Dear OMB Office of Information and Regulatory Affairs:

The Society of Toxicology (SOT) respectfully submits the attached comments on the "Proposed Risk Assessment Bulletin," which was issued by the OMB on January 9, 2006. This compendium of comments represent the submission from 14 members of the Risk Assessment Specialty Section (RASS) of the Society of Toxicology based on a request for comment from all Risk Assessment Specialty Section members and based on notes taken during the Risk Assessment Specialty Section business meeting held during the 2006 SOT Annual Meeting held in San Diego. Comments were solicited via an announcement to all members of RASS and this compendium has been reviewed and edited by the officers of RASS and SOT Council. Submitted comments were reviewed, organized by category, edited and transitional wording added if deemed necessary, but the wording is essentially that of the individual contributors with only minor modifications. No effort has been made to develop this as a consensus document and is not to be considered a SOT position paper, but rather should be viewed as an SOT Council Commentary for consideration by the OMB as the office works to finalize its Bulletin.

The stated purpose of the OMB document is "to enhance the technical quality and objectivity of risk assessments prepared by federal agencies by establishing uniform, minimum standards." The Society of Toxicology believes that transparent and accurate risk assessment standards are necessary for wise risk assessment decisions and we appreciate the opportunity to submit these comments.

We recognize that a peer review panel of the National Academies of Science will review the Proposed Risk Assessment Bulletin, as well as public and agency comments before a final Bulletin is released. Should there be a need for potential reviewer names or outside technical expertise, the SOT would be happy to assist.

Sincerely,
James A. Popp, SOT President
Michael L. Gargas, SOT Risk Assessment Specialty Section President

Comments on the "Proposed Risk Assessment Bulletin"
from the Office of Management and Budget
(Document released January 9, 2006)

Comments prepared on behalf of the
Society of Toxicology
by members of the
Risk Assessment Specialty Section
2 June 2006

Introduction

The U.S. Office of Management and Budget (OMB) has released a Proposed Bulletin on risk assessment for peer review and public comment. Along with this Bulletin, OMB has provided extensive supplementary information, including a discussion of the uses and types of risk assessments and an expanded explanation of the requirements of the Proposed Bulletin. In preparing our comments, we have focused on the apparent intent of the Proposed Bulletin, including the explanations in the supplementary information, rather than just the specific wording of the Proposed Bulletin itself. While we recognize that there will be a need for the affected agencies to assure that the language of the Bulletin is clear and consistent with the amplifications in the supplementary materials, our concern is for the potential impact of the Bulletin on the agencies' ability to conduct risk assessments in accordance with good science.

The stated purpose of the OMB document is: "to enhance the technical quality and objectivity of risk assessments prepared by federal agencies by establishing uniform, minimum standards." The Bulletin is being issued pursuant, in part, to OMB's responsibilities under the Information Quality Act to "provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility,

and integrity of information" disseminated by the agencies. OMB identifies six standards that apply to all risk assessments:

1. A risk assessment should clearly state the informational needs driving the assessment as well as the objectives of the assessment
2. Every risk assessment should clearly summarize the scope of the assessment, the hazard of concern, the affected entities, the relevant exposure scenarios, and the dose-response relationship for the relevant exposure ranges
3. Every risk assessment should provide a characterization of risk, qualitatively and, whenever possible, quantitatively. When a quantitative characterization of risk is provided, a range of plausible risk estimates should be provided.
4. Risk assessments must be scientifically objective, neither minimizing nor exaggerating the nature and magnitude of the risks. They should use the best available data and should be based on the weight of the available scientific evidence.
5. Risk assessments should explain the basis of each critical assumption and those assumptions that affect the key findings of the risk assessment. Whenever possible, a quantitative evaluation of reasonable alternative assumptions should be provided.
6. Every risk assessment should contain an executive summary that discloses the objectives and scope, the key findings of the assessment, the key scientific limitations and uncertainties in the risk assessment, and a context/perspective for the risks.

