Children's Health Protection Advisory Committee

Administrator Stephen Johnson
US Environmental Protection Agency
1200 Pennsylvania Ave NW
Washington, D.C. 20460

December 14, 2007

RE: Framework for Determining a Mutagenic Mode of Action (MOA) for Carcinogenicity

Dear Administrator Johnson:

The Children's Health Protection Advisory Committee (CHPAC) has reviewed the "Framework for Determining a Mutagenic Mode of Action (MOA) for Carcinogenicity." The CHPAC finds that the Framework falls far short of adequately protecting public health, specifically with respect to protecting against childhood exposure to carcinogens. The Agency needs to redraft the Framework based on the principle that genotoxic carcinogens have a mutagenic MOA as the default risk assessment position, and that assessment of risk from such carcinogens warrants application of age-dependent-adjustment factors (ADAFs) to account for early-life susceptibility. The CHPAC strongly urges the Agency to revise the Framework before the document undergoes peer review.

Background

The CHPAC has followed with great interest the development of EPA's 2005 *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (See, for example, the CHPAC's June 8, 2004 letter to Administrator Michael Leavitt and to then-Acting Administrator Stephen Johnson March 3, 2005.). The Supplemental Guidance (SG) recommends applying ADAFs when assessing risks from early life exposure to carcinogens with a mutagenic mode of action. The ADAFs adjust the portion of risk that occurs from early-life exposure upwards to account for susceptibility of developing children. The Framework was developed to aid in the implementation of the SG by guiding assessors in determining whether a carcinogen has a mutagenic mode of action. The CHPAC is concerned that the Supplemental Guidance already is limited with respect to protection against childhood exposure to carcinogens (the ADAFs are only applied in risk assessment for carcinogens with a mutagenic MOA). The

Framework would further severely restrict the application of the ADAFs. This is a critical issue because exposure to some carcinogens early in life results in higher cancer risk relative to adulthood exposure. Below, the CHPAC provides comments on the Framework, makes recommendations, and offers related considerations.

Comments on the Framework

Although the Framework states that there is no default MOA, in fact the implicit default is that mutagens do not cause cancer via a mutagenic mode of action. The Framework requires a high degree of evidence to demonstrate a mutagenic MOA, even for genotoxic carcinogens, in order to apply the ADAFs to account for early-life susceptibility. According to the Framework, evidence of mutagenicity or genotoxicity alone is not sufficient to conclude that the carcinogen operates via a mutagenic MOA. As outlined below, this approach is inconsistent with established cancer risk assessment methodologies, impedes assessment for early-life exposure, and relies on data that are generally not available. More specifically:

1) Under the draft Framework, when assessing cancer risk from early-life exposure, ADAFs would be applied only if additional data beyond standard genetic toxicology tests are available. However, in many cases, these additional data will not be available or are highly uncertain (e.g., where in the carcinogenic process the mutation occurs; whether the agent causes DNA adducts in the cancer target organ). Thus, even for well-established mutagens, incorporating ADAFs for early-life exposure into the cancer risk assessment will be detoured by consideration of uncertain, controversial and data-poor issues. As noted in EPA's 2005 cancer risk assessment guidelines, many carcinogens act via multiple mechanisms; determining which is the predominant mechanism, at what life-stage and at what doses is extremely difficult.

2) The Framework seriously limits the application of ADAFs, which is counter to basic public health protective risk assessment procedures designed to treat uncertainty in a predictable manner (NRC, 1994). The Framework itself notes on Page 27 that "Mutagenesis is routinely accepted as part of the carcinogenic process." This statement points to the appropriateness of a default assumption that a mutagenic carcinogen has a mutagenic MOA unless evidence exists to the contrary. The Agency should change the default to assume that carcinogens positive in genotoxicity tests cause cancer via a mutagenic MOA.

3) The Framework creates a disincentive to new data generation because the default position is that no ADAF is necessary without additional detailed mechanistic data. For most chemicals, these data do not exist and are unlikely to be generated with this default.

