United States Environmental Protection Agency | Science Advisory Board (1400) Washington DC | EPA-SAB-EC-99-015 July 1999 *ww.epa.gov/sab*

REVIEW OF REVISED SECTIONS OF THE PROPOSED GUIDELINES FOR CARCINOGEN RISK ASSESSMENT

Review of the Draft Revised Cancer Risk Assessment Guidelines by a Subcommittee of the Science Advisory Board

July 29, 1999

EPA-SAB-EC-99-015

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Subject: Review of Revised Sections of the Proposed Guidelines for Carcinogen Risk Assessment

Dear Ms. Browner:

At the request of the Office of Research and Development (ORD), a Subcommittee of the Science Advisory Board's (SAB) Executive Committee (augmented with representation from the Scientific Advisory Panel), reviewed selected sections of the Proposed Guidelines for Carcinogen Risk Assessment (GLs). The Committee subsequently met in Washington, DC, on January 20-21, 1999 and generated the report discussed below.

The SAB's 1997 review (EPA-SAB-EHC-97-010) of the 1996 Proposed Guidelines for Carcinogen Risk Assessment generally commended the efforts of the Agency to update its GLs in keeping with new scientific information and commentaries by authoritative groups (e.g., the Presidential/Congressional Commission Report on Risk Assessment and Risk Management in Regulatory Decision Making(GPO #055-000-00568-1, 1997). However, the review also identified a number of areas where further improvements/clarifications could be made - hazard descriptors, the use of mode of action information, and dose response (DR) analysis. These particular sections contained the Agency's response to recommendations contained in the SAB's 1997 review of the GLS as proposed in 1996. EPA consequently revised selected sections of the GLs to respond to these comments and discussions within the Agency. These revisions to the GLs were reviewed by the Subcommittee at a meeting held in Washington, DC, on January 20-21, 1999 and addressed in this report.

The Charge for this review (see section 2.2 of the enclosed report for the complete Charge) addressed the adequacy of the proposed narrative summaries and hazard descriptors as a basis for characterizing the evaluation of carcinogenic potential; the use of Mode of Action (MOA) information; the use of DR analysis as a basis for calculating the point of departure; and the use of margin of exposure (MOE) analysis, including consideration of the nature of the response, steepness of the DR curve, and human intraspecies variability (including susceptible populations), as well as inter-species variability.

The Subcommittee's deliberations resulted in several major recommendation to the Agency concerning the GLs. The first of these recommendations, although not a specific technical finding, is perhaps the most important. **We believe strongly that these GLs should become operative, as soon as judiciously possible.** The Agency has been working on the revised GLs since 1990, and has sponsored several public workshops on GLs issues; the SAB has held a Consultation and two reviews, with at least one more in the offing to address GLs issues related to children. Clearly, there are issues noted in this report that need to be addressed and/or re-visited (some continually); in addition, new ones will arise. However, it is important to consolidate the progress that has been made in the current document, and have it officially issued at the earliest possible date.

Other major overall findings and recommendations include:

a) **Primacy of public health protection:** It is essential that the GLs state at the outset that "..the primary goal of EPA actions is public health protection and that, accordingly, as an Agency policy, the defaults used in the absence of scientific data to the contrary should be health protective." These defaults should be clearly explained in the revised GLs text, including the assumptions of low dose linearity and the relevance of animal data to humans. The basis for the various default uncertainty factors should also be clearly described.

b) **Loss of flexibility:** The Subcommittee is concerned that EPA, in responding to the SAB's 1997 request for more definition in several areas, actually reduced, rather than increased, flexibility in moving from the 1996 to the 1998 version. Examples included the addition of numerous new defaults, standard dose-response models, restrictions on the use of the No Observed Adverse Effects Level (NOAEL) approach, and fixation on the 10% excess as a point of departure.

c) **Sensitive subpopulations**: EPA should include a discussion of sensitive subpopulations for all agents to which the general public (as opposed to healthy workers) is exposed. Although not part of this review, we wish to endorse the Agency's plan to hold a meeting later this year on GLs issues related to children.

d) **Background and multiple exposures**: EPA should discuss the need for the risk assessment to consider background exposures/processes and concurrent exposures with which the chemical (mixture) of interest may display additivity or interact multiplicatively.

Other, more specifically focused findings directly addressing the Charge include:

a) The Subcommittee strongly supports the proposed "Framework" as a means for providing a working model for incorporating and interpreting data in a clear and transparent manner. This model was developed as part of a World Health

Organization working group to deal specifically with differences between the approaches used by various countries to evaluate the same data with respect to the risks posed by a given chemical.

b) There was agreement that the narrative descriptor "known to be carcinogenic to humans" or “known human carcinogen” should be retained. Although the majority of the Subcommittee held that assignment to this category requires human (e.g., epidemiological) data, several Members opined that animal data demonstrating strong mechanistic linkages between common human and animal pathways could be used to support this classification.

c) The use of a narrative is a key component of the hazard identification section. Flexibility in how the hazard narrative is written is laudable, but a common format is essential. All of the relevant data should be included.

d) EPA should continue efforts to achieve compatibility with international organizations such as the International Agency for Research on Cancer, the World Health Organization, and European regulatory bodies.

e) The Subcommittee recommended that specific criteria for judging the adequacy of data on a mode of action approach are needed, and that specific examples should be included to illustrate the application of these criteria.

f) The proposed GLs document remains (perhaps necessarily) vague about what specific data are required to reject defaults assumptions. Some additional clarification on this issue is needed. The Subcommittee does recognize that the Agency does not want to be prescriptive, as the science will continue to evolve.

g) The SAB recommended in 1997 that a single risk level (e.g., 10%) be selected as the point of departure for (low dose) non-linear extrapolation in order to facilitate comparisons across chemicals, and provide more clarity to the risk manager. The draft GLs now propose a value of 10%, while noting that, in some situations (e.g., large experiments), it may be preferable to use a non-standard value. In the current Agency proposal, it is noted that a lower point for linear extrapolation can be used for tumor incidence study of “greater than usual sensitivity.” This is a reasonable approach, and one that the Subcommittee endorses.

h) In the case of Margin of Exposure (MOE) analysis, the Subcommittee continues to be concerned about the linkage between the selected risk level and the incorporation of adjustment and uncertainty factors. Use of a risk level less (greater) than 10% should, other things being equal, require a smaller (larger) uncertainty factor. The Agency is encouraged to develop explicit guidance regarding the selection of uncertainty factors for points of departure other than 10%. Also, because of this problem, the Agency should strive to use the standard

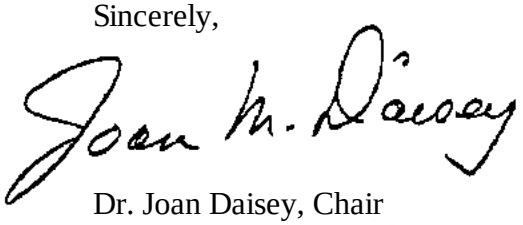
point of departure whenever possible.

i) There is continuing confusion about the relationship between the LED_{10}, or ED_{10} and the NOAEL. The GLs should seek to clarify, not reinforce this confusion. In addition, the new GLs propose two new ten-fold adjustment factor to be used in specified situations. Some Subcommittee Members questioned whether the need for, or the magnitude of, these new factors is sufficiently justified in the GLs; other Members supported the basic thrust of these factors, but noted that further refinements were needed.

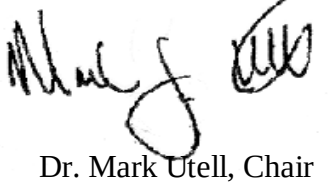
Finally the SAB's Executive Committee wishes to point out a generic problem not addressed by the reviewing Subcommittee. There is a substantial literature which shows that qualitative probability terms such as “likely" and "unlikely" can mean very different things to different people (see for example, G. Morgan in Human and Ecological Risk Assessment, pp. 25-39, February 1998). Some rough quantification will have to be associated with these or any similar probability words if they are to have useful meaning.

We appreciate the opportunity to review these proposed revisions, and look forward to receiving your response to the issues raised.

Sincerely,



Dr. Joan Daisey, Chair
Science Advisory Board



Dr. Mark Utell, Chair
Cancer Guidelines Subcommittee
Science Advisory Board

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ABSTRACT

A Subcommittee of the Science Advisory Board reviewed EPA's revised Cancer Risk Assessment Guidelines (GL) on January 20-21, 1999, addressing the proposed narrative summaries and hazard descriptors; the use of Mode of Action (MOA) information; the use of dose response analysis to calculate the point of departure; and margin of exposure analysis, including human intraspecies variability.

The Subcommittee recommended that the GLs should be released as soon as possible and found the GLs were a significant improvement. Other general findings/recommendations included:

a) State that "..the primary goal of EPA actions is public health protection..."
b) Re-consider the loss of flexibility for risk assessors.
c) Discuss sensitive subpopulations for all agents to which the public is exposed.
d) Discuss the need consider background and concurrent exposures.
e) Provide guidance on the use of biologically-based models

More specific findings are:

a) The narrative descriptor "known to be carcinogenic to humans" or "known human carcinogen" should be retained. The Subcommittee did not agree on whether to restrict use of this category to scenarios in which there was conclusive epidemiological data.
b) A common format for the hazard narrative is essential.
c) Continue efforts to achieve compatibility with international organizations.
d) Specific criteria for judging the adequacy of data on a mode of action are needed .
e) The GL remain vague about what data are required to reject default assumptions.
f) The GLs should require testing of the hypothesis before rejecting the default assumption.
g) There should be guidance on whether mode of action data support linear or non-linear extrapolation of risk
h) The Subcommittee is concerned about the linkage between selected risk levels and the incorporation of adjustment and uncertainty factors.
i) Clarify the relationship of the LED_{10}, ED_{10} and the NOAEL.

Keywords: cancer risk assessment; linear multi-stage model; narrative description; margin of exposure; mode of action; sensitive subpopulations; adjustment factors

US EPA SCIENCE ADVISORY BOARD
CANCER GUIDELINES SUBCOMMITTEE OF THE EXECUTIVE COMMITTEE
ROSTER

January 20-21, 1999

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[2]Ms. Martin is an EPA Intern assigned to the Science Advisory Board and assisted in the conduct of this review.

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1. EXECUTIVE SUMMARY

In 1997, the Science Advisory Board's (SAB) Environmental Health Committee (EHC), augmented with representation from the Scientific Advisory Panel (SAP), reviewed a draft of EPA's 1996 revised Cancer Risk Assessment Guidelines (GLs) (SAB, 1997). Although generally applauding the efforts of the Agency to update its GLs in keeping with new scientific information and commentaries by authoritative groups, the Board identified a number of areas where further improvements and clarifications could be made - hazard descriptors, the use of mode of action information, and dose response (DR) analysis. EPA revised the pertinent sections of the GLs and requested that the SAB review the updated materials. A Subcommittee of the SAB, including representation from the SAP reviewed revised GLs at a meeting held in Washington, DC, on January 20-21, 1999. The findings stemming from that meeting are addressed formally in this report.

The Charge for this review (see section 2.2 for the complete Charge) addressed the adequacy of the proposed narrative summaries and hazard descriptors as a basis for characterizing the evaluation of carcinogenic potential; the use of Mode of Action (MOA) information; the use of DR analysis as a basis for calculating the point of departure; and the use of margin of exposure (MOE) analysis, including consideration of the nature of the response, steepness of the DR curve, and human intraspecies variability (including susceptible populations), as well as inter-species variability.

The Subcommittee developed several major recommendation to the Agency concerning the GLs. The first of these recommendations, although not a specific technical finding, is perhaps the most important. We believe strongly that these GLs should become operative, as soon as judiciously possible. The current GLs have been around for more than a decade; the Agency has been working on the revised GLs since 1990, including sponsoring several public workshops on GLs issues; and the SAB has had a Consultation (SAB, 1991), the 1997 review noted above, the review just completed; and one more in the offing to address issues related to children. Clearly, there are GLs issues noted in this report that need to be addressed and/or re-visited, continually (and new ones which will arise). However, it is important to consolidate the progress that has been made in the current document, and have it officially issued at the earliest possible date.

