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Subject: EPA responses to NRC questions re OMB Risk Assessment Bulletin

Good Afternoon;

Attached please find EPA's responses the questions posed by NRC in relation to its peer review of the proposed OMB Risk Assessment Bulletin.

Answers were prepared in the Office of the Science Advisor with input from other Offices. Many answers were based on the general comments presented by EPA to NRC at its public meeting in June. Others were written specifically in response to this request or were drawn from existing EPA publications

(See attached file: NASquestionsfinal.doc)

We hope that the attached responses will be useful to the Committee.

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EPA Answers to Questions posed by NRC in its review of the Proposed OMB Risk Assessment Bulletin – August 3, 2006

I. Introduction

Below please find EPA's answers to the questions posed by NRC to EPA (and other federal agencies) about the Proposed OMB Risk Assessment Bulletin. We have numbered the questions for readability. (In some cases, the order of the questions has been re-arranged, e.g. question 1).

Answers were prepared in the Office of the Science Advisor with input from other Offices. Many answers were based on the general comments presented by EPA to NRC at its public meeting in June. Others were written specifically in response to this request or were drawn from existing EPA publications, primarily:

US EPA 2004; An Examination of EPA Risk Assessment Principles and Practices. EPA/100/b-04/001; www.epa.gov/osa/ratf.htm

US EPA 2002; Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity, of Information Disseminated by the Environmental Protection Agency. EPA/260R-02-008; www.epa.gov/oei/quality/informationguidelines

US EPA 2006; EPA's Peer Review Handbook, 3rd Edition; EPA/100/B06/002; http://www.epa.gov/peerreview

II. NRC Questions and EPA Responses

QUESTIONS FOR ALL AGENCIES POTENTIALLY AFFECTED BY THE OMB BULLETIN

General questions about current risk assessment practices

NRC Question 1. A. Please provide a brief overview of your current risk assessment practices.

In 2004, EPA published a staff paper entitled "An Examination of EPA Risk Assessment Principles and Practices" (*Staff Paper*) that described its risk assessment practices at that time. This paper was developed in large part in response to public comments[1] requested by OMB on EPA's risk assessment practices. While it does not represent official EPA policy, it was reviewed and approved for publication and presents an analysis of EPA's general risk assessment practices at that time. Chapter 1, pages 1-6, and Chapter 2, pages 11-16 provide a good overview of our current practices.

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[1] On February 3, 2003 (68 FR 22, pp. 5492-5527) OMB requested public comment on "ways in which 'precaution' is embedded in current risk assessment procedures through 'conservative' assumptions in the estimation of risk" and "Examples of approaches in human and ecological risk assessment...which appear unbalanced."

NRC Question 1 B. Specifically, do you conduct probabilistic risk assessment?

EPA typically uses deterministic approaches to characterize risk, although, increasingly often, in the Office of Pesticide Programs (OPP), in the Office of Solid Waste and Emergency Response (OSWER), and for criteria pollutants in the Office of Air Quality Planning and Standards (OAQPS), EPA applies probabilistic techniques for characterization of exposure or risk.

EPA has published a number of documents related to probabilistic assessments: these include the March 1997 *Guiding Principles for Monte Carlo Analysis* (USEPA, 1997b), the May 1997 Policy Statement (USEPA, 1997c), and the December 2001 Superfund document *Risk Assessment Guidance for Superfund: Volume III — Part A, Process for Conducting Probabilistic Risk Assessment* (USEPA, 2001a)"

Section 3.4.3 of Chapter 3 of the *Staff Paper* described generally how EPA uses probabilistic analyses with respect to hazard assessment.

" EPA cancer and other risk assessments have not included full probabilistic uncertainty analyses to date, primarily due to the need to develop relevant probability distributions in the toxicity part of risk assessment. However, quantitative statistical uncertainty methods are routinely applied in evaluation of fitting of dose-response models to tumor data, and quantitative uncertainty methods have been used to characterize uncertainty in pharmacokinetic and pharmacodynamic modeling."

OPP increasingly is using probabilistic techniques for characterization of exposure.

OSWER routinely uses probabilistic techniques for evaluating risks from wastes, specifically in the fate, transport and exposure components of assessments used for a variety of management decisions and rules. OSWER has also used PRA to characterize variability and uncertainty in exposure assessments on a site-specific basis. Superfund has a guidance document (US EPA 2001).

For criteria air pollutants, OAQPS has conducted probabilistic exposure analyses and for some air pollutants (e.g., particulate matter, ozone) and health endpoints it has conducted probabilistic risk assessments incorporating statistical uncertainty in exposure-response and concentration-response relationships.

