Children's Health, Susceptibility, and Regulatory Approaches to Reducing Risks from Chemical Carcinogens

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Risk-based regulation of chemical exposures from the environment generally relies on assumptions about the extent of people's susceptibility to chemically induced diseases. Those assumptions are intended to be health-protective, that is, they err on the side of overstating susceptibility. Recent concern about children's special susceptibilities has led to proposals that would make risk-based regulations one-tenth more stringent, unless data are available to refute the assumption that children are more susceptible than adults. In this paper we highlight some of the questions that should be addressed in the context of risk assessment to determine whether such increased stringency would accomplish the desired result of improving children's health. In particular, characterizing benefits of greater stringency requires more information about dose-response relationships than is currently available. Lowering regulatory levels has attendant costs but may not achieve benefits, for example, if the previous level were already below an actual or practical threshold. Without an ability to understand the potential benefit (or lack thereof) of the additional stringency, an appropriate consideration of benefits and costs is not possible. Key words: age, carcinogens, children's health, dose-response assessment, pesticides, risk analysis, risk assessment, susceptibility, uncertainty. Environ Health Perspect 109:187–192 (2001). [Online 26 January 2001] http://ehpnet1.niehs.nih.gov/docs/2001/109p187-192charnley/abstract.html

Few issues in risk analysis have generated as heated controversy as that of how best to protect children's health from chemical contaminants in the environment. The issue is not whether to protect children, because few would argue against protecting children; the issue is how best to protect them. Insults that occur during development in utero or during childhood can have tragic consequences in terms of birth defects and greater likelihood of disease throughout both childhood and adulthood, having great social and emotional costs. The proportion of birth defects and other problems attributable to environmental exposures to chemicals is not known, but even if that proportion is small, it could constitute a public health problem by virtue of the number of people affected. Many are questioning the extent to which methods used by regulatory agencies to assess risks from environmental chemicals are adequate to protect children.

Much of the current concern surrounding children's health and risks from chemicals in the environment is attributed to the National Academy of Sciences report Pesticides in the Diets of Infants and Children (1). That report concluded that there can be profound differences between children and adults, that children may experience quantitatively and qualitatively different exposures to chemicals than do adults, that children may be more or less sensitive to chemically induced toxicity than adults, and that standard approaches to risk assessment and regulation may not always account explicitly for potential age-related differences in exposure and toxicity. The resulting concern that, at least in some cases, children may not be protected adequately by current regulatory policies provided the momentum that led to the children's health provisions of the 1996 Food Quality and Protection Act (2), to President Clinton's 1997 executive order, Protection of Children from Environmental Health Risks and Safety Risks (3), to establishment of the U.S. Environmental Protection Agency's (U.S. EPA's) Office of Children's Health Protection and Children's Health Protection Advisory Committee, and to a renewed research focus through the U.S. EPA's voluntary children's Chemical Evaluation Program and the Child Health grants program administered by the U.S. EPA and the National Institute of Environmental Health Sciences.

Although the policy concerns regarding children's environmental health risks include different types of chemical exposures and different kinds of health effects, an issue of particular concern is cancer. There is a fear that chemical exposures during childhood or in utero could increase cancer incidence both during childhood and later in life. Reported increases in rates of brain cancer in children and of testicular cancer in young men are cited as evidence that environmental exposures may have a public health impact. The U.S. EPA's proposed cancer risk assessment guidelines have not been finalized because of wide disagreement about whether they are appropriately child protective.

An issue of continuing concern is children's exposures to pesticides. The debate about the need for an additional 10x uncertainty factor to address children's sensitivity in safety assessments involving pesticide registrations endures. The need for an additional 10x factor in cancer risk assessment has also been raised. By conventional practice in the United States, safety assessment generally involves dividing the highest chemical exposure level that does not cause toxicity according to animal tests or human data by uncertainty or safety factors because people may be more sensitive to toxicity than laboratory animals or than other people. The magnitude of the combination of all of these factors increases when we have less information about a chemical's toxicity to humans, reflecting a need to be health-protective when we are uncertain. The current debate addresses the advisability of making acceptable exposure limits 10 times more stringent than they already are, specifically to protect children.