In the context of standard number three, the Proposed Bulletin extends to all risk assessments a requirement from the 1996 amendments to the Safe Drinking Water Act, to specify to the extent possible:

- The expected risk or central estimate of risk for the affected populations
- Each appropriate upper-bound or lower-bound estimate of risk
- Studies that would assist in resolving the uncertainties identified in the assessment

- The methodology used to reconcile inconsistencies in the available scientific data

An additional standard is specified for risk assessments that will support regulatory analysis. To a large extent, the additional requirements of this standard relate to information required to support decision-making and cost-benefit comparisons.

More stringent standards are specified for influential risk assessments (those having a clear and substantial impact on important public policies or private sector decisions):

- Capable of being substantially reproduced by an external expert
- Comparison with previously conducted risk assessments on the same topic
- Providing central estimates as well as high-end and low-end estimates of risk
- Quantitative uncertainty analysis and sensitivity analysis
- Discussion of alternative theories, data, studies, and assessments
- Characterization of variability of risk
- Characterization of the adversity of effects on which the assessment is based
- Discussion of research that could resolve key scientific limitations/uncertainties
- Consideration of external comments

The Proposed Bulletin also specifies that agencies should have in place procedures to ensure it is aware of new, relevant information that might alter a previously conducted influential risk assessment, and that the need for revision of the assessment is considered.

The supplementary information accompanying the Proposed Bulletin described the wide variety of uses, types, and scopes of risk assessments, and acknowledges that a rule of reason should prevail in the appropriate application of the standards in the Proposed Bulletin. For example, in a screening assessment it might be appropriate to provide only a conservative (e.g., plausible worst-case) estimate of risk. However, some requirements (e.g., transparency, characterization of uncertainty) should be met by all risk assessments.

What follows are a compendium of comments received from fourteen members of the Risk Assessment Specialty Section (RASS) of the Society of Toxicology (SOT). These comments also include the notes of one RASS member taken during the presentations given on the OMB Bulletin during the RASS Business Meeting held during the 2006 SOT meeting in San Diego, California. Comments were solicited via an announcement to all members of RASS and this compendium has been reviewed and edited by the officers of RASS and SOT Council. Submitted comments were reviewed, organized by category, edited and transitional wording added if deemed necessary, but the wording is essentially that of the individual contributors with only minor modifications. No effort has been made to develop this as a consensus document and is not to be considered a SOT position paper, but rather should be viewed as an SOT Council Commentary for consideration by the OMB as the office works to finalize its Bulletin.

General Comments

Most contributors to these comments indicated that in general the Proposed Bulletin was comprehensive and clearly written with adequate detail. It was also indicated that the Proposed Bulletin appropriately sets a high standard for risk assessments, a standard that probably has never been fully achieved. Also, and perhaps obviously, it should be stated that considerably more resources and time would likely need to be allocated to conduct adequate risk assessments. Another commenter thought that, given some of the recommendations, the proposal had not been fully evaluated by scientists practicing risk assessment.

From the viewpoint of insuring the incorporation of as much scientifically grounded information as possible into risk assessments, the OMB Proposed Bulletin appears to represent an important step forward. In a general sense, the desired characteristics of risk assessments specified in the Proposed Bulletin, such as quality, objectivity, transparency, and utility, are already requirements of agency policies, particularly in response to the requirements of the Information Quality Act. Many of these issues are noted in the two National Academy of Sciences books on risk assessment. The important contribution of

the OMB Proposed Bulletin is to provide a more detailed description of the specific attributes of risk assessments that set the bar for minimal expectations. A number of these attributes will increase the likelihood of the incorporation of good science in risk assessment. In particular, the emphasis of the Bulletin on the use of the best available science and the identification of assessment-specific research needs would provide a valuable impetus for the development and application of new scientific data in risk assessments.

On the other hand, some of the required elements of risk assessments specified in the OMB Proposed Bulletin represent a significant departure from current practice, and implementing these new requirements may present a serious challenge to the affected agencies. Particularly noteworthy is the specification that risk assessments should present a central estimate of risk. While central estimates of risk would clearly be of great value for decision analysis and cost-benefit comparisons, some additional specific guidance needs to be offered about how these should be calculated as there is currently no generally accepted approach for how to offer such central risk estimates. This is not to say that they cannot be offered, but rather some guidance about the various methods that should be pursued deserves to be developed.

