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September 26, 2000

Carol Browner
Administrator
US Environmental Protection Agency
1200 Pennsylvania Avenue
Washington, DC 20460

Re: Evaluation With Respect to Children's Environmental Health of
OPP/EPA's June 2000 Draft Cumulative Risk Guidance

Dear Administrator Browner:

The Children's Health Protection Advisory Committee (CHPAC) is submitting these written comments and questions to the Agency and the FIFRA Science Advisory Panel (SAP) to suggest considerations they should take into account during the review of EPA's "Proposed Guidance on Cumulative Risk Assessment of Pesticides That Have a Common Mechanism of Toxicity" (hereafter the Guidance). We seek to inform discussions during the next meeting of the SAP, which will address the Guidance on September 27-28, and again as the Agency and the SAP review comments on and further refine the document.

In general, the CHPAC believes the Guidance is a comprehensive, thoughtful, and reasonable work in progress. However, the CHPAC also believes the Guidance does not adequately focus on risks to children. Starting with the executive summary and in each subsequent section, children's risk should be comprehensively addressed. For example, the Guidance could be strengthened by addressing children's differential risk to pesticides due to rapid growth and development of organ systems, during windows of susceptibility, and resulting from greater exposures due to crawling, mouthing behaviors, and disproportionate food and water consumption per unit body mass.

Recognizing the Guidance is a work in progress, and that we do not fully understand how it will be utilized and how it will be adapted as the result of new information, we offer the following questions and suggestions for improvement prior to implementation:

Aggregate and Cumulative Exposure Assessment

- The CHPAC does not believe it will remain acceptable to assess the cumulative risk of exposure to pesticides from residential sources separately from dietary sources because residential sources could lead to more significant exposures than dietary sources for some groups of children. Better guidance is needed to cumulate residential (for example) and dietary exposures to pesticides with a common mechanism of toxicity in the absence of adequate data on residential exposure. In that same vein, the Guidance, as it relates to the use of bridging or surrogate data, should be expanded and include a case study. Is the relationship of the adequacy of data to the ability to aggregate and cumulate exposures adequately and appropriately defined? What is the plan to develop adequate data? And how can this be accomplished through research and industry data call-ins?
- Does the Guidance enable the agency to account for patterns of behavior that change rapidly during early childhood, including mouthing behaviors and crawling, and the effect on the aggregation and cumulation of exposures to pesticides and other residential exposures over time?
- In the absence of an individual aggregate assessment on each chemical, how does the agency plan to ensure that available data have been carefully evaluated for their ability to describe the potential exposure for each chemical and population of interest, including children, when undertaking a cumulative risk assessment?
- The Guidance states, and we agree, that a benchmark approach is preferred to derive the point of departure for each chemical, but that an NOAEL will be used until the toxicological databases improve to permit reliable benchmark analysis. The Agency should clearly define the shortcomings of the databases, and the plan for how and when the transition to benchmark doses will occur.
- The CHPAC is concerned that the cumulative risk over time and over various life stages or over a lifetime may be qualitatively and quantitatively different from the cumulative risk related to an exposure to multiple chemicals at a point in time. What methodology will the Agency will set forth in the Guidance for integrating risk over time and through developmental life stages?

Fitting Mechanisms to Endpoints

- The Guidance should more explicitly state how it will use other EPA documents/guidance to group chemicals with a common mechanism of action and how the Agency will select among proposed or documented modes of action to ensure the maximal protection of children.

Use of Case Studies

- A case study that considers a chemical with both acute and chronic potential health effects would better illustrate how the cumulative risk assessment will work in practice. For example, acetylcholinesterase inhibition is a recognized molecular mechanism underlying acute organophosphate neurotoxicity. Inhibition of neuropathy target esterase is most closely associated with chronic neurotoxic effects (neuropathy). The case study in the Guidance mentions the former, but not the latter.

- The CHPAC has serious concerns about how the Guidance will be applied for specific chemicals or toxicants. The Agency should provide several case studies, in addition to the organophosphate example, to clarify and explain how the Guidance could be applied to specific chemicals and toxicants. These case studies should include acute, chronic reversible, and chronic irreversible effects from a broad range of chemical classes.

Validation of Assumptions

The Guidance is based on numerous assumptions (e.g., additivity of toxic effects, exposure parameters) and underlying models. Although we agree this approach is necessary to enable the use of the Guidance to protect humans in the near term, the CHPAC believes that reliance on this approach will inhibit empirical studies and observations that are necessary to ensure that children are adequately protected from prevalent environmental exposures.

- What is EPA's plan to validate the assumptions and models in the Guidance, including epidemiological studies that link exposure to biomarkers or health effects for prevalent exposures, to ensure that the Guidance adequately protects children?
- In EPA's plan to validate assumptions and models, the Guidance must be clear that some assumptions can be tested in the lab, others can be tested in the field, and both are important in testing the model's validity.
- The CHPAC recommends that the Guidance include a description of the assumptions and uncertainties included in the document. This description should include research and industry data call-ins, underway or proposed, to provide data to validate or replace the assumptions or define the uncertainties. Such an analysis should include a specific description of the data gaps related to children, and of the plan to develop critical information.

In the CHPAC's April 14, 2000 letter to Administrator Browner regarding EPA's strategy for research on environmental risks to children, the Committee recommended that EPA place the highest priority on conducting fundamental research which generates *actual data* about children rather than relying on extrapolations. One of the high priority areas concerned the issue of mixtures and cumulative risks to children. In addition, the Committee expressed its concern as to whether EPA had sufficient resources to adequately fund all the research that is widely considered to be a very high priority. The CHPAC reemphasizes its earlier recommendation that the necessary research identified in the Guidance receive high priority.

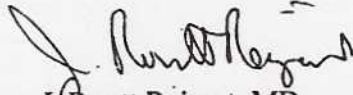
Childhood as a Susceptible Life Stage

- The Guidance does not adequately address cumulative exposures *in utero* or during childhood.
- There are children who are likely to have special susceptibility to environmental chemicals as a result of prematurity, previous exposure to toxicants, pica, inadequate nutrition, chronic illness, genomic polymorphisms, etc. To what extent will these factors be entered into cumulative risk assessments? For example, should the well-known genomic polymorphism that results in deficiency of butyrylcholinesterase be considered in relation to organophosphates and carbamates?

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The Committee supports EPA's efforts to develop the Guidance, and seeks to focus energy and thought in your review of the proposed document on specific guidance in determining the cumulative risks to children. We thank you for the opportunity to comment.

Sincerely,



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

cc. R. Kendall (SAP Chair), S. Wayland, N. Noonan, S. Galson, R. Trovato, P. Goode