Our goal in this paper is to articulate some of the questions that must be addressed in the context of dose-response assessment to determine whether an extra 10x uncertainty factor is appropriate, necessary, or adequate to protect children from chemical carcinogens or other environmental chemicals.

Comparing Sensitivities

Potential differences in exposures and in inherent biological susceptibility will affect the likelihood that a child will experience risk differently from an adult. Sensitivity to a risk is thus influenced by both exposure and susceptibility. In risk assessment, scaling exposures on a body-weight basis and using data on behavior patterns and other factors that affect exposures (when available) yield exposure assessments that more accurately reflect age-related exposure differences. Accounting for age-related differences in inherent susceptibility as part of dose-response assessment is much more complex. Here we focus on susceptibility issues in dose-response assessment, not on exposure issues, and the term “sensitivity” is used to...
mean the impact that differences in susceptibility have on risk.

Concern about the appropriateness of an additional 10× factor to account for children’s sensitivity arises for several reasons. Some authors have suggested that interindividual variation in susceptibility can exceed 10×, so a factor of 10 is not protective enough (4). Others suggest that an additional 10× factor is not needed at all because the default assumptions used in regulatory risk assessments already are conservative enough to account for variation in susceptibility among individuals, including that due to age (5). Here we evaluate the data and analyses required to resolve this controversy.

Dividing a cancer potency or a no-observed-adverse-effect level by 10 to account for sensitivity due to age implies that a substance could be up to 10 times more potent, or more effective at inducing toxicity, in children as compared to adults. One of the fundamental problems with trying to evaluate whether the 10× factor is appropriate is that biology is not so straightforward. Describing a chemical (or pharmaceutical) as “twice as potent” or “five times more effective” than another chemical is simplistic. Few, if any, chemicals maintain such a constant relationship between dose and response for all levels of exposure. What toxicologists and pharmacists generally understand is that one chemical can be “twice as potent” as another within a defined, and often relatively limited, range of doses or responses and b) our ability to detect a variation from the expected potency, given that we know individuals will respond somewhat differently. Thus, such measures of relative potency are useful, but not strictly accurate. The concept of relative potency can be equally useful in toxicology and risk assessment, but the limitations on accuracy, including the need to restrict the response range for the comparison, also apply.

Similarly, the difference in response between two groups within the general population (eg, children and adults) will rarely be the same for all exposures. Consider some of the potential mechanisms that could account for a difference in response between groups. The following are simplistic but illustrative examples.

- To produce a response, the chemical must bind to receptors (in the most general definition of that term), and the extent of binding is the critical step in determining the response. Assume that adults are less efficient at binding the chemical to the receptors than children. For a constant relationship to hold, an adult would have to bind a constant percentage less than a child. At the exposure where a child’s receptors are 100% occupied, increasing the concentration would increase the response of an adult, but not of a child. Similarly, at exposures where an adult binds (effectively) none of the chemical, a child could bind 0–10% (if children are 10 times more sensitive). Given that the difference in the amount bound by adults and by children cannot be a constant for the complete range of doses, the issue of concern is the size of the deviation and whether it matters in the context of the decision to be made.

- The chemical must be metabolized by a particular form of the enzyme cytochrome P450 to become biologically active and produce a response. In adults, the P450 of concern is inducible, and in children it is not. The relationship between the child’s and adult’s formation of the toxic derivative will be constant at very low doses and for a brief period of time at higher doses until the adult’s P450 is induced. The rate of formation of the toxic derivative by the adult will then greatly increase compared to the child’s, increasing the difference between the child’s and the adult’s sensitivities. If the potential difference is estimated at the highest exposure level, the child’s risk at a lower level could be substantially overestimated.

