Science Policy Council Cancer Guidelines Implementation Workgroup

FACT SHEET: Implementation of the S*upplemental Guidance* in Cancer Risk Assessment

June 2006

Purpose

Many questions on implementation of the 2005 *Cancer Guidelines* and *Supplemental Guidance* have been asked or can be anticipated. This Fact Sheet was created as a tool for risk assessors and provides information that may be useful for communication with the public. Also, a series of questions and answers on the *Cancer Guideline*s are available on the EPA *Cancer Guidelines* website (www.epa.gov/cancerguidelines).

Introduction

The Science Policy Council (SPC) Cancer Guidelines Implementation Workgroup (Workgroup) has provided information to facilitate the development of new carcinogenicity risk assessments and to promote consistency with Agency policy, guidance, and guidelines. The issues addressed by the workgroup were:

1) The process for weight of evidence determinations of a mutagenic mode of action (MOA) for carcinogenicity;

2) Application of the *Cancer Guidelines* and *Supplemental Guidance* in each of the four steps of a risk assessment;

3) Appropriate application of the *Supplemental Guidance* to chemicals described in the *Supplemental Guidance* as having a mutagenic MOA for carcinogenicity;

4) Suggested revisions to the Integrated Risk Information System (IRIS) assessment format to accommodate mutagenic MOA determinations and use of Age-Dependent Adjustment Factors (ADAFs);

5) Internal and external communication of determinations of mutagenic MOAs.

The Risk Assessment Forum Website (link provided below) provides general information about the *Cancer Guidelines* and *Supplemental Guidance*. The Workgroup also has provided two communications (Communications I and II, links provided below) that convey further information on the first three topics, and this fact sheet provides additional information to support external communications.

Definitions

Cancer or carcinogenicity – Cancer refers to a group of diseases involving abnormal, malignant tissue growth. The development of cancer involves a complex series of steps, and carcinogens may operate in a number of different ways. Ultimately, cancer results from a series of defects in genes controlling cell growth, division, and differentiation. (Fact Sheet: EPA's Guidelines for Carcinogen Risk Assessment, March 29, 2005, http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=119032)

Mutagenicity - For its use in relation to mutagenic modes of action, mutagenicity is the capacity of either the carcinogen or its metabolite to react with or bind to DNA in a manner that causes mutations. Mutagens usually (though not always) produce positive effects in multiple test systems for different genetic endpoints, particularly gene mutations and structural chromosome aberrations, both *in vitro* and *in vivo.*

Mode of Action - As explained in the *Cancer Guidelines* (p. 1-10), a carcinogenic *"mode of action"* is a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in the formation of cancer.

Mutagenic Mode of Action - In order to have a mutagenic MOA, the carcinogen is determined to be mutagenic, and this mutagenicity is a key early event in carcinogenesis. The text of the *Supplemental Guidance* describes effects that are indicators of mutagenicity for determining a mutagenic MOA in the following words.

> "Key data for a mutagenic mode of action may be evidence that the carcinogen or a metabolite is DNA reactive and/or has the ability to bind DNA. Also, such carcinogens usually produce positive effects in multiple test systems for different genetic endpoints, particularly gene mutations and structural chromosome aberrations, and in tests performed *in vivo* which generally are supported by positive tests *in vitro*."

As explained in the *Cancer Guidelines* (p. 2-30), many, but not all, mutagens are carcinogens. In addition, compounds that are both mutagenic and carcinogenic may not cause cancer through a mutagenic MOA. There are many other possible modes of carcinogenic action, such as mitogenesis (the stimulation of cell division), inhibition of cell death, cytotoxicity (cell damage or death), and immune suppression (footnote, *Cancer Guidelines*, p.1-10).

Key Information to Address Frequently Asked Questions

1. The *Supplemental Guidance* focuses on early-life exposures; it recommends quantitative adjustment of cancer slope factors only for chemicals having a mutagenic MOA for carcinogenicity.

The *Supplemental Guidance* recommends consideration of all studies on the effects of early-life exposures. The *Supplemental Guidance* addresses carcinogens with a mutagenic MOA in detail based on an analysis of currently available early-life studies for carcinogens with that MOA. The *Supplemental Guidance* concludes (p. 28) that there can be greater susceptibility for the development of cancer as a result of exposures to chemicals acting through a mutagenic MOA, when the exposures occur early in life as compared with later in life. In the case of non-mutagenic carcinogens, or when the mode of action is unknown, EPA judged the data to be too limited and the modes of action too diverse to apply a general default adjustment factor approach.

