

Center for Regulatory Effectiveness

1601 Connecticut Ave, NW – Suite 500

Washington, DC 20009

Tel: (202) 265-2383 Fax: (202) 939-6969

www.TheCRE.com secretary1@mbsdc.com

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Stephen F. Sundlof, DVM, Ph.D.
Director, Center for Food Safety and
Applied Nutrition
U.S. Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Dear Dr. Sundlof:

We are concerned that the peer review of the draft FDA risk assessment for bisphenol A currently being conducted by the BPA Subcommittee of the FDA Science Board does not comply with the explicit peer review requirements of the OMB and HHS information quality guidelines. In brief, those deficiencies, which are explained further in the accompanying white paper, are:

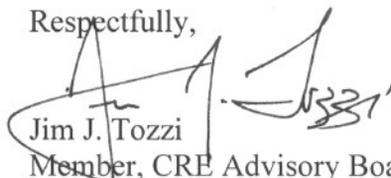
- The charge to the BPA Subcommittee does not comply with the requirements for peer review charges specified in the information quality guidelines.
- There is no indication that the Subcommittee members have been informed of the relevant quality standards of the information quality Act and guidelines, as required.

As we note in the attached paper, these are binding requirements, and the agency would be foreclosed from taking any regulatory action based on its risk assessment unless it can certify that it has complied with those requirements.

Because the Subcommittee is actively engaged in its review, and is expected to report its views to the Science Board at its October 31 meeting, we hope that these deficiencies will be corrected very expeditiously.

Thank you for your attention to this matter.

Respectfully,


Jim J. Tozzi
Member, CRE Advisory Board

Attachment

cc w. attach: Laura M. Tarantino, Ph.D.
Frank M. Torti, M.D., MPH
Martin Philbert, Ph.D.
Barbara J. McNeil, M.D., Ph.D.
Carlos Peña, Ph.D., MS

**Applicability of the Data (Information) Quality Act Guidelines
To Peer Review of FDA's BPA Risk Assessment:
Deficiencies in the Charge to the BPA Subcommittee**

The FDA risk assessment for bisphenol A is subject to the Data (Information) Quality Act ("DQA"), the IQA guidelines promulgated by OMB and the HHS and FDA IQA guidelines promulgated to conform to the OMB guidelines.¹ Those guidelines cover both agency information disseminations in general, and agency "pre-dissemination review" to ensure compliance with the guidelines.

The applicability of the DQA and its guidelines to the BPA risk assessment and the Subcommittee peer review was recognized explicitly in the FDA slide presentation at the September 16, 2008 public hearing held by the FDA Science Board's Bisphenol A Subcommittee. The third FDA slide, immediately after the "Outline" slide², states:

The information in the draft assessment has been distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines.

Such a statement is specifically required by the IQA peer review guidelines. 70 Fed. Reg. 2664, 2674 3d col. (Jan. 14, 2005).

The data quality guidelines also require that when an agency takes regulatory action based on scientific information such as a risk assessment, an agency must certify that it has complied with the DQA (IQA) and its peer review guidance, and place in the administrative record relevant materials demonstrating compliance:

Section VII: Certification in the Administrative Record

If an agency relies on influential scientific information or a highly influential scientific assessment subject to the requirements of this Bulletin to support a regulatory action, the agency shall include in the administrative record for that action a certification explaining how the agency has complied with the requirements of this Bulletin and the Information Quality Act. Relevant materials are to be placed in the administrative record.

70 Fed. Reg. at 2677 1st col. There can be no doubt that the final FDA BPA risk assessment will be either "influential" scientific information or a "highly influential" scientific assessment.

¹ The Paperwork Reduction Act of 1995 ("PRA"), which the IQA implements, states that agencies "shall be responsible for . . . complying with the requirements of this subchapter and related policies established by the Director [of OMB]." 44 U.S.C. § 3506(a)(1)(B). The text of the IQA can be found as a note to section 3516 of the PRA, 44 U.S.C. § 3516.

² Available at <http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-0038s1-01.pdf>. The OMB government-wide general information quality guidelines were published at 67 Fed. Reg. 8452 (Feb. 22, 2002). The pre-dissemination review requirement is at 67 Fed. Reg. 8459.

Accordingly, FDA will not be able to take any regulatory action on BPA unless it can certify compliance with the peer review guidance and other requirements of the IQA.

As explained below, the FDA charge, and other information provided, to the BPA Subcommittee does not currently comply with the information quality peer review guidelines, and therefore FDA could not make such a certification unless it corrects those deficiencies.