Other major overall findings and recommendations are:

a) Primacy of public health protection: It is essential that the GLs state at the outset that "..the primary goal of EPA actions is public health protection and that, accordingly, as an Agency policy, the defaults used in the absence of scientific data to the contrary should be health protective." These defaults should be clearly explained in the revised GLs text, including the assumptions of low dose linearity and the relevance of animal data to humans. The basis for the various default uncertainty factors should also be clearly described.

b) Loss of flexibility: The Subcommittee is concerned that EPA, in responding to the SAB's request for more definition in several areas, actually reduced, rather than increased, flexibility in moving from the 1996 to the 1998 version. Examples included the addition of numerous new defaults, standard dose-response models, restrictions on the use of the No Observed Adverse Effects Level (NOAEL) approach, and fixation on the 10% excess for a point of departure.

c) Sensitive subpopulations: EPA should include a discussion of sensitive subpopulations for all agents to which the general public (as opposed to healthy workers) is exposed. Specifically, this discussion should include consideration of pregnant females, the fetus, young children and adolescents, the ill, and the elderly. The basis for the uncertainty factor or alternative modeling procedure used to account for susceptibility of the young should be clearly stated. EPA should also discuss other known or likely sensitive populations due to susceptibility factors *in addition to* young age: nutritional deficits, preexisting disease, ethnicity, gender, pregnancy – which may occur simultaneously (in combination) in various subsets of the population.

In addition, the Agency should conduct systematic reviews to explore quantitatively the extent of variability among individuals in the human population. In doing so the Agency should consider modeling approaches, as well as comparisons of risks across populations. Although not addressed in this review, we wish to endorse the Agency's plan to hold a meeting later this year on GLs issues related to children.

d) Background and multiple exposures: EPA should discuss the need for the risk assessment to consider background exposures/processes and concurrent exposures with which the chemical (mixture) of interest may display additivity or interact multiplicatively.

e) Guidance on the use of biologically-based models: The 1998 draft does not provide greater guidance than the 1996 GLs regarding the use of biologically based DR models. No clear example has been provided of DR models "that would be relied upon for low dose extrapolation." (SAB, 1997, p. 23) As in the 1997 report, we continue to support the view that "if no such model can presently be identified, a statement to that effect would be helpful."

Other, more specifically focused findings directly addressing the Charge are:

a) There was agreement by the current Subcommittee that the revised GLs were a significant improvement over the earlier version. In particular, the majority of the Subcommittee strongly supports the proposed "Framework" as a means for providing a working model for incorporating and interpreting data in a clear and transparent manner. This model was developed as part of a World Health

Organization working group to deal specifically with large differences between the approaches various countries were using to evaluate the same data with respect to the risks posed by a given chemical (WHO 1999; Sonich-Mullin, *et al.*, in press).

b) There was a majority position that the narrative descriptor "known to be carcinogenic to humans" or “known human carcinogen” should be retained. The Subcommittee did not agree on whether to restrict use of this category to scenarios in which there was conclusive epidemiological data. The majority of Members favored this more restrictive approach believing that this position represents the most reasonable interpretation of the phrase “known to be carcinogenic in humans.”

c) The use of a narrative is a key component of the hazard identification section. Flexibility in how the hazard narrative is written is laudable, but a common format is essential. All of the relevant data should be included.

d) EPA should continue efforts to achieve compatibility with international organizations such as the International Agency for Research on Cancer, the World Health Organization, and European regulatory bodies

e) The current guidance allows for departure from the linear default when supported by mode of action information in favor of a non-linear or combined linear/non-linear approach. The Subcommittee recommended that specific criteria for judging the adequacy of data on a mode of action are needed and that specific examples should be included to illustrate the application of these criteria.

f) The proposed GLs document remains (perhaps necessarily) vague about what specific data are required to reject defaults assumptions. Some additional clarification on this issue is needed. The three examples provided help the reader to understand this issue. Providing additional examples should further advance understanding of the specific data required to reject defaults in the assessment step. The Subcommittee recognizes that the Agency does not want to be prescriptive, as the science will continue to evolve.

g) The GLs should require specific, challenging testing of the proposed hypothesis before rejecting the default assumption. The proposed assessment framework appears to have sufficient flexibility to accommodate these developments.

h) As part of the GLs’ conclusions, there should be guidance on whether the data on mode of action support, either strongly or moderately, a linear or non-linear extrapolation of risk, or whether the data are inconclusive and that the linear default should be used. Some Members expressed their strongly held view that the GLs should require a much higher threshold of evidence for departure from

defaults than the "more likely than not" level currently found in the GLs, although most of the Subcommittee accepted the Agency's position.

i) To standardize calculations, facilitate comparisons across chemicals, and provide more clarity to the risk manager, the SAB recommended in 1997 that a single risk level (e.g., 10%) be selected as the point of departure for (low dose) non-linear extrapolation. The draft GLs now propose a value of 10%, while noting that, in some situations (e.g., large experiments), it may be preferable to use a non-standard value. In the current Agency proposal, it is noted that a lower point for linear extrapolation can be used for tumor incidence study of "greater than usual sensitivity." This is a reasonable approach, and one that the Subcommittee endorses.

j) In the case of Margin of Exposure (MOE) analysis, the Subcommittee continues to be concerned about the linkage between the selected risk level and the incorporation of adjustment and uncertainty factors. Use of a risk level less (or greater) than 10% should, other things being equal, require a smaller (or larger) uncertainty factor. The Agency is encouraged to develop explicit guidance regarding the selection of uncertainty factors or MOE GLs for points of departure other than 10%. Also, because of this problem, the Agency should strive to use the standard point of departure whenever possible.

k) There is continuing confusion about the relationship between the LED_{10}, or ED_{10} and the NOAEL. The GLs should seek to clarify, not reinforce this confusion. In addition, the new GLs propose two new ten-fold adjustment factors to be applied in specific situations. Some Subcommittee Members questioned whether the need for, or the magnitude of, these new uncertainty factors is sufficiently justified in the
GLs. Other Members supported the basic direction laid out in the draft GLs, but noted that some further refinements were needed.

2. INTRODUCTION

2.1 Background

In September 1986, EPA published Guidelines for Carcinogen Risk Assessment (GLs) (51 Federal Register 33992-34003). Since that time, significant gains have been made in understanding the carcinogenic process. Concurrently, the Agency's experience with the 1986 GLs has revealed several limitations in their approach to cancer risk assessment. In April 1996, EPA proposed revisions to the 1986 GLs (61 Federal Register 17960-18011). These revisions were the result of a number of EPA-sponsored meetings, e.g., a 1994 peer review workshop (EPA, 1994), recommendations contained in the National Academy of Sciences report (NAS, 1994) S*cience and Judgment in Risk Assessment*, the U.S. Commission on Risk Assessment and Risk Management in Regulatory Decision Making (GPO, 1997), and extensive EPA and Federal reviews.

The intent of the revised GLs is to take into account the available knowledge about the carcinogenic process and to provide flexibility for additional changes in the future to more realistically assess data, recognizing that the GLs cannot always anticipate future research findings. Compared to the 1986 GLs, the revised 1998 GLs are intended to emphasize more complete evaluation of all relevant information and to provide more guidance on the use of information on the way an agent produces cancer (mode of action). Further, the revised GLs will be structured on an analytical framework that recognizes a variety of conditions under which the cancer hazard may be expressed (e.g., route or magnitude of exposure to the agent). The revised GLs promote the evaluation of data related to mode of action as the first step. If the available data support a linear relationship at low dose or if no clear alternatives exist, then a linear low dose extrapolation will be utilized. However, guidance is provided as to when departure from this presumption is possible if available mode of action information supports non-linearity at low doses.

It should be noted that the SAB and SAP have been involved with risk assessment GLs, including those for cancer, for many years. In 1986, the SAB/SAP (SAB, 1986) conducted a review of the GLs as proposed at that time. The Board has continually encouraged the Agency to update all of its GLs in order to reflect the continuing advances of science. In 1991 the Executive Committee of the SAB conducted a Consultation with the Agency on the GLs and their future evolution (SAB, 1991). In 1997, the SAB's Environmental Health Committee (EHC), augmented with representation from the Scientific Advisory Panel (SAP), reviewed a draft of the revised GLs as they existed at that time (SAB, 1997). Although generally applauding the efforts of the Agency to update its GLs in keeping with new scientific information and commentaries by authoritative groups (e.g., the National Academy of Science and the National Research Council (NAS/NRC) and their 1994 report “Science and Judgment in Risk Assessment, and the report of the Presidential/Congressional Commission Report on Risk Assessment and Risk Management (US GPO, 1997), the Board identified a number of areas where further improvements/clarifications could be made - hazard descriptors, the use of mode of action information, and dose response (DR) analysis (SAB. 1997). Revisions have been developed for

these areas in response to these comments and discussions within the Agency and it is these revised sections of the GLs that the SAB Subcommittee reviewed at a meeting held in Washington, DC, on January 20-21, 1999 and addresses in this report.

2.2 Charge

The Charge addressed three major areas noted above, and within these areas, posed specific questions. The elements of the Charge are:

a) Hazard Descriptors

1) Do the proposed narrative summaries and the five hazard descriptors provide an appropriate and adequate basis for characterizing the technical evaluation of carcinogenic potential?
2) Is the guidance supplied for each of the proposed hazard descriptors sufficiently clear and complete?

b) Use of Mode of Action Information

1) Is the guidance provided in the revised Sections 2.3.5 - 2.5 clear and transparent?
2) Please comment on the proposed key elements and their use in supporting a mode of action conclusion via the framework (section 2.5).

3) Are the case studies useful as illustrations of the guidance and framework?

c) Dose Response Analysis

1) Defining a Point of Departure: Please comment on the soundness of the scientific rationale provided for the standard approach and options for selecting departure points.
2) Please comment on the adequacy and clarity of the guidance on this subject.
3) Margin of Exposure Analysis: Please comment on the adequacy and clarity of the guidance regarding how to perform a MOE analysis. Are the proposed approach and the factors for consideration in determining the appropriate magnitude of the MOE appropriate? Specifically address the use of factors to account for:
4)
   i) the nature of the response (i.e., tumors or key events selected as the point of departure for extrapolation)
   ii) steepness of the DR curve
   iii) human intraspecies variability, including susceptible populations
   iv) inter-species variability.

3 DETAILED FINDINGS

3.1 Hazard Descriptors

3.1.1 Narrative Summaries and the Five Hazard Descriptors

The 1997 SAB review (SAB, 1997) of the 1996 draft Cancer Risk Assessment Guidelines (GLs) (EPA, 1996) endorsed the (at the time, new) emphasis on the use of narrative discussion to describe the weight of evidence (WOE). However, the reviewers found problems with its implementation, particularly in the use of multiple terms (i.e., categories, descriptors, and sub-descriptors). Given the complexities involved, the Committee could not come to a consensus as to how this problem should be addressed. Some Members suggested eliminating categories in favor of a narrative with selections made from the proposed thirteen sub-descriptors. Other Members proposed use of the eight descriptors proposed by Ashby *et al.*, (1990) .

Questions posed by the Agency for this review addressed the adequacy of the proposed narrative summaries and the five hazard descriptors in providing an appropriate and adequate basis for characterizing the technical evaluation of carcinogenic potential, and the clarity and completeness of the guidance supplied for each of the proposed hazard descriptors.