Other general comments as received from multiple commenters include:

- The requirement for an extensive risk appraisal implied that virtually anything could be used safely, and therefore could be registered for use, because of uncertainty inherent in risk assessment. This seems to be getting close to risk management, despite the statement to the contrary on page 3 of the Bulletin.
- There was considerable repetition of essentially identical concepts in different parts of the guidelines. There is a significant need for editing to ensure that key points are not lost.
- One commenter indicated there was little distinction between different toxicological endpoints, such as cancer vs. non-cancer, which will generally require different approaches in the risk assessment methods.

- Another commenter, on the other hand, encouraged OMB to strive for harmonization of cancer and non-cancer risk assessments and pointed out that there should be more similarity in the way cancer and non-cancer endpoints are evaluated.
- The OMB seems to want to limit these guidelines to "significant risk assessments". It is suggested that these guidelines apply to all risk assessments, especially in regard to the quantification of population risks. The USEPA has seemed reluctant to do this in the past for CERCLA risk assessments, but this is important because it can help provide a measure of the level of effort really necessary for a remedial action. If only a fraction of a person is going to be protected by a removal action for example, then it might be wise to consider "capping" instead of a more costly approach that does not help that much.
- Over time, different expectations regarding the thoroughness of risk assessments should be related to the size of the exposed population, the severity of the risk, and the relative importance of the hazard vs. others.
- OMB did an excellent job of portraying various aspects of the risk assessment process that should also aid in transparency.
- The comprehensive nature of the guidance is laudable, but this is detracted by the lack of definition and prioritization for implementation of the guidance.
- It is very difficult to understand the degree of flexibility intended by the guidance. There are vast implications in this that come down to nuances of interpretation as currently written.
- There is no guidance on what to do when data are lacking.
- The guidance appears to exempt all pesticides and the FDA regulatory process.
- The role of mechanistic information and models to help integrate diverse databases are ignored despite recent emphasis in the scientific arena.

Additional comments are provided below, separated into (1) those relating to the potential positive benefits of the OMB Proposed Bulletin with regard to fostering the use of good science in risk assessment, (2) those relating to the possible scientific challenges associated with implementing the requirements of the Bulletin, and (3) some specific suggestions.

Benefits

Overall, the development of uniform guidance for risk assessment such as proposed by OMB is supported by the majority of the commenters. Such guidance, when refined and finalized has the opportunity to formalize the implementation of commonly used risk assessment principles, promote a series of best practices, and improve the harmonization of risk assessments. Achieving these objectives will strengthen the scientific underpinnings of risk assessment. Much of the proposal as laid out in the Supplementary Information and more briefly in the Bulletin itself is very consistent with evolving practice in risk assessment. Many of the general principles outlined relate to increased transparency, clarity, and balance in presenting scientific conclusions or enhanced communication with users of the assessments. These are well-accepted principles in current risk methods guidance, including in US EPA's Risk Characterization Guidelines (US EPA, 2000), recommendations of the Commission of Risk Assessment and Risk Management (CRARM, 1997), and the principles described by the National Academy of Sciences (NAS, 1983, 1994). These basic principles are endorsed and the proposal is supported to promote their implementation throughout the federal government. When OMB revises this Bulletin, they would do well to evaluate suggestions for conducting risk assessments that have been proposed by other countries since some of these suggestions reinforce issues that appear to be of concern to the OMB.

Use of Best Available Science

The OMB Proposed Bulletin specifies that all risk assessments should use the best available data and be based on the weight of the available scientific evidence. It extends to all risk assessments the SDWA Amendments of 1996 requirement to use "(i) the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and (ii) data collected by acceptable methods or best available methods".

Identification of Research Needs

The OMB Proposed Bulletin extends to all risk assessments the requirement in the SDWA Amendments of 1996 to specify each significant uncertainty identified in the process of the assessment and to identify the studies that would assist in resolving the uncertainty. Identifying the specific studies considered of value to the risk assessors should be of help to researchers in their design of studies that could have an impact on decisions affecting the protection of human health, and should provide an impetus for funding of important research.

