Patricia Kablach Casano
Senior Counsel - Environmental
Corporate Environmental Programs

GE
1299 Pennsylvania Avenue, NW
Suite 900
Washington, DC 20004-2407
T 202-637-4228
F 202-637-4414
pat.casano@ge.com

June 11, 2013

Dr. Andrew Rooney
Deputy Director,
OHAT, Division of NTP, NIEHS
P.O. Box 1223,
K2-04
Research Triangle Park, NC 27709
Andrew.rooney@nih.gov

Re: Draft Office of Health Assessment and Translation Approach for Systematic Review and Evidence Integration for Literature-Based Health Assessments – February 2013, 78 Fed. Reg. 12764 (Feb. 25, 2013)

Dear Dr. Rooney:

The General Electric Company (GE) appreciates the opportunity to comment on the Draft Office of Health Assessment and Translation (OHAT) Approach for Systematic Review and Evidence Integration for Literature-Based Health Assessments – February 2013 ("Draft Approach"). We offer these comments in support of OHAT's mission to adopt systematic review procedures in order "to assess the evidence that environmental chemicals, physical substances, or mixtures (collectively referred to as "substances") cause adverse health effects and provide[] opinions on whether these substances may be of concern given what is known about current human exposure levels."[1]

GE supports OHAT's effort to adopt systematic review procedures for its evaluations of the human health effects of substances. We are concerned, however, that OHAT's articulated goal for the use of such procedures is too narrow, and the Draft Approach too generic, to prevent or reduce the scientific controversy that too often accompanies such evaluations.

The Goal of Systematic Review Should Be To Enhance the Quality, Objectivity, Utility and Integrity of OHAT's Evaluations As Well As Their Transparency

OHAT's goal in adopting systematic review procedures appears to be limited to "enhanc[ing] transparency for reaching and communicating evidence assessment conclusions." Draft

[1] Health Assessment and Translation. June 7, 2013. http://ntp.niehs.nih.gov/?objectid=497C419D-E834-6835-8AF15D389859AF07.

Approach, p. 1. While enhancing transparency is a laudable goal, it should not be, and cannot be, the only goal. Instead, the focus on enhancing transparency should be matched by an equal focus on "ensuring and maximizing the quality, objectivity, utility and integrity of" NTP's hazard evaluations. This broader goal is dictated by the Information Quality Act (IQA)[2] and the implementing guidelines issued by the Office of Management and Budget, the Department of Health and Human Services, and the National Institutes of Health. Quality, objectivity, utility and integrity should be given weight and expression throughout the Draft Approach and the protocols used to implement that Approach.

Congress enacted the IQA to "ensur[e,] and maximiz[e,] the quality, objectivity, utility and integrity of information . . . disseminated by Federal agencies."[3] To that end, Congress required the Office of Management & Budget (OMB) to issue government-wide implementing guidance.[4] Congress also instructed each agency to issue its own guidelines.[5]

Pursuant to the IQA, HHS has issued department-wide information quality guidelines,[6] and NIH has issued its own agency-specific guidelines.[7] NTP's hazard evaluations must comport with the OMB, HHS and NIH guidelines.

OMB's Guidelines require all disseminations to meet "a basic standard of quality . . . appropriate to the nature and timeliness of the information."[8] "Quality" is defined in terms of objectivity, utility and integrity.[9] "Objectivity" is critically important in cases of scientific health assessments such as OHAT's hazard evaluations, and encompasses both the substance of the information and the way it is presented. "Utility" also is important, as it refers to the usefulness of the information for its intended users, including the public.