In addition, in July of 2005, EPA was a co-sponsor of a Contemporary Concepts in Toxicology Workshop on Probabilistic Risk Assessment (www.toxicology.org/AI/MEET/PRA_meeting.asp) and has a workgroup within the Risk Assessment Forum that is considering ways to promote probabilistic analyses, including a risk assessor –risk manager dialogue, and a clearinghouse for EPA probabilistic assessments.

U.S. Environmental Protection Agency (USEPA). (1997). Guiding principles for Monte Carlo analysis. EPA/630/R-97/001. Risk Assessment Forum, Office of Research and Development, Washington, DC.

U.S. Environmental Protection Agency (USEPA). (1997). Policy for use of probabilistic analysis in risk assessment at the U.S. Environmental Protection Agency. Fred Hansen, Deputy Administrator. Science Policy Council, Washington, DC. (http://www.epa.gov/osa/spc/2polprog.htm)

U.S. Environmental Protection Agency (USEPA). (2001). Risk assessment guidance for Superfund: Volume III - Part A, Process for conducting probabilistic risk assessment. EPA 540-R-02-002. Office of Emergency and Remedial Response, Washington, DC. **http://www.epa.gov/oswer/riskassessment/rags3a/**

NRC Question 1 C. How do you currently address uncertainty and variability in your agency's risk assessments?

EPA has been increasingly making efforts to more completely characterize uncertainty in its risk estimates. EPA's 1986 set of Risk Assessment Guidelines explicitly stated the importance of characterizing uncertainty. EPA's Exposure Assessment Guidelines developed this theme further for the exposure assessment part of risk assessment. EPA's Risk Characterization Policy provided even more direction for describing uncertainty in risk estimates.

Chapter 3 of the *Staff Paper* discusses EPA's practices in the areas of uncertainty and variability. Below is an excerpt from the overview of the chapter.

"Uncertainty and variability exist in all risk assessments. Even at its best, risk assessment does not estimate risk with absolute certainty. Thus, it is important that the risk assessment process handle uncertainties in a predictable way that is scientifically defensible, consistent with the Agency's statutory mission, and responsive to the needs of decision makers (NRC, 1994). Instead of explicitly quantifying how much confidence there is in a risk estimate, EPA attempts to increase the confidence that risk is not underestimated by using several options to deal with uncertainty and variability when data are missing. For example, in exposure assessment, the practice at EPA is to collect new data, narrow the scope of the assessment, use default assumptions, use models to estimate missing values, use surrogate data (e.g., data on a parameter that come from a different region of the country than the region being assessed), and/or use professional judgment. The use of individual assumptions can range from qualitative (e.g., assuming one is tied to the residence location and does not move through time or space) to more quantitative (e.g., using the 95th percentile of a sample distribution for an ingestion rate). This approach can also fit the practice of hazard assessment when data are missing. Confidence in ensuring that risk is not underestimated has often been qualitatively ensured through the use of default assumptions."

Most recently, EPA has begun to place increased emphasis on use of quantitative uncertainty analyses in its risk assessments, and, in its IRIS assessments, will be moving away from promoting a single value for both non-cancer and cancer effects and will instead recognize and quantify the range of uncertainty in estimates of potential hazard and risk.

NRC Question 1 D. Is there a common approach to both risk assessments and uncertainty analysis?

EPA has a long history of the development of risk assessment guidance to foster consistent practices between and within different effect areas, e.g. carcinogenicity, neurotoxicity, or for different categories of assessments, e.g. cumulative risk assessment, benchmark dose analysis. Approaches to uncertainty analysis are less well developed at this point, but are a goal for the Agency. Section 3.3.3 of the *Staff Paper* on uncertainty analysis describes a general EPA tiered approach.

"Over the years, improved computer capabilities have created more opportunities to characterize uncertainty. As a result, advocates promote such characterization in all cases. We need to be judicious in which methods we apply, such as Monte Carlo analysis. Uncertainty analysis is not a panacea, and full formal assessments can still be time- and resource-intensive. Further, the time and resources needed to collect an adequate database for such analyses can be a problem. While uncertainty analysis arguably provides significant information to aid in decision making, its relative value is case-specific and depends on the characteristics of the assessment and the decision being made. In some cases, a full probabilistic assessment may add little value relative to simpler forms. This may occur where more detailed uncertainty analysis (or analysis focused on non-critical uncertainties) does not provide information which has any impact on the overall decision."

