THE ENDOCRINE SOCIETY

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Dr. Andrew Rooney, Deputy Director
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Research Triangle Park, NC 27709

RE: Draft OHAT Approach for Systematic Review and Evidence Integration for Literature- Based Health Assessments—BPA exposure and obesity protocol

Submitted via email 06-12-13

Dear Dr. Rooney:

The Endocrine Society appreciates the opportunity to comment on the BPA exposure and obesity protocol proposed by the Office of Health Assessment and Translation (OHAT) of the National Toxicology Program (NTP). Founded in 1916, The Endocrine Society is the world's oldest, largest and most active organization devoted to research on hormones and the clinical practice of endocrinology. Today, The Endocrine Society's membership consists of over 16,000 scientists, physicians, educators, nurses and students in more than 100 countries. Society members represent all basic, applied and clinical interests in endocrinology. Among the Society's members are the world's leading experts in the field of endocrine disruption.

The Endocrine Society is pleased that the NTP has taken steps to improve its evaluation of candidate endocrine-disrupting chemicals (EDCs). The new framework and the proposed protocol to evaluate BPA and its potential link to obesity represent significant improvements over past processes to perform such evaluations; nonetheless, the protocol could benefit from relatively minor modifications, and its ultimate success will greatly depend on attention to detail during implementation. Given the long-term impact this archetypal protocol will likely have in the larger program, it is critical to minimize and correct any problems that might undermine the overall validity of the framework.

Endocrine Society experts have examined the BPA-obesity protocol, and we would like to offer both general and protocol-specific feedback. The former, which we address first, concerns general issues that pertain to both the current and future protocols that adopt the new framework.

<u>General comments</u>

We support the general goal of developing a framework that can be applied either by experts or by non-expert scientists with the same outcomes and conclusions. However, we are concerned that this goal will be very difficult to achieve in practice, particularly in a field as nuanced as

endocrine disruption. Therefore, it is of utmost importance to ensure that individuals with appropriate expertise are engaged and contribute to the analysis. If the selected individuals are also free of financial conflict of interest, they will be equipped to provide an informed and unbiased evaluation of all the relevant literature.

It is unclear from our reading of the framework itself and the BPA-obesity protocol whether the evaluation of study quality and relevance will rely on an independent assessment of the data in the literature or rather on the original authors' interpretation of the data as presented in their scientific publications. This distinction is critical and we suggest that the evaluation rely on an assessment of the data. Individuals engaged in the evaluation process should therefore possess sufficient expertise to evaluate study designs and interpret all data in the context of the larger body of scientific knowledge, rather than relying exclusively on the conclusions drawn by the original authors. Researchers deeply engaged in the study of endocrine effects have first-hand knowledge and understanding of how seemingly inconsequential experimental details can have measurable effects on study outcomes. Many of The Endocrine Society's members have the requisite expertise; we would value the opportunity to identify such individuals for your consideration.

<u>Protocol-specific comments</u>

The protocol is comprehensive and detailed, and we are encouraged by much of its content. For example, we support the approach to missing data described on page 11, wherein evaluation team members will approach authors to gather missing data rather than simply excluding studies on this basis. We also support the designation of "no downgrade" for routes of exposure other than oral, including dermal exposure, subcutaneous injection, and inhalation. Nonetheless, there remain points of potential concern, which we address below.

Dose response

The Endocrine Society supports the consideration and inclusion of non-monotonic dose responses, but this section of the protocol would benefit from revision. First, hormone actions are often non-linear and non-monotonic; therefore, the findings of non-linear or non-monotonic dose-responses of candidate EDCs should not, *a priori,* rule out the data for consideration for hazard identification or characterization. Moreover, many important endocrine questions that inform hazard identification will have three or fewer doses, which would preclude determination of the overall shape of the dose-response curve. Thus, the protocol should not require that a dose-response curve be established for a study to be considered in the evaluation, nor should single-dose studies be excluded. While dose-response curves provide valuable information and are critical to hazard characterization, they are not required for hazard identification.

We propose that the protocol adopt the underlying assumption that there are low dose effects and that studies should be evaluated in this context.

Inclusion/exclusion process

The protocol describes a process to eliminate bias in the selection of studies for inclusion in the evaluation; however, in our view, some of the criteria may actually introduce bias. For example, the first sentence on page 52 states, "Early positive studies, particularly if small in size, are suspect." This language introduces inclusion bias toward large negative studies. If this is not the intention, the text should be revised. In our view and experience, an early study that shows an effect is no more or less intrinsically flawed than an early study that fails to show an effect. We are also concerned that the stated bias against "small" studies may skew inclusion toward large GLP studies and away from academic studies. Such a bias does not appear to be science-based. Specifically, academic studies directed at focused endpoints, using sophisticated methods, may be statistically powered in a manner comparable to a GLP study that uses more animals per group. Moreover, academic studies can be tailored to address issues that have been revealed by human studies, providing important mechanistic insight—endocrine or otherwise—into the relationship between a chemical exposure and health endpoint.

As written, the protocol fails to clearly address the following questions:

- In the context of a large study, do negative results on one end point relegate the entire study to the negative category?
- Do negative results on a secondary endpoint relegate the study to the negative category?

In both of these cases, the exclusion of such "negative" studies might represent the loss of critical information.

Additionally, there must be some consideration given to bias and/or conflict of interest (COI) based on the study's funding source(s). The protocol states that funding data are to be collected but not used to determine COI or risk of bias; but the literature shows that there is indeed a link between funding sources and the potential for bias in results and their interpretation. For example, financial COI has been empirically shown in the pharmaceutical literature to influence study outcomes[1,2]. As such, the NTP should include COI as a relevant element in risk of bias. We do not suggest the exclusion of all studies funded by potentially bias-inducing sources; however, there must be acknowledgement of this potential, and steps should be taken to develop systematic approaches to minimizing their effects on the evaluation.

Finally, though there is a systematic approach to inclusion/exclusion deliberations, in cases of uncertainty, the ultimate decision falls to the judgment of the principals involved. This further highlights the need to ensure that individuals with both broad and deep knowledge of the field are involved in the evaluation process.

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[1] http://onlinelibrary.wiley.com/doi/10.1002/14651858.MR000033.pub2/abstract

[2] 10.1377/hlthaff.2010.1219, HEALTH AFFAIRS 30, NO. 5 (2011): 931–937

Again, The Endocrine Society thanks you for the opportunity to comment on the BPA exposure and obesity protocol. We understand that it will serve as proof-of-principle in the larger framework. We therefore hope there will be another opportunity to evaluate the protocol after its implementation. As with any new program or approach, we expect this protocol to raise new considerations requiring refinements and improvements in the future.

The Endocrine Society stands ready to serve as a resource. Please contact Loretta Doan at ldoan@endocrine.org, if we can be of assistance.

Sincerely,
[Redacted]

William F. Young, M.D.
President, The Endocrine Society