

EDITORIAL

Using Best Science in Cancer Risk Assessment

Our understanding of the biological basis of toxicity is continuously evolving, and it is important for risk assessment approaches to keep pace. The U.S. Environmental Protection Agency's (USEPA's) recently completed revision to its *Guidelines for Carcinogen Risk Assessment* (USEPA 2005) represents an important milestone in support of science-based decision-making, and is the result of an extensive multi-year effort. The new guidelines provide a powerful tool to risk assessors, by encouraging the use of the most robust approaches currently available, increasing flexibility to adjust to chemical-specific data, and improving transparency in the cancer risk assessment process. The guidelines also allow for further revision when “substantial changes are necessary,” and supplemental guidance on special topics as needed. Indeed, the first such supplemental guidance, on susceptibility from early life exposure to carcinogens, accompanies the completed guidelines. This editorial focuses first on the main body of guidelines, and then addresses the supplemental guidance for assessing early-life exposures. In addition, we focus on the USEPA guidelines to frame the discussion, but similar principles apply to international practices in cancer risk assessment. Overall, the new guidelines are an excellent example of a risk assessment approach that encourages the development and use of evolving scientific knowledge.

A key aspect of the new guidelines is the increased emphasis on the use of all data in developing weight-of-evidence conclusions, with particular attention to mode of action (MOA) for carcinogenesis, and on the identification of key events in the carcinogenic process. Under the new guidelines, the MOA identifies the conditions (if any) under which a chemical is believed to cause cancer, which then determines the approach for low-dose extrapolation. The guidelines allow for the consideration of MOA in the use of different descriptors by route or by dose level. For example, a chemical may be “likely to be carcinogenic to humans” via the inhalation route, but “not likely to be carcinogenic to humans” via the oral route. Similarly, a chemical may be “likely to be carcinogenic to humans” under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues, and “not likely to be carcinogenic to humans” under exposure conditions that do not cause cytotoxicity and cell regeneration.

As part of the increased emphasis on use of chemical-specific data, the guidelines state that the preferred approach for quantitative assessment is a physiologically based toxicokinetic model for interspecies extrapolation and a biologically based dose response (BBDR) model for low-dose extrapolation. Although this approach is data- and labor-intensive, such models reduce uncertainties in complex risk assessment problems. Furthermore, the continued development and use of such models

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will lead to less labor-intensive, more generalizable models. If the preferred approach of BBDR modeling is not possible, then linear extrapolation is used for chemicals thought to cause cancer through mechanisms assumed to be non-threshold (*e.g.*, direct reactivity with DNA) or for chemicals for which the MOA is not clearly identified, whereas an uncertainty factor approach is used for a MOA expected to generate a threshold response. This major improvement in the use of basic science directly reflects our increasing understanding of cellular biology.

The guidelines reflect a significant and welcome change in the approach to defaults. Instead of starting with defaults, and “departing from default” if data are available, the guidelines emphasize starting with a critical analysis of all the data, and invoking defaults “if needed to address uncertainty or the absence of critical information.” Beginning with the data helps to emphasize the use of the best science, whereas retaining use of defaults as needed in the face of inadequate data.

The guidelines also highlight the need for carrying multiple approaches through the assessment based on chemical-specific data. Fully evaluating multiple MOAs is important, because uneven levels of experimental support for different MOAs can reflect the true biology, or may reflect disproportionate resources spent investigating different MOAs. Improved transparency in the guidelines is provided by an appendix that explicitly lays out default options for various decision points in an assessment, along with the rationale behind the defaults. Presentation of the defaults and accompanying rationale also aids in developing chemical-specific data that address the rationale, and in clarifying cases when the defaults do not apply.

Consistent with other initiatives in the USEPA, the guidelines emphasize discussion of uncertainty, and requires the presentation of narrative characterization of the weight of evidence (with accompanying descriptors), rather than a single alphanumeric categorization of carcinogenic potential. The narrative characterization provides an integrated summary of the hazard assessment and its implications for human carcinogenic potential, including strengths and limitations of the assessment. Presentation of central estimates, as well as both upper and lower bounds of risks is encouraged. This aids in the characterization of uncertainty and allows the central estimate to be used where appropriate (*e.g.*, for some risk-ranking exercises).