"Accordingly, EPA's practice is to use a "tiered approach" to conducting uncertainty analysis; that is, EPA starts as simply as possible (e.g., with qualitative description) and sequentially employs more sophisticated analyses (e.g., sensitivity analysis to full probabilistic), but only as warranted by the value added to the analysis and the decision process. Questions regarding the appropriate way to characterize uncertainty include:

a) Will the quantitative analysis improve the risk assessment?

b) What are the major sources of uncertainty?

c) Are there time and resources for a complex analysis?

d) Does this project warrant this level of effort?

e) Will a quantitative estimate of uncertainty improve the decision? How will the uncertainty analysis affect the regulatory decision?

f) How available are the skills and experience needed to perform the analysis?

g) Have the weaknesses and strengths of the methods involved been evaluated?

h) How will the uncertainty analysis be communicated to the public and decision makers? "

NRC Question 2. Please identify any substantial scientific or technical challenges that you may encounter when conducting risk assessments for your agency.

The principal scientific challenge relates to limited data.

Data limitations relate to reliance on available data and may include qualitative hazard characterization without identification of the full range of potential hazards; quantitative analyses with limited data points; reliance on animal data for estimating risks to humans; an absence of hazard or exposure data on susceptible lifestages at potential risk; and reliance on data on individual chemicals when estimating risks likely to involve exposure to multiple agents.

Specific data limitations may be seen: for evaluation of countervailing risks, e.g. for implications of reduced income, as an indirect impact; for defining the timing of exposure and onset of the adverse effects, reduction, or cessation of adverse effects; or for estimating population risk from safety assessments, e.g. reference doses.

There are many places within the exposure to outcome continuum where additional data can be quite instrumental either in establishing the adversity of exposure or in reducing the uncertainty in an assessment. EPA encourages, wherever possible, the development of more biological data, or other data for refining risk assessments.

EPA has recently placed increased emphasis on mode of action information in its cancer risk assessments as a way of evaluating alternative (non-linear) dose response models. These data can play an important role in defining the biological plausibility of alternative models.

EPA has also recently emphasized a preference for data-derived uncertainty factors rather than the default assumptions used in safety assessment (Reference Dose) calculations, such as the data-derived factors used in intra-species extrapolation.

Another important consideration is the increasing role of biochemical data or newer types of data, e.g., genomics, in defining events that may be linked with adverse outcomes and become valid endpoints for risk assessment.

Technical challenges may include application of multiple models with limited datasets, estimation of indirect countervailing risks of alternatives, and others.

There are areas of risk assessment for which the application of some probabilistic and statistical methods is not straightforward and additional guidance may need to be developed. For example, quantitative uncertainty analysis (of which 2-dimensional Monte-Carlo assessments is one example) and probabilistic hazard assessment are areas in which techniques are available but for application within the Agency, EPA believes there could be benefit from development and articulation of guidance in their application for some risk assessments. As another important example, consider that much of the historical effort in risk assessment has been devoted to "safety assessment" - development of adequate margins of exposure or safety for key variables to prevent toxicity of products, failure of structures, etc. Such safety analyses may not be quickly replaced with more extensive calculations of statistical bounds and probabilities.

Application of central estimates and confidence bounds in dose response assessments may also require further development prior to routine application. Development of guidance, and in some contexts, derivation of central estimates and statistical bounds may require further methods development. These proposed methods and applications should be subject to peer review prior to application. What is meant by central estimates may need more discussion or guidance. The definition of central estimates may be context specific, i.e. may vary or even not be appropriate, depending on the regulatory and statutory context. There is a need for flexibility to make these determinations.

There are a number of additional areas in risk assessment where there may be technical challenges.

These include:

the state of development of methodologies, and understanding statutory needs and specific context as issues for e.g. reporting results as population risks;

the need for clear definitions, an understanding of the needs for the decision, the statutory environment, and the specific context, in distinguishing between central estimates and expected risks;

limited or no data to support a quantitative measure of the relative plausibility of alternative risk estimates; and

the need for caution (See NRC, 1994) in treating fundamentally different predictions as quantities that should be averaged.

Level of uncertainty in risk estimates is a central issue addressed in EPA risk assessments. This uncertainty is inherent in both exposure estimates and estimates of potential effects (e.g., weight of evidence and dose/response). For our most influential assessments (e.g., National Ambient Air Quality Standards (NAAQS)), EPA conducts quantitative uncertainty analysis for both exposure and effects. However, because of unquantifiable model uncertainty, the large number of input parameters and limited data on their distribution, even the most comprehensive uncertainty analyses do not present the true distribution of uncertainty. EPA has efforts underway to further develop methods to address uncertainty including expert elicitation.

In many assessments (especially for exposure assessments) where distributional information is not available, uncertainty is partially characterized by providing several discrete sets of assumptions that span the range of potential values. In many cases where data are inadequate, default values or high end values (intended to not underestimate risks) are used in the analysis. In such cases their potential impact on the assessment is characterized.