Deficiencies in the charge and other information given to the BPA Subcommittee

At its September 16, 2008, public hearing, a number of commenters urged the Subcommittee to factor into its peer review a sufficient degree of "precaution," or to follow the "precautionary principle." The IQA peer review guidance expressly prohibits peer reviewers from injecting any such conservative bias into their review, and the guidance requires the agency to include in its charge to the peer reviewers instructions against injecting policy into their review and to inform the reviewers of all pertinent IQA guidance requirements. The OMB peer review guidance states:

Peer reviewers **shall be charged** with reviewing scientific and technical matters, leaving policy determinations for the agency. Reviewers **shall be informed** of applicable access, objectivity, reproducibility and other quality standards under the federal laws governing information access and quality.

70 Fed. Reg. 2675 2d col. This requirement for the charge is explained more fully in the preamble to the IQA peer review guidance as requiring peer reviewers to exclude any judgments regarding uncertainty factors or precaution:

[T]he charge should make clear that the reviewers are not to provide advice on the policy (*e.g.*, **the amount of uncertainty that is acceptable or the amount of precaution that should be embedded in an analysis**). Such considerations are the purview of the government.

70 Fed. Reg. at 2669 (emphasis added; footnote omitted).

The charge that FDA gave to the BPA peer reviewers does not contain these required instructions on not injecting policy considerations, such as the acceptable amount of uncertainty or the use of precaution. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-0038b1_01_01_Charge%20to%20the%20Subcommittee.pdf. There is also no indication in the public administrative record that the Subcommittee³ was informed of other relevant IQA guidance such as its definitions of "objectivity" and "utility", the applicability of the IQA standards to "third-party" information on which the agency might rely, or the "reproducibility" requirement for influential scientific information. These omission must be corrected as soon as possible to enable the agency to certify compliance with the IQA guidance in any regulatory decision it might make.

³ The peer review guidance applies not only to the BPA Subcommittee, but also to the Science Board when it conducts its review.

Applicable IQA quality standards

"objectivity"

"Objectivity" is one of the basic IQA standards for agency and "third-party" information. The OMB definition is mirrored in the HHS guidelines. As described in the HHS IQA guidelines, the "objectivity" standard "involves a focus on ensuring that information is accurate, reliable, and unbiased and that information products are presented in an accurate, clear, complete, and unbiased manner. Objectivity is achieved by using reliable data sources and sound analytical techniques, and carefully reviewing information products prepared by qualified people using proven methods."⁴ Prior peer review is regarded as raising a rebuttable presumption of objectivity, but it is recognized that journal peer review is not always adequate and a substitute for more rigorous and transparent peer review.⁵

"utility"

This means simply that the information is suitable for its intended purpose. Thus, if the purpose is to produce a quantitative risk assessment, the information must be suitable for use in a quantitative risk assessment. For example, if *in vitro* or animal studies cannot be determined to have relevance for an assessment of human risk, or they are inconsistent with similar studies, they might lack sufficient utility.

"reproducibility"

In the case of "influential" scientific information -- that which is likely to have a clear and substantial impact on important public policies or important private sector decisions -- there must be "sufficient transparency about data and methods that an independent reanalysis could be undertaken by a qualified member of the public." This "reproducibility" requirement, means that, as a result of sufficient transparency about data and methods, "the information is capable of being substantially reproduced, subject to an acceptable degree of imprecision."⁶

"third-party information"

The OMB government-wide information quality guidelines cover not only information developed by an agency, but also third-party information relied on or used by an agency when it disseminates information. Thus, if the agency were to rely on and use any of the studies other than the Tyl et al. studies that various commenters urged the Subcommittee and the agency to

⁴ Sec. D.4.d. See also sec. D.2.c. An example of bias is the use of the term "endocrine disruptor" by some commenters. That terminology is biased because it assumes that *a priori* that a substance "disrupts" the endocrine system, implying that a relevant adverse effect has been determined. The term "hormonally active agent [or substance]" employed by FDA during the hearing avoids that *a priori* bias.

⁵ The OMB guidelines recognize that journal peer review is not always adequate and is not transparent. Journal articles are often published based on whether they are interesting or might add to a developing data base, not because they are deemed to be reliable and useful by themselves. See 67 Fed. Reg. at 8455.

⁶ 67 Fed. Reg. at 8460 1st & 3d cols.

consider and incorporate, those studies must meet IQA guidance standards for objectivity, utility, and reproducibility.