In its 1998 GLs document (EPA, 1998), EPA responded to the SAB and public comments with a revised system of narratives and descriptors, incorporating five categories:

a) *known to be carcinogenic to humans*

b) *likely to be carcinogenic to humans*

c) *suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential*

d) *inadequate data for an assessment of human carcinogenic potential*

e) *not likely to be carcinogenic to humans*

At the current Subcommittee's public meeting, there was considerable discussion of alternatives to the EPA's proposed term "Known to be Carcinogenic to Humans." Suggested options included:

a) Restricting use of the descriptor "*Known to be Carcinogenic to Humans*" to those agents for which conclusive epidemiologic data exists.

b) Substituting "*Carcinogenic* to Humans"or "*known/as if known* to be carcinogenic to humans" for" *known to be carcinogenic to humans.*"

c) Retaining the term, clarifying that the epidemiological evidence, while not necessarily conclusive, should be substantially positive and. supported by mechanistic data of known relevance

As with the 1997 SAB review, the Subcommittee did not reach a full consensus on this issue at the 1998 public meeting. There was however, a majority position, that the descriptor "known to be carcinogenic to humans" or "known human carcinogen" should be retained.[3] The Members did not agree on whether to restrict use of this category to scenarios in which there was conclusive epidemiological data. Most Members favored this more restrictive approach believing that this position represents the most reasonable interpretation of the phrase "known to be carcinogenic in humans." Consequently, to base assignment to this category upon non-human data could be misleading, particularly to the general public.

However, some Members recommended that, even with less than sufficient epidemiologic data, an agent with strong animal evidence plus evidence (in exposed humans) that the chemical is causing measurable changes that are on the causal pathway to cancer in humans, should be considered to be carcinogenic to humans. This latter approach is consistent with the findings of the National Toxicology Program (NTP, 1998; Olden, 1998) and the International Agency for Research on Cancer's (IARC, 1994)) scheme which includes under the heading "the Agent (mixture) is carcinogenic to humans" language stating that "...a chemical (mixture) for which the evidence in humans is less than sufficient but for which there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity." It was suggested that in such a case, EPA qualify the necessary epidemiologic evidence to be "a moderate amount of evidence from human studies to suggest carcinogenicity, although it is not considered definitive." There should be strong evidence linking the key event(s) known or likely to be related to carcinogenicity in animals with the event(s) observed in humans exposed to the agent in question. The text should stipulate that all four of the criteria listed in the draft GLs (section 2.6.2 p.2) (EPA, 1997) be met.

Also, as a general comment, the Subcommittee noted that the ultimate choice of categories must be accurate, clear, and transparent in title and content if the document and the EPA are to retain trust of the scientific and general population.

In summary, the Subcommittee's recommendations on each of the five proposed classifications follow below. These recommendations are intended to express the underlying rationale for each category, rather than prescriptive guidance on exact wording.

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[3]The reader will note that, throughout the body of this report, the terms "consensus," "a majority," "most," "some," "several," and the singular "Member" are used to denote the degree of support within the Subcommittee for a given finding or observation. As listed above, these terms denote a decreasing level of support within the Subcommittee for a given position, ranging from full agreement to a position held by one Member. These adjectival assignments are based on a combination of positions taken (or comments made) at the public meeting, and comments provided by the Subcommittee Members during the report preparation process. They do *not* represent the results of a formal vote or count.

a) Known human carcinogen. Use of this descriptor is appropriate when there is convincing evidence from studies in humans demonstrating causality between human exposure and cancer. Although, as noted above, this was the majority position, the Subcommittee recognized that there might be other situations and circumstances that could lead to placement in this category. These situations include cases wherein (as proposed by the IARC (1994) and NTP (1998) there is strong animal evidence [plus evidence in exposed humans]) that the substance causes measurable changes in the causal pathway to cancer in humans). The Subcommittee did not reach any other specific conclusions or consensus on this topic.

b) Likely to be carcinogenic to humans. Typically, findings based on human data that are generally supportive of carcinogenicity but of insufficient strength or consistency to be definitive, or strong animal data, support assignment to this category. This descriptor is appropriate for use when there is either limited epidemiological evidence or strong evidence from animal studies. This categorization might also be used if the limited human and animal evidence is buttressed by findings that the carcinogenesis is mediated by a mechanism that also operates in humans. It should also include definitive animal data in the absence of definitive data establishing mechanistic relevance. Some Members felt that strong mechanistic and structure activity data in the absence of epidemiological evidence are sufficient to place an agent in this category (This position is consistent with that taken by the Agency for some dioxin and PCB congeners, as well as IARC's (1991) position on Benzedrine-based dyes.) Another Member suggested that this category needs a clear statement regarding exposure conditions under which this scenario is possibly true.

c) Suggestive evidence of human carcinogenicity. This category encompasses cases in which there is mixed evidence of carcinogenicity in humans or animals, or suggestive mechanistic data, but for which the data are insufficient to conclude there is a likely causal relationship between exposure and cancer.

d) Inadequate data for an assessment of human carcinogenic potential. This classification should be used when there is a paucity of pertinent data on which to base a judgment.

The Subcommittee recommends that the concept expressed by the term "conflicting data" be narrowed by replacing it with "irreconcilable data" (e.g., a significant effect at one dose in one study, but negative responses at this dose and higher doses in a replicate study that are statistically incompatible with the positive response seen in the one study). Apparent inconsistencies in data may result from a number of reasons including chance, differences in design, and the fact that complementary component(s) may not be present in all studies (Rothman (p. 18), 1986)

e) Not likely to be carcinogenic to humans. The Subcommittee found the supporting text for this category to be quite good, but has some recommendations. Because agents in this category are unlikely to be tested further, the criteria for this finding should be stringent (e.g., negative data from several rodent and non-rodent studies incorporating relevant routes of exposure). The GLs text should state that there must be strong evidence for finding a lack of effects in animals. Stringent test requirements are needed to discount carcinogenicity by specific routes of exposure. When using epidemiological data to support the finding, multiple studies should be required.

The GLs' text should also state that route specificity must be supported by a range of other relevant data. Under the requirement for "evidence that carcinogenic effects are not likely by a particular route of exposure," EPA should add words to the effect that "This conclusion is relevant only to this route of exposure."

3.1.2 Clarity and Completeness of the Guidance

The use of a narrative is a key component of the hazard identification section. Flexibility in how the hazard narrative is written is laudable, and a common format is essential. All of the relevant data should be included.

In developing the revised GLs, EPA should strive whenever possible, to achieve compatibility with international organizations such as the IARC , the World Health Organization and European regulatory bodies. Within that context, an emphasis should be placed on the factors of weight of the evidence, conditions of exposure, and relevance to humans. The wording for the descriptors is suggested above, with an emphasis on integrating all of the available data. Some Members felt the a need to address the relevance of animal data to human risk at environmentally relevant doses, while others held that this should occur in the risk characterization, but not at the hazard identification stage. However, all Members agreed that this is an important consideration, and the Subcommittee was in full agreement that the actual environmental concentration was an essential factor to consider in assessing the potential carcinogenic *risk*. There was a range of opinion on the question of whether and how anticipated environmental concentrations should be factored in when describing the potential carcinogenic *hazard*.

Some Members felt that it did not make sense to label a substance as "carcinogenic" when all anticipated exposures in the environment were well below that level at which a carcinogenic mechanism might come into play; e.g., formation of stones, following by irritation that leads to a carcinogenic response--but only at high doses. For these Members, the question being asked in the Hazard Identification stage is: "Does this substance pose any carcinogenic risk at anticipated environmental exposures?" Other Members felt that the concentration considerations are appropriately reflected in the Exposure Assessment and in the Risk Characterization steps of the risk assessment process. For these individuals, the Hazard Identification question is: "Does this substance pose any carcinogenic risk under any possible exposure conditions

In the end, the Subcommittee concluded that the determination of which question is being asked in the Hazard Identification step is a really a policy decision. In either case, the Agency has an obligation to be very explicit about which question it is asking. In addition, in order to be consistent and thereby enhance public understanding of the risk assessment process, the question in the Hazard Identification stage for cancer should be consistent with the question in the Hazard Identification stage for non-cancer effects, such as reproductive effects. Also, these questions must be so posed that take into account the fact that a biological response such as carcinogenicity or reproductive toxicity is a function of both dose and exposure (rate and duration of exposure), as well as the genetic background of the host.

3.2 Mode of Action

The 1996 EPA GLs proposal called for the use of mode of action (MOA) information to guide both decisions about the human relevance of animal responses, and decisions on the conduct of dose response (DR) assessment. Although the 1997 SAB EHC agreed in general about the importance of mode of action data, some expressed concern that the 1996 GLs did not provide a means of judging the sufficiency of the evidence to assess mode of action data. The current guidance allows for departure from the linear default when supported by mode of action information in favor of a non-linear or combined linear/non-linear approach. The Subcommittee recommended that specific criteria for judging the adequacy of data on a mode of action are needed and that specific examples should be included to illustrate the application of these criteria.

EPA believes that developing precise criteria for evaluating a mode of action is not possible. Any attempt to do so would quickly become out of date and restrictive. Instead, the Agency put forward a framework for evaluating a mode of action that is loosely adapted from the considerations developed by Bradford Hill for judging causality in epidemiologic studies (Hill, 1965). The proposed approach was found to be acceptable by most, but not all, Members of the Subcommittee. EPA's revised Sections 2.3.5 -2.5 of the 1996 GLs proposal (EPA, 1966, pp. 17977-17981) now include a framework for using mode of action information. Three case studies were included in the draft GLs to illustrate the application of the framework to judge the adequacy of available data to support a postulated mode of carcinogenic action. The case studies are intended to be included in Appendix D of the final GLs.

3.2.1 Clarity and Transparency of the Guidance

When the revised GLs and public comments were reviewed in 1997, the SAB Committee (SAB, 1997) requested that EPA provide additional guidance on evaluating "Mode of Action" (MOA) data. There was general agreement by the current Subcommittee that the revised GLs were a significant improvement over the earlier version. In particular, the majority of the Subcommittee strongly supports the proposed "Framework" as a means for providing a working model for incorporating and interpreting data in a clear and transparent manner. This model was developed as part of a World Health Organization (WHO 1999; Sonich-Mullin, *et al.*, in press) working group to deal specifically with large differences between the approaches various

countries were using to evaluate the same data with respect to the risks posed by a given chemical. It was not meant to dictate final interpretations, but rather to ensure that the available data are reviewed in a comprehensive manner that. The model also draws on the use of the Bradford Hill criteria employed by epidemiologists for many years (Hill, 1965). By applying this type of rationale to mechanistic data, one is forced to look at such basic issues as identifying key events in the mode of action, examining the strength, consistency and specificity of the associations between these key events and cancer, evaluating the dose-response and temporal relationships of key events and cancer, determining the biological plausibility and coherence of the data, and discussing alternative modes of action. Such a framework will provide a clear path for data presentation that should be scientifically rigorous and transparent.

While expressing this strong general support for this revised section of the GLs, the Subcommittee also suggested revisions to strengthen the section, including:

a) It was suggested during the public meeting that the question "*Do the key events*[4] *suggest possible sensitive populations?*" be added to the mode of action section. Furthermore, if data on humans, such as enzyme induction and disease are available and indicate that they may place a subset of the population at greater risk due to age, gender, disease state etc., this finding should be addressed in relevant sections. E.g., the variation in individual enzyme levels and disease states should be stated in the hazard identification document.

b) EPA should add a statement noting that lack of strength, consistency, specificity of association or dose-response weakens the mode of action. As presently written, the document focuses only on those factors that strengthens the association. It was also pointed out that the WOE derived from such associations should not just be a statistical evaluation. Rather, it should be a thorough evaluation of the data that identifies coherent, versus flimsy data sets. For example, WOE statements should be worded in the context of whether the hypothesis associating a mode of action with a carcinogenic response has survived multiple experimental challenges. I.e., that there is a consistent association under a variety of conditions.

c) The proposed GLs document remains (perhaps necessarily) vague about what specific data are required to reject defaults. Some additional clarification on this issue is needed. The three examples provided help the reader to understand this issue. Providing additional examples should further advance understanding of the specific data required to reject defaults in the assessment step. The Subcommittee recognizes that the Agency does not want to be prescriptive, as the science will continue to evolve. The GLs should require a thorough evaluation and specific,

[4] Subcommittee Members noted that the term "Key Event" is not the ideal designation for a process which is a biological continuum. In addition, the list for consideration for evaluation of data on "key events" as provided in the proposal needs to be prioritized. The first point should address the presence of a direct or indirect effect on DNA; also, the time course "bullets" need to be combined.

challenging testing of the proposed hypothesis before rejecting the default. The framework appears to have sufficient flexibility to accommodate these developments.

d) As part of the GLs' conclusions, there should be a statement about whether the data on mode of action support either (strongly or moderately) a linear or non-linear extrapolation of risk, or whether the data are inconclusive and that the linear default should be used. Some Members expressed their strongly held view that the GLs should require a much higher threshold of evidence for departure from defaults than the "more likely than not" level currently found in the GLs, although most of the Subcommittee accepted the Agency's position.