Consideration of New Data

The OMB Proposed Bulletin specifies that agencies should have in place procedures to ensure they are aware of new, relevant information that might alter a previously conducted influential risk assessment, and that the need for revision of the assessment is considered. This requirement would provide an important stimulus for undertaking research that could impact risk assessment.

Challenges

The input from several commenters was grouped into the specific sections that follow. Comments that did not seem to fit in a particular category are simply grouped under "*Other Challenges*" for completeness.

Central Estimates of Risk

The OMB Proposed Bulletin specifies that risk assessments should provide a central, or expected, estimate of risk. Central estimates of risk would clearly be of great value for decision analysis and cost-benefit comparisons; however, it is not certain how, using presently available science, a central estimate of risk could, in general, be determined. As an example of this issue, one commenter attempted to address central estimates of risk for chloroform liver carcinogenicity. In this example, the alternative risk estimates would be limited to (1) a low-dose linear potency estimate (assuming a genotoxic mode of action) and (2) a determination that the margin of exposure between a dose associated with 10% incidence of tumors in animals and the reference dose for noncancer effects was acceptable (assuming a non-genotoxic mode of action). The latter approach does not actually provide a quantitative risk estimate; it only suggests a dose below which risks are considered negligible. The determination of a central estimate of risk from these two disparate approaches would seem to be highly problematic.

The OMB Proposed Bulletin suggests the use of formal probability analysis with expert elicitation to obtain a weighted average of risk results from alternative models, but the use of such an approach is highly controversial and has not yet been generally accepted by the scientific community. A good deal of research and evaluation will probably be necessary before generally accepted approaches for determining central estimates of risk become available. Having said this, it is suggested that perhaps OMB should convene a special science panel, symposia or workshop where a minimum (and perhaps desired) set of approaches be recommended for estimating central tendency or the “best estimate”. Scientifically, requiring that a number of approaches be offered and justified should advance the objectives of the risk assessment process.

Another commenter believed the focus on a central estimate does not address important emerging issues such as susceptible populations (e.g., infants, children, elderly, compromised health status).

Definition of Risk Assessment

The definition of risk assessment in the Bulletin includes the determination of whether a potential hazard exists. As defined in the Red Book, this determination is a "hazard assessment", not a risk assessment. If this type of determination was indeed a risk assessment, then it would be hard to satisfy the general standards that are required in the Bulletin; e.g., determination of the affected populations...that are the subject of the assessment; the exposure/event scenarios....; and the type of event-consequence or dose-response relationship... Thus, it appears that either the "determination of whether a potential hazard exists" should be stricken from the definition or the definition of risk assessment be changed from its current form.

This same commenter noted that the part of the definition that states that risk assessment is a "scientific and/or technical document" does not correspond to current practice. Presently, the products of risk assessment include significant policy components in addition to scientific and technical considerations and it could well be argued that these policy judgments are paramount. For example, the "risk assessment" values published on IRIS explicitly include value judgments in the form of the multiple assumptions made as to: what studies to include, how to interpret these studies, and how to extrapolate these studies from animals to humans. Similar value judgments are included in carcinogenic "risk assessments." In light of this, the Bulletin should be explicit as to whether it is indeed proposing to replace (not just modify) current practice and, if so, exactly what the form of the replacement should be.

Another commenter indicated that risk assessment is ill defined - is the intention to apply guidance to address full-fledged risk assessment (e.g., comprehensive evaluation from exposure through benefit: cost valuation)? What about other types of risk assessments or

components, such as the following: Exposure assessment alone? Hazard ID or screening assessments alone? CDC biomarker results? In addition, this commenter indicated there is no guidance on integration of these components.