4) The additional data needed to demonstrate a mutagenic MOA, as described in the Framework, are vague. This creates the potential for inconsistent and arbitrary decision-making about when to apply the ADAFs. The Agency may find it difficult to defend a mutagenic MOA determination because defining the precise mechanism whereby a chemical causes cancer can be an extensive research effort with many uncertainties.

5) The definition of mutagen in the Framework is too limiting, focusing only on carcinogens, or their metabolites, that have a direct interaction with DNA. Such a narrow view of mutagenicity is problematic. Mutagens that damage DNA indirectly (e.g., via formation of oxygen radicals) should still be considered to have a mutagenic MOA. Further, positive responses in genotoxicity tests indicate an ability to modify DNA. Such DNA modification is particularly critical at early-life stages when cells are rapidly dividing and differentiating, and DNA repair is less efficient in some tissues (e.g., Anderson et al., 2000; Slikker et al., 2004, Barton, et al., 2005). Moreover, the Framework ignores the uncertainty of extrapolating MOA across different life stages and is therefore inconsistent with the recently adopted EPA Framework for assessing children's risk (EPA 2006).

6) The Framework would likely fail when tested against some of the 12 mutagenic carcinogens upon which the Supplemental Guidance is based. Data on these chemicals spurred the development of the Supplemental Guidance because they showed considerably greater cancer potency when juvenile rodents were exposed as compared to exposures to adult rodents. However, it is unclear that the Framework would identify an agent such as safrole, for example, as having a mutagenic MOA, because of its complex metabolism, mixed mode of action, and data gaps for some of the supporting data sought in the Framework (e.g., whether mutagenic action occurs early in the carcinogenic process) (Liu, et al., 1999; Rietjens, et al., 2005). Yet the potency of safrole in juvenile mouse liver was 46-fold greater than in adults.

CHPAC Recommendations

The CHPAC finds that the Framework seriously restricts the utility of the Supplemental Guidance and must be revised significantly prior to peer review. **The CHPAC recommends that the Agency redraft the Framework such that genotoxic carcinogens are assumed to have a mutagenic MOA unless proven otherwise.** The revised Framework should use an inclusive default approach that considers both direct- and indirect-acting mutagens and genotoxic carcinogens as possessing a mutagenic MOA that warrants application of the ADAFs for early-life susceptibility. The revised Framework should include criteria necessary to demonstrate those cases in which the ADAFs are not applicable to a specific genotoxic carcinogen. The data for superseding the default should be robust and the criteria for using these data clearly articulated.

Related Considerations

The CHPAC notes that protection provided by the SG is already limited by only applying the ADAFs for carcinogens with a mutagenic MOA. This goes against the standard approach of using conservative MOA assumptions in the face of uncertainty. Since the 2005 Cancer Guidelines assume that chemicals which have a mutagenic MOA or for which the MOA is unknown have linearity at low dose (USEPA, 2005), it is also appropriate that the ADAFs be applied in assessing risks to these carcinogens. Indeed, the Agency needs to consider expanding the application of ADAFs. Instead, the Agency has created a Framework which greatly limits the application of ADAFs, making it difficult to apply ADAFs even for known genotoxicants. These problems can be remedied by following the CHPAC recommendations for known genotoxicants and by reevaluating the application of ADAFs to carcinogens with an uncertain MOA.

The Agency has delayed implementation of the Supplemental Guidance over the two years since it was published. The CHPAC urges the Agency to apply the ADAFs developed in the Supplemental Guidance now, unless chemical-specific data are available to indicate that it is not necessary. We believe our recommendations will open the way to fully assessing cancer risks resulting from childhood exposure in a prudent manner that is protective of public health and consistent with current scientific understanding of the carcinogenic process.

Sincerely,

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Children's Health Protection Advisory Committee

Cc: Dona DeLeon, Acting Director, U.S. EPA Office of Children's Health Protection and Environmental Education
George Gray, Assistant Administrator, Office of Research and Development
Elizabeth Lee Hofmann, Executive Director, Risk Assessment Forum
Joanne Rodman, Acting Director, Child and Aging Health Protection Division

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