For cancer potency assessments EPA follows the approach in its 2005 Cancer Guidelines (i.e., provide confidence limits, based on the point of departure (POD), and indicate risks may be as low as zero). In some cases a range of potency estimates is presented. In others alternative approaches (which EPA believes are adequately supported) are discussed.

For most non-cancer effects (e.g. RfDs in IRIS), EPA typically presents confidence limits where PODs are derived from benchmark dose analyses. However, RfDs are typically presented as point estimates and the uncertainty around those estimates are unknown. As for cancer assessments, the risk often may be as low as zero. Uncertainty factors and a qualitative confidence characterization are also presented.

Alternative models/Model Uncertainty: EPA utilizes expert judgment based on the available data to focus the choice of models to be evaluated. For our most significant assessments (e.g., NAAQS), the quantitative implications of these alternatives are more fully explored. For most Agency exposure assessments programs typically use a single preferred exposure model to develop exposure estimates. Such models have been peer reviewed and their performance and limitations are well documented. Where new models are used, model uncertainties are presented.

As noted in EPA's Cancer Guidelines, many aspects of model uncertainty in risk assessment related to human health hazards (e.g., the use of animals as a surrogate for humans) are difficult to quantify. Further, the bases for analyses of many of these aspects of risk assessment often rest on science policy choices or inference guidelines that have been justified based on the available general evidence and peer reviewed as generic science policy default choices.

Defining adversity is both a challenging and complex issue.

Endpoints chosen as points of departure or as critical effects are not always adverse *per se*. However, they may well be associated with adverse outcomes, and if the evidence is sufficient, appropriately and often serve as the critical endpoints in risk assessments. Example: The use of blood acetylcholinesterase inhibition as an endpoint, or the use of precursor effects to prevent frank toxicity (as in the recent NRC recommendations regarding perchlorate).

Adversity is not a yes/no phenomenon in many, many situations, so endpoint selection is governed by the considerations in EPA's risk assessment guidelines and professional judgment.

Evidence comes in many levels of quality and detail, and it is the weight of the evidence, or its integrated whole, that will often support a judgment, not simply the "best evidence".

Finally, as another technical challenge facing EPA, there is also our evolving understanding of both the science and engineering processes involved in improving the conceptual model for describing and modeling chemical fate/transport in the environment. A recent example is the consideration of organic chemicals in the generation of gases for waste placed in a landfill.

NRC Question 3. What is your current definition of risk assessment, and what types of products are covered by that definition?

From EPA *Staff Paper*, section 1.1.1

" The most common basic definition of risk assessment used within the U.S. Environmental Protection Agency (EPA) is paraphrased from the 1983 report *Risk Assessment in the Federal Government: Managing the Process* (NRC, 1983), by the National Academy of Sciences' (NAS's) National Research Council (NRC):

Risk assessment is a process in which information is analyzed to determine if an environmental hazard might cause harm to exposed persons and ecosystems."

EPA has long embraced the idea that a risk assessment consists of analyses that embrace the four steps described in NRC 1983: hazard identification, dose response assessment, exposure assessment, and risk characterization. Implicit in the completion of these steps is the notion of the characterization of the magnitude or extent of the potential hazards.

In carrying out its mission, EPA conducts a wide range of analyses that fall within this definition. A series of presentations to the NRC committee examining Toxicity Testing and Assessment of Environmental Agents (1-19-06), made by EPA speakers from programs that regulate air, water, solid waste, toxic substances and pesticides, describes the regulatory environment and the range of EPA products. Many of EPA's programs rely on hazard identification and dose response assessments developed by the Office of Research and Development under its IRIS program.

NRC Question 4. About how long (that is, from initiation of the risk assessment to delivery to the regulatory decision maker) does it take to produce the various types of risk assessments?

Assessments vary widely in their complexity and in the time needed for their production and completion.
For examples:

review of pre-manufacture notices under the Toxic Substances Control Act to support a concern for significant hazard or exposure must take place within ninety days of submission;

provisional peer review toxicity values for Superfund sites may be completed in weeks or a few months;

more complex assessments including Integrated Risk Information System (IRIS) assessments, site-specific assessments, or pesticide registration risk assessments may take one to five years; and

some of the most complex assessments (e.g. dioxin, Libby Montana site-specific risk assessment) in which there is significant controversy and significant new data, the time needed may extend well beyond five years.

It should be noted that much of this time is due in part to requirements not only for rigorous scientific evaluation, but also coordination across the Agency, internal peer review, interagency review, external peer review and final approvals.

Questions about OMB's definition of risk assessment and applicability

NRC Question 5. Using the definition of risk assessment described in the OMB Bulletin, are there work products that would now be considered risk assessments that were not previously considered risk assessments? If so, what are they?