Non-carcinogen Risk Assessment

The most significant "risk assessment" value for quantitatively estimating the risk of adverse effects in humans from non-carcinogens is the RfD, which is defined as: "...an estimate (with an uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime." As can be seen from the definition, the RfD does not provide an estimate of risk; rather, it provides an exposure value that is "likely to be without appreciable risk". One commenter stated that since the term "appreciable risk" is not defined scientifically, there is no way to be scientifically objective about it and thus the RfD cannot be scientifically objective. In addition, examination of current practice reveals that RfDs contain a variety of assumptions that have not been established scientifically; e.g., that humans are more sensitive than the animals to adverse effects of all agents. Thus, it does not seem possible to carry out many of the prescriptions of the Bulletin; e.g., to be scientifically objective or to provide a quantitative evaluation of the assumptions or reasonable alternative assumptions within the RfD framework. As is the case with the definition of risk assessment, the Bulletin should be explicit if it is proposing to reject the current approach - and also be explicit in suggesting what should replace it. Another commenter indicated that although the harmonization of approaches to conducting cancer and non-cancer risk assessments has been discussed for nearly a decade, and this deserves to be mentioned here, much work needs to be done to achieve consensus on this matter.

Carcinogen Risk Assessment

There are two parts to carcinogen risk assessment. The first is the categorization of the risk into broad classes based on a qualitative assessment of the risk to humans and the use

of these categories to identify those agents for which more detailed quantitative assessments should be performed. One commenter stated that the classification system, although it has undergone significant revisions in recent years, is not based on a comprehensive scientific assessment of the evidence. For example, it does not include recognition of the influence of dose. As practiced it does not necessarily utilize a weight of evidence approach; rather a variety of triggers that can be used individually to assign an agent to a category. Further, it is based on the scientifically unproven assumption that any agent that causes cancer in the experimental animals will also cause it in humans. It is therefore not surprising that the names of the resulting categories; e.g., likely to be a human carcinogen" are not defined scientifically. This commenter stated that again, as is the case for the RfD as a measure of risk of non-carcinogens, it is not possible for this categorization to be scientifically objective.

The second part of carcinogen risk assessment is the quantitative estimation of the risk. For genotoxic carcinogens, the result of this exercise is the cancer potency factor, which by definition "is estimated as the 95% upper confidence limits of the slope of the dose response in the low dose region. This method provides an upper estimate of the risk; the actual risk may be significantly lower and may actually be zero. It is important to recognize that the use of this model results in risk estimates that are protective, but not predictive of cancer incidence." The commenter indicated that it is very clear from this definition that the methodology used in making this estimate is neither scientifically objective nor designed to provide best estimates of risk; rather it is designed to provide a risk estimate that includes a variety of value judgments. These value judgments are included in the assumptions as to what studies to use, what extrapolation method to apply and how to interpret the results of the extrapolation. Thus, as in the previous cases, it is not possible for this methodology to be scientifically objective.

Other Challenges

While there is general support of the guidance as proposed, a number of specific details in the Bulletin or in the Supplementary Information Section presented in the front matter

may have practical implications on how risk assessments are presented in the future, and should be carefully considered. For example, a major focus in the proposal is a more complete presentation of salient uncertainties. While such a presentation is already included in many comprehensive assessments, a broader discussion of alternative risk estimates, quantitative analysis of uncertainties, and ranges of risk values, will require additional detailed guidance for the risk managers on methods and implications for using such data presentations. Such guidance should include scientific methods for choosing among competing risk estimates and evaluating what may appear to be inflations in uncertainty rather than decreases in uncertainty with more information.

Few would not want to present intellectually honest assessments as suggested by the OMB guidance. However, increasing the complexity of risk assessment presentation in this way is already an issue in the context of questions that site managers have related to risk values presented as a range (or distribution) of values. Presentation of timely guidance and training on such issues will be essential for ensuring that implementation of the guidelines improves risk assessments, but does not slow progress in their development and use by risk managers.

In addition, potential interpretations of current methods or new requirements (at least in some risk assessment contexts) presented in the Proposed Bulletin need clarification before scientific comment on the intent of the language is possible. Two examples are noted here. The text on Page 20 regarding the use of mild effects, as the basis for risk estimates, needs further elucidation as many risk assessors would argue that the immediate precursor of an adverse effect could be a useful determinant of dose-response for protection of human health. This is consistent with EPA's definition of critical effect: the first adverse effect or its known, *and immediate,* precursor (italicized words added by former EPA author for clarity). A second example is the recommendation on page 20 that data gaps and research needs should be presented along with cost and feasibility for filling these gaps. The suggestion to address cost (and implications for identifying a specific research plan) will increase the scope of at least some types of assessments. Details on how such requirements should be implemented will be needed.