In the preamble explaining its final government-wide guidelines of Feb. 22, 2002, OMB explained that "if an agency, as an institution, disseminates information prepared by an outside party in a manner that reasonably suggests that the agency agrees with the information, this appearance of having the information represent agency views makes agency dissemination of the information subject to these guidelines" 67 Fed. Reg. 8454. Several months later, in reviewing the agency-specific guidelines, OMB further explained how the IQA guidelines covered "third-party" information relied upon by an agency in a rulemaking, using the draft Department of Transportation guidelines as an example:

DOT incorporated these principles from the OMB guidelines by stating that an agency disseminates information if it relies on information in support of a rulemaking. "If the Department is to rely on technical, scientific, or economic information submitted by, for example, a commenter to a proposed rule, that information would need to meet appropriate standards of objectivity and utility" (DOT, 3). "The standards of these guidelines apply not only to information that DOT generates, but also to information that other parties provide to DOT, if the other parties seek to have the Department rely upon or disseminate this information or the Department decides to do so" (DOT, 8). . . . Other agencies – particularly those likely to be involved with using and/or disseminating "influential" information – must include similar provisions in their guidelines.⁷

Issues regarding the IQA quality of third-party studies raised during the hearing

During the September 16 public hearing, FDA and NTP scientists raised a number of concerns regarding the quality, reproducibility, and utility of many of the third-party studies that some NGO commenters argued the agency and the Subcommittee should rely on.

As FDA stated at the public hearing, its draft relies principally on the two Tyl et al. multi-generation rodent studies because the agency regards them as the best available data. The agency also made clear that it had reviewed the hundreds of other studies on BPA, and it had evaluated them as being of lower, or lacking, quality and utility.

For example, the FDA and NTP presenters noted the following with regard to the studies other than the two Tyl et al. studies:

- The animal studies involving a non-oral route of administration were of limited utility for human risk assessment due to the differences in metabolism and insufficient information. Hearing DVD at 40:30 - 43:00.

⁷ *Memorandum for the President's Management Council*, June 10, 2002, on "Agency Draft Information Quality Guidelines," from John D. Graham, Administrator of OMB's Office of Information and Regulatory Affairs, at 6-7 of Attachment. http://www.whitehouse.gov/omb/inforeg/iqg_comments.pdf.

- Many of the studies were intended only to generate discussion or to make recommendations for additional research, not for the purpose of being used in quantitative risk assessment. 4:20.
- The studies on prostate development in animals were of questionable utility. 48:00. It is unclear whether prostate PIN lesions are relevant to human risk assessment because it is unclear whether they progress to cancer. 1:29.
- The neurobehavioral studies were difficult to interpret and lacked consistency. 49:00. It was difficult to evaluate their reproducibility and relevance (utility) for human risk assessment. 1:26.
- Many of the studies were not useful for quantitative risk assessment and were only useful for hazard identification screening purposes. 1:07, 1:21.
- The data on mammary gland development had many limitations. 1:30.
- The mouse puberty studies were inconsistent. 1:32.

The IQA requirement for use of the "best available" scientific evidence, not all evidence

A number of public commenters at the September 16 public hearing held by the BPA Subcommittee appeared to argue that the Subcommittee must give some weight to all BPA studies in weighing the evidence in support of the FDA draft assessment, regardless of their quality or utility for quantitative human health risk assessment. This appears to be a suggestion that an evaluative approach must be somehow quantitative rather than qualitative -- *i.e.*, counting or considering numbers of studies rather than weighing based on quality. Such a view is contrary to the IQA guidance, which requires agencies to use the "best available scientific data", not all data regardless of its quality and utility.

The OMB IQA guidelines required agencies to either adopt or adapt the risk assessment principles specified in the Safe Drinking Water Act ("SDWA").⁸ The SDWA risk assessment principles require use of the "best available" science, not use of all available data. The HHS IQA guidelines, in following the OMB and SDWA requirements, state that HHS agencies will use "a.) the **best available** science and supporting studies conducted in accordance with sound and objective scientific practices, including peer reviewed studies when available and b.) data collected by accepted methods (if reliability of the method and nature of the decision justify use of the data.)" Sec. d.g. (emphasis added).⁹ The OMB/OSTP risk assessment principles, promulgated to complement the other IQA guidelines, also require use of the "best reasonably obtainable scientific information."¹⁰

⁸ 67 Fed. Reg. 8460 2d col.

⁹ See also sec. VII, C of the FDA guidelines. <http://aspe.hhs.gov/infoquality/Guidelines/fda.shtml>.

¹⁰ <http://www.whitehouse.gov/omb/memoranda/fy2007/m07-24.pdf>, at 5.

The term "weight of the evidence" was invoked or mentioned a number of times during the public hearing. Because the agency must use the "best available science," not all science regardless of quality and utility, this term has a qualitative, rather than quantitative, meaning.

In view of the many comments on this subject at the public hearing, it would be advisable for the BPA Subcommittee and Science Board to state specifically that they recognize that FDA must use the "best available" data, not all data regardless of quality and utility, and that the peer reviews are likewise based on this approach.