UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

October 4, 2005

SCIENCE POLICY COUNCIL

MEMORANDUM

SUBJECT: Implementation of the Cancer Guidelines and Accompanying Supplemental Guidance - Science Policy Council Cancer Guidelines Implementation Workgroup Communication I: Application of the mode of action framework in mutagenicity determinations for carcinogenicity

FROM: William H. Farland, Ph.D.
Chair, Science Policy Council

TO: Science Policy Council
Science Policy Council Steering Committee

In his memo of March 29, 2005, Administrator Johnson provided general direction on implementation of EPA's 2005 Guidelines for Carcinogen Risk Assessment (*Cancer Guidelines*, CG) and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (*Supplemental Guidance*, SG). The Administrator's memo says that the Cancer Guidelines and the Supplemental Guidance should be used:

- for all carcinogenicity risk assessments that are newly initiated;
- on a case-by-case basis for assessments that currently are being performed, based on consideration of the potential effects of their use on the expected decision and timeline; and
- on a case-by-case basis for assessments that were completed before issuance of the *Cancer Guidelines*, when a new program-specific or site-specific decision is required that needs to be supported by an updated carcinogenicity risk assessment.

I have asked the Science Policy Council (SPC) Cancer Guidelines Implementation Workgroup to provide information to facilitate the development of new carcinogenicity risk assessments and to promote consistency with Agency policy, guidance, and guidelines. I anticipate providing additional information on these topics in the future as the Agency gains experience with the new *Cancer Guidelines* and *Supplemental Guidance* and as new questions and issues arise.

The information in the attached communication is intended for Agency risk assessors who are involved in conducting or reviewing risk assessments for carcinogens. The scope of Agency assessments varies widely, from screening level exposure and risk assessments involving hundreds of chemicals, to comprehensive toxicological assessments of single chemicals such as

those in the Agency's Integrated Risk Information System (IRIS). The activities of Agency risk assessors are equally diverse, so risk assessors will need to consider their specific roles and responsibilities when deciding how best to use the information provided here. Agency risk assessors are strongly urged to become familiar with the sections of the *Cancer Guidelines* and *Supplemental Guidance* that are relevant to their particular activities, and to consult these documents for a fuller description of the topics discussed in this communication.

The purpose of the attached communication is to provide summary information for applying the *Cancer Guidelines'* mode of action (MOA) framework in determining whether a chemical has a mutagenic mode of action. This communication also provides information on applying the new *Supplemental Guidance* when assessing risks for carcinogens that have a mutagenic mode of action. Specifically,

- Section 1 summarizes the key steps in the process of determining whether a weight of evidence evaluation supports a mutagenic MOA for carcinogenicity.
- Section 2 outlines how to consider both the *Cancer Guidelines'* mode of action framework and the *Supplemental Guidance* in each component of a risk assessment (hazard characterization, dose-response assessment, exposure assessment, and risk characterization).

It focuses on these particular topics because the new *Cancer Guidelines* emphasize the importance of MOA in assessing cancer risk, and the MOA determination is critical to the application of the new *Supplemental Guidance*. Additionally, while much of the *Cancer Guidelines* focus on hazard characterization and dose-response assessment, the *Supplemental Guidance* includes guidance for risk assessors who are using slope factors and exposure data to estimate cancer risk for early-life exposures in risk characterization.

This communication clarifies how risk assessors should apply the *Cancer Guidelines* and accompanying *Supplemental Guidance* within the context of the current practices and activities of their offices or programs. For example, if a program generally relies on cancer risk assessment information contained in IRIS, that program can continue this practice. When IRIS states that a weight of evidence evaluation supports a determination that a chemical is carcinogenic by a mutagenic mode of action, the program would utilize that determination and the appropriate application of recommended age dependent adjustment factors (ADAFs) or chemical specific estimates of lifestage susceptibility. In cases where the IRIS assessment on a chemical has not addressed application of the *Supplemental Guidance*, each office or program will need to consider application of the *Cancer Guidelines* and *Supplemental Guidance*.