Although the new guidelines are a welcome improvement in cancer risk assessment, challenges and potential areas for improvement remain as the underlying science develops further. For example, an ongoing issue in applying the prior draft guidelines was the determination of “how much information is enough” to demonstrate a nonlinear mode of action, and whether data that are contrary to the default assumptions (*e.g.*, data on the absence of DNA reactivity) would lessen this “how much” requirement. The clarifications in the current document provide a useful framework for addressing this issue. Ultimately, however, the best guidance is likely to result from the development of case examples, such as USEPA’s assessments of chloroform (nonmutagenic mode of action; USEPA 2001) and atrazine (mode of action not relevant to humans, USEPA 2002a,b). Similar work is proceeding at the international level, as evidenced by the mode of action paradigm adopted by the International Programme on Chemical Safety (IPCS; Sonich-Mullin *et al.* 2001), and efforts to develop harmonized cancer risk assessment guidelines.

Other useful case studies and generalizations are being developed using the International Life Sciences Institute (ILSI) framework for evaluating the human relevance

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of carcinogenic effects (Cohen *et al.* 2003, 2004). In early work applying the framework, ILSI held a workshop in 2004 on the use of mode of action data in evaluating the relevance of rodent tumors to human cancer (see Dragan and Holsapple (2005) and related abstracts). Generalizations from such case examples can help to define the approaches and data requirements for addressing specific tumor types, as was done for alpha-2 μ globulin and male rat kidney cancers (USEPA 1991), and for thyroid tumors (USEPA 1998). For example, the guidelines allow for extrapolation from related chemicals. Such extrapolation may be done, for example, in cases where the MOA is known to occur for a given chemical, even if a cancer bioassay for that chemical does not exist. Although such assessments would clearly include more uncertainty than one for which MOA data and well-conducted bioassays exist, allowing for extrapolation recognizes the need to protect the public health in the face of thousands of new chemicals entering commerce yearly. Extrapolation from related chemicals is also consistent with anticipated European Union initiatives, such as REACH (Registration, Evaluation, and Authorization of CHemicals).

In addition to the case studies being conducted by ILSI, there are a number of other recurring issues and challenges in applying the guidelines. For example, although the option is available to conduct nonlinear extrapolation, the guidelines do not explicitly address the approach for tumor promoters, such as phenobarbital, that are carcinogenic in combination with other chemicals, but do not cause cancer as a single chemical exposure. Application of the guidelines would suggest that the approach would be to identify a point of departure based on key event(s) for promotion, and then apply a nonlinear extrapolation approach. However, the guidelines do not address the approach for a chemical that is a known promoter, but for which the MOA and key events are not known. In addition, we are not aware of any consensus in the scientific community regarding what degree of change would be appropriate for a point of departure based on such key events as enzyme induction or receptor binding. The classical approach of determining an "adverse" degree of change may or may not be appropriate for such endpoints.

Further consideration of the implications of metabolic saturation would also be useful. For example, how should one evaluate chemicals that cause cancer in animals at doses that deplete the reserves of reduced glutathione (GSH)? GSH depletion could result in a shift in metabolism, with tumorigenicity resulting from direct DNA reactivity of reactive metabolites that are not prevalent under low exposure conditions. GSH depletion could also result in oxidative stress, with this oxidative stress resulting in tumorigenicity through indirect DNA-damage or cell growth promotion through activation of signal transduction pathways. Some scientists have considered GSH depletion to have a threshold (based on the degree of GSH depletion needed for a shift in metabolism or for oxidative stress), whereas others consider these events (particularly competing metabolic pathways) to be a matter of degree, rather than an on/off distinction.

Additional guidance would also be useful for evaluating chemicals for which human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process. The guidelines specify that a linear extrapolation approach should be used for such chemicals, because the background exposure (as well as exposure to other agents operating through a common MOA) are in the increasing, approximately linear, portion of the dose-response curve.

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Guidance would be useful for determining when the background exposure is near the doses of concern.

