

Workshop report

# EPA's new guidance for assessing cancer risks from early life exposures: Genotoxic mode of action and implications for human health-based standards

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## 1. A workshop's report

The International Society of Regulatory Toxicology and Pharmacology (ISRTP) hosted a workshop on February 10, 2005 in Baltimore, MD, to explore scientific and policy issues related to the implementation of EPA's Proposed Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens, an extension of the Agency's Guidelines for Carcinogen Risk Assessment. Subsequent to the ISRTP Workshop, EPA released the final Guidelines for Carcinogen Risk Assessment (hereafter called "the Guidelines") as well as the final Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens (hereafter denoted as SG).<sup>1</sup>

Seven speakers addressed a broad range of issues that included how EPA formulated, and may apply, the proposed SG to chemicals that are carcinogenic via a mutagenic mode of action; the scientific issues and uncertainties associated with application of the proposed Guidance; and, how implementation of this Guidance might affect risk-based human health exposure limits in regulatory programs. The presentations were followed by a panel discussion. The workshop identified a number of key issues that may require policy clarification and research to strengthen the scientific foundation for, and provide consistency to, assessments developed in accordance with the proposed SG. These included: approaches for defining and determining a mutagenic mode of action for carcinogens; research and analysis

for resolving physiological uncertainties in the manner by which exposure and dose parameters are evaluated; and, guidance for determining how threshold dose–response characteristics could be considered. The proposed SG has the potential for impacting drinking water and site remediation regulatory programs, and perhaps to a somewhat lesser extent, air toxics and pesticide regulatory actions. The workshop agenda and slide presentations are posted at <http://www.isrtp.org>.

## 2. Background and summary of presentations

For more than 10 years, EPA has been working to improve the Agency's scientific approaches for assessing carcinogenic risks from chemicals. In addition to its overarching Guidelines for Carcinogen Risk Assessment, in March 2003, EPA made public its Draft *Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens* (68 Fed. Reg. 10,012 (March 3, 2003)). This draft stimulated considerable scientific and policy comments as well as suggestions from the Agency's scientific advisory panel. The objective of the February 10, 2005 ISRTP Workshop was to foster scientific discourse on the considerable challenges facing the Agency in refining and then implementing the proposed SG. A number of general issues pertaining to cancer risks associated with early-life exposures are addressed in the proposed SG, but more importantly, based on the assumption that certain chemical carcinogens exhibit a greater effect from exposures early in life, the proposed SG provides specific guidance on adjusting quantitative carcinogenic risk estimates for early-life exposures to substances acting

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<sup>1</sup> <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283>.

through a mutagenic mode of action. The proposed SG defines a mutagenic mode of action as one that produces cancer via irreversible changes to DNA, a determination that is to be reached by a weight-of-evidence approach as described in the Guidelines.

Although the science underlying the proposed SG was discussed extensively during EPA's public comment period in 2003, there has been only modest public dialog subsequent to 2003 concerning revised scientific analyses by the Agency. Furthermore, there has been little public discussion to date concerning how the new proposed SG would impact risk-based regulatory and public health programs. These factors prompted ISRTP to organize the February 10, 2005 Workshop. Seven speakers, including speakers from EPA, State regulatory agencies, and the private sector were invited to discuss scientific issues related to risk estimation and potency adjustments for the carcinogens to which the proposed SG may be applied, and how implementation of this new policy might affect risk-based human health exposure limits, action levels, and remediation standards for regulatory and public health programs.

The morning session of the workshop focused on the Supplementary Guidance, risk estimation and potency adjustments. Dr. Hugh Barton of the US EPA, and one of the principal authors of the Supplementary Guidance, presented a detailed overview of the proposed SG and explained various revisions to the final document that were made subsequent to the 2003 public comment period and peer review of the Agency's initial draft. He presented the updated analysis of 18 chemical carcinogens, some considered mutagenic and others non-mutagenic, for which the Agency judged the data sufficient to quantitatively evaluate possible differences in cancer risk arising from early-life exposures compared to adult exposures. Based on their new quantitative analysis, EPA concluded that substances producing cancer through a mutagenic mode of action demonstrated site- or tissue-specific enhanced potency associated with early-life exposure. Although the requisite data for substances acting through other modes of action was much more limited, the Agency's analyses indicated no consistent increase in potency for early-life exposures compared to exposures later in life. Therefore, EPA concluded the guidance offered for mutagenic carcinogens is not applicable to chemical carcinogens acting through other modes of action.

