

Leslie Kux
Assistant Commissioner for Policy
Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

February 10, 2015

Dear Assistant Commissioner Kux,

The Endocrine Society appreciates the opportunity to provide comments on certain topics related to the Toxicological Principles for the Safety Assessment of Food Ingredients, hereafter referred to as the “Redbook.” 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. The Society’s membership of over 18,000 includes researchers who are making significant contributions to the advancement of knowledge in toxicology, especially in the field of endocrine disrupting chemicals (EDCs). We are therefore extremely interested in a potential update to and expansion of the scope of the Redbook.

In our comments, we identify specific endocrine principles that should be considered as important aspects of the safety and risk assessment of food ingredients and other CFSAN-regulated products. We also make several general recommendations that will serve to update the Redbook to more fully support the development of safety assessments for substances introduced into food and increase transparency and consistency in risk assessments. We believe that these recommendations, when brought into effect, will help achieve the goal of applying the most appropriate analysis for specific contexts such as EDCs.

Specific Principles of EDCs

The Endocrine Society maintains that current testing guidelines and regulatory apparatus are insufficient for identifying and characterizing risks associated with exposure to EDCs. For example, chemical interference with hormone actions during early development can have long-lasting, even permanent, consequences on hormone action that might manifest years later. Therefore, it is important to ensure that explicit guidance exists to examine sensitive periods of development such as pre-natal, infancy and adolescence.



Furthermore, hormones act at very low concentrations, so the effects of very small amounts of EDCs must be taken into account systematically. We stress that dose-response relationships should be carefully examined in light of mechanistic data. Specifically, EDCs may exhibit non-monotonic dose responses based on receptor affinity at low vs. high doses¹. Mixtures of EDCs may also have additive or synergistic effects, where the compounds in combination induce responses that are not predicted based on studies of single chemicals alone²³⁴. The Endocrine Society therefore urges the FDA to consider non-monotonic dose response relationships for chemicals that may have endocrine disrupting features.

Finally, we note that a single hormone will have changing effects at different life phases and places in the body during development and the sensitivity at a particular phase and location may differ. For example, while testosterone acts during sexual development to cause the development of the male reproductive tract, in adult animals it exerts action on the brain through conversion to estradiol. Sensitive endpoints with predictive ability must therefore be prioritized to identify endocrine disruptors⁵. Current endpoints used in guideline assays are insufficient and we believe that prioritizing the review guideline endpoints in updates to the Redbook will provide more “state of the art” assessments of the effects of chemicals.

General Updates to the Redbook

The Endocrine Society cautions against an over-reliance on the use of Good Laboratory Practices (GLP) in updates to the Redbook. While GLP is an appropriate approach for standardization and consistency in recording and reporting of results, GLP compliance in and of itself is not a reflection of the quality of the science or the plausibility of the hypothesis under examination. Furthermore, academic laboratories may not have resources needed to achieve GLP certification; however these same academic laboratories are fully capable of producing excellent, reproducible research results.

¹ Vandenberg et al., Hormones and EDCs: Low Doses and Nonmonotonicity. *Endocrine Reviews*, June 2012, 33(3):378 – 455

² Ermiler S, Scholze M, Kortenkamp A.. The suitability of concentration addition for predicting the effects of multi-component mixtures of up to 17 anti-androgens with varied structural features in an in vitro antagonist assay. *Toxicol Appl Pharmacol* 2011. 257:189-197.

³ Kortenkamp A. Low dose mixture effects of endocrine disrupters: Implications for risk assessment and epidemiology. *Int J Androl* 2008. 31:233-240.

⁴ Crofton KM, Craft ES, Hedge JM, Gennings C, Simmons JE, Carchman RA, et al. Thyroid-hormone-disrupting chemicals: evidence for dose-dependent additivity or synergism. *Environ Health Perspect*. 2005 Nov;113(11):1549-54

⁵ Zoeller et al., Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society. *Endocrinology*. Sep 2012; 153(9): 4097–4110.



For these reasons, we recommend that updates to the Redbook incorporate guidance on the inclusion of both GLP and non-GLP studies that are based on the most relevant and up-to-date science.

The Society believes that the transparency and consistency of risk assessments will also be improved by the implementation of systematic review methodologies. Systematic reviews will minimize subjectivity and improve evidence integration from various complicated data streams. Implementation of such methodologies could be facilitated by coordinating with other agencies that regularly conduct risk assessments. We refer specifically to those strategies in development by the Environmental Protection Agency's Integrated Review Information System and the National Toxicology Program Office of Health Assessment and Translation⁶.

Finally, we encourage the FDA to explicitly develop guidance to address cumulative biological effects of chemicals. Cumulative exposure is particularly relevant to EDCs⁷; however this concept can in principle be extended to other classes of toxic chemicals.

Summary

In conclusion, we believe that the following specific principles of EDCs should be taken into account in updates to the Redbook:

- Windows of sensitivity or susceptibility in development
- Low-dose effects and nonmonotonicity
- Appropriate endpoints with predictive ability

Furthermore, we recommend that the updates to the Redbook incorporate the following general recommendations:

- Reduce over-reliance on GLP in study evaluation
- Develop systematic review methodologies to better incorporate various data streams
- Explicitly include guidance on the evaluation of risks due to cumulative exposures

As an overarching consideration, we strongly support the involvement of experts in the evaluation of technical data and scientific information to ensure that studies are of sufficient quality and

⁶ http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf Accessed January 20, 2015.

⁷ http://dels.nas.edu/resources/static-assets/materials-based-on-reports/reports-in-brief/phthalates_final.pdf Accessed January 20, 2015.



relevance. We assert that for specialized sub-disciplines, scientists with discipline-specific expertise need to be involved in these processes. We define “scientists with discipline-specific expertise” as individuals with a research-based understanding of relevant system(s) and mechanisms, and who have recently made or are currently making significant contributions to the advancement of knowledge in the specific field of inquiry.

The Endocrine Society stands ready to assist the FDA in its efforts to improve the Redbook and we look forward to additional opportunities to help the FDA update and expand the scope of the Redbook. We believe that the Redbook can be a useful tool, and we encourage the FDA to expand the scope of the Redbook to include products such as cosmetics and dietary supplements. We believe that such an expansion of scope will help harmonize the regulatory apparatus for chemicals. Thank you for considering the Endocrine Society’s comments. If we can be of any assistance in your efforts, please do not hesitate to reach out to Dr. Joseph Laakso, Associate Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

A handwritten signature in black ink, reading "Richard J. Santen", enclosed in a thin black rectangular border.

Richard J. Santen, MD
President, Endocrine Society