While there was general agreement among the commenters with the principle that uncertainty should be fully communicated, it is recommended that the Bulletin include technical guidance and a training component on use and interpretation of such data presentations to aid risk managers in the interpretation and appropriate application of risk assessments.

The Bulletin tends to focus on exposures to single agents or conditions. We generally are exposed to multiple agents and conditions that can influence the risk of adverse effects. Although a difficult issue, some more discussion is merited on exposures to mixtures or combinations of interacting factors, as well as, cumulative exposures as a function of age and duration of exposures.

Inasmuch as EPA risk assessments serve the purpose of identifying potential human exposures, below which the risk of adverse effects is unlikely to be increased, the next logical step in quantifying the impact of risk management decisions is to assign an economic value to the avoided illness/injury. When risk assessments include findings from human populations or groups, uncertainty in forecasting a likely adverse human health outcome is reduced as compared to such a forecast made solely on the basis of effects observed in studies with experimental animals. The inclusion of this forecasting of likely human effects and a statement of confidence in such in risk assessments may be of value.

It is apparent that the consideration of gene-environment (chemical) combinations as they relate to health effects is becoming increasingly important and deserves more discussion in the Bulletin.

The guidance does not capture the iterative process of performing preliminary risk assessment with subsequent reviews and refinements as requisite data emerge. Often a preliminary assessment will direct necessary research. This needs to be added to the guidance.

The guidance is too vague regarding expectations. This is particularly problematic when needing to set priorities for resources and regulatory agendas. Without establishing this context, this guidance could be used to delay and bring to a standstill the regulations required to protect the public health.

The discussion of designating "adverse" versus "adaptive" / "non-adverse" is too skeletal and needs to be expanded within the Bulletin. Functional impairment was not covered nor was the role of precursor lesions, both of which need to be added to the Bulletin.

Specific Suggestions

Page 6, 3rd paragraph, last sentence. Remove the word "precise".

Page 6, 4th paragraph, last sentence. After developed insert "and are under modification".

Page 16, paragraph 5). Include the "median" as a central estimate.

Page 17, Section 3, 1st paragraph. Add: "However, if a high-end estimate of risk results in an acceptable level of risk, further analysis may not be necessary".

Page 20, 2nd paragraph. In the absence of a definition of an adverse effect, an abnormal effect (that may or may not always be adverse) may be identified by examining the observed extreme effect levels (e.g., 1st and 99th percentile) in the general population, subpopulation, or control group not exposed to the agent in question. Then, at least, a risk assessment can be performed for the occurrence of abnormal effects.

Summary Statements Made By Commenters

One commenter noted that currently, the aim of risk assessment is not the estimation of risk but rather the generation of values that can be used for risk management. As such, risk calculations include "conservative" assumptions that have not been scientifically validated. Most of the discussions about improving risk assessment have implicitly accepted this and involve tweaking the current system to provide a somewhat better estimate of risk. If the prescriptions included in the Bulletin under discussion are taken seriously and adopted, then risk assessment would have to be radically changed from its current state. This is something that should be explicitly stated in the Bulletin and it should be recognized that the Bulletin does not provide anything but the barest framework for what a new risk assessment paradigm might be. In the view of this commenter, this is an appropriate time to start a discussion of a new framework and so the main value of this document may be to catalyze the beginning of such discussions.

The majority of the contributors to this document support the development of uniform federal guidance for risk assessment such as that proposed by OMB. Such guidance, when refined and finalized, will formalize the implementation of commonly used risk assessment principles, promote best practices, and improve the harmonization of risk assessments. Achieving these objectives will strengthen the scientific underpinnings of risk assessment in the federal government.

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The list of references that follow not only include those cited in this document, but also a list of additional references provided by two of our commenters that we believe would be useful to the OMB as they strive to finalize the Bulletin.

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