1. Objectivity

Insofar as the substance of information is concerned, "objectivity" means that information must be accurate, reliable and unbiased.[10] Scientific information must be generated using sound statistical and research methods.[11] "Influential" scientific information must be sufficiently transparent to be reproduced, subject to several caveats.[12] Agencies must provide "sufficient transparency about

---

[2] Pub. L. No. 106-554, § 515, 114 Stat. 2763A-153 to 2763A-154, 44 U.S.C. § 3516 note (2000).
[3] Id. at § 515(a).
[4] Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, 67 Fed. Reg. 8452 (Feb. 22, 2002).
[5] Pub. L. No. 106-554, supra note 1, at § 515(b)(2)(B) (emphasis added).
[6] HHS, Guidelines for Ensuring the Quality of Information Disseminated to the Public, available at http://aspe.hhs.gov/infoQuality/Guidelines/index.shtml .
[7] NIH, Guidelines for Ensuring the Quality of Information Disseminated to the Public, available at http://aspe.hhs.gov/infoquality/Guidelines/NIHinfo2.shtml.
[8] 67 Fed. Reg. at 8458.
[9] Id. at 8459.
[10] Id. (emphasis added).
[11] Id.
[12] Id. at 8460.

data and methods that an independent reanalysis could be undertaken by a qualified member of the public."[13]

Insofar as the presentation of information is concerned, "objectivity" means that information must be presented in an accurate, clear, complete and unbiased manner in the proper context.[14] The sources of the information must be disclosed subject to confidentiality and privacy limits, and data should have full, accurate and transparent documentation, with sources of error identified and disclosed to users.[15] Scientific, financial and statistical information must be accompanied by supporting data and models.[16]

In addition to these requirements, influential scientific information that is used to analyze risks to human health or the environment must meet the standard for risk assessments adopted by Congress in the Safe Drinking Water Act of 1996.[17] Under that standard, OHAT must ensure that the information that it disseminates is based on "(i) the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices and (ii) data collected by accepted methods or best available methods." 42 U.S.C. § 300g-1(b)(3)(A). In carrying out that mandate, OHAT must ensure that "the presentation of information on public health effects is comprehensive, informative and understandable. [OHAT] shall . . specify . . . to the extent practicable . . . (v) peer-reviewed studies known to [OHAT] that support, are directly relevant to, or *fail to support* any estimate of public health effects and the methodology used to reconcile inconsistencies in the scientific data." 42 U.S.C. § 300g-1(b)(3)(B)(emphasis added).

OHAT's evaluations of substances "can lead to NTP opinions on whether these substances may be of concern given what is known about current human exposure levels."[18] The output from an evaluation can include, but is not limited to, NTP Monographs, state-of-the-science workshop reports, or peer-reviewed journal publications.[19] Clearly, OHAT's evaluations are influential information.

2. Utility

As defined in the OMB Guidelines --

> 2. "Utility" refers to the usefulness of the information to its intended users, including the public. In assessing the usefulness of information that the agency disseminates to the public, the agency needs to consider the uses of the information not only from the perspective of the agency but also from the perspective of the public. As a result, when transparency of information is relevant for assessing the information's usefulness from the public's perspective, the agency must take care to ensure that transparency has been addressed in its review of the information.

67 Fed. Reg. at 8459. In the context of OHAT's hazard evaluations, "utility" can be understood to mean information that provides a realistic assessment of the human health hazards that might result

---

[13] Id.
[14] 67 Fed. Reg. at 8459 (emphasis added).
[15] Id.
[16] Id.
[17] OMB Guidelines, 67 Fed. Reg. at 8460.
[18] About OHAT. June 7, 2013. http://www.niehs.nih.gov/research/atniehs/dntp/ohat/
[19] OHAT Implementation of Systematic Review. June 7, 2013. http://ntp.niehs.nih.gov/?objectid=960B6F03-A712-90CB-8856221E90EDA46E

from exposure to a chemical, such that the hazards are neither exaggerated nor minimized. Evaluations that exaggerate the hazards will lead to misdirected government resources and unnecessary public concern. Evaluations that inappropriately minimize the risk might lead to adverse human health effects.

Adoption of systematic review procedures will go a long way towards enabling OHAT to "ensure and maximize the quality, objectivity, utility and integrity" of OHAT's evaluations. In order to perform a systematic review, however, and to do so consistently across chemicals, OHAT needs to move beyond the Draft Approach, and develop a system that details the common procedures to be followed, information to be considered, and rules to be applied whenever OHAT evaluates the hazards of a chemical.

Systematic Review Requires More Than An Approach; It Requires A System

As the Draft Approach's name indicates, it is not a system; it is an approach. It provides a high-level, seven-step framework for conducting evaluations using principles of systematic review. The Draft Approach lacks the details needed to ensure that chemicals are evaluated consistently, and that the use of scientific judgment is limited to those situations where scientific judgment truly is necessary.

