out that evaluating the effectiveness of an uncertainty factor also depends on whether differences between adults' and children's susceptibilities, where they exist, can be accounted for by current risk assessment models, noting the limitations of such models. We commented on the regulatory use of statistical upper bounds on cancer risk estimates instead of maximum likelihood estimates and suggested that, even if a particular uncertainty factor were found to be consistent with the best estimate of the risk for children, there is no reason to assume that the upper-bound risks would have the same relationship as the best estimates. Finally, we concluded that determining whether additional regulatory stringency will demonstrably improve public health in general or children's health in particular is unknown and cannot be evaluated without far more information than is currently available. Such a conclusion should be interpreted as encouraging the generation of such information (and serves only to promote the interests of researchers such as Landrigan et al.) presuming, of course, that one is interested in whether environmental health regulation does, in fact, protect public health. As Landrigan points out frequently, use of a child-protective safety factor is policy based, not science based. As scientists, we are interested in the question of whether and to what extent additional science might improve public policy.

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