3.2.2 Proposed Key Elements and the Framework

Previous versions of the EPA GLs recognized the importance of mechanism of action and the need to include this type of information in the WOE analysis. Such considerations were not a major factor in the actual decision making phase of the assessment process. The 1996 GLs not only reversed this approach but give mode of action a central role in the cancer risk assessment process. In the April, 1996, version of the GLs, the mode of action section included a listing of the uncertainties and factors that need to be considered in any cancer risk assessment, and folded these factors into a WOE approach. The current revision improves significantly on the earlier GLs version by providing a specific framework which includes a new "Bradford Hill" (Hill, 1965) type of evaluation.

However, the most important part of this framework is its focus on identifying the key or critical elements in the carcinogenic process. This is a significant refocusing for the GLs. The outcome could be further improved if, in addition to identifying the critical elements, the process would identify which of these elements are rate-determining or rate-limiting, enabling a focus on the important steps of the risk determination, rather than on a multitude of factors as is now the case with the WOE evaluation. The mode of action approach can be used to establish actual dose thresholds. Exposures not exceeding the dose and time thresholds are not toxic. We can use toxicokinetics to identify the risk limiting processes associated with metabolism of the agent and toxicodynamics to do the same for the effects or injury. For agents with a long half-life (such as mirex, dioxins, asbestos, etc.), the toxicokinetic processes are more likely to be rate determining/limiting than the toxicodynamic processes. Conversely, for agents with a short half-life (such as benzene and most other solvents), the toxicodynamic processes are more likely to be rate determining/limiting. The Agency should follow closely work in progress by two National Research Council/National Academy of Science Subcommittees (NAS/NRC, in preparation) to develop a mathematical approach for dealing with these issues.

One final concern emphasized during the public meeting is the need for the Agency to include an evaluation of cancer risks to sensitive subpopulations (such as children, pregnant women, other females, the aged, specific disease states, etc.). Since the mode of action section is one place to address this issue, further revision of this section to incorporate these factors may be

appropriate. There was also some discussion of the need to provide a characterization of how the Agency might use human data in this process. This information should also be folded into the MOA section. These issues pose important, but difficult problems. The Subcommittee is concerned that attempts to rework the present document to include these areas may result in a significant further delay. If it appears that these problems cannot be resolved expeditiously, perhaps the best solution would be to provide some wording in the MOA section indicating that guidance on the use of MOA data would follow as the susceptible population and human data evaluation procedures were developed; and concurrently, publish the current product as a final document, but one explicitly recognizing the need for future updating on a regular basis. (see section 4.0).

3.2.3 Case Studies

The three case examples addressing mode of action present two overarching concepts. First, the case examples are meant to present three different modes of action: a) thyroid tumor/thyroid hormone interaction; b) bladder tumor/urinary calculi interaction; and c) stomach tumor/direct irritation interaction. Second, the cases are meant to present different levels of scientific support, i.e., a) from a complete, rich data set; b) to one with adequate, but not complete data; and c) to one with insufficient data. Each case example meets these requirements, and each is organized in accordance with the GLs. One Subcommittee Member believed that the cases would be more valuable if the actual agent was identified.

The Subcommittee believes that adding specific information on the relevance of mode of action to humans to the three case examples would improve them. In each case example, it would be useful to mention the relevance of the particular mode of action to population subgroups, especially children and child-bearing women. Some Members felt that, in each case example, it would be useful to include a statement about the potential levels of human environmental exposures, compared to exposure levels used in animal studies; other Members, however, felt that such information should be taken into account at later stages in the risk assessment process after the Hazard Identification stage.

As part of the conclusions, it would be useful for the GLs document to point out specific limitations of the data in each case. In particular, identification of the data gaps that are *critical* to the risk assessment should be identified.

3.3 Dose-Response Analysis

3.3.1 Defining a Point of Departure

The 1996 draft GLs employed a "point of departure" dose level to mark the beginning of low dose extrapolation. The lower 95% confidence bound on the 10% effect level for tumor (or precursor response) incidence (LED_{10}) was proposed as the standard point of departure in order to be consistent with approach taken in the proposed benchmark approach for non-cancer endpoints (EPA, 1997).

The Agency specifically requested the Subcommittee's comments on the selection of the LED_{10} as the point of departure. In its previous review (SAB, 1997), the SAB voiced a number of preferences that included a lower limit as well as central estimates (ED_{10}) and standard versus case-by-case choice of response level (1.0% to 50%). The 1997 SAB review concluded that the approach to determining the point of departure should be harmonized for non-linear carcinogens and the benchmark methodology for non-carcinogens. The SAB also recommended that a single risk level be utilized, e.g., 10%when the low dose non-linear approach is applied, and that both the point estimate as well as upper and lower confidence bounds should routinely be reported.

3.3.1.1 Soundness of the Scientific Rationale

The Agency's 1996 Proposed GLs for Cancer Risk Assessment employed a "point of departure" as the starting point for low dose extrapolation. The selection of the point involves selecting a DR model, selecting a risk value, and calculating statistical confidence bounds. In the 1997 review, the SAB advised the Agency to provide further specific guidance on these aspects of the procedure and offered a number of suggestions. The Agency has been very responsive to the advice and has thought through a number of difficult issues to develop the current proposal. We understand that the Agency plans to make the overall procedure available on the World Wide Web for public use, and the Subcommittee endorses this action and commends the Agency for this initiative. Nonetheless, the Subcommittee has some remaining concerns about the definition of the point of departure and the overall procedure.

To standardize the calculation, facilitate comparisons across chemicals, and provide more clarity to the risk manager, the SAB recommended in 1997 that a single risk level (e.g., 10%) be selected as the point of departure for (low dose) non-linear extrapolation. A value of 10% was proposed, while noting that, in some situations (e.g., large experiments), it may be preferable to use a non-standard value. In the current Agency proposal, a risk value of 10% has been selected for (low dose) linear and non-linear applications, although it is noted that a lower point for linear extrapolation can be used for tumor incidence study of "greater than usual sensitivity." This is a reasonable approach, and one that the current review endorses.

The EPA's scientific rationale for selection of 10% for cancer endpoints is based on findings for cancer and non-cancer endpoints. The draft GLs correctly note the work of Haseman (1983) indicating that for typical cancer bioassays a 10% response is at or just below the limit of sensitivity. Therefore, it is very important to be accurate about the strength of the scientific evidence for selection of 10% for non-cancer health effects. However, the current draft GLs also state that "Because the NOAEL in study protocols for non-tumor toxicity can range from about a 5% to a 30% effect level" (Faustman *et al.*, 1994) adopting the 10% effect level as the standard point of departure will accommodate most of these data sets without departing from the range of observation." (EPA, 1997). This statement needs to be corrected to reflect that the Allen *et al*. and Faustman *et al*. papers (1994) evaluated only a few developmental toxicity endpoints and not "non-tumor toxicity," in general.

As noted above, the use of 10% risk value as a point of departure may not be appropriate in all situations. A lower point for linear extrapolation can be preferable for studies of greater than usual sensitivity, and a higher point may be necessary to remain within the range of observation for certain insensitive studies.

In the case of MOE analysis, the Subcommittee continues to be concerned about the linkage between the selected risk level and the incorporation of adjustment and uncertainty factors. Use of a risk level less (or greater) than 10% should, other things being equal, should require a smaller (or larger) uncertainty factor. The Agency is encouraged to develop explicit guidance regarding the selection of uncertainty factors or MOE GLs for points of departure other than 10%. Also, because of this problem, the Agency should strive to use the standard point of departure whenever possible.

Guidance on the use of NOAELs versus LED or ED values is ambiguous. Thus, the Subcommittee continues to be concerned there may be unnecessary confusion and inconsistency in the application of GLs. It is also concerned that a risk manager may improperly apply these approaches without a clear understanding of how and why they differ. The argument that the NOAEL approach is the most practicable way of proceeding with a mixed data base (of continuous and quantal data) was not compelling. However, some Members felt that, until the Agency gains more experience with the GL, it might be useful to encourage evaluation of both the NOAEL approach and approaches that use more quantitative methods (e.g., the LED or ED). At present, they felt that it may be premature for the Agency to develop a science policy default to use the LED or ED value over the NOAEL while there is sufficient experience with application of these quantitative approaches to cancer bioassays but limited experience with other toxicity studies. The quantitative methods (including decisions of whether LED vs ED should be used as point of departure, or how to apply this approach to continuous data) are not sufficiently well-established to support the LED/ED approach as the method of choice in all cases. In any event, the proposed GLs should encourage a decision process driven by careful scientific evaluation, rather than a default assumption that a mathematically calculated point of departure is automatically more scientifically sound. In addition, the Subcommittee recommends that EPA pursue a modeling approach for continuous data, together with efforts to gain a quantitative understanding of the relationship between precursor data and tumor incidence.

There is continuing confusion about the relationship between the LED_{10}, or the point estimate of the ED_{10} and the NOAEL. The GLs should seek to clarify, not reinforce this confusion. The draft proposal indicates that the LED_{10} can be regarded as an improved and harmonized estimate of the NOAEL (GLs Section 3, page 7, line 15). Statements such as this contribute to the general misunderstanding of the relationship between these DR indices. To facilitate an understanding of the quantitative relationship between the LED_{10} and the NOAEL, the Agency is encouraged to compare them systematically across a wide range of cancer data sets, and to make the results available to the public.

Under the draft proposal, the Agency will apply a standard curve-fitting procedure to model the DR relationship and will make the procedure available to the public on the Agency's

Website. EPA should conduct a rigorous peer review of this procedure. The Agency also expressed its intention to include procedures to identify situations where the standard procedure fails. The Agency is commended for this effort, which is responsive to the 1997 SAB recommendation that the Agency select a default procedure for use in calculating the point of departure. The examples presented by the Agency at the January, 1999 public meeting incorporate some of the specific model suggestions made by the EHC . In addition to the suggestion that EPA's standard models be made available for peer review, several Members suggested that the GLs provide more flexibility and allow consideration of other possible models, particularly for epidemiological data.

As in the 1997 review, the current Subcommittee encourages the Agency to develop specific guidance to address problematic data sets, such as those with poor fits, extreme curvature or large intercurrent mortality. Another area needing guidance pertains to the modeling of dose rate and age effects. Specific, detailed guidance could be developed separately from the more general GLs, and following peer review, posted on the Agency's Website.

The current Draft GLs indicate that when time-to-tumor information is available, more elaborate, time-dependent models, are appropriate. This is the case when mortality is sufficiently high, but the use of time dependent models may not be necessary in most cases. Detailed guidance on this should be developed, with new procedures and provided on the Agency's Website after an appropriate level of external peer review. Another related issue, and one for which considerably more guidance is needed, has to do with differences in time scale for the different species. This is a particular concern when precursor data are used.

During the Subcommittee's meeting, there was a lively discussion on the use of confidence bounds and point estimates in DR analysis. The 1998 draft GLs selected as the point of departure for linear and non-linear approaches the LED_{10}, that is the lower 95% confidence limit on a dose associated with a 10% excess risk – noting that the "use of the lower limit takes experimental variability and sample size into account." The current draft GLs also state that the central estimate (i.e., the point estimate of the ED_{10}) is appropriate in some situations, for example, in ranking chemical potencies across chemicals. In addition, the GLs state that the point estimate of the ED_{10} and upper and lower confidence limits will always be presented for reference.