Science Policy Council Cancer Guidelines Implementation Workgroup

Communication I. Application of the mode of action framework in mutagenicity determinations for carcinogenicity

Section 1. Essential Components in the Process for Determining a Mutagenic Mode of Action for Carcinogenicity[1]

Carcinogenesis is a complex process requiring that assessors sometimes consider more than one MOA for carcinogenicity. This memo addresses the evaluation of the potential for a mutagenic MOA for carcinogenicity, but nothing in this discussion is meant to exclude consideration of other carcinogenic MOAs as part of the evaluation process.

An Agency determination regarding a mutagenic mode of action (MOA) for human carcinogenicity may be part of a new complete hazard and dose-response assessment, part of an updated assessment, or an addition to an existing assessment. The determination should address the quality standards described in the Agency's Information Quality Guidelines. The process of making each MOA determination has three essential components, which are discussed below. Their description is not intended to imply duplicative analytical steps.

1.A. Analysis of a mutagenic MOA for carcinogenicity.

Risk assessors should implement the following steps when determining whether a chemical is considered carcinogenic by a mutagenic MOA.

1.A.1. Consult Critical Agency Documents

The *Cancer Guidelines* and *Supplemental Guidance* (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283) discuss the MOA analysis and considerations for mutagenicity as a MOA for carcinogenicity (See CG Sec. 2.4; SG Secs. 3.2.1-2). Other documents, such as EPA publications on modes of action for certain classes of chemicals may also be relevant.

1.A.2. Evaluate Relevant Data

The EPA Risk Assessment Forum's Mutagenic Mode of Action Working Group is working on guidance on the scientific aspects of making mutagenic mode of action determinations, and to assist in determinations of mutagenic MOAs for carcinogenicity. Their product will elaborate on the essential elements of such determinations which include:

- reviewing the available mutagenicity data to determine if the chemical is mutagenic;
- applying the Cancer Guidelines' mode of action framework to ascertain if the weight of the evidence supports a determination that a mutagenic mode of action (as described in

---

[1]The phrase, 'determination that a chemical is carcinogenic by a mutagenic mode of action', and similar phrases, are intended to indicate a weight of the evidence determination that includes an evaluation of the mode of action in animals as well as its relevance for humans, as part of the broader weight of evidence narrative "that explains an agent's carcinogenic potential and the conditions that characterize its expression"[CG, sec 2.5]. The slightly shorter phrase is used to improve the flow of the text.

the *Cancer Guidelines* and *Supplemental Guidance)* is (1) applicable to animals and (2) relevant to humans; and

- reaching an Agency conclusion for a mutagenic MOA for carcinogenicity when a mutagenic MOA is determined, and applying the *Supplemental Guidance.*

(For further information, contact Resha Putzrath, 202 564-3229; putzrath.resha@epa.gov).

In addition to evaluating mutagenicity as a MOA for carcinogenicity, the MOA analysis should also evaluate the strengths and weaknesses of other plausible modes of action. If there is significant biological support for more than one mode of action, each should receive a separate analysis (See CG Sec.2.4.3). Information on all modes of action should be integrated to better understand which mode(s) may be relevant for different human exposure scenarios, i.e., risk characterization (See CG Sec. 2.4.3.3). Alternative modes of action for which there is significant biological support should, along with their strengths and uncertainties, be part of the risk characterization (See CG Sec.5.1). When developing an MOA analysis as a companion to an existing assessment that may contain a considerable amount of data and analysis, an application of the mode of action framework may largely rely on citations and analyses from the existing assessment.

1.A.3. Provide the Conclusion of the Analysis and Supporting Rationale

Assessors can make one of three major conclusions:

- a weight of evidence evaluation supports a determination that the chemical is carcinogenic by a mutagenic MOA;
- the weight of the evidence evaluation does not support a mutagenic MOA; or
- a weight of evidence evaluation supports the conclusion that a determination of a mutagenic MOA for carcinogenicity cannot be made because there are insufficient data for determining the mutagenicity, or for defining an MOA.