A particularly challenging issue is how to assess chemicals that cause cancer in laboratory animals and are mutagenic (or have mutagenic metabolites), but for which there is a body of evidence suggesting that tumors may occur via a nonmutagenic MOA, or via multiple MOAs. Chemicals in this category (with varying weights of evidence regarding the MOA) include formaldehyde (a high production volume industrial chemical), dichloroacetic acid (a drinking water disinfection byproduct), acrylamide (a byproduct of frying or baking foods, and an industrial chemical), acrylonitrile (a high production volume industrial chemical), and captan (a pesticide). For chemicals that act via several MOAs, determining if a particular MOA is a “significant” contributor to the overall tumor response remains difficult. As with any other endpoint, mutagenicity needs to be considered carefully based on the overall weight-of-evidence (WOE), recognizing that chemicals may differ in both potency of mutagenicity and regarding the conditions of mutagenicity. For example, when evidence exists that *in vivo* mutagenicity occurs only at doses in excess of those causing the tumorigenic response, it may not be appropriate to default to a linear dose-response assessment, even in the absence of good data for other MOAs (Moore *et al.* 2005). Evaluation of such chemicals requires careful consideration of the entire body of evidence, ranging from molecular toxicology and basic cancer biology to epidemiology data, in light of the modified Hill criteria. Professional judgment is required in using the best science in the assessment while protecting public health, particularly in the face of uncertainties.

An additional area for future improvements is in the continued harmonization between noncancer and cancer methods. The guidelines take the first step in stating that nonlinear extrapolation for chemicals that act via a nonlinear MOA should follow methods for development of reference doses (RfDs) and reference concentrations (RfCs). In addition, the approach for calculation of human equivalent concentrations (HECs) for inhalation exposure follows that of the RfC guidelines (USEPA 1994). Further harmonization in the approach for interspecies extrapolation for the oral route would be useful, preferably taking into account dosimetric considerations. (Currently, the noncancer approach uses a default uncertainty factor for the toxicokinetic extrapolation between humans and experimental animals, whereas the cancer methods use a body weight to the 3/4 power scaling.)

Although the cancer guidelines specify that one should use the lowest point of departure (POD) of the critical effect that is adequately supported by the data, the interplay between the POD and the uncertainty factors used to derive RfCs and RfDs has not been fully considered. For example, use of a lower POD for a tumor endpoint (*e.g.*, use of an ED01 instead of an ED10) corresponds to moving lower on the dose-response curve, suggesting that the use of a lower POD should be accompanied by a reduction in the intraspecies variability uncertainty factor (which corresponds to moving lower on the dose-response curve for humans). Further consideration of the implementation of these considerations is needed.

The guidelines raise the possibility of using precursor data for the POD, and note that this is an ongoing area of research that may result in supplemental guidance. Further research is needed on how to use data on tumor precursors or early biomarkers of effect to inform the dose-response curve for tumor induction below the level of

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observation. Judicious use of precursor data may decrease the need for extrapolation from the high doses typically used for animal testing to environmentally relevant levels. On the other hand, use of very early molecular events can result in cancer potency calculations that are not clearly linked to the outcome of concern. Better guidance is needed on the criteria for identifying precursors that can be quantitatively linked to tumors, particularly if early biomarkers are being considered as precursors. Key issues to be addressed include identifying approaches for *quantitatively* linking the precursor and tumors (current methods focus on qualitative links in the absence of a BBDR), and the best approach for accounting for precursor events having steeper low-dose slope than the tumors.

Additional work will also be needed in the future in order to incorporate the burgeoning field of genomics and other measures of early events into cancer risk assessment (as well as noncancer risk assessment). These types of data are currently perhaps best used for informing the hazard characterization and MOA conclusions, but future developments may allow for their use quantitatively in risk assessment. This issue will be worth revisiting as the field of toxicogenomics and other molecular biology approaches mature and researchers develop more experience in application of the data. Other issues where additional research is needed and guidance is needed include the approach for addressing intermittent exposures (*e.g.*, less-than-lifetime exposure of adults, or peak exposures), and the approach for addressing site of contact carcinogenicity for the skin.

SUPPLEMENTAL GUIDANCE

In contrast to the revised guidelines, which appear fairly mature in their development, the first supplemental guidance on susceptibility from early life exposure to carcinogens would have benefited from more work and analysis. Although some evidence exists that young experimental animals and humans are more susceptible to carcinogenic insult than older juveniles and adults—evidence that the USEPA summarizes nicely—other evidence that the USEPA cites indicates that they are less sensitive.