- The mode of action that quantitatively determines the toxic response is not the same for all levels of exposure. For example, dose–response modeling for enzyme- or receptor-mediated toxicity is often assumed to be first order at low doses. The model frequently used for that assumption (Michaelis-Menten kinetics or related algorithms) further assumes that the chemical of concern is present in quantities significantly greater than the enzyme or receptor. Clearly, this assumption will be accurate for only higher levels of exposure. Similarly, the critical or rate-determining step for the toxic effect, and hence for the dose–response relationship, may change with dose (6).

- Two molecules of the chemical must work together to produce toxicity. For example, two molecules must bind to a receptor to produce (maximal) activity, or a dimer must form to produce the response of concern. (Perhaps the best known example of multiple sites for ligand interaction with a receptor is hemoglobin, with its four binding sites for oxygen.) If two molecules are necessary to produce a response, the response is more likely to vary with dose squared, or with some other nonlinearly proportional relationship with dose, rather than dose. The 10× factor implicitly assumes the response varies in a linearly proportional relationship with dose.

Because the concept that chemicals’ relative potencies can be calculated by simply multiplying by a constant is an approximation, whether a 10× factor will be sufficiently (or overly) protective depends on the dose at which the measurement is made compared to the exposure of interest. Thus, comparison of the doses required to produce any specified level of response will only provide information regarding that dose, or reasonably similar doses. Although such information is likely to be useful for doses near those evaluated, the information may prove significantly faulty for doses that are 10- to 100-fold lower or higher, a significant consideration given that differences between doses used in the laboratory and actual human doses often vary by several orders of magnitude. Evaluating the appropriateness of a 10× factor for age-related differences in susceptibility thus depends on how the dose-response relationships for children and adults change with level of exposure.

Age and Susceptibility to Carcinogenesis

In the context of chemical carcinogenesis, arguments for and against an additional 10× factor to account for age-related differences can be made on both theoretical and experimental grounds. The developing organism experiences many complex, integrated events involving the regulation of cell growth, differentiation, and morphogenesis. Interfering with those events through mutation or through altered mitosis, nucleic acid biosynthesis, membrane function, enzyme function, or energy sources can have significant adverse impacts on development (7,8). Many factors can have an impact on normal development, including nutrition and folic acid availability, maternal smoking and alcohol consumption, prescription drugs, and environmental contaminants such as lead and organic mercury. (For a useful review of the factors that underlie developmental susceptibility to environmental toxicants, see Faustman et al. (7).]

Factors that have an impact on development obviously cannot be characterized as a fractional response of the adult to chemical carcinogenesis. Many of those responses will never be observed in the adult, making the ratio of adult’s to children’s responses zero. Identifying developmental responses requires that they be tested for specifically. The in utero carcinogenic effects of diethylstilbestrol, for example, would not have been detected using standard rodent bioassays, so neither could it have been identified nor prevented using a 10× uncertainty factor.

Age can have an impact on susceptibility, specifically to chemical carcinogenesis in rodents. Pesticides in the Diets of Infants and Children (1) included a table summarizing the results of studies that had been performed through 1983 in which the effects of age on chemically induced carcinogenesis in rodents
had been evaluated (Table 1). Table 2 shows those results updated to include studies performed since 1983. Both the original and updated tables indicate that the number of studies showing that younger animals are less susceptible than adults (53%) to chemically induced carcinogenesis is similar to the number showing that they are more susceptible (37%) under the conditions of the bioassays (Figure 1). A number of studies showed that age played no role at all in susceptibility (10%). What those results demonstrate is that it is difficult to make generalizations about the effect of age on susceptibility to chemical carcinogens. Age can affect metabolism, cell proliferation rates, and hormone levels, for example, which can in turn affect tumor incidence, latency, and tumor type, as can myriad other interactions that are genetically, behaviorally, and environmentally determined. The National Academy of Sciences report (1) concluded that those results clearly demonstrate that age may be an important factor in susceptibility to chemically induced carcinogenesis, but they do not support the conclusion that younger animals are always more susceptible than older animals. This database also illustrates the difficulty associated with assessing the need for a 10× factor to address children’s sensitivity. Virtually all of the studies listed used only one dose level, so the underlying dose-response relationships are unknown, and comparison of sensitivities is possible only at the relatively high dose levels used.