EPA based its potency evaluation for early-life sensitivity on an analysis of repeated dose studies for four mutagenic chemical carcinogens whose data sets included complete or nearly complete data on parameters such as sex, strain, species, target site, etc. The data from these studies allowed for evaluation of 45 cancer potency ratios comparing responses from early-life to later in life. Of these ratios, 42% were greater than unity, which EPA interpreted as indication that mutagenic carcino-

gens have greater potency for exposures occurring early in life versus later in life. For three chemicals, data were sufficient to evaluate six potency ratios for lifetime exposure when started early in life versus somewhat later; 67% showed a potency ratio  $>1$ , indicating greater potency for early-life exposures. For the acute exposures, there were 42 chemicals, 515 ratios in total, and 55% of those ratios were  $>1$ .

From the data on mutagenic carcinogens, EPA developed adjustment factors for quantitative risk calculations to be used when assessing human cancer risk for three age groups, which are intended to be applied when the existing data for a chemical does not specifically include assessment of corresponding early-life exposure periods. These age groups are birth to  $<2$  years (adjustment factor of 10), 2 years to  $<16$  years (adjustment factor of 3), and  $>16$  years (adjustment factor of 1). The proposed SG (see Footnote 1) presents EPA's quantitative analyses in detail and emphasizes the use of data instead of default assumptions whenever possible. In addition, EPA indicates it plans to hold workshops for its employees responsible for interpreting and applying the Guidance to ensure that it is properly utilized (i.e., adjustment factors are not applied blindly when other relevant data are available).

Dr. Lorenz Rhomberg (Gradient Corporation) outlined various concerns regarding use of relevant data, species extrapolation, and statistical analysis of the studies and methodologies serving as the foundation of EPA's proposed SG. He explained that when estimating the received dose, it is necessary to delineate the substantial differences between children and adults, particularly when using studies that rely solely on measurements of exposure (i.e., ppm/ppb in air/water/food, etc.). In particular, the dose transferred through milk is not generally quantified in animal studies, making dose calculations, and thus, potency ratios for pre-weaning animals subject to assumption rather than quantification. He also illustrated how known metabolic differences between children and adults could lead to either greater or lesser sensitivity to specific mutagenic carcinogens, making it difficult to generalize regarding sensitivity to all mutagenic carcinogens. Rhomberg pointed out that one of the most important factors complicating the approach is that the existing database of relevant animal studies is generally from the older published literature, which often suffers from poor or incomplete data reporting (e.g., no individual animal data; no time to tumor data, etc.) To increase scientific certainty, new age-specific models need to be developed. Rhomberg also illustrated the methodological inappropriateness of using end-of-life tumor incidence to compare those exposed early versus later in life since in principle, early exposure allows a longer "lifetime" for tumor development to occur. He argued that time to tumor data would be a better approach, but these data are lacking, making

age-specific hazards impossible to calculate with the requisite degree of scientific certainty. Rhomberg concluded his presentation by noting that the apparent increased “susceptibility” of young animals may be an artifact of receiving a larger dose, since most toxicology studies have not estimated doses for pre-weanling animals, which is the early-life stage at which exposure appears to have the greatest impact on tumor incidence.

Dr. Gary Burin (Technology Sciences Group, Inc.) focused on the evidence for increased sensitivity of young animals to mutagenic carcinogens, and argued that a weight of evidence evaluation, as recommended in the proposed SG, should lead to the use of threshold dose–response models for at least some mutagenic carcinogens. Although very few pesticides used today are mutagenic, orthophenyl phenol and benomyl are pesticides that show clear thresholds for both genotoxicity and carcinogenicity. Burin argued that these pesticides, and other chemicals whose data sets include multiple genotoxicity studies, may be best evaluated by the qualitative weight-of-evidence approach for evaluating chemicals with multiple genotoxicity studies, as used by the International Commission for the Protection Against Environmental Mutagens and Carcinogens (IC-PAEMC). The approach was first published by David Brusick in the 1980s, and has been applied to a number of pesticides. Burin stated that, in general, few pesticides would be affected by the proposed SG if mutagenicity is defined by the qualitative weight-of-evidence approach used by the Office of Pesticides within EPA. Concerns of the pesticide industry include that “mutagenic” mode of action needs to be defined more clearly in the proposed SG, that greater attention be given to the potential for threshold mechanisms of mutagenicity, and that the adjustment factors stipulated in the proposed SG should not be applied to chemicals that exhibit thresholds.

The workshop focused on implementation issues during the afternoon session. Each speaker was invited to address a range of questions, including a comparison of the current approach to the new approach that would arise from using the proposed SG, how the procedure for evaluating mutagenic mode of action might affect the new approach, the implications of the new approach for allowable exposure levels, and costs associated with the new approach.

