

August 16, 2018

Charlotte Bertrand
Acting Principal Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Re: EPA-HQ-OPPT-2018-0210

Dear Dr. Bertrand,

Thank you for the opportunity to provide comments on the Application of Systematic Review in TSCA Risk Evaluations. Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization dedicated to the understanding of hormone systems and the clinical care of patients with endocrine diseases and disorders. Our membership of over 18,000 includes researchers who are making significant contributions to the advancement of systematic review methodologies, especially in the field of endocrine-disrupting chemicals (EDCs).

We share the concerns articulated by the University of California, San Francisco Program on Reproductive Health and the Environment (UCSF-PRHE) and enthusiastically support their recommendations submitted separately to docket EPA-HQ-OPPT-2018-0210. We intend for this letter to be complementary to that effort. In our comments we propose additional recommendations and identify issues that should be clarified to ensure that the Guiding Principles can help EPA effectively characterize harmful effects on endocrine systems in the context of risk evaluations.

We acknowledge that the Toxic Substances Control Act (TSCA) requires EPA to use a "weight of scientific evidence" during risk evaluations and we are encouraged that the definition within the TSCA context includes features that are equivalent to systematic review. However, we are concerned about the use of expert judgment throughout the process and encourage EPA to instead use review by experts in the context of systematic review rather than professional judgment-based weight of evidence approach. The use of expert review also necessitates careful selection of expert reviewers during the planning phase of the data evaluation steps. **We encourage the EPA to clearly define the criteria used to select reviewers and ensure that expertise in the fundamental biological systems affected by chemicals is prioritized.** For EDCs, this means that experts in endocrine systems and hormone biology are included in review panels. Reviewers should document and describe potential conflicts of interest, including financial conflicts, and a transparent process for managing conflict should be articulated in the guiding principles.



We appreciate that EPA clarified that reference to study guidelines “should not be construed to imply that non-guideline studies have lower confidence than guideline or Good Laboratory Practice (GLP) studies,” and that EPA will consider all information sources that conform to the TSCA science standards. The Endocrine Society has consistently argued that GLP standards, while an appropriate approach for standardization and consistency in recording and reporting of results and has been useful in limiting fraud in contract laboratories, is not a reflection of the quality of the science or the plausibility of the hypothesis under examination. GLP compliance also does not automatically ensure a low risk of bias. **It is imperative that the evaluation of study quality will treat GLP and non-GLP studies in the same way and that this be made explicit in future iterations of the Guiding Principles.**

In addition to implementing the recommendations above, upon careful review of the document, there are several issues that EPA should clarify in revisions to the Guiding Principles, specifically:

- EPA should better describe what “fit-for-purpose” means in the context of implementing systematic review approaches and how EPA will evaluate different systematic review methodologies.
- EPA should articulate the aim of evaluating studies and data to ensure that they are “consistent with the intended use of the information”. I.e., does this mean that studies should be designed to comply with specific regulatory systems?
- EPA should clarify how literature search terms will be selected and if the list of terms will be reviewed to ensure a comprehensive assessment of the relevant literature.

Thank you for considering the Endocrine Society’s comments. We look forward to continuing to work with EPA on future revisions and refinements to the Guiding Principles to ensure that EPA can protect the public from harms due to EDC exposures. If we can be of any further assistance, please contact Joseph Laakso, PhD, Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

A handwritten signature in black ink that reads "Susan Mandel".

Susan Mandel, MD, MPH
President
Endocrine Society