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May 12, 1999

Carol Browner
Administrator
Environmental Protection Agency
401 M Street SW
Washington, D.C. 20460

Dear Administrator Browner,

The Children's Health Protection Advisory Committee met on May 5-6, 1999 to consider, among other topics, the appropriate consideration and protection of children under EPA's proposed revisions to the Guidelines for Cancer Risk Assessment (the Cancer Guidelines). The Committee strongly supports EPA's plans to convene an expert panel under the auspices of the Science Advisory Board to review the pediatric implications of the proposed Cancer Guidelines. The purpose of this letter is to suggest questions to include in the charge to be given to this panel, which we understand will meet in July 1999, and to comment on critical next steps in the process. In addition, members of the Committee have proposed the names of several pediatric experts for nomination to this panel.

In preparing these comments, the Committee's Science Work Group reviewed the following documents:

- The April 1996 notice of the proposed Cancer Guidelines in the *Federal Register*,
- The Science Advisory Board's September 1997 report commenting on the 1996 proposal,
- The March 1998 reply by EPA to the Science Advisory Board, and
- The briefing materials to and minutes of a January 1998 Science Advisory Board meeting.

The Committee and the Science Work Group also heard presentations on what is and is not known about the causes of cancer in children from research scientists specializing in pediatric cancer. In addition, the Committee received very useful briefings by EPA at its May 1999 meeting.

Obviously, the state of science has advanced significantly since the 1986 version of the cancer guidelines and continues to develop rapidly. The EPA appropriately wishes to apply current scientific knowledge and to maintain the flexibility to incorporate new knowledge that will further improve the accuracy of its cancer risk assessments. Because the Cancer Guidelines represent critical regulatory policy and cancer risk assessments are the basis for specific regulatory decisions, it is essential that all proposed changes to the Cancer Guidelines are carefully reviewed to ensure that future Agency decisions fully consider the risk of prenatal and childhood exposures and cancer and, in this way, fully protect all children's health. The proposed guidelines allow use of a non-linear (threshold) model to assess risk in addition to the prior, linear default model. While use of a nonlinear model may be a correct decision, it should be chosen only with great care and assurance that the nonlinear model and curve are applicable in that case to the fetus and children.

Generally, the Committee's comments are based on the understanding and concern that the cancers associated with childhood are of at least three types: (1) those that occur uniquely in children, either in a form different from that seen in adults or through different biological processes; (2) those that also occur in adults, but may appear more rarely in childhood perhaps because of unique susceptibility in certain children; and (3) those that occur in adult life after a latency period but are associated with an exposure during a sensitive developmental window during gestation, infancy and childhood.

Overall, the Committee wishes to know how EPA met its commitment found in the March 13, 1998 letter to Dr. Joan Daisey to incorporate human variability in susceptibility into the proposed guidelines reflecting "the Administrator's policy on evaluating health risks to children...recogniz[ing] developing infants and children as a subgroup..."

The Committee urges the SAB, at its July meeting, to examine and comment on the extent to which EPA's 1996 draft Cancer Risk Assessment Guidelines address the recommendations regarding infants, children, and differential susceptibility (including children's susceptibility) found starting on p. 11 of the NAS 1994 report, *Science and Judgment in Risk Assessment*, the consideration of which was mandated by Section 112(o) of the Clean Air Act.

We submit the following questions and request that EPA include them in the charge to the proposed SAB panel in July. We look forward to the insights that emerge from their thoughtful consideration. In particular, the Science Advisory Board panel should consider:

1. What constitutes sufficient animal and human data to depart from a low dose linear default extrapolation for a particular chemical while maintaining the appropriate level of protection for children? What policy or processes should be implemented in the absence of such data to assure the protection of children? What policy should be followed if there is sufficient data to establish a mode of action in an adult, but not in a fetus or child?
2. Are the modes of action for chemical agents different for children than for adults?
3. What factors should be reviewed to determine the latent risks from exposures at different stages of development: pre-conception, in utero, in childhood and in adolescence?
4. How do the proposed cancer guidelines take into account the timing of exposure, especially the effects of acute exposures during particularly sensitive developmental stages?
5. How do the proposed guidelines take into account the sequencing of sensitizing and subsequent potentiating events in the manifestation of cancers both in childhood and in later adolescent or adult life (e.g. how might an exposure to a medical intervention such as radiation, chemotherapy, vaccine or virus affect an individual's sensitivity to later environmental or developmental stress factors, such as the onset of puberty or exposure to a chemical agent)?
6. When scientific data suggests a particular mode of action for a specific chemical, what data should be required, if any, to establish that this is the relevant carcinogenic mode of action for that chemical?
7. How should EPA apply the Cancer Guidelines in relation to exposure assessments in assessing risks to special populations and, in particular, in developing regulatory policy and regulations such as the Worker Protection Standard where consideration needs to be given to the actual exposures of children in farm worker families? Should the guidelines set forth examples of such applications?
8. What research should EPA sponsor or develop to improve its ability to evaluate unique susceptibility of children in general and in high-risk populations in particular.
9. What examples of the application of the guidelines to cancers that occur uniquely in childhood, or to cancers that occur later in adolescent or adult life resulting from childhood exposures, have been considered in developing these Cancer Guidelines? Are new models based on acute or combinations of acute and chronic exposures needed?

In addition, the Committee understands that EPA intends to prepare risk assessments for both chloroform and atrazine using the proposed revisions to the Cancer Guidelines and to submit them to the Science Advisory Board panels for review. The Committee strongly urges EPA to wait until the written Cancer Guidelines review from the SAB Pediatric Panel is available before conducting the chloroform and atrazine SAB reviews. The Committee also recommends that EPA include the pediatric experts invited to participate in the July panel in those subsequent panels to review the risk assessments on chloroform and atrazine.

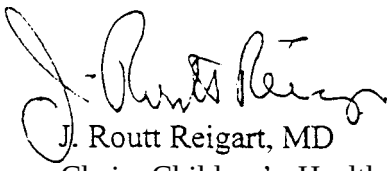
Finally, members of the Committee have offered the following experts for nomination as participants in the proposed July panel:

- Dr. Lucy Anderson, National Cancer Institute
- Dr. Genevieve Matanoski, Johns Hopkins University
- Dr. Les Robison, University of Minnesota
- Dr. Lorenzo Tomaz, NIEHS/NTP

The Children's Health Protection Advisory Committee strongly urges EPA to actively pursue methods of evaluating risks of mixtures, particularly in cases where mixtures are already suspected of having synergistic effects or where certain populations are regularly exposed to mixtures of carcinogenic agents or initiators.

In summary, the Committee supports EPA's efforts to improve the accuracy of its risk assessments but urges continued research to fill gaps that remain in scientific knowledge. Thank you for the opportunity to comment.

Sincerely,



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

cc. R. Trovato, P. Goode, W. Farland, W. Wood, J. Wiltse, D. Barnes