The 1998 draft GLs, in essence, adopted the SAB's suggested guidance from its 1997 review (SAB, 1997), which stated:

> *"The consensus of the Committee was that both point estimates and statistical bounds can be useful in different circumstances, and recommended that the Agency routinely calculate and present the point estimate of the ED_{10} and the corresponding upper and lower 95% statistical bounds. It may be appropriate to emphasize point estimates in activities that involve ranking agents as to their carcinogenic hazard. On the other hand, it may be appropriate to emphasize lower statistical bounds in activities designed to develop an appropriate human exposure value, since such activities require*

accounting for various types of uncertainties and a lower statistical bound on the ED_{10} (LED_{10}) is a scientifically-based approach for accounting for the uncertainty in the true value of the ED_{10}."

Although there was continued support for this position and the one taken by the Agency in their draft GLs, there were some divergent views expressed during the 1999 review. One such view held that using the lower confidence limit as the point of departure addressed uncertainty at the wrong stage in the analysis, and that it would be more appropriately taken into account at a later stage in the process, namely the reporting of a recommended MOE. Another Member noted that if this viewpoint were to be adopted, the ratio of the point estimate of the ED_{10} to the LED_{10} could be used to estimate an additional adjustment factor addressing the statistical uncertainty associated with the point estimate of the ED_{10} (Further discussion of this topic is located in section 3.3.1.2).

For linear extrapolation, the point of departure is expressed as a human equivalent dose, including those scenarios where default inter-species scaling is applied. Under the MOE analysis, the point of departure appears to be expressed in terms of the animal dose, with the default adjustment factor accounting for differences in body size taken into account in developing the default MOE. This inconsistency in the definition contributes to the over all confusion about what the MOE factors represent.

As noted by the SAB in its 1997 review, there is considerable room for confusion and misinterpretation by risk managers and the public about the use of the term "MOE,"especially how it relates to terms like "margin of safety" or "margin of error." To address this issue, some Members recommend that instead of, or in addition to, a MOE, the Agency report an advisory or reference concentration for cancer endpoints.

The 1997 SAB review also noted the need for more guidance on DR analysis for human data, particularly in the application of the new approach to DR analysis, and to locating the point of departure. There may be insufficient time and resources to provide more detailed guidance in this version of the GLs. If so, the Agency is encouraged to proceed to develop further detailed guidance, through workshops and perhaps extramural research and development. Improved procedures could be posted on the Agency Website as they are developed and peer reviewed. Whenever a risk level other than 10% is used, the uncertainty and adjustment factors should be modified accordingly.

3.3.1.2 Adequacy and Clarity of the Guidance

As noted above, the current draft GLs present the ED_{10} point estimate, and both upper and lower confidence limits. They also propose the use of the statistical lower bound on the ED_{10} (the LED_{10}) as a the point of departure for MOE analysis.

The presentation by EPA at the Subcommittee meeting outlined four main reasons for use of the LED_{10} (rather than the point estimate of the ED_{10}) as the point of departure: a) harmonization with non-cancer risk assessment; b) the LED_{10} rewards better experimentation (e.g. larger sample size); c) the LED_{10} is stable to changes in experimental design (e.g. group size), and d) the LED_{10} takes into account uncertainty in the experimental data. Each of these points is discussed in detail below; the final paragraph of this section summarizes the Subcommittee's findings and advice on the use of the Ed_{10} versus the LD_{10}.

a) Harmonization: It was pointed out by some Members that harmonization between cancer and non-cancer endpoints could be achieved by using the central estimate for both endpoints. When EPA sought expert advice about whether to use the central estimate or the lower confidence estimate on the dose for non-cancer endpoints, the majority of the expert peer consultants at the EPA Benchmark Dose Peer Consultation Workshop (conducted by the International Life Sciences Institute) (Barnes, 1995) recommended that the central estimate should be used. Other Members of the Subcommittee disagreed, noting that previous benchmark dose-analyses seen by the EHC in its 1997 review used the LED_{10} as the point of departure, and EPA does not seem to have adopted the central estimate for non-cancer endpoints.

b) Rewards better experimental design: Although the LED_{10} theoretically rewards better experimentation, it may have little practical effect in many cases. For example, the effect of doubling the number of animals in each dose group increases the LED_{10} by only 20-35%, and the gains appear to be minimal. In any event, most bioassays for carcinogenicity are conducted according to FIFRA/TSCA test rules and must meet standards calling for minimal use of animals to address animal welfare issues and be acceptable to the Agency. It should be noted that not all studies, especially mechanistic studies, are performed according to specified guidelines. In these cases, the LED-based approach may provide incentives to conduct studies with greater statistical power. It is important to consider the impact on study designs resulting from an ED- versus LED- based approach.; i.e., the potential incentives for small insensitive studies and disincentives for more powerful studies under the ED-based approach.

c) Stability of the LED_{10}: The Subcommittee generally agreed with EPA's position that use of the LED_{10} provides a measure with lower variance than does the ED_{10}. On the other hand, the ED_{10} point estimate is the best estimate of the target dose.

d) Accounting for experimental uncertainty: The MOE guidance provided by the EPA involves application of several factors that account for various types of uncertainties. The Subcommittee agreed that the uncertainty in the experimental data should be taken into account, and most Members thought that the use of the LED_{10} is a scientifically sound method for accomplishing this goal.

The Subcommittee discussed other factors regarding the use of the ED_{10} as the point of departure:

a) The variability of the point estimate of the ED10 versus the LED_{10}: The point estimate of the ED_{10} is an unbiased estimate of the dose that causes an increased risk of 10%, although the variance of this estimate is often relatively large. The LED_{10} (95% statistical lower bound of the ED_{10}) generally is less variable than the point estimate

b) The ED_{10} provides for clearer exposition: Some Members found that the meaning, calculation, and communication of the ED_{10} concept to be more straightforward for an ED_{10} point estimate than for LED_{10}. Therefore, the point estimate of the ED_{10} is likely to be more readily interpreted by risk managers and by the public. Other Members felt that this introduced difficulties later in the process because the rationale for using the ratio of the point estimate of the ED_{10} to the LED_{10} will be difficult to communicate to risk managers.

In summary, the Subcommittee still supports presenting the point estimate of the ED_{10} along with both lower (LED_{10}) and upper (UED_{10}) bounds as called for in the Agency draft. The Subcommittee also supports the use of the ED_{10} as the primary statistic for relative hazard/potency ranking, although statistical confidence bounds on the ED_{10} (both the LED_{10} and the UED_{10}) could be used to evaluate the uncertainty in the rankings. There were differences of opinion within the Subcommittee regarding the use of the LED_{10} for the point of departure. Some Members believed strongly that use of the point estimate of the ED_{10} was preferable, but others (equally strongly) preferred use of the LED_{10}.. These latter Members suggested that, as a compromise, the ED_{10} be used as the point of departure, and that the ED_{10} /LED_{10} ratio be incorporated as an index which could be used to develop an Reference Concentration (RfC). This alternative approach would provide exactly the same advisory exposure level as would the approach proposed in the draft GLs. If an RfC or Reference Dose (RfD) was derived, concern over the use of an ED_{10} would be lessened; also, some felt that this alternative approach is more transparent, and would treat the uncertainty in the experimental data in a manner that is more consistent with how other uncertainties are handled.

3.3.2 Margin of Exposure Analysis

The 1996 proposed GLs called for the use of a margin-of-exposure (MOE) analysis as a default dose-response procedure. This approach was to be used when there is sufficient evidence to support a non-linear mode of action at low doses (in those cases when available data are inadequate for development of a biologically based DR (BBDR) model. The MOE is the ratio of the point of departure (e.g., the LED_{10}) to the dose associated with the environmental exposure(s) of interest. The purpose of the MOE analysis is to provide information on how much reduction in risk may be associated with a given target exposure level so that a risk manager can make a determination of the adequacy of a given MOE.

The 1997 SAB Committee felt that there might be confusion and misinterpretation of the concept and recommended additional guidance and examples of the MOE approach be provided in the GLs. The 1998 draft GLs treatment of this issue (section 3.1.3 of the revised text) includes expanded guidance on how to perform a MOE analysis and is intended to replace section 3.1.2 of the 1996 proposal . Three case studies are included (in the draft GLs' Appendix E) to illustrate how to perform a MOE analysis. However, concern was expressed that the risk manager may be less inclined to use the advisory MOE than the RfC, and in the end the uncertainty index (the ratio of point estimate of the ED_{10} to the LED_{10}) may not be used.

The Agency asked the Subcommittee to comment on the clarity of the GLs' guidance, addressing a) nature of the response; b) steepness of the DR curve; c) the proposed use of data from key events; and d) inter-species variability. In addition to the four factors identified by the Agency, the Subcommittee has identified two other factors that should be considered, as well, comprising: e) human intraspecies variability, including susceptible populations; and f) comments on mode of action. The Subcommittee's responses follow below in sections 3.3.2.1 and 3.3.2.2.

3.3.2.1 Adequacy and Clarity of the Guidance

The current draft contains several examples illustrating MOE analysis. The Subcommittee commends the Agency for preparing these examples. They provide very useful insight into how the Agency would apply the GLs.

When it first became known that the Agency was adopting new GLs that would permit the wider use of scientific data in risk assessment, it was generally assumed that these GLs would allow some of the assumptions, including the adjustment and uncertainty factors used in the 1986 GLs, to be replaced by factors or procedures derived from scientific data. However, as it has turned out, most of the assumptions and factors present in the old GLs are still present in the new GLs (one exception to this is the use of pharmacokinetic data in the new GLs for making animal to human extrapolations). In addition, the new GLs propose two new ten-fold factors, one to account for the slope of the DR in the observable range and the other to account for limitations in amount and quality of precursor data. Some Subcommittee Members questioned whether the need for, or the magnitude of, these new uncertainty factors can be sufficiently justified in the GLs. Other Members supported the basic direction laid out in the draft GLs, but noted that some further refinements were needed. A majority of the Subcommittee questioned the rationale for the new safety factors.

3.3.2.2 Critical Factors in Margin of Exposure Analysis

The major factors are:

a) Nature of the Response: Some Members felt that the proposed MOE approach does not use the existing direct data on tumor incidence well. It may not use the tumor incidence data at all (i.e., it may use"key event" incidence/measurements instead), or it may use the tumor data somewhat to define a LED_{10} for animals,

but then proceeds with a whole series of assumptions whose applicability and accuracy are often unknown when developing a level that might be considered to be sufficiently protective for humans. In cases where there is little information about the adjustment factors (key events, steep/shallow slope, inter-species extrapolation, or heterogeneity in sensitivity), some Members felt that the MOE procedure is overly conservative. Others noted a number of additional factors that should be addressed if one wishes to proceed from a dose causing a 10% cancer incidence in animals to one that could be considered safe for a heterogenous human population. These other factors include background exposures of agents functioning via the same mechanism; inter-individual variability; adjustments for differences in body size of animals versus that of humans; and severity of endpoint. For example, in the GLs' Appendix E, Example 1, even though there were no significant findings of liver cancer below the highest dose, the MOE extrapolation advocated a dose 3,000-fold lower. Given that the EPA's policy aim is to be conservative with regard to health protection, the multiplication of layers of conservative factors is likely to produce an overly conservative result.