For additional information, see:

1) 2005 *Cancer Guidelines*, section 1.3.6, p. 1-19 to 1-20
2) Barton *et al.*, 2005. "Assessing Susceptibility from Early-Life Exposure to Carcinogens." Environmental Health Perspectives 113(9): 1125-1133; available at www.epa.gov/cancerguidelines)
3) EPA's 2005 *Guidelines for Carcinogen Risk Assessment* and *Supplemental Guidance from Assessing Susceptibility from Early-life Exposure to Carcinogens* - Questions and Answers (March 29, 2005) http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=119031

2. The Age-Dependent Adjustment Factors (ADAFs) from the *Supplemental Guidance* are not to be applied to all categories of carcinogens.

a. ADAFs are not recommended for agents for which the carcinogenic MOA has not been determined.
b. ADAFs are not recommended for agents with a carcinogenic MOA other than a mutagenic MOA.
c. When data are available for a sensitive lifestage they would be used directly to evaluate risks for that chemical and lifestage on a case by case basis. In general, the Agency prefers to rely on analyses of data, rather than general defaults, so generic ADAFs may not be recommended in those situations.

Regardless of a chemical's MOA for carcinogenicity, the *Cancer Guidelines* and *Supplemental Guidance* recommend that available data on any susceptible lifestage or population be considered in any future quantitative dose-response assessment. It is the Agency's long-standing position that use of the default linear low-dose extrapolation approach (without further adjustment) provides adequate public health protection in the absence of chemical-specific data indicating differential population or lifestage sensitivity or when the mode of action is not mutagenicity.

EPA intends to focus its research and to work collaboratively with its federal partners to improve understanding of the implications of early-life exposure to carcinogens. The Agency expects to produce additional supplemental guidance for other modes of action as data from new research and toxicity testing indicate it is warranted. (http://www.epa.gov/sab/pdf/sab_04003_resp.pdf; p.7)

For additional information, see:
2005 *Cancer Guidelines*, pp. 1-20; *Supplemental Guidance*, Preface

3. EPA has, to date, identified 13 agents with Mutagenic MOA for Carcinogenicity. The *Supplemental Guidance* provided an analysis of early-life exposure data for twelve chemicals that the Agency described as having a mutagenic MOA for carcinogenicity. In addition, 70 Federal Register 19992 describes the Agency's determination that coke oven emissions have a mutagenic MOA for carcinogenicity. Although future assessments may identify additional chemicals for which the weight of evidence supports a mutagenic MOA, the Agency cannot predict how many chemicals will be determined to have a mutagenic MOA for carcinogenicity. While the EPA has evaluated many chemicals for carcinogenicity, those assessments, primarily conducted under earlier versions of the *Cancer Guidelines*, did not usually include a MOA analysis. MOA analyses are needed before conclusions can be drawn regarding how many of these chemicals may have a mutagenic MOA for carcinogenicity.

4. EPA Staff responsible for conducting hazard and dose-response assessment are responsible for determining whether agents are carcinogenic by a mutagenic MOA. For agents (for example, chemicals or substances) under review in the Integrated Risk Information System (IRIS) program, the determination that an agent has a mutagenic mode of carcinogenic action will be part of the standard IRIS evaluation process that examines the available scientific literature for the agent. For IRIS assessments, EPA evaluates all relevant modes of action with substantial biological support simultaneously. The MOA evaluation is integral to the evaluation of the data for the agent and to decision-making about the agent's toxicity. EPA also may assess agents through Agency processes other than the IRIS process. For example, EPA's Office of Pesticide Programs (OPP) conducts risk assessments to support the registration of pesticides and the setting of pesticide tolerances. Like the IRIS process, these alternative processes have requirements for data evaluation, peer review, and public involvement.

For additional information, see Communication I,
(http://www.epa.gov/osa/spc/cancer.htm)

5. The time involved for conducting a cancer MOA determinations is generally similar to or less than that for a full cancer hazard and dose-response assessment.

The MOA determination generally will be part of a larger toxicological review. Once initiated, IRIS assessments typically take two to five years to complete due in part to requirements for rigorous scientific evaluation, coordination across the Agency, internal

peer review, interagency review, external peer review and final approvals. Assessments conducted through other Agency processes are likely to require a similar amount of time, although they may be conducted in less time depending on the nature of the assessment and the urgency of a particular program's need.

For additional information, see:

1) US EPA's Process for IRIS Assessment Development and Review (http://www.epa.gov/iris/process.htm)

2) Setting Tolerances for Pesticide Residues in Foods (http://www.epa.gov/pesticides/factsheets/stprf.htm)

Additional Sources of Information

If you would like more information about the *Cancer Guidelines*, please visit the Risk Assessment Forum website, (http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=116283);

If you would like more information about the *Cancer Guidelines* Implementation Workgroup communications, visit the Office of the Science Advisor website, http://www.epa.gov/osa/spc/cancer_guidelines.htm

Communication I. " Application of the Mode of Action Framework in Support of a Mutagenic Mode of Action for Carcinogenesis," October 4, 2005, available at http://www.epa.gov/osa/spc/pdfs/CGIWGCommuniation_I.pdf

Communication II. "Performing Risk Assessments that include Carcinogens Described in the *Supplemental Guidance* as having a Mutagenic Mode of Action," June 14, 2006 available at http://www.epa.gov/osa/spc/pdfs/CGIWGCommunication_II.pdf