OMB's definition applies the term "risk assessment" to work products that are less than complete risk assessments, e.g. hazard characterization and dose response assessments such as IRIS entries. EPA does not see a big change in its practices as a result of this new, more inclusive definition. EPA recognizes, that many of these products, do end up as a major basis of subsequent, fully developed risk assessments.

Questions about type of risk assessment (tiered structure)

NRC Question 6. In your agency, is there currently a clear demarcation between risk assessments used for regulatory analysis and those not used for regulatory analysis? Is this clear at the outset of the risk assessment?

In general, most EPA risk assessment activities are tied to some aspect of a regulatory analysis, even if they do not result in a full (four step) risk assessment.

While the regulatory purpose should generally be apparent at the outset of the assessment in the planning and scoping phase, the ultimate regulatory needs and uses may only evolve over time and may be different for different settings, and different customers.

With respect to actions that may need regulatory impact analyses (RIAs), and that could be subject to OMB Circular A-4, some actions clearly do, some do not, and for some the need may only become apparent as an assessment is developed.

OMB Circular A-4 advocates a flexible approach to these analyses, stating (p. 3):

> *"You will find that you cannot conduct good regulatory analysis according to a formula. Conducting high-quality analysis requires competent professional judgment. Different regulations may call for difference emphases in the analysis, depending on the nature and complexity of the regulatory issues and the sensitivity of the benefit and cost estimates to the key assumptions."*

EPA agrees with this emphasis on professional judgment and consideration of the differences in the nature and purpose of an Agency's assessments related to A-4 and to all risk assessments.

There is a need for flexibility given the variety of statutory mandates and types of assessments to which the section would apply. Differences between RIAs and risk analyses conducted for other purposes mean that not all standards should be applicable to all regulatory risk assessments. They should, of course, where appropriate, maintain consistency with the requirements of Circular A-4.

NRC Question 7. In your agency, is there currently a clear demarcation between "influential risk assessment" used for regulatory purposes and other risk assessments used for regulatory purposes? Is this clear at the outset of the risk assessment?

EPA has set out a number of criteria for determining whether an assessment is an influential risk assessment and considers it a case by case process, with, then, no clear demarcation point. These judgments are made in part to determine what upcoming assessments are subject to peer review, and so are made early in the process.

EPA interprets *influential risk assessment* to mean any risk assessment (or component), as defined above, that meets the OMB Peer Review Bulletin's definition of "influential scientific information," which is, "scientific information the agency reasonably can

determine will have or does have a clear and substantial impact on important public policies or private sector decisions," as described in EPA's Peer Review Handbook, 3rd edition. The Handbook states:
"Generally, determinations whether a scientific and/or technical work product is "influential" will occur on a case-by-case basis. The continuum of work products covers the range from the obviously influential, which clearly need peer review, to those products which clearly are not influential and don't need peer review. There is no easy, single "yes/no" test that applies to the whole continuum of work products for determining whether a work product is influential scientific information.

The novelty or controversy associated with the work product may determine whether it is influential scientific information. Influential scientific information may be novel or innovative, precedential, controversial, or emerging ("cutting edge"). An application of an existing, adequately peer-reviewed methodology or model to a situation that departs significantly from the situation it was originally designed to address may make peer review appropriate. Similarly, a modification of an existing, adequately peer-reviewed methodology or model that departs significantly from its original approach may also make peer review appropriate. Determining what constitutes a "significant departure" is the responsibility of the decision maker (SPC Peer Review Handbook, 3rd edition, section 2.2.3). "

The Handbook also provides criteria to evaluate whether products should be considered influential. " Generally, scientific and/or technical work products that are used to support a regulatory program or policy position and that meet one or more of the following factors would be considered to be influential scientific information:

a) Establishes a significant precedent, model, or methodology;
b) Likely to have an annual effect on the economy of $100 million or more, or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, Tribal, or Local governments or communities;
c) Addresses significant controversial issues;
d) Focuses on significant emerging issues;
e) Has significant cross-Agency/interagency implications;
f) Involves a significant investment of Agency resources;
g) Considers an innovative approach for a previously defined problem/process/methodology;
h) Satisfies a statutory or other legal mandate for peer review."

Questions about impact of the Bulletin on agency risk assessment practices

NRC Question 8. If applicable, please specify provisions in the Bulletin that can be expected to have a substantial positive effect on the quality, conduct, and use of risk assessments undertaken by your agency.

EPA supports the broad goal of this OMB Bulletin to improve the quality, objectivity, utility, and integrity of risk assessments. Many of the Bulletin's standards are drawn from National Research Council (NRC) reports that EPA supported and whose recommendations have been endorsed by EPA. Many of the approaches presented in the supplementary information section of the proposed Bulletin ("Preamble") have already been adopted by EPA:

- in our quality system which includes our implementation of the OMB Information Quality Guidelines and OMB Peer Review Bulletin;
- in the EPA Risk Characterization Handbook (www.epa.gov/osa/spc/2polprog.htm)
- in the EPA Staff Paper on Risk Assessment Principles and Practices; and
- in other EPA guidance, guidelines, and policies.