Assessors should explain the rationale for their conclusion clearly and in appropriate detail. In some cases, where there are few data and where the data are insufficient to support a mutagenic MOA determination, this rationale may be quite brief.

1.B. Peer Review of the MOA Analysis

The *Cancer Guidelines* discuss peer review of MOA analyses in section 2.4.2.1. MOA analyses, including evaluation of a mutagenic MOA for carcinogenicity, should be peer reviewed in accordance with EPA's Peer Review Policy, and conduct of the peer review should be in accordance with EPA's Peer Review Handbook (http://www.epa.gov/osa/spc/2peerrev.htm).

1.C. Communication of Agency Determinations.

For informational purposes, chemical-specific mutagenic MOA analyses for carcinogenicity should be shared across the Agency prior to any public release. Communication with the public should be conducted in accordance with the Agency's Information Quality Guidelines and the

practices of the specific program office or region making the determination. These analyses should make clear, across the Agency (and to the public, when appropriate):

- whether a determination of a mutagenic MOA has been made; and
- whether age-dependent adjustment factors (ADAFs) should be applied; or
- if chemical- specific data incorporating lifestage susceptibility were available for derivation of cancer slope factors.

For IRIS assessments, communication of the MOA determination across the Agency occurs during the IRIS Agency Review. Communication with the public occurs when the toxicological assessment is released for external peer review, and when the final assessment is posted on IRIS. When the IRIS program makes a mutagenic MOA determination for a chemical, the IRIS assessment for the chemical will contain the MOA determination. When a mutagenic MOA determination for a chemical has been made outside of the IRIS assessment process, the analysis and determination, while not necessarily part of the IRIS assessment for the chemical, generally will be accessible from the IRIS assessment (e.g., via hyperlinks).

Section 2. Implementing the MOA Framework and *Supplemental Guidance* in Risk Assessment

Implementing the MOA framework described in the *Cancer Guidelines* requires particular considerations in each component of a risk assessment: hazard characterization, dose-response assessment, exposure assessment, and risk characterization. The purpose of this section is to describe how to use the MOA framework and consider the *Supplemental Guidance* in each component. Figure 1 (adapted from Figure 3 of the *Supplemental Guidance*) provides a flow chart of the MOA framework. Reference to a "box" in the following text means one of the boxes in Figure 1.

2.A. Hazard Characterization

In this step, the assessor weighs the evidence for carcinogenicity and makes a conclusion regarding carcinogenicity to humans. In addition, the assessor analyzes information on possible MOAs for carcinogenicity, including a mutagenic MOA in animals, to determine whether there is sufficient information to support a MOA determination and if any proposed MOAs are relevant to humans (Box 1 of Figure 1). Section 1, "Essential Components in the Process of a Determination of a Mutagenic Mode of Action for Carcinogenicity," provides additional guidance on the key steps in determining a mutagenic MOA. If plausible mutagenic MOAs for carcinogenicity have been considered and rejected, and no other MOA can be determined, the *Cancer Guidelines* recommend assessing cancer risk for exposures of interest using slope factors derived via the default linear extrapolation, without further adjustment (Box 2). If a mutagenic MOA for carcinogenicity is supported by the database and is relevant to humans, then the assessor flags susceptible lifestages and populations for application of chemical specific quantification in the dose-response step or application of ADAFs in the risk characterization step.

2.B. Dose-Response Assessment

In the dose-response step of a risk assessment, the conclusions of the MOA analysis influence the method used to extrapolate from the range of exposures in the available studies to environmental exposure levels. Generally, the *Cancer Guidelines* recognize various implications for low-dose extrapolation.

The decision to use a particular extrapolation approach is based on the analysis of the entire database and the conclusion on the MOA. A non-linear approach is used for agents having a carcinogenic MOA sufficient to conclude that it is non-linear at low doses; the RfC/RfD method is the default approach. A linear approach is used either as a default in the absence of sufficient toxicological information to determine a MOA or when the MOA is consistent with low-dose linearity, such as may be the case with a mutagenic MOA.