At least for the foreseeable future, it appears that the details of how to apply the Draft Approach are to be provided through protocols to be developed on a chemical-by-chemical basis, such as the Draft BPA and PFOA protocols. Though not perfect, those protocols contain the details that can constitute a system for reviewing and evaluating scientific evidence that can be applied to every chemical that OHAT evaluates. To fully embrace systematic review, instead of simply applying principles of systematic review, OHAT should combine the Draft BPA and PFOA protocols, substitute "Chemical of Interest" (or the equivalent) for the references to those specific chemicals, and substitute the resulting document for the current Draft Approach. That more detailed, systematic document (hereinafter, the "System") then can be used to guide and document OHAT's evaluations of BPA and other chemicals. Unless that is done, there will be ample opportunity for (1) inconsistency in the way that chemicals are evaluated, (2) significant duplication of effort in development of protocols, and (3) subjectivity to influence the outcome of the evaluation.

The Draft BPA Protocol's treatment of missing information provides an example of the need for more rules than the Draft Approach provides. The Draft BPA Protocol sets out a number of situations in which information needs to be obtained, but does not always state what the result will be if the information cannot be obtained. For instance, on p. 11, there is a heading -- "Missing Data" -- followed by a one sentence statement: "We will attempt to contact authors of included studies to obtain missing data considered important to summarize study findings (Table 2) or evaluate risk of bias." A parallel entry on page 18 under "Rules for non-reporting" does a more complete job: "When additional information is required to address an item that is not reported we will attempt to contact the corresponding author of the original reports to provide further details. If we are unable to obtain sufficient information to evaluate the risk of bias question, 'probably high risk of bias' will be used as the response except where indicated otherwise based on the guidance." To have a system, one needs rules that will be applied whenever information is not provided, and to have the exceptions to those rules carefully spelled out and justified. In the case of missing information, an increase in the risk of bias appears to be appropriate when data cannot be obtained.

We recognize that, for any given chemical, not all of the components of the System might apply, and factors not included in the System might be relevant. For example, the list of potential confounders to be considered in a review of Chemical X might be different from the list of potential confounders to

be considered in a review of Chemical Y. Both evaluations, however, can and should start with the same generic list of confounders. To the extent that confounders on the list are not relevant to a particular chemical, they can be deemed "not applicable". To the extent that additional confounders are relevant, they can be added. The System should recognize the potential need for, and permit, those types of adjustments, provided that they are justified appropriately. The need to make such adjustments, however, does not mean that all evaluations should not have the same detailed System as a starting point.

We turn now to the specific steps of the framework described in the Draft Approach.

Step 1: Prepare Topic

The Draft Approach provides that "the topic for the evaluation and the protocol are developed through an iterative process in which information is obtained by outreach to federal partners, use of technical experts as needed, comment from the public and consultation from the NTP Board of Scientific Counselors." Draft Approach at 1. This indicates that the public is to have an opportunity to provide input on the topics to be evaluated. If the public was invited to provide input on the topics to be considered for BPA and PFOA, we can find no record of it. NTP should make it clear that public input on the questions to be investigated should be solicited before a detailed protocol is developed for a specific chemical.

Step 2: Search for and Select Studies for Inclusion

In designing literature searches, OHAT should take into account publication bias. This well-known phenomenon favors publication of studies showing "positive" results – an association between the chemical and a biological effect – over those that do not. In risk assessments, the determination of the dose at which there is no observable effect is very important. OHAT needs to capture the results of research showing that, at given doses, a chemical has no effect on human or animal biological systems. Accordingly, the System should require reviewers to look for grants that were awarded to researchers who studied the chemical of interest, but did not publish any results. When such grants are identified, the System should require reviewers to contact the researchers and determine why they did not publish the results of their research. If the results were not published because the researchers did not find an association between the chemical and human health effects, that research should be included in the evaluation.

The public should be given the opportunity to provide input on the literature search strategy and the criteria for inclusion and exclusion of studies. The public also should be provided the opportunity to identify literature and other studies for consideration in the evaluation.