Further, EPA is engaged in a wide variety of activities to advance risk assessment practices:

- agency wide workgroups including a Probabilistic Analysis Workgroup, and a task force on Expert Elicitation;
- in specific activities in different program offices and regions, particularly the National Center for Environmental Assessment (NCEA); and
- in support of intramural research in EPA labs and support of extramural research on risk assessment practices (e.g. Resources for the Future report on uncertainty analysis).

EPA supports the general goals described in section III of the Proposed Bulletin. These goals call for dialogue between risk assessors and decision makers in order to define the objectives of the assessment. This dialogue, in turn defines the scope and content of the risk assessment considering professional judgment and the costs and benefits of acquiring additional data before initiating the assessment. The goals provide flexibility in the type of risk assessment based on the hazard, the data, and the decision needs; furthermore the goals indicate that the level of effort be matched to the importance of the assessment. In contrast, sections IV and V describe the twenty standards referred to above as requirements in categorical and mandatory terms; for example, "All influential risk assessments shall..." (Sec V), or "...the agency shall include a certification explaining that the agency has complied with the requirements of this bulletin".

The contrast between the flexibility described in the general goals and the prescriptive nature of the twenty proposed standards makes unclear what will be required in any one of the enormous variety of circumstances under which EPA and other agencies work. This in turn may lead to unrealistic expectations within and outside the Federal government regarding compliance with the proposed Bulletin.

The Bulletin should integrate the flexibility described in the goals in Section III with the standards in Sections IV and V.

Because of the breadth of the areas covered in the standards, and the complexity of their application and implementation, EPA suggests that OMB consider the model used for the Information Quality Guidelines, that is, to issue general guidance, and to ask each Agency to develop guidance appropriate for the scope of its activities, which OMB would review.

EPA believes that it could provide substantial compliance with the standards in the proposed Bulletin through compliance with its Information Quality Guidelines, Peer Review Policy, Risk Characterization Policy, Monte Carlo Policy, its Risk Assessment Guidelines, and other existing, related guidelines, policies, and guidance. Development of EPA guidance based on compliance with those specific Agency policies, guidelines, and guidance, EPA believes, would provide considerably greater detail and thereby promote greater transparency and clarity in its practices, for those within and outside the government.

EPA believes that this process would ensure greater consistency and integration with current practices, while advancing the practice of risk assessment in the specific areas described in the standards.

NRC Question 9. If applicable, please specify provisions in the Bulletin that can be expected to have a substantial negative effect on the quality, conduct, and use of risk assessments undertaken by your agency.

We see the issues here as essentially related to clarity, transparency, and conduct of risk assessments.

Aspects related to clarity and transparency include:

Sections VIII and IX

While Section IX gives OIRA and OSTP responsibility for overseeing implementation of the Bulletin, it does not outline any roles and responsibilities for decision-making, resolution of disagreements between agencies and OMB, certifications, waivers, exemptions, and other areas. The document should describe how interactions between OMB and the Agencies will work in implementing the Bulletin.

Implementation of the deferral and waiver section VIII is unclear and ambiguous in what is required; that is, when is a standard being "waived" as opposed to just being applied "flexibly"?

While the proposed Bulletin does provide an opportunity to waive or defer some or all of the indicated standards, this opportunity is defined in a very limited way. Under Section VIII, only the agency head may waive or defer the standards, which would likely result in an undue expenditure of great effort and time within the Agency. In addition, deferral

only delays the implementation of full compliance with the Bulletin and does not provide any real relief. The proposed Bulletin does not describe any criteria for granting a waiver or for providing for exemptions, but it indicates that even deferral is expected to be a rare event.

Scientific "defaults" or "inference guidelines" play an important role for EPA in providing a consistent and peer reviewed means of addressing recurring, fundamental issues of science policy in its risk assessments. The proposed Bulletin does not address this aspect of risk assessment practice that is discussed in the 1983 NRC "redbook" and specifically described for different areas in the EPA Risk Assessment Guidelines. However, as emphasized in the 2005 Cancer Guidelines, EPA sees that a critical analysis of all the available information relevant to assessing risk is the starting point from which default options may be invoked to address uncertainty or the absence of critical information.

Aspects related to Conduct of Risk Assessments

Those aspects of the Bulletin that could have the greatest negative impact on conduct, in addition to those that may pose technical challenges, are those that have a potentially broad scope, e.g., those that call for multiple analyses. The primary negative effect might be increased need for time and/or resources.