An aim of the GL's MOE approach is to provide a method to estimate safe doses for non-linear modes of carcinogenic action that will more firmly rooted in scientific data than a linear model. Some believe that such an approach would yield a less conservative result than does the linear approach, but there is no measure of how much less conservative it actually is when applied with defaults. Again, examining Example 1 in Appendix E of the draft GLs, a rough calculation shows that the estimate generated using the MOE approach may be nearly as conservative as a produced by application of a linear model. Specifically, applying the derived MOE dose-reduction factor of 3,000 to a linear curve produces an estimate of risk of $\sim 10^{-5}$, which is not dissimilar to a level one would choose using the linear extrapolation procedure. Without further specifics on the mode of action discussed in the example, it is not possible to determine whether or not the MOE approach is appropriate.

b) Steepness of the Dose Response Curve (also affecting the severity of the endpoint): The GLs introduce a new adjustment factor of 10 to be applied to the point estimate of the ED_{10} (except in exceptional cases when the observed DR slope at the LED_{10} is very large; this will be discussed in more detail below). This factor would not be applied if the DR were "steep enough" at the point of departure. Specifically, it is proposed that a 10-fold default factor be applied if the slope of the estimated dose- response curve at the point of departure is less than a factor of three steeper than a straight line drawn from the point of departure to the origin. This approach assumes that an observed slope will continue into the low dose range; consequently, this adjustment is intended to account for differences in observed slope. Although not stated explicitly in the revised GLs document, EPA scientists at the review meeting confirmed that the

steepness of the slope would be evaluated using the lower bound DR curve defining the LED_{10}, rather than on the best estimate of the DR curve that defines the point estimate of the ED_{10}.

Although the specified approach implies that this new adjustment factor would not be applied to very steep DRs, it appears that the conditions necessary to exclude use of the uncertainty factor are so severe that its use would be required in almost all cases. The steepness/shallowness of the dose-response curve at the LED_{10} appears to be largely a function of the power (k) of the polynomial dose-response curve that is selected, which, in turn, is largely driven by the spacing of doses in experiments if only the highest dose shows an increase in incidence. Insofar as the GLs' Appendix E (Example 1 and Example 2) are fairly typical, one is likely to find that a value of three for k provides an adequate fit for many/most of the animal data sets in which only the highest dose shows any tumor effect (or "key event" effect), and the MOE procedure will therefore dictate an additional factor of ten. If one looks at the actual data presented in these examples, one sees that, at the two lower doses in both examples, the incidence does not differ significantly from controls, even though in one case, the incidence in the mid-dose group is double that of the controls. The lack of steepness of the dose-response curve is likely to be primarily an artifact of the experimental design (namely, the spacing of doses) and the sparseness of the data.

Some Members felt that if there is any applicability of the concept of shallow/steep slope, it would be in the case where there is some evidence of elevation at one or more doses below the highest dose, yet a linear curve does not fit the data well (although one would suspect this will seldom occur; a linear curve will frequently fit in such situations given the usual sparseness of the incidence data). There may also be continuous data where the linear fit is poor. Some Members also felt that the shallow/steep slope operational definition needs a major reformulation. If the adjustment factor for shallow/steep slope is to be used, it should be reserved for the cases where there is actual evidence for a shallow slope (e.g., with two or more elevated data points) and should not be applied when only the highest dose shows an elevation, since the inference of a shallow slope in such cases may be largely an artifact of the spacing of the doses, and is not based on any actual evidence of a shallow slope (i.e., the next-to-highest dose point is already down to baseline). Some other Members emphasized the importance of some procedure for moving to a point below that of 10% risk was needed and any changes to the current proposals should address this issue.

The reason given by the Agency for this new uncertainty factor is to "Lower the dose from the LED_{10} to approach a zero to 1% effect level (or from a LOAEL to NOAEL)." Some Members found this an appropriate motivation for an additional factor; others did not. Here the GLs appear to be equating LED_{10} with a LOAEL,

despite the fact that the LED_{10} was characterized earlier as"an improved and harmonized estimate of the NOAEL," and despite data relied upon by the Agency indicating that the LED_{10} is, on average, less than the NOAEL already. The Agency is now moving to the use of a measure (the LED_{10}) that, based on currently available information, appears to be generally more protective than the NOAEL, and it is also adding a new 10-fold adjustment factor.

The addition of this new adjustment factor raised a number of concerns with many Members of the Subcommittee. For them, the reasons given for incorporating the new factor in the GLs' assessment were not convincing. First of all, the LED_{10} is already generally lower than a NOAEL, so adding an adjustment factor to lower the dose from a LOAEL to a NOAEL was not thought to be appropriate. Others strongly disagreed, noting the importance of reducing exposure below a level producing a 10% cancer incidence. Second, since the factor is arbitrary; why should one stop at 1% risk? Speaking rhetorically, why not divide by 100 and reduce the dose from the LED_{10} to one approaching a zero to 0.1% risk? Third, although the rationale for the new adjustment factor may not be conceptually related to cancer, it is apparently being proposed only for cancer. Some found this to be at odds with the earlier recommendation by the Subcommittee that approaches for cancer and non-cancer be harmonized to the extent possible Some Members noted, however, that the EHC, in its 1997 report (SAB, 1997), stated that harmonization does not necessarily mean the adoption of the same factors. Furthermore, it may point out a problem in the analytical framework for RfC derivation from severe non-cancer endpoints. Fourth, the use of this new adjustment factor is apparently limited to cases in which the LED_{10} is used as the departure point, and would not be applied to the NOAEL. Some Members felt that this introduces an intolerable incompatibility between the two approaches. Since the LED_{10} is already (in general) lower than a NOAEL, this approach means that assessments that employ the LED_{10} will generally be at least 10-fold more conservative than assessments that employ the NOAEL. (redline text above inadvertently deleted by the editor when revising the previous draft)On the other hand, some Members felt that the NOAEL should not be used without any adjustment factor.

The specific proposed adjustment introduces a "bright line" decision point based upon arbitrary criteria, as there is no specific rationale for either the factor of three for differences in slopes nor the 10-fold adjustment factor. Also, as noted above, the measured slope can be highly influenced by both the experimental design (dose spacing) and the selected DR model, so its reliability is questionable. This latter point is well-illustrated by Example One presented in the draft GLs' revised Appendix E (EPA, 1998). According to the reported analysis, the slope at the LED_{10} was 0.37, the slope from the LED_{10} to the origin was 0.15, and since $0.37/0.15 = 2.5 < 3$, an additional factor of 10 was required. However, when the model is modified to include a fourth degree term, the fit is even better.

Furthermore, with this model, the slope at the LED_{10} is 0.46, and the slope from the LED_{10}, the origin is 0.12. Since 0.46/0.12 = 3.8 > 3, according to this modeling, no additional factor of 10 is warranted. (These calculations are based on the best estimate curve and were made before it became known that EPA intends to employ the curve defining the LED_{10} rather than the point estimate of the ED_{10}.). This illustrates that this three-fold slope ratio rule is likely to be highly model dependent and, consequently, unreliable. Some Subcommittee Members were also concerned that the use of the curve defining the LED_{10}, rather than the best-estimate curve defining the point estimate of the ED_{10}, is not justified. These Members felt that the best-estimate curve should be used so that the focus is on the biological DR curve instead of a curve defining the statistical uncertainty of the biological response.

It is instructive to compare the result of the example in Appendix E (EPA, 1998)) to what would have been obtained if the NOAEL approach has been applied. The NOAEL in this case is 0.65 mg/kg/d, which by chance is also the value of the LED_{10} obtained by EPA. However, if the NOAEL were used as the take-off point, no additional factor of 10 for steepness of slope would be applied. This, therefore, illustrates the imbalance in the currently proposed approach of allowing either the NOAEL or the LED_{10} to be used as the point of departure. But again, some
Members found this to be appropriate because of the severity of the endpoint, and that the use of the NOAEL would require an additional adjustment factor.

In order to avoid the "bright line" decision regarding whether or not to use the ten-fold adjustment factor, one could apply a factor equal to 10*[slope from the point estimate of the ED10 to origin]/[slope at the ED_{10}]. Although this approach (supported by several Members of the Subcommittee) suffers from most of the same shortcomings as that currently proposed (arbitrariness and model dependency), it would at least provide a sliding scale that would avoid "bright line" decision rule of the proposed approach.

In addition to the new 10-fold uncertainty factor that is added for steepness of slope (per the criteria noted above), EPA also proposes that an additional 10-fold uncertainty factor be applied automatically when the NOAEL for a key event is used as the point of departure (section 3.1.3.2, pg. 12, lines 14-17, EPA, 1998). There is no clear scientific rationale provided for this additional 10-fold factor, and the criterion for its removal ("...when the full array of data sets supports a conclusion that the NOAEL is probably a no effect level or very close.") (ibid) is not sufficiently defined in the GLs document provided to the Subcommittee. However, EPA staff provided one rationale for using this 10-fold factor at the SAB meeting. The NOAELs in a large number of developmental toxicity studies were found to be approximately equivalent to the calculated LED_{10}. Since EPA's stated goal (EPA, 1998, pg. 13) is to lower the dose to approach a 1% effect level

as a point of departure for cancer EPA felt that it is necessary to use an additional 10x uncertainty factor. If this is an accurate reflection of EPA's rationale, then EPA essentially regards the traditional NOAEL as a LOAEL and believes that additional 10x uncertainty factor should be added to reach a "true" NOAEL. EPA is essentially stating that the current practice of using the NOAEL plus default 100-fold uncertainty factor has not been sufficiently protective, and that 1000-fold should now be the default uncertainty factor. Some Members felt that there is no scientific evidence to support this position and, if this position is adopted the Agency, they should make very clear that it is a policy decision, based on added concern posed by the cancer endpoint, i.e., a value-driven decision, not a science-driven decision, but remaining consistent with the Administration's 1995 risk characterization policy. Other Members found this approach to be supported by data and justified, noting that an adjustment to go from a dose associated with a 10% incidence of health effect to one with a minimal level of effect was needed. These Members questioned why a similar factor was not applied for other chronic endpoints, particularly when the effect observed is severe.

In summary, many Members of the Subcommittee believe that the rationale presented for this new adjustment factor is weak, and questioned whether it is justified. Other Members agreed with the rationale but thought further work on the method is desirable. If the Agency decides to retain some such correction factor, the specific approach to be applied needs to be reworked.

c) The Proposed use of Data from Key Events: For carcinogen GLs, defining risk based on evidence of actual tumor induction (rather than on putative, but perhaps poorly correlated, key events) is a solid bottom line and should not be abandoned without strong justification. Incorporating the shape of the dose-response of "key events" is consistent with the objective of incorporating more science, particularly mechanistic data related to mode of action. However, reliance on one or more early events, that may be necessary but not sufficient for causation, can lead to incorrect inferences about the shape (and steepness) of the dose-response curve in the low-dose region. Nevertheless, one could make the case that key events that are fairly proximal to the tumor induction step in tumor pathogenesis have some biological plausibility as events to consider. On the other hand, use of those events that are further removed and earlier in the possible chain of pathogenetic events becomes questionable. The early events are likely to have a poor correlation with tumor induction, suffering especially from lack of specificity, i.e., many "false
positives." If key events are to be used quantitatively, there should be much fuller specification and justification of events to be considered "key."

The shape of the dose-response relationships depends on the dose-dependence of all component events in the multistage process and not just a single event -- even

an early event. One key event might be linear with respect to dose and another key event might be non-linear or even have a threshold. Hence one event being linear does not imply that the whole process is linear. However, non-linearity of one event does imply that the whole process is non-linear, although the dose-response may be linear in the low dose range. Each "event" is a process and the overall sum of events is not first order. Furthermore, an earlier event may be associated with a steeper slope and be reversible. Thus, the shapes of the dose-response relationships of all known necessary and sufficient key events and the dose-response of the tumor incidence must be jointly considered.