The EPA’s March 2003 draft proposed SG is already being used by Minnesota’s Department of Health (MDH) to develop their own methodology for calculating Health Risk Levels of water contaminants with the intent of protecting children’s health (Laura Plunkett, Integrative Biostrategies, LLC). However, although the MDH cited the EPA guidelines, Plunkett illustrated how the novel algorithm MDH developed for exposure and risk is different in many respects from EPA’s published Guidance and methods, which raises concern

regarding difficulties in the uniform application of available science. This example of a novel approach, based in part on EPA’s proposed SG, but which lacks transparency, scientific documentation and justification, highlights the need for EPA to be extremely clear on how to interpret and apply the new proposed SG for early-life exposure.

The case studies presented for air (Deirdre Murphy, US EPA Office of Air Quality Planning & Standards), drinking water (Erin Snyder, Black & Veatch), site remediation—soil clean up (Steve DiZio, California Department of Toxic Substances Control and Interstate Technology and Regulatory Council) demonstrated to what degree the proposed Guidance would make a difference in public health risk assessments for decision making by regulatory programs. These presentations showed that:

- The proposed SG will affect air regulation of mutagenic carcinogens depending on the assumptions used regarding exposure levels, exposure duration, and age of exposure in individual situations.
- The proposed SG will most likely lower the maximum contaminant level (MCL) for mutagenic carcinogens allowed in drinking water. These levels may or may not be attainable (measurable) with current analysis techniques. Attaining these levels will be costly and harder to obtain at small treatment facilities due to their limited budgets. The cost of reducing the MCLs for mutagenic carcinogens would need to be weighed against the benefit of reducing the early-life exposure cancer risk.
- The proposed SG would lead to an increase in the quantitative cancer risk to children from exposure to a soil contaminated with mutagenic carcinogens. Therefore, remediation costs would likely increase. Cleanup of contaminated urban areas could also be significantly more expensive, and in some cases cost-prohibitive. DiZio pointed out that implementing the approach recommended by the proposed SG in regulatory decision making brings with it the complex task of communicating to the public at large and to parents in particular both science—with its uncertainties and limitations—and policy—with its inherent assumptions and nuanced applications. DiZio discussed how such dialogs are often problematic because risks arise not only from contaminated sites but also from exposures to background levels of chemicals in the ambient environment, the latter of which can dominate risk estimates in some cases.
- Although not discussed in great detail, some panelists offered their perspective that the proposed SG is unlikely to affect the regulation of pesticide active ingredients to a great extent. Currently, all modern pesticide active ingredients must be tested for carcin-

ogenicity, and of the few that indicate carcinogenic potential in rodent assays, a demonstrated mutagenic mode of action is not observed; therefore the proposed SG would not apply.

### 3. Conclusions

The workshop concluded with a panel discussion led by Dr. Gail Charnley (HealthRisk Strategies). She summarized the assumptions that underlie and reflect the proposed SG and its application:

- The proposed SG concludes that children are more sensitive than adults to mutagenic carcinogens; sensitivity in humans is greatest between ages birth and 2 years, and declines as age increases, until it achieves a comparable value to an adult at age 16.
- Underlying EPA's approach is the presumption that the current quantitative risk guidelines are not sufficiently protective for mutagenic carcinogens, even with all of the health-protective, default assumptions used to evaluate carcinogenic risks.
- The rodent models are appropriate surrogates for childhood development; however, age mapping issues must be addressed.
- Sensitivity differences observed in laboratory animal studies of high dose, acute exposures accurately reflect sensitivity differences expected at environmental exposure levels.
- Data for the four mutagens evaluated by EPA in the proposed SG are representative of all mutagenic carcinogens.

- Quantitative adjustment of cancer risk calculations is warranted for all mutagenic carcinogens, although the data for the four substances evaluated by EPA indicated that 58% of ratios early-life: later in life indicated no increased potency, equal potency or less potency.
- The differences in potency observed in the datasets relied on by EPA are due to susceptibility, not dose.
- Risks from early and later exposures can be added to estimate lifetime exposure, but the approach may not always be appropriate.

Overall, the presenters and panelists generally agreed that the complexity and extent of the assumptions embedded in the proposed SG would challenge its interpretation and application. The greatest challenge would be clearly defining criteria for determining a "mutagenic" mode of action for chemical carcinogens, in a manner that considers the totality of the data from all relevant assays and that applies the criteria in a consistent way. Additional concerns and challenges noted by the panelists included addressing thresholds for mutagenicity in relation to induction of cancer. Noted also was the relatively scarcity of substances with sufficient scientific data to convincingly warrant adding more conservative health protective default factors in the quantitative adjustment of cancer risk estimates for humans. An overarching challenge identified by the panelists was communication to the public, for both the underlying science and EPA's Guidance are complex, often ambiguous, and not meant to be applied across the board for all substances.