If a weight of evidence analysis supports a mutagenic MOA for carcinogenicity and the extrapolation approach is linear, then as described in the *Supplemental Guidance*, it is necessary to analyze the available data on potential susceptibility of early lifestages (lower box in Figure 1) to determine whether chemical-specific slope factors incorporating lifestage susceptibility are to be developed or ADAFs should be applied in the risk assessment. Specifically:

- If appropriate chemical-specific data on susceptibility from early life exposures are available, then these data are used to develop cancer slope factors that specifically address any potential for differential potency in early lifestages. An example is the IRIS assessment of vinyl chloride (http://www.epa.gov/iris/subst/1001.htm).

- If appropriate chemical-specific data are not available on susceptibility from early life exposures, the dose-response assessment should indicate that the ADAFs should be used with the cancer slope factors and age specific estimates of exposure in the development of risk estimates. See Section 2.D, Risk Characterization, below.

The Agency is currently considering how this information will be presented and formatted in IRIS assessments, and will provide further information on this.

2.C. Exposure Assessment

According to the *Supplemental Guidance*, "when developing quantitative estimates of cancer risk, the Agency recommends ***integration of age-specific values for both exposure and toxicity/potency where such data are available and appropriate***," since "children, in general, are expected to have some exposures that differ from those of adults (either higher or lower), due to differences in size, physiology, and behavior." Further, "this approach is adopted because risk estimates based on an average daily exposure pro-rated over a lifetime do not consider the potential for higher cancer risks from early-life exposure."

Section 6 of the *Supplemental Guidance* provides several examples of how to integrate age-dependent estimates of exposure and potency to estimate risks from lifetime and less-than-lifetime oral exposures. EPA's Risk Assessment Forum is also nearing completion of guidance for selecting age groups for monitoring and/or assessing childhood exposures. (http://cfpub.epa.gov/ncea/raf/index.cfm ; or see http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=55887). The *Supplemental Guidance* establishes ADAFs for three specific age groups (< 2 years, 2 to < 16 years, 16 years and above). If the dose-response assessment indicates that ADAFs should be applied, any grouping of ages in the exposure assessment will need to be integrated with the ADAF age groupings to derive age group-specific risk estimates. For example, an assessor may determine that an exposure is age-dependent, necessitating the use of age-specific exposure factors in the risk assessment (for example, age-specific body weights). In this case, the assessor may find that age groups for which exposure factors are available do not match the ADAF age groupings, such that the assessor will need to sub-divide an exposure age group to accommodate the age groupings for the ADAFs. In the risk characterization, cancer risk is derived for each age group, as appropriate, and summed across age groups, to obtain the total risk for the exposure period of interest (See SG Sec.6).

2.D. Risk Characterization

The risk characterization should explicitly discuss the MOA conclusion, the low-dose extrapolation approach, and consideration of the potential for early lifestage susceptibility. In assessments for chemicals for which a mutagenic MOA for carcinogenicity has been determined and a linear low-dose extrapolation performed, one of the following pertains:

- If chemical-specific data on susceptibility from early-life exposures were available for derivation of cancer slope factors, those slope factors are used for risk characterization, and the ADAFs are not applied.
- If chemical-specific data on susceptibility from early life exposures were not available, the ADAFs are applied in calculating or estimating risks associated with early-life exposures (see SG, Sec.6).

In some EPA programs, different people are involved in the different steps of the risk assessment. In those cases, there will need to be clear communication concerning the decisions made in the various steps of risk assessment and there will need to be a clear understanding of who is responsible for implementing each of the various elements of the *Supplemental Guidance*. For example, risk assessors who use slope factors from IRIS or any other source of hazard and dose-response assessments are responsible for assuring that ADAFs or chemical specific data are appropriately used given the exposure scenario.

For additional information, contact the workgroup co-chairs:

Lee Hofmann, 202 566 1928; hofmann.lee@epa.gov
Bill Sette, 202 564 0693; sette.william@epa.gov

Figure 1. Flow Chart for Early-Life Risk Assessment Using Mode of Action Framework

(Source: Figure 3. *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*)