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May 30, 2002

Honorable Christine Todd Whitman
Administrator
U. S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20406

Dear Administrator Whitman:

The Children's Health Protection Advisory Committee has continuing interest in the EPA's proposed revisions to its Guidelines for Cancer Risk Assessment (the Cancer Guidelines). We sent two previous letters to Administrator Browner raising questions and concerns we wanted U.S.EPA to consider during its process of revisions to the cancer guidelines. The purpose of this letter is to offer further comments on the guidelines as currently written (e.g., the July 1999 version) with respect to the adequacy of children's health protection. The Committee looks forward to continued dialogue with EPA on the revised guidelines as well as input into future revisions.

We recognize that EPA has been working towards revised guidelines for a number of years and believe it is important to release the revised guidelines as soon as possible. Clearly EPA needs to base the guidelines on the state-of-the-science at the present time. Clear recommendations that make use of existing science, as well as consideration of guidelines under development for FQPA, could:

- improve the utility of the July 1999 draft cancer risk assessment guidelines
- provide appropriate protection for potentially higher-susceptibility early life stages
- and increase consistency in risk assessment across the Agency.

The Committee is concerned that there is no clear recommendation for default methods of accounting for potential increased sensitivity of early life stages to the effects of carcinogens. While not all carcinogens would be expected to be more potent when exposure occurs early in life, there are many examples where this is true.

The guidelines do not have adequate criteria for deciding whether to adopt a margin of exposure (MOE) approach versus a linear approach for dose-response assessment. The MOE approach generally assumes the carcinogen has a threshold below which carcinogenesis would not be expected to occur. This is a critical

decision for children because it a) assumes that the mode of action in adult animals applies equally to embryonic life stages, infants, and children as well as adult humans; and b) usually results in a less health-conservative analysis of risk (because one assumes zero risk below some threshold in the MOE approach but assumes non-zero risk for any dose in the linear approach). There are few chemicals for which data are sufficient to conclude that the mode of action is a threshold phenomenon. In addition, the vast majority of carcinogens have not been tested in studies that exposed animals *in utero*, or perinatally. Although the guidelines state that a more conservative linear approach should be used if the assessor is not sure of the mode of action, there is little guidance to the assessor regarding the type and strength of evidence needed to make that determination. Clear criteria should be presented in the guidelines for the evidence needed to conclude a threshold mode of action. These criteria should address the need for data that adequately tests the hypothesis of a threshold mechanism of action. Such criteria have been proposed, for example, for chemicals that act as α–2-u-globulin inducers in rodent kidney. In addition, the finding of a threshold should be clear from studies which provide mechanistic support for an MOE approach, as the routine carcinogenicity bioassay is generally not adequate to determine a threshold mechanism. Finally, the additional data available on the compound should be consistent with the selection of a threshold mechanism, (e.g., lack of genotoxicity in a number of assay systems and studies).

Another concern regarding the MOE approach is the lack of clear guidance on the adequate size of the margin of exposure when evaluating risks. Specifically, there is a need to address whether the MOE should be larger when evaluating risks from early life stage exposures. The ratio of the existing exposure to the point of departure (typically the 95% lower confidence limit on the dose effecting a 10% response rate) is the MOE. As noted above, there is uncertainty in assuming that the mode of action is the same when exposure occurs early in life as when exposure occurs at maturity. One approach to address this uncertainty is to use a larger MOE when risks to children are being evaluated unless certain that the mode of action and potency identified for later life stage exposures would be sufficiently similar to those following exposures at early life stages. The Agency has recently developed guidance for the Food Quality Protection Act additional ten-fold safety factor for pesticide tolerance assessment to protect children. Similar general approaches could be used to help decide whether the MOE should be larger, and how much larger, when evaluating risks to children.

The linear approach proposed moves away from the linearized multistage model to a simpler model. The simple linear model defines a point of departure as the 95% lower confidence limit on the dose effecting a 10% tumor response rate (the LED_{10}, equivalent to the point of departure for the MOE methodology). A line is drawn from that point through the origin. As noted in the guidelines, the results of the linearized multistage model and this simpler linear approach are generally comparable. However, the data used to define the point of departure will almost always be data obtained from

bioassays in which exposure started at sexual maturity (or from epidemiological studies of adults). It has been argued by some that the linear model itself is fairly health-protective and can be considered to be protective even when exposure starts in early life stages. However, many argue that this approach ignores examples where potency is clearly larger if calculated based on early-life exposures (e.g., vinyl chloride, nitrosamines, others). Where data are unavailable to quantitate differences in potency by life-stage at exposure, generic approaches to address possible increased sensitivity from early life stage exposure could be applied. A weighting factor for age-at-exposure could be developed for use when conducting a quantitative dose-response assessment using a linear model for carcinogens suspected of greater potency following early life stage exposures. For example, the Agency could suggest a range for a default weighting factor based on knowledge of the differences in potency by life stage for carcinogens where data are available to quantify this risk. Another possible approach is to use structure-activity relationships for structurally similar compounds (e.g., vinyl bromide as analogous to vinyl chloride) or classes of compounds (e.g., polycyclic aromatic hydrocarbons, nitrosamines). As written, the July 1999 guidelines are basically silent on this issue except where there are existing chemical-specific data sufficient to quantify early-life-stage sensitivities.

The guidelines are also silent on the issue of exposure to carcinogens prior to conception, and the potential increased risk of cancer in the offspring. The Committee recognizes that the data on this issue are inconclusive, but believe it deserves mention as an unresolved issue.

We are attaching copies of two earlier letters sent to Administrator Browner which contain specific considerations and questions the Agency should evaluate in revising the cancer guidelines. These issues are still appropriate for consideration as you finalize the next draft of the cancer guidelines.

The Committee encourages EPA to include experts in children's health on peer review committees for chemical-specific carcinogen potency assessments. This is particularly important since the guidelines do not contain guidance for default approaches accounting for potential increased sensitivity from early life stage exposures. Thus, assessment of this potential increase in sensitivity to carcinogens will likely be conducted on a case-by-case basis. This makes the peer review all the more important to ensure adequate protection of infants and children.

We encourage the EPA to continue developing methods to explore cancer risk assessment that adequately accounts for early life stage exposures. The Committee recognizes that there are many unresolved scientific issues and hopes for a lengthy discussion of such issues in the guidelines themselves. We recommend that EPA work with the National Toxicology Program to encourage research into the effects of early life stage exposure to carcinogens. We also recommend that EPA compile a database of

studies of carcinogens where early life stage exposures as well as exposures to mature animals have been evaluated, and conduct comparisons of the effects of life stage at exposure on estimated cancer potencies for a number of compounds. We recommend that USEPA work with the California EPA and other states agencies who are evaluating the issue of early life sensitivities to carcinogens. As the scientific understanding of carcinogenesis moves forward, it is our hope that EPA will revise the guidelines on a regular basis to incorporate new information emerging in this field, particularly as it relates to early life-stage sensitivity.

Sincerely,

J. Routt Reigart, M.D.
Chair, Children's Health Protection
Advisory Committee

JRR/pc