The standards of the proposed Bulletin would come into play for a large class of agency products and, if categorically adopted, would mandate a high level of analysis and development of characterization that goes beyond most current EPA practice in risk assessment.

While EPA appreciates that fact that the Bulletin does not create legal rights (Section XI), challenges that claim that the risk assessment or supporting analyses have not fully carried out the practices established by the Bulletin come in many other fora. Such claims could pose an additional burden.

Several standards discuss multiple analyses, including: IV 5, a quantitative evaluation of reasonable alternative assumptions; and V 5, portrayal of results based on different effects observed and/or different studies; We have some general concerns about these analyses as drafted:

- their scope may be impractical;
- one should consider the value added (benefits) of these analyses versus their costs as a function of the importance of the assessment, and their relative value in comparison to collecting data;
- multiple analyses may pose risk communications challenges;
- and in some cases, the complexity of the analyses may limit their feasibility.

Section V 9. states: Consider all significant comments received on a draft risk assessment report and:

> a. issue a "response-to-comment" document that summarizes the significant comments received and the agency's responses to those comments; and
> b. provide a rationale for why the agency has not adopted the position suggested by commenters and why the agency position is preferable.

EPA conducts its peer reviews and public involvement in line with its defined policies in these areas and consistent with the OMB Peer Review Bulletin, which provides for different processes for influential scientific information and highly influential scientific assessments. This section goes beyond those guidelines by calling for a response to comment package for all influential risk assessments, and also in its call not only to explain the basis for the agency position, but also to explain why other approaches were not taken, and why. This goes beyond the peer review procedures even for highly influential scientific assessments and most practice we know of in this area.

NRC Question 10. If your agency followed the procedures described in the Bulletin, would it affect the time course for production of the risk assessment (that is, the time required from initiation of the risk assessment to delivery to the regulatory decision maker)? If so, please explain why?

If EPA followed all of the procedures described in the twenty standards, assessments could take considerably longer. If alternatively, scoping and planning lead to an appropriately defined assessment in terms of its scope, as noted in the goals section, then those assessments should be efficient, and there would be a limited impact on current timelines.

NRC Question 11. One of the Bulletin's reporting standards states the need to be scientifically objective by "giving weight to both positive and negative studies in light of each study's technical quality." Please give an example of how this would be implemented by your agency or department.

Weight of Evidence analyses, to which the Agency subscribes, embrace the notion of consideration of all the evidence, consistent with its quality. Thus, any published EPA risk assessment, should satisfy this standard in that sense. The phrase "giving weight to both positive and negative studies" has quantitative connotations and the term "consideration" may be preferable.

See also, section 4.4.2, page 72 of the *Staff Paper* which illustrates how positive evidence has not uncritically been accepted in analysis of carcinogenicity data.

NRC Question 12. Does your agency use risk assessments conducted by external groups? Would it be helpful to you if risk assessments submitted to your agency by

external groups, such as consultants and private industry, met the requirements proposed in the OMB Bulletin?

Yes, in some cases the Agency has relied upon assessments conducted by external groups, including NRC panels, the World Health Organization, the Canadian government, ATSDR, and CAL-EPA. In general, their conformity with the requirements of the Bulletin, as feasible and appropriate, would be a laudable goal both for those whose assessments may be used as well as more broadly for those who might wish to propose alternative analyses for consideration.

ADDITIONAL QUESTIONS FOR SPECIFIC AGENCIES: EPA

NRC Question 13. Regarding pesticides specifically, what risk-assessment activities will be covered by the Bulletin and what risk-assessment activities will be exempted?

The Agency agrees with the OMB bulletin that risk assessments for permitting or licensing programs should be exempt. Thus, pesticide risk assessments or actions under FIFRA would be excluded given that pesticide registration/re-registration program is a licensing program. However, the proposed Bulletin did indicate that actions that involve assessment / reassessment of tolerances for pesticide residues on food would be subject to the Bulletin (page 10, par. 2). EPA's Office of Pesticide Programs conducts risk assessments in support of the establishment of tolerances under Federal Food Drug and Cosmetic Act (FFDCA). Because pesticide risk assessments supporting tolerances are tied to the pesticide registration/re-registration program (i.e., licensing), such risk assessments should also be exempted from the OMB bulletin. Furthermore, all new food tolerances are impacted by the short PRIA (Pesticide Registration Improvement Act) time frames (2 years and less). Although pesticide risk assessment tied to the registration/re-registration program (licensing) should be exempted, we agree with OMB that certain pesticide risk assessments that have significant science issues that are debated by the scientific community and that have intra- and inter-agency impact on regulatory decisions of broad consequences (e.g., arsenicals) should be subject to the Bulletin.