Step 3: Extract Data From Studies

Step 3 provides that "[r]elevant data are extracted from individual studies selected for inclusion using separate templates for human, animal and in vitro studies that are customized as needed for specific evaluations." Draft Approach at 2. This implies that there are generic templates that can be customized. If there are generic templates, they should be included in the final System. To the extent that "generic templates", per se, do not exist, they can be derived from the templates included in the draft BPA and PFOA protocols. These generic templates are an example of the elements needed to have a system for reviewing scientific evidence.

Step 4: Assessing the Quality of Individual Studies

We do not understand why OHAT would wait to assess the quality of studies until after OHAT has extracted data from the studies. Extracting data from studies that subsequently are determined not to be useful because they are of poor quality would be a complete waste of time and resources. ***Study quality should be assessed before data are extracted***, and data should be extracted only from studies that pass that initial screen. Another quality review should be conducted after the data are extracted to confirm that there is nothing in the data or the statistical analyses that generated the data that undercuts the initial conclusion that the study is of sufficient quality to be reliable.

In assessing study quality, OHAT's system should include the following steps:

1. The System Should Account For All Outcomes Measured

In ascertaining the quality of an individual study, one of the questions that OHAT will consider is whether the authors of the study reported all measured outcomes. Failure to report all measured outcomes is a reason to downgrade confidence in the results of the study.

It is important to know whether the authors of a study reported all measured outcomes in order to determine whether any positive findings were due to chance. For example, assume that a scientist who is investigating whether a chemical causes neurodevelopmental effects in rats performs 20 different tests on the treated rats and control rats. Assume also that he finds one association at the 95% confidence level, and reports that result, without reporting the results of the 19 tests that did not show an association. Having made 20 comparisons at the 95% confidence level, at least one association is likely to be spurious – the result of chance. Unless the reader knows how many tests were performed or comparisons made, he/she cannot make a fair judgment as to the value to give to the reported result. OHAT therefore needs to know how many comparisons a researcher made and what the results were in order to determine the likelihood that a reported association is real. Where multiple comparisons have been made, OHAT should consider the likelihood that an association reported in a study is due to chance.

Neither the Draft Approach nor the Draft Protocols for BPA and PFOA indicates how OHAT will determine whether the authors of a study reported all measured outcomes. Authors do not always report every test that they conducted, or every outcome that they measured. Unless an article explicitly states that the authors have reported all tests conducted and all measured outcomes, OHAT should contact the authors, ask them what tests they conducted and what outcomes they measured, and confirm (or not) that all outcomes that were measured were reported. If the researchers decline to provide this information, OHAT should not rely on the study.

2. The System Should Require Review of Original Data For Key Studies

With no falsification, there are a number of ways to present data that will affect its ultimate implications. Statistical treatment is the most obvious example. In one well-documented instance, NTP requested data from study authors in order to examine study quality. The NTP "used a unique and novel approach to evaluate the validity of [an] important and controversial environmental health issue [endocrine disruption]. Fifteen principal investigators of primary research groups active in this field were asked by the organizing committee to provide their individual animal data on selected parameters for independent statistical reanalysis by the statistics subpanel." Melnick et al., Summary of the National Toxicology Program's Report of the Endocrine Disruptors Low-Dose Peer Review, 110 Environmental Health Perspective 427 (2002). NTP found that its independent review of the

researchers' data "provide[d] greater insight on the experimental data than is typically apparent in most peer-reviewed research articles; consequently, the statisticians' report was critical for each of the subpanel reviews." Id. at 428. NTP's statistical analyses resulted in another paper that concluded: "[We] identified a number of important statistical considerations that must be addressed in the design, analysis, and interpretation of experimental studies. Increased awareness of these issues should reduce the frequency of problems such as those encountered in our reanalysis." Haseman et al., Statistical Issues in the Analysis of Low-Dose Endocrine Disruptor Data, 61 Toxicol. Sci. 201 (2001).

Understanding the importance of researchers' disparate statistical treatment of data was only possible because the researchers' data were independently analyzed. It is very important that the data on which human health risk assessments are based are verified by independent analysis. Accordingly, at least for the critical studies, OHAT should routinely ask that the data underlying published articles be made available to NTP and the public. OHAT then should examine the data and its characterization, and rely upon the reported results only when they are fully supported by the data.

3. The System Should Downgrade Confidence in Studies that Fail to Adjust or Control for Relevant Confounders

The draft Guidance for Assessing Risk of Bias in the BPA-Obesity Systematic Review states (at p. 10):

> It is understood in environmental health that people are exposed to complex mixtures of environmental contaminants and other types of exposures that make it difficult to establish chemical-specific associations. Thus, we will not penalize studies if other exposures are not adjusted or controlled for in most cases.

This truly is an astonishing statement. OHAT is saying, in essence, that even though it is entirely possible that another chemical or nonchemical stressor, or combination of stressors, caused an effect found in a study that shows an association between Chemical X and an effect, OHAT typically will treat the study as establishing an association between Chemical X and the effect. There is no scientific justification for that position; it most certainly should not be carried forward into the final Approach or BPA/PFOA Protocols. Studies that do not properly account for confounders should be considered, at best, as hypothesis-generating. They should not be relied upon as proof of an association, or combined with other similarly deficient studies to reach a conclusion that the body of evidence supports the association.

Step 5: Rate the Confidence in the Body of Evidence

This step identifies the factors to be considered in determining the level of confidence that a body of evidence establishes the true relationship, if any, between a chemical and a human health effect. After an initial confidence rating is determined, five factors are considered to downgrade confidence, and four specific factors are considered to upgrade confidence. The factors that might lead to a downgrade in confidence are risk of bias of the body of evidence; unexplained inconsistency; indirectness; imprecision and publication bias. The factors that might lead to an upgrade in confidence are large magnitude of effect; dose-response; all plausible confounding; and cross-species/population/study consistency.

The distinction between the factors that are used to downgrade confidence and those that are used to upgrade confidence appears to be artificial. For example, if a high risk of bias can be used to

downgrade confidence, a low risk of bias should be used to upgrade confidence. If evidence of dose-response can be used to upgrade confidence, lack of such evidence should be reason to downgrade confidence. If consideration of all plausible confounders can be used to upgrade confidence, then failure to consider plausible confounders should be used to downgrade confidence.

The artificial distinction between the factors used to upgrade and downgrade confidence should not be maintained. Instead, all of the factors listed above should be applied neutrally to evaluate the body of evidence.

Step 6: Translate Confidence Ratings into Level of Evidence for Health Effect

This portion of the Draft Approach essentially assumes that every chemical causes some adverse effect after some exposure ("Although the conclusions describe associations, a causal relationship is implied" (Draft Approach at 6)). While that might be true (e.g., even too much water can be toxic), whether a chemical will cause an adverse or positive human health effect depends upon the dose, the route and duration of exposure, and other factors. In many cases, an effect will occur only at doses well beyond the "current human exposures levels" that are of concern to OHAT. All of the confidence ratings for the various levels of health effects should be related to whether the effects are seen, or likely to be seen, at "current human exposure levels."

Step 7: Integrate the Evidence to Develop Hazard Identification Conclusions

As we have suggested for the confidence ratings described in Step 6, the hazard identification conclusions described in Step 7 should be related to whether the effects are seen, or likely to be seen, at "current human exposure levels." In addition, the fourth hazard identification conclusion category – "not classifiable or not identified to be a hazard to humans" – should be split into two: (1) Not identified to be a hazard to humans; and (2) insufficient evidence to determine whether a hazard to humans. The two categories are not equivalent, and therefore should be distinguished. "Not classifiable" does not tell the reader anything about the state of the evidence.

Conclusion

The draft Approach, in combination with the Draft Protocols for BPA and PFOA, can be used to develop a true system for evaluating the human health effects of chemicals that details the common procedures to be followed, information to be considered, and rules to be applied whenever OHAT evaluates the hazards of a chemical. Development and implementation of such a system will enable OHAT to ensure and maximize the quality, objectivity, utility, integrity and transparency of OHAT's literature-based health assessments.

We appreciate your consideration of these comments. Should you have any question regarding these comments, please contact me.

Sincerely,

[Redacted]

Patricia Kablach Casano