**Effect of Age on Dose-Response Relationships**

In most cases, chemical carcinogens have the same mechanism of action in children as in adults (64). If children are more or less susceptible than adults, however, the difference in susceptibility would affect the shape of the dose-response curve, which is the cumulative distribution of the responses. Rather than only considering this cumulative distribution, examining the distribution itself is instructive when evaluating the need for an additional 10× factor.

Characterizing the distribution of probability of a response for additional (or incremental) responders as a function of dose is important for the usual interpretation of current safety or uncertainty factors. Those factors are said to account for the uncertainty and/or variability within the human population or between the human population and a test species (65). Various analyses have examined the variability within the population(s); these factors are likely to encompass the distribution of the incremental responders as an indication of that variability, and the extent to which a safety or uncertainty factor may overestimate or underestimate those distributions (2,66).

Normal and log-normal distributions are often assumed for risk assessment parameters such as the distribution of the probability of response for incremental responders. If children are best characterized by a different distribution than adults, then the changes in the distribution of the incremental responders would be smaller for children than for adults.

### Table 1. Effect of aging on latency, incidence, and size of tumors at different sites.

| Site                  | Animal species | Carcinogenic agent | Age group (months) | Effect of aging | Reference |
|-----------------------|----------------|--------------------|--------------------|-----------------|-----------|
| Skin                  | Mouse          | MC, BP, TC, MC, DM BA | 2-4 and 12-13      | No effect       | (9,10)    |
|                       |                | DM BA, UV-light    | 1.5-4 and 12-13   | Decrease        | (10,11)   |
|                       |                | Fast neutrons      | 2 and 11          | Increase        | (12)      |
|                       |                | Electrons          | 14-20 and 22-24   | Increase        | (13)      |
|                       |                | BP, DBA, M C       | 2-3 and 10        | Decrease        | (14)      |
|                       |                | M C                | 3 and 6           | Increase        | (15)      |
|                       |                | DM BA              | 6 and 20          | Increase        | (16)      |
|                       |                | Plastic films      | 2-6 and 13        | Increase        | (17)      |
|                       |                | Monolocyte sarcoma | 1 and 15.5        | Increase        | (18)      |
|                       |                | virus              | 3 and 30          | Increase        | (19)      |
| Soft tissues          | Mouse          | BP, MNU            | 1-3 and 6         | Increase        | (20)      |
|                       |                | M N U              | 4 and 11-14       | Increase        | (21)      |
|                       |                | FBAA               | 3-6 and 12        | Increase        | (22)      |
|                       |                | Estrogens          | 1-3 and 16        | Increase        | (23)      |
|                       |                | 3-Se-selenomethionine | 3-24 and 26 | Increase        | (24)      |
| Liver                 | Mouse          | DM H               | 2-3 and 12-13     | No effect       | (25)      |
|                       | Rat            | CC12               | 1-6 and 12        | Increase        | (26)      |
|                       |                | DBA, DMBA, AFB2     | 1-6 and 12        | Decrease        | (27)      |
|                       | Frog           | DENA               | 2 and 12-18       | Increase        | (28)      |
| Kidney                | Mouse          | M N U              | 2,3, and 12-18    | No effect       | (29,30)   |
|                       | Rat            | FBAA, M N U, DM NA | 1-6 and 12-18     | Increase        | (31)      |
| Bladder               | Mouse          | DM BA (in vitro)   | 1.5-2 and 28-30   | Increase        | (32)      |
| Lung                  | Mouse          | M N U              | 2.5 and 12        | Decrease        | (33)      |
|                       | Rat            | DBA, urethane      | 3 and 24          | Increase        | (34)      |
|                       |                | Fast neutrons      | 3 and 21          | Increase        | (35)      |
| Pleura                | Mouse          | Asbestos           | 2 and 10          | Increase        | (36)      |
| Uterus                | Mouse          | DM H               | 2 and 12          | Increase        | (37)      |
| Vagina                | Mouse          | DM BA              | 3 and 18          | Increase        | (38)      |
| Ovary                 | Mouse          | X-ray              | 2 and 12          | Decrease        | (39)      |
| Tests                 | Mouse          | Fast neutrons      | 2 and 11          | Increase        | (40)      |
| Vascular wall         | Mouse          | DENA               | 2.5 and 17        | Increase        | (41)      |
| Hematopoietic system  | Mouse          | X-rays             | 1.5-4 and 12      | Increase        | (42)      |
|                       | Rat            | M N U              | 3 and 12, and 24  | Decrease        | (43,44)   |
|                       |                | PM S               | 6 and 10          | No effect       | (45)      |
|                       | Frog           | M N U              | 3 and 14          | No effect       | (46)      |
|                       |                | Radionucleides     | 3 and 8-10        | Increase        | (47)      |