NRC Question 14. Does EPA have any examples of the application of the 1996 requirements of the Safe Drinking Water Act, as described on page 13 of the Bulletin? Can any examples be provided to the committee? If none are available, can EPA provide an explanation?

EPA has *adapted* these requirements in its implementation of the Information Quality Guidelines (US EPA, 2002[2]). Thus, any assessments published subsequent to our completion of that document should be consistent with the elements described therein.

In issuing its IQGs, EPA *adapted* the SDWA principles. As EPA explained in its IQGs, "EPA conducts and disseminates a variety of risk assessments. When evaluating environmental problems or establishing standards, EPA must comply with statutory requirements and mandates set by Congress based on media (air, water, solid, and hazardous waste) or other environmental interests (pesticides and chemicals). Consistent with EPA's current practices, application of these principles involves a "weight-of-evidence" approach that considers all relevant information and its quality, consistent with the level of effort and complexity of detail appropriate to a particular risk assessment." EPA committed to ensure, to the extent practicable and consistent with Agency statutes and existing legislative regulations, the objectivity of our dissemination of influential scientific information regarding human health, safety or environmental risk assessments by applying an adaptation of the SDWA principles.

EPA adapted the SDWA principles in the Agency's IQGs, "in light of our numerous statutes, regulations, guidance and policies that address how to conduct a risk assessment and characterize risk" in order to:

- Implement SDWA principles in conjunction with and in a manner consistent with Agency statutes, existing legislative regulations, and our existing guidelines and policies for conducting risk assessments;

- Accommodate the range of real world situations that EPA confronts in the implementation of our diverse programs. For example, EPA's adaptation covers situations where EPA may be called upon to conduct "influential" scientific risk assessments based on limited information or in novel situations, and recognizes that all "presentation" information called for in the SDWA principles may not be available in every instance. Our adaptation recognizes that the level of effort and complexity of a risk assessment should also balance the information needs for decision making with the effort needed to develop such information.
- Enable EPA to use all relevant information, including peer reviewed studies, studies that have not been peer reviewed, and incident information; evaluate that information based on sound scientific practices as described in our risk assessment guidelines and policies; and reach a position based on careful consideration of all such information (i.e., a process typically referred to as the "weight-of-evidence" approach). As noted in our IQGs, EPA uses a weight of evidence approach, in which a well-developed, peer-reviewed study would generally be accorded greater weight than information from a less well-developed study that had not been peer-reviewed, but both studies would be considered.

[2] US EPA (December 2002). Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency (EPA/260R-02-008). Washington, DC, Office of Environmental Information.

- Allow EPA to use terms that are most suited for environmental (ecological) risk assessments. EPA assessments of ecological risks address a variety of entities, some of which can be described as populations and others (such as ecosystems) which cannot.

The Bulletin should clarify that it does not modify or supersede OMB-approved agency adaptations of the SDWA risk assessment principles in their Information Quality Guidelines.

NRC Question 15. Does EPA have a working definition of "expected risk" or "central estimate"? The agency indicated in its 1986 cancer guidelines (51FR33992-34003) that central estimates of low-dose risk, based on "best fit" of the observed dose-response relationship, were meaningless—that "fit" in the high-dose region provided no information about "best fit" in the region of extrapolation. The newer cancer guidelines appear to adopt the same thinking. Has the Agency changed its view on this point? If so, why?

EPA finds the terms central estimate and expected risk to be quite different and does not use them interchangeably. EPA documents discuss central estimates from a specific model, for example, with respect to both cancer dose response assessment and for derivation of maximum likelihood estimates for points of departure (PODs). In contrast, discussion of the notion of expected risk, (not a specifically defined term, to our knowledge) in a risk assessment usually involves a particular exposure distribution, and relies on a series of judgments about whom (average consumer, top 5% of those exposed) we expect to be exposed. For safety assessment, an additional complication is a limited ability to describe what effect is expected above a reference dose.

EPA's 2005 cancer guidelines differ significantly from its 1986 guidelines with regard to the treatment of the "central estimate" of cancer risk. In particular, the 2005 guidelines distinguish between the dose-response function within the range of data from that which is used to extrapolate to lower doses. In contrast, the 1986 guidelines use one model (the linearized, multistage model) both to fit the data and to extrapolate to lower doses. The 2005 guidelines discuss the following issues not mentioned in the 1986 guidelines.

1. A preference for biologically-based dose-response models when there is adequate scientific support for them.

2. The potential for biologically based modes of action that are non-linear at low doses (even in the absence of a biologically based dose-response model).

3. The utility of central estimates, and estimates of confidence limits, when practicable, conforming with OMB and EPA guidelines on data quality.