A key analysis in the supplemental guidance is the comparison of cancer potency in juveniles and adults, based on acute, repeated, and lifetime exposures. EPA's analysis found that the median juvenile to adult potency ratio was 1, with a very wide range of ratios. The weighted geometric mean ratio (based on number of ratios, not chemicals; combined repeated and lifetime) was 10.4 for mutagenic chemicals. Based on this analysis, the USEPA recommends that an adjustment factor of 10 be used for exposures before 2 years of age, and a factor of 3 (as midway between 1 and 10) for ages 2 to <16 for mutagenic chemicals. This factor would be replaced by chemical-specific data, if available. No general adjustment is recommended for chemicals for which the MOA is not known, or for chemicals with a non-mutagenic MOA, because the data were judged by the USEPA to be too limited and the MOAs too diverse for developing a general default adjustment factor approach. Given that the median ratio for the mutagenic chemicals was approximately 1, the choice of ratios appears to be based on the desire to be health-protective by covering a large percentage of the larger ratios.

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There are a number of issues with the current analysis. USEPA's specific quantitative adjustments of 3- and 10-fold are primarily based on 5 or 6 chemicals, and mostly on male rodent liver tumors, for which careful analysis is often needed to determine relevance to humans of the MOA. The analysis is based on a number of studies of varying designs, using experiments that were generally not designed to address relative potency in adults and juveniles. The USEPA used complex statistical analyses to evaluate these disparate studies, and included outliers in the analysis. Although such complex analyses may have been needed in light of the study limitations and limited dose-response data, they decrease overall transparency and highlight the importance of conducting a sensitivity analysis. For example, the use of different mathematical models by the USEPA would have resulted in different ratios and different choices of factors. The USEPA should encourage other scientists to analyze these data and evaluate the results/implications of alternative interpretations. In the face of multiple approaches to any particular problem, risk assessment scientists need to guard against being overly precise where data are not sufficient to support the precision. Such over-precision is of particular concern in light of the numerous uncertainties in the analyses supporting the supplemental guidance.

A final and compelling reason to proceed cautiously with the use of this new supplemental guidance is that the linear approach to low-dose extrapolation is already considered to be conservative by many scientists, a conservatism that is acknowledged by the USEPA for consideration of lifetime risk and also historically in general by many risk assessors. Thus, low dose cancer risks have been described as plausible upper bounds (*e.g.*, the risk can be as high as 1×10^{-6} , but it is likely lower, and it may even be zero).

A major challenge that the USEPA faced in considering children's risk issues was developing guidance when additional research is needed on key scientific issues. The supplemental guidance lists a number of aspects of biological processes (toxicodynamic processes) leading to cancer that could increase childhood susceptibility; other processes may decrease childhood susceptibility and also need to be examined. Similarly, differences in toxicokinetics could increase or decrease childhood susceptibility. Several issues need to be further considered in evaluating carcinogenic risk resulting from early-life exposures, many of which would benefit by further research. Does the current use of the linear low-dose extrapolation already account for sensitive individuals, including children? Should our testing strategy be changed to more adequately and systematically test experimental animals in a manner that reflects exposure during early development and juvenile periods? For which types of chemicals are children at lower or higher risk due to differences from adults in metabolic capacity? (These toxicokinetic differences between fetal and neonatal experimental animals and post-weanling adult animals have been reviewed in other investigations, such as Scheuplein *et al.* 2002.)

For chemicals where increased metabolism in children is protective, what is the impact on cancer risk of age-related differences in toxicodynamics, such as the increased rate of cell division in the growing organism? How do differences in immune function between children and adults affect tumor incidence and growth? These and other questions are reasonable, and properly conducted studies can deliver answers that can inform the risk assessment process. The challenging issue is determining

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how these competing processes combine to determine cancer risk. We believe that studies to answer these questions should be a high priority, although we also acknowledge that proper design of studies to address these questions is not a simple matter. The USEPA has also acknowledged the need for additional data. Sponsorship by the USEPA and/or others of a workshop to design a testing strategy for obtaining critical data would be most helpful.

In light of the issues highlighted here regarding the analyses in the supplemental guidance and the supporting science, the USEPA may wish to acknowledge that the available data are insufficient to make precise calculations, that these factors may not be needed for most chemicals (because the juvenile potency was less than the adult potency for about half of the ratios), and that the choices of 3 or 10 are policy decisions—similar to what the USEPA did for its choice of linear extrapolation in 1986.

SUMMARY

Overall, risk assessment scientists should take heart at the official release of USEPA's *Guidelines for Carcinogen Risk Assessment*, which provide a solid platform for making maximum use of chemical-specific data and improved methods. We look forward to future development of the underlying science and resulting methods, and interactions with our colleagues in the assessment of chemical risk to best protect public health.

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