**Abbreviations:** AFB2, aflatoxin B2; BP, benzo[a]pyrene; DBA, 1,2,5,6-dibenzanthracene; DENA, N-nitrosodiethylamine; DM BA, 7,12-dimethylibenz[a]anthracene; DM H, 1,2-dimethylhydrazine; DM NA, N-nitrosodiethylamine; DM N, N-nitrosodimethylamine; FBAA, N-4-fluorobiphenylacetamide; M C, 3-methylcholanthrene; M N G, N-methyl-N-nitro-N-nitrosoguanidine; M N U, N-nitrosomethylurea; TC, tobacco smoke concentrate.

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characteristic parameters of a distribution must be known to evaluate whether a 10× factor is needed. Consider, for example, a case where the mean (for normal) or median (for log-normal) of a distribution is the same for adults and children, but the children's distribution is broader; that is, it allows for more variability and therefore more sensitivity within the population of children (Figure 2). The relative responses of children and adults will depend on the response level at which the comparison is made. Only if the distributions are truncated at some low level of exposure would it be possible to state whether the 10× factor is appropriate for all exposures above that level. But truncating exposure assumes a threshold for the effect of concern, which is often a point of controversy, especially for carcinogenesis. A similar analysis can be performed by identifying a response level below which exposure is not of concern, which would serve as a practical threshold, established either as a policy choice or as a response that is undetectable (for example, a probability of 1 case occurring among 1 million exposed people).

If the width of the distributions for children and adults (standard deviation for normal distributions, or appropriate parameters for other distributions) is the same, but the distributions are moved relative to each other (i.e., the means or other measures of central tendency differ), it is possible to have a constant relationship between the response of a child and the response of an adult for any given exposure (Figure 3). This shift in the location of the distribution on the axis for dose would result in a relationship where the relative sensitivities are constant for all levels of exposure. Mathematically, this can be achieved if either the dose-response curves are straight lines through the origin or the log(dose)-response curves are parallel. The former algorithm, an assumption often used for cancer risk assessment, is assumed only for doses that produce very low levels of response. At higher response levels, the dose-response curves must become curvilinear. The latter algorithm is assumed for toxic equivalency factors and some methods for evaluating noncancer risks of mixtures (e.g., U.S. EPA's hazard index), but is based on the pharmacologic concept of relative potency, the limitations of which have previously been discussed.

In either case (or in the case where both the central tendency and width of the distributions vary), current risk assessment procedures do not provide the appropriate starting point for evaluating case-by-case needs for a 10× factor to account for age-related differences in susceptibility. The characteristics of a distribution require more information than is available either from potency estimates of carcinogens or from the point estimate of acceptable levels of exposure such as acceptable daily intakes (ADI's) or reference doses (RfDs) used for noncancer effects. Using these limits as starting points for the application of a 10× factor assumes information about the distributions of the probability of response for children and adults that is not knowable from the information provided. To determine if a 10× factor is appropriate, the types and characteristics of distributions for both adults and children must be known for a sufficient number of chemicals to permit a reasonable analysis, such as that performed for other safety/uncertainty factors. Such an analysis would also require identification of a desired level of protection because comparing responses, and even determining which age group is more sensitive, may depend on the point of comparison. Thus, comparison of relative sensitivity at any one response level, whether an ADI, a median effective dose, or a point of departure for linear extrapolation, is not sufficient to determine the relative sensitivity for another level of response.

Limitations of Risk Assessment Methods

Evaluating the effectiveness of a 10× factor also depends on whether differences between adults' and children's susceptibilities can be accounted for by current risk assessment models. For example, if childhood exposure to a carcinogen leads to a reduced latency period for the appearance of adult cancer, that difference cannot be accounted for by parameters explicitly considered in current risk assessment algorithms. The usual method for calculating cancer risk estimates the incremental increase in risk over the lifetime of the people exposed, but does not consider when during a lifetime the cancer occurs. Even when cancer bioassay results include information that allows a time-to-tumor analysis of the data, the results are usually used to estimate only a lifetime cancer potency factor. Only the lifetime cancer risk, not the age at which cancer occurs, is evaluated. If the difference in a child's susceptibility is due to a change in latency, not to a change in potency, lifetime cancer risk will appear unchanged using current regulatory methods for estimating cancer risks. Need for a 10× factor to account for that type of change cannot be evaluated using current methods. Even if latency were considered, another question must be answered before the need for a 10× factor can be assessed: Is the factor an adjustment of dose so that the latency period is the same regardless of age at exposure, or so that the disease manifests itself with the same age distribution regardless of when the exposure occurs? The former is the usual hypothesis tested, but even if an additional 10× factor were applied, the result would still be an earlier occurrence of cancer due to the earlier exposure. That is, an additional 10× factor would not necessarily have an impact on the age at which cancer occurs. Thus, the goal of any adjustment for a more sensitive population should be clear.

A final consideration in evaluating the need for another 10× factor is the regulatory use of statistical upper bounds on cancer risk estimates instead of maximum likelihood estimates. Even if the 10× factor were found to be appropriate for 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. For

Table 2. Effect of aging on incidence of tumors at different sites: update of Table 1.

| Site            | Animal species | Carcinogenic agent                  | Age group (months) | Effect of aging | Reference |
|-----------------|----------------|-------------------------------------|--------------------|----------------|-----------|
| Thymus          | Rat            | N-Propyl-N-nitrosoureia             | 1.25, 2.5, 5, 10   | Decrease       | (57)      |
|                 | Mouse          | Ethylenethiourea and sodium nitrite | 1, 6, 12           | Increase       | (58)      |
| Mammary gland   | Rat            | 7,12-Dimethylbenz(a)anthracene      | 0.3–2, 3, 5, 15    | Increase       | (59)      |
|                 | Mice           |                                     |                    |                |           |
| Prostate        | Rat            | N-Nitroso-N-methylurea              | 1, 2.5, 4.5, 6.5   | Decrease       | (60)      |
|                 | Mouse          | 3,2'-Dimethyl-4'-aminophenol        | 1, 9, 16           | No effect      | (61)      |
| Kidney          | Mouse          | N-Butyl-N-(4-hydroxybutyl)-nitrosamine | 1.5, 4, 11      | No effect      | (62)      |
| Urinary bladder | Rat            | N-Butyl-N-(4-hydroxybutyl)-nitrosamine | 1.5, 12, 23    | Increase       | (63)      |

Figure 1. Percentage of total studies performed evaluating the effect of age on chemical carcinogenesis in rodents.
example, if the linear, no-threshold model for carcinogenesis were accurate for both the child and the adult, then it would be mathematically possible to have a constant relationship between the response for the child and the response for the adult. However, either the upper-bound dose–response curves could have this relationship or the true dose–response curves could have this relationship, but not both. Assuming that both have this relationship is to assume that uncertainty decreases at lower doses, when we know instead that uncertainty must increase (67, 68). Thus, if the true relationship between the child and the adult responses were a constant, the upper-bound risks that we currently estimate could not have this relationship. If the upper-bound risks have this relationship, the actual risks cannot. If the data indicate that children are more sensitive, this effect should be evaluated in the regulatory context of the usual upper-bound risk estimate. Simply adjusting the upper-bound risk is likely to result in a demonstrably incorrect result based on an artifact of the method we use to calculate the carcinogenic risk, not the true toxicologic relationship.

Conclusions

Experimental evidence clearly shows that young animals are not always more sensitive than older animals to chemically induced carcinogenesis (1). Because the biological modes of action involved in carcinogenesis are multiple and varied, many factors may account for differences in sensitivity. Rates of metabolism and clearance in the young are generally faster than those in adults, which may increase or decrease toxicity. For example, many cytostatic agents must be administered to children at up to five times greater doses on a per body weight basis than the dose to adults. Although it is true that developing organisms may be of special sensitivity simply because they are developing, whether environmental contaminants are having a disproportionate impact on the young is a matter primarily of conjecture (with some obvious exceptions, such as lead). However, much is known about the special sensitivity of the elderly to pharmacologic agents (69), and the elderly have also been viewed as a population at special risk from environmental insult due to their enhanced sensitivity (70). An argument could be made on that basis that an extra 10x factor is needed to protect the elderly as well as the young.

It is possible to identify many people within the general population who may have greater sensitivity to some chemicals. Indeed, any life stage or group that is identified based on physiologic or pharmacologic parameters would be expected to have some greater and lesser sensitivities than the general population. Current risk assessment procedures account for at least some of this variability, and the extent to which they already protect a life stage or group should be examined as part of any quantitative analysis of the need for additional safety factors. Requiring additional factors for all possible groups with special sensitivities would likely result in restrictions on exposure without additional protection of public health (71).

For those cases in which a different mechanism causes the toxicity in one group, such as developmental effects in utero, no scientific method is available to estimate the effect quantitatively based on another toxic effect. The effect-specific experiments must be performed. In those cases in which the mechanism of toxicity is assumed to be the same among groups, information on the distribution of probability of response—not just one response level—is required to determine the relative potencies for exposures of interest. If an uncertainty or safety factor is desired for general use in evaluating chemicals, a particular response level to be evaluated must be selected because the distribution of relative potencies varies with response levels.

Standard risk management practice based on regulatory risk assessment allows reductions in permissible exposures using uncertainty factors when data considered critical (based on type of chemical or its intended use) are not available. Determining which data are critical usually includes policy considerations as well as toxicology. Selecting the size of an uncertainty factor is usually pragmatic rather than scientific: 10 and 3 (considered a reasonable approximation of half a log unit) are the most common values, with occasional use of 5 or 2. Approximations abound. When distributions in variability have been examined, the values are rounded up to an order of magnitude. Adding another uncertainty factor to those approximations is possible, but must be viewed as a policy-driven approximation, not a scientifically derived value.

The potential benefits and drawbacks of using an additional 10x uncertainty factor to account for potentially greater susceptibility of children to chemicals should be weighed carefully. Application of the precautionary principle in the absence of a risk analysis framework would support the need for an additional factor where data on sensitivity are unavailable because, although experimental evidence suggests that young animals are more sensitive to chemically induced carcinogenesis about half the time, it is appropriate to err on the side of caution. Application of the precautionary principle within a risk analysis framework would involve weighing the costs of more stringent standards, considering the risks of substitutes, and determining the benefits of a 10x factor which, as we have demonstrated, cannot be evaluated without far more information than is currently available. It therefore remains unclear whether
making regulation of chemical exposures 10 times more stringent will demonstrably improve public health in general or children’s health in particular. Without a clearer demonstration of the benefits of greater stringency, whether and to what extent adding another 10 x uncertainty factor to risk decisions will have the effect of protecting or improving children’s health is unknown.

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