The proposed adjustment factor of 10 to account for difference in dose between the occurrence of the key event and the observation of tumors was not sufficiently justified in the GLs. Some Members questioned the existence of data indicating that a factor is needed at all, while others noted this addressed, in part, the contributions of background exposures. Some questioned the magnitude of the factor, and whether it was a policy-driven decision, or one based on the available science. The Subcommittee recommends that the data available be studied and used to inform this decision.

d) Inter-species Variability: If the point of departure is calculated as a "human equivalent dose" determined from a body weight scaling factor (such as inter-species equivalence on a (body weight)$^{3/4}$ basis), then no additional factor should be included for animal-to-human extrapolation. The proposed 3-fold factor is (incorrectly, to some Members) justified as corresponding to toxicodynamic species differences, as if the (body weight)$^{3/4}$ scaling from animal dose to human equivalent dose only accounted for toxicokinetic differences. Some Members argued that the (body weight)$^{3/4}$ scaling from animal dose to human equivalent dose includes both toxicokinetic and toxicodynamic differences. For example, in the paper by Travis and White (1988) which contributed to the adoption of (body weight)$^{3/4}$ scaling from animal dose to human equivalent dose, the inter-species equivalence refers to the inter-species differences in maximum tolerated dose, and maximum tolerated dose reflects both toxicokinetics and toxicodynamics. An alternative viewpoint is that toxicodynamics for carcinogenesis and for the acute endpoints studied by Travis and White differ considerably, and that, in the case of cancer, inter-species differences in toxicodynamics will be greater. Recent research by Rhomberg and Wolff (1998) on empirical scaling of single oral lethal doses across mammalian species provides further evidences of differences for acute versus chronic endpoints (in particular, see pages 752-753 of the article). It should also be noted that subsequent analyses of the data used by Travis and White (ibid) pointed out the possibilities of significant underestimation of risk in certain cases when 3/4 scaling is used (Watanabe *et al.*, 1992).

e) Human intraspecies variability, including susceptible populations: Heterogeneity in susceptibility among humans is clearly an appropriate factor for consideration

by the GLs. The Subcommittee recognizes the importance of inter-individual variability and the need to consider the range among individuals in the population, rather than focusing on the comparisons of one large population group (e.g., males, females, children, adults) with another. It is quite difficult to determine (epidemiologically) how the most sensitive members of a large variable population differ from the average. Recent work with biomarkers may eventually provide better means of characterizing the range of variability (Perera, 1997). Unfortunately, with regard to carcinogenesis there are relatively few systematic data of good quality that shed light on this issue, although data are emerging to explore further this issue. The research area that has perhaps the most extensive human data on susceptibility factors is radiation carcinogenesis. With regard to ionizing radiation and carcinogenesis by gender, there are (if we ignore the obvious differences -- breast, ovarian, uterine, prostate cancers), modest differences between sexes at other sites, such that females are at slightly higher risk than males, although the differences are nearly all less than two-fold. With regard to age at radiation exposure, children are at increased risk compared to adults, but the factor is only about two- to four-fold, and certainly not as much as 10-fold more than the average for all ages. (NAS/NRC, 1990; ICRP, 1991). There are two cases where there are strong radiation age effects, namely for thyroid and breast cancer. For breast cancer the increased sensitivity at young ages is less than 10 times the average for all ages, but the increased sensitivity may be on the order of 10-fold for thyroid cancer (because thyroid cancer risk drops to virtually zero for irradiation after age 30). For childhood cancer risk following in utero exposure, the risk is probably several times as great as when irradiation occurs in childhood (although the evidence regarding this is mixed), but the two groups seem to have similar radiogenic cancer risks in adulthood.

With regard to genetic factors and radiation, there are very few human data. The most extensive study, that of persons who received radiotherapy for bilateral retinoblastoma (homozygous mutation of the Rb gene), showed about a 5-fold greater radiation risk for cancer induction than expected (Wong, 1997). However, this risk was largely limited to a few uncommon types of cancer, especially sarcomas, and did not include the common cancer types (breast, lung, colon, etc.) At the present time, radiation risk with regard to a number of other hereditary mutations has not been defined, e.g., for BRCA1/2, APC, and HNPCC. There is some evidence that hereditary p53 mutations (Li-Fraumeni syndrome) may confer added radiation risk, but the data have not been systematically evaluated (Malkin *et al.*,, 1992; Strong, 1993). There are also two controversial studies suggesting increased radiation risk for breast cancer in those with the ataxia-telangiectasia mutation (ATM) (Swift *et al*., 1991; Athma, *et al.*, 1996). If the ATM-radiation risk is real, it is probably two- to five-fold.

Thus, the evidence from radiation epidemiology suggests that a 10-fold factor for susceptibility would be a health-conservative factor, although a caveat should be

added that radiation does not require any metabolic processes for its carcinogenic action, so it may not be representative of some chemical carcinogens .

Key factors that explain variability in human disease risk are age, socioeconomic status (which is often a surrogate for other risk factors), smoking, gender, routes of exposure, nutritional factors, and genetic factors. Because cancer causation is multi factorial and there are both protective attributes as well as risk factors in the same individual, population overall variability may be less extreme than variability on a single factor might suggest. The distribution of risk among subpopulations studied for the disease of interest can be informative in the assessment of human variability. For example, lung cancer risk among subpopulations that differ according to factors such as diet, ethnicity and gender vary by about two fold to six fold. The highest risk group for lung cancer, male smokers, have a 10-fold higher risk for lung cancer than non-smokers. It is rare for an epidemiology study to identify risks greater than six when comparing subpopulations. Interactive effects have been observed in rare circumstances. Furthermore, methods exist to define a point of departure in the presence of interacting agents. Some Members felt that a careful analysis of all relevant information should precede a decision to apply a default factor to account for human variability; other Members found it imperative to apply a factor to account for human variability in the absence of more definitive information. Flexibility should exist to use uncertainty factors other than 10 (or higher or lower than 10), should scientific data exist to support some other value.

Frequently, experimental data are available on male and female animals of different species, and the risk assessment is based on the most sensitive species and sex. Consequently, some variations in risk across populations, such as between males and females, may already be accounted for and may not require an additional uncertainty factor, or the full value of a default factor. It also should be noted that a 10- fold range between most- and least- sensitive individuals might generally be accounted for by a factor nearer to three than to 10, because the departure point is presumed to apply to the average individual rather than to the least sensitive. However, research on variability suggests the existence of ranges considerable greater than this for specific chemical carcinogens (e.g., benzene [Rothman *et al*., 1997] and 4-aminobiphenyl [Bois *et al.*, 1995]).

The Subcommittee Members recommended that the EPA evaluate the data on chemical carcinogens and make a more scientific determination of an appropriate uncertainty factor to employ for protecting more sensitive individuals. The Subcommittee also recommends that any such review be conducted as a peer-review so that a credible and balanced evaluation is produced.

f) Comments on Mode of Action: The GLs call for the use of a margin-of-exposure (MOE) analysis when there is sufficient evidence to support a non-linear mode of

action. A procedure modeled after the Hill causality criteria for epidemiological studies (Hill, 1965) has been provided to assist in determining MOE. Whereas these criteria are useful, it needs to be clearly recognized that they only provide a means of determining whether the MOA of a chemical is sufficiently well understood. They are not designed to determine whether the mode of action is linear or non-linear at low doses. The GLs include the use of a margin of exposure approach as a new default procedure to accommodate cases in which there is sufficient evidence of a nonlinear dose-response, but not enough evidence to construct a mathematical model for the relationship. However in the examples, the focus appears to be on determination, first, that a MOA is reasonably well understood qualitatively and second, that it is an indirect mode of action. The question of whether the dose-response is linear or non-linear is ignored. It appears to be an unstated assumption that an indirect mechanism will be non-linear. This issue is key to the non-linear approach and must be addressed in the GLs. Linearity is a very specific type of dose-response, and the hypothesis is that a DR is linear and can be tested within the observable range using standard statistical tests.

As noted in the 1997 EHC report the terms 'linear' and "non-linear" as used in the GL can lead to some misunderstanding and confusion. Many well-studied agents associated with a DNA reactive mode of action are observed to have non-linear dose response relationships (e.g., vinyl chloride and diethylnitrosamine). Non-linear tumor dose response relationships (due to increased mortality in high dose groups and dose dependent pharmacokinetics) are frequently observed. Alternative terminology could be employed to address this problem is. e.g., the use of "linear at low doses" and "non-linear at low doses;" "low dose linear" and 'low dose non-linear;" or "non-threshold' and "presumed threshold-like."

Although not addressed in detail at the Subcommittee's review meeting, we wish to point out that the issue of background additivity is also overlooked in the GLs. In cases when there is considerable exposure to exogenous and endogenous chemicals operating by similar mechanisms, the DR in the population can be linear even if the DR from zero exposure to higher doses is significantly non-linear.

4. CONCLUSIONS AND COMMENTS

The Agency stated that the current draft of the GLs is intended to provide greater flexibility to the risk assessor, so that new scientific data can be used, when they exist, in place of traditional defaults. While the draft, in being responsive to the SAB's 1997 request for more definition and explanation in some areas, certainly moves in the direction of greater flexibility, some flexibility has actually been lost; e.g., the incorporation of several new defaults, standardization of dose-response models, restrictions on the use of the NOAEL approach, and a decision to use the LED_{10} as a point of departure. The current version demonstrates, however, the Agency's progress and commitment to implementing the recommendations of the NAS/NRC Committee report "Science and Judgment in Risk Assessment (NAS/NRC, 1994) and the Commission on Risk Assessment and Risk Management (GPO, 1997) to harmonize GLs for cancer and non-cancer risk assessment.

Given the above findings, the Subcommittee wishes to make a major recommendation to the Agency. We believe strongly that these GLs should become operative, as soon as judiciously possible. The old GLs have been around for more than a decade; the Agency has been working on the revised GLs since 1990, including sponsoring several public workshops on GLs issues; and the SAB has had a Consultation and two reviews -- with at least one more in the offing to address GLs issues related to children. Clearly, there are GLs issues noted in this report that need to be addressed and/or re-visited, continually (and new ones that will arise). However, it is important to consolidate the progress that has been made in the current document, and have it officially issued at the earliest possible date.

In summary, the Subcommittee is aware of the difficulty that the Agency faces in trying to 'titrate' just the right amount of flexibility into the GLs. In point of fact, however, the issue cannot be settled *a priori*. The Agency should continually consider the matter as the GLs move into common practice and experience demonstrates how the flexibility should be adjusted. Therefore, we encourage the usage of the GLs and that the Agency gain valuable experience with them as soon as judiciously possible.

The above accomplishments, and the preceding detailed discussion notwithstanding, the Subcommittee wished to highlight for the Agency several additional issues (both within, and without, the scope of the Charge).[5] These issues are:

a) Primacy of public health protection: The Subcommittee believes that it is essential that, as noted in the previous review (SAB. 1997, p.18) the GLs state at the outset that "the primary goal of EPA actions is public health protection and that, accordingly, as an Agency policy, the defaults used in the absence of scientific data to the contrary should be health protective." These defaults should be

[5] In addition, detailed comments from individual Members of the Subcommittee are provided in Appendix A.

clearly explained in the revised GLs text, including the assumptions of low dose linearity and the relevance of animal data to humans. The basis for the various default uncertainty factors should also be clearly described.

b) Lost flexibility: Some Members expressed concerns that EPA, in responding to the SAB's request for more definition in several areas, actually reduced, rather than increased, flexibility in moving from the 1996 to the 1998 version of the GLs. They cited several examples, including the reliance on the LED_{10} as a point of departure, the addition of numerous new defaults, standard dose-response models, and restrictions on the use of the NOAEL approach.

c) Sensitive subpopulations: EPA should include a discussion of sensitive subpopulations for all agents to which the general public (as opposed to healthy workers) are exposed. Specifically, this discussion should include consideration of pregnant females, the fetus, young children and adolescents, the ill, and the elderly. There should be a summary of existing data (including biomarker data), acknowledgment of gaps in knowledge, and a discussion of the factors that make or may place the population at increased or decreased risk to this agent. Differences between the young and adults in metabolic pathways, DNA repair, cell proliferation, immune surveillance or other critical or important processes that may alter susceptibility, as well as cancer risk, should be addressed to the extent that data are available on how these biomarkers translate into population risk. The basis for the uncertainty factor or alternative modeling procedure used to account for susceptibility of the young should be clearly stated. EPA should also discuss other known or likely sensitive populations due to susceptibility factors *in addition to* young age: nutritional deficits, preexisting disease, ethnicity, gender, pregnancy – which may occur simultaneously (in combination) in various subsets of the population (see Perera, 1997). It should also be noted that interindividual differences in enzyme activities, etc., do not necessarily imply similar changes in cancer susceptibility when they are not the rate limiting step.

The Agency should conduct systematic reviews to explore quantitatively the extent of variability among individuals in the human population. In doing so the Agency should consider modeling approaches, as well as comparisons of risks across populations. In performing such comparisons, it is noted that (typically) average risk serves as the basis of comparisons, and that such comparisons may substantially underestimate the variability among individuals in populations. For certain applications, such as the MOE approach, it is particularly important that variability not be significantly underestimated.

d) Consideration of background and multiple exposures: EPA should discuss the need for the risk assessment to consider background exposures/processes and concurrent exposures with which the agent (mixture) of interest may display additivity or inhibition, or interact multiplicatively.

e) Guidance on the use of biologically-based models: The 1998 draft does not provide greater guidance than the 1996 GLs regarding the use of biologically based DR models. No clear example has been provided of DR models "that would be relied upon for low dose extrapolation." (SAB, 1997, p. 23) As in the 1997 report , we continue to support the view that "if no such model can presently be identified, a statement to that effect would be helpful."

f) The preceding technical discussions notwithstanding (sections 3.3.2.2 (b)), the ultimate answer to the question of whether or not to include a special adjustment factor because the endpoint under discussion is cancer is not actually a scientific question, but a policy decision.

APPENDIX A
DETAILED COMMENTS FROM INDIVIDUAL SUBCOMMITTEE MEMBERS

The following comments from individuals on the Panel are offered to the Agency for its information. They do not represent a Subcommittee consensus position on any point, but they are worthy of further consideration as these GLs continue to evolve. The Subcommittee does not expect the Agency to address these comments in its response to this report.

a) One reviewer found the argument in the thyroid dose example to be internally inconsistent, especially regarding rodent sensitivity, given the findings in the dog. For that example, it is recommended that values based on the LED_{10} approach be presented. There is no good rationale for using the NOAEL over the LED_{10} in this example.

b) It was clear from the Subcommittee discussion on mode of action at the meeting that the EPA GLs will be used as a blueprint for testing by chemical manufacturers. They must therefore be rigorous and specific as to the types of data to be considered. It is important to explicitly include the following types of data:

   1) Are there parallel data in humans (e.g.; in the thyroid case, on liver enzyme induction and Thyroid Stimulating Hormone)? Gaps in knowledge should be noted.
   2) Data available on populations known or likely to be sensitive to the chemical alone or in combination with other chemicals (e.g., children, people with preexisting thyroid disorders etc.) should be discussed.
   3) Discuss whether background exposures/processes occur in the human population.
   4) Data on interactions known, or likely to occur, between the chemical of interest and other exposures should be provided.
   5) Gaps in testing and scientific knowledge should be identified.
   6) Are the IARC (1991) criteria for species-specificity or qualitative differences between species met?[6]

[6]"The available evidence may show that similar mechanisms are acting in humans and experimental animals. Of particular concern are those situations in which the possibility is considered of species-specific activity. One concern would be raised when humans are the more affected or susceptible species. This could be evaluated on the basis of knowledge of mechanisms and the comparative relevance of a mechanism to animal and human responses. Another concern is raised when the putatively unaffected species is human beings. Certain principles should be applied before such species-specific activity can be concluded. It should be established, (1) for the tumor site in question, that the mechanism in question is the primary one in the tumorigenesis in that species; (ii) that the same or a similar mechanism does not operate in humans; and (iii) whether the agent induces other types of tumors in experimental animals. If other types of tumors are induced, then (i) and (ii) would have to be fulfilled for each of them. Qualitative differences, in which effects occurring in one species are not expected to occur in another, should be distinguished from quantitative differences (such as different rates of biotransformation), which may influence only the degree of response rather than the presence or absence of a response." [IARC, 1991]

c) The narrative summary is the key component of this section. The current discussion does not convey an understanding that the effects of chemicals are a function of dose, exposure duration, and the background of the exposed individual.

d) The proliferative effects section needs to be rewritten to clarify the last several sentences that are on a different topic than the rest of the paragraph. The immune surveillance point should be removed. The mutagenicity section could go one step further to suggest a technique for the combination of disparate data sets (Brusick *et al*., 1992). The primary problem in this section is that it is unclear what is necessary and sufficient to suggest a plausible mode of action (see Scheuplein, 1995) for a useful discussion of this area). The flexibility to this should be retained since this is the strength of this version of the GLs.

e) In the special subchronic studies section, it seems unlikely that doses in excess of the MTD will be helpful in characterizing the biological effects and providing mechanistic data for these assessments. In this case several points need to be clarified. Do the data to be obtained support a specific tenet in carcinogenesis? Is an oncogene over expressed, a tumor suppressor gene silenced, or an expression of genes associated with cancer development altered? Is a secondary mechanism for cancer development supported? The latter case permits one to link the induction of tumors with a previously occurring event through a physiological or pathological change that has a threshold.

f) In section 2.3.5.3 of the GLs, the listing needs to be prioritized- genotoxic evidence should be first, then the dose-dependence and temporal and spatial nature of the effects should be documented. Both the biology and the statistical analyses should be consistent and the biology should drive the assessment.

Selection of a single marker is insufficient evidence to link it causally to cancer. For example an increase in cell proliferation that is not sustained or that is below a certain level may be without risk; judgments need to be case-by-case. Information that helps to define the biological plausibility of the mode of action and not just provide additional mechanistic detail is needed to support decision making. Rule out mechanisms that are directly genotoxic and demonstrate a plausible link to mechanisms that may not be operative at all doses. These studies must demonstrate that the secondary mechanism exists in animals, that this mechanism can be interrupted to block tumor development and that a no effect level for the secondary mechanism exists. The second point is that the induction of hyperplasia and other precursor lesions should be reversible upon cessation of the agent being tested (Scheuplein, 1995). This is followed very clearly in the Appendix D thyroid hormone example.

g) In section 2.4, dose and duration of exposure need to be included along with biology of the organism and chemical properties of the agent. Inputs to mode of action section needs to be rewritten to reflect PK considerations, and remove the discussion of TCDD on page 9. Figure 2-1 needs to be amended to indicate that in the absence of all of the necessary data a default assumption of linear or nonlinear can be used. The flexibility of this part is the key to the utility of this document. This entire section needs to indicate that the effects of compounds are dependent upon the dose and duration of exposure to the agent and that the administered dose is of less relevance than the dose at the target site. The most relevant factors would be WOE, exposure conditions, and relevance to humans.

h) Use of the mode of action data- the flexibility in this section is to be recommended.

i) Remove sentences on "key event" this terminology is confusing since one is describing a process that is a continuum of biological response.

j) The discussion on genotoxicity states that determining whether genetic damage occurs from chemical exposure is an important part of risk assessment. This section needs to speak to the method for combining data from many disparate studies and what the minimally acceptable criteria are for inclusion of a specific study in this context. It is also important to include a discussion of non-genotoxic effects that may impact on carcinogenicity. It is however insufficient to indicate that a chemical can alter gene expression with acute exposure without specifically linking this change or chronic change to the carcinogenic potential. Transient alterations that can be reversed would in this context be of a lesser concern than chronic effects that can be linked in a temporal and dose-dependent manner with the induction of cancer. The that needs to be emphasized is that the effects of all agents are dose dependent.

Specific points which should be addressed in these sections include: what to do in the absence of a BBDR model for the chemical and endpoint of interest. The data should define whether linearity or non linearity is assumed. For example is the background incidence of tumors in the target tissue (for example mouse liver) is 20%, then why are we extrapolating to zero? Second, what should be done if the high and low dose give the same tumor incidence or if the high dose gives a lower incidence than the low dose? Or the most likely scenario in which there is no detectable biological response (i.e. no tumors at the low dose and an increased incidence at the higher dose- how does this indicate a linear process. The lower dose is statistically at most a 10% response that was not detected given the constraints of the animal bioassay, but may be zero

k) Decision criteria for judging adequacy of WOE for a specific mode of action need to include both the biological endpoint and an appropriate measure of PK/PD to help define default assumptions for the MOE.

l) All of page 9 needs to be rewritten.

m) Evidence of non linearity should include information on the biology of the response under consideration. For situations in which both linear and non-linear components of the assessment are required this should proceed based on the expected exposure dose and duration. In dose range X, a nonlinear mode of action is most appropriate. Figure 2-1 should be reconsidered to reflect that the default should be non linearity and that the presumption of risk should have some biological support. The onus should be to prove linearity.

n) The listing in section 2.5 needs wordsmithing. The term key events should be changed. The section on mode of action is fine in content but needs rewording. In general, the writing style lacks precision. Obtaining precision should not eliminate flexibility- the inclusion of more biology will strengthen the risk assessments performed.

o) The examples included in the GLs require additional refinement. Although it is clear how the Agency intends for the MOE analysis to be performed, the discussion of the uncertainty factor issue needs some careful revision.

p) The appendix D portions are fine with the exception that in both the thyroid and bladder cases a good analysis of potential human risk is not provided. On the GLs' Page 8 (line 5) the number provided should be 1000 not 100. The last clause on page 12 should be removed. If the animals were maintained on a caloric restricted diet and lived for 3 years, the likelihood of female thyroid tumors would be limited. The real issue here is the question of whether these tumors in rodents are predictive of human cancer risk at doses achievable in humans (see McClain, 1995; 1992).

q) A paper (*Use of Mechanistic data in Assessing Human Risks from Exposures to Particles)* (McClellan, 1997) offers a template for the conduct of research directed toward reducing uncertainties in assessing human health risks from exposure to particles. The guidance provided in this paper has broad relevance to developing information pertinent to assessing cancer risks. It addresses:

1) the design of mechanistic studies
2) dose levels related to environmental levels for both *in vivo* studies and *in vitro* studies

3) the use of dose levels for *in vitro* studies which provide a gradient of response (relative to dose) and can elucidate how underlying mechanisms are influenced by dose and dose rate
4) when practical, observations made with animal tissues studied *in vitro* should be extended to human tissues
5) when practical, the results of mechanistic studies should be presented quantitatively, within the framework of an exposure (dose)-time-response matrix
6) investigators should place substantially greater weight on data obtained over a range of exposure (dose) levels when interpreting mechanistic data for carcinogenic classification schemes.
7) mechanistic data should be used for risk assessment purposes only when they represent a mechanism operative in humans at plausible exposure levels

r) There is confusion about what the MOE factors represent. Contributing to this confusion are the varying viewpoints, expressed in the draft GLs, on the point of departure. The draft indicates that the "ideal would be to identify the dose at which the key events just begin to occur in a heterogeneous, human population and to use that dose as the point of departure." Under this viewpoint, (one that some members of the Subcommittee supported), the point of departure would represent a population threshold dose, expressed as the equivalent human dose. The dose would reflect human and inter-species variability, differences in effect level doses associated with key events and tumor, and adjustments to move from a point estimate of the ED_{10} to a vanishingly small risk level. A major reason for this alternative viewpoint, is the potential confusion over the use of advisory MOE.

s) Ultimately, the issue of using the NOEL and point estimate of the ED_{10} versus the LED_{10} will need to be resolved with real data rather than with opinions. Hypothetical statistical arguments about how DR curves will vary under real-world conditions often yield us "attractive" curves that have no biological relevance. The next step is up to the researchers, who need to try out all these suggestions and illustrate for EPA what works well and what needs further work.

t) When the NOAEL approach is used to derive an MOE under these GLs (or if the LED_{10} approach is used without the steepness factor), the approach is essentially the same as that for non-cancer effects. However, the severity of the effects being addressed may vary widely (from cancer mortality to subtle sub-clinical effects). Although this specific use of a severity adjustment factor was not discussed at the public meeting, it would be reasonable for EPA to account for severity of the health effect under consideration. If this approach is adopted, it is recommended that the Agency extend the procedure to similarly account for relative severity of different non-cancer health effects. During the preparation of

this report, several Members did comment on the idea of adding another adjustment factor to account for severity of the health effect. These Members believe that EPA needs to be careful about adding factors with borderline justification, because they cascade and lead to recommendations that lack credibility.

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