ENDOCRINE SOCIETY
Hormone Science to Health

April 26, 2018

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

Re: EPA-HQ-OPPT-2017-0559

Dear Dr. Bertrand,

On behalf of the Endocrine Society, I appreciate the opportunity to provide comments to EPA on the draft Strategic Plan to Promote the Development and Implementation of Alternative Test Methods. 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 our understanding of the effects of exposures to manufactured chemicals that interfere with hormone systems, called endocrine-disrupting chemicals (EDCs). The Society has closely followed the development and implementation of the Frank R. Lautenberg Chemical Safety in the 21st Century Act and we appreciate the need to develop, build, and implement reliable and relevant new and alternative methods (NAMs) to reduce vertebrate animal testing. In our comments, we identify improvements that, if included in the strategic plan, would result in better protection from harms due to EDC exposures.

NAMs Must Be Able to Predict Effects on the Endocrine System

The Endocrine Society maintains that testing strategies must account for effects on hormone biology and endocrine pathways. NAMs must therefore be able to assess chemicals with non-monotonic dose response (NMDR), low-dose effects, sex-specific effects, imbalances and reactive/feedback changes in complex hormonal systems (e.g., hormone synthesis, transport, and metabolism), reactive effects that may indicate adversity (e.g., phthalate exposure and effects on anogenital distance), sensitivity to exposure during critical developmental stages, and context dependent features such as tissue, receptor type, and co-factors that may affect hormone signaling. The evaluation of NAMs must reflect their ability to replicate diseases and dysfunctions that occur in animal models and human studies. This includes obesity, diabetes, liver diseases, learning and behavioral problems. As science, including animal research, discovers additional

2055 L Street NW
Suite 600
Washington, DC
20036

T. 202.971.3636
F. 202.736.9705

endocrine.org

mechanisms through which hormonal systems are perturbed, NAMs must be updated to include additional endpoints/diseases/dysfunctions.

As we stated in our comments on identifying potential candidates for prioritization under the amended Toxic Substances Control Act[1], we are concerned that existing high-throughput screening assays, exposure models, and other test systems have not been sufficiently validated and demonstrated effectiveness in identifying EDCs. The models used to evaluate data on estrogen receptor (ER) and androgen receptor (AR) bioactivity discounted potential low-dose effects or NMDR, resulting in an excessively high false-negative rate, which reflects low reliability and confidence in the assays. Non-classical ER and AR signaling pathways, including rapid and membrane-initiated activity, are not accounted for. Moreover, an exclusive focus on the ER and AR pathways will result in a lack of coverage for other endocrine pathways, including complex pathways such as reproduction and development, that could be disrupted by EDCs.

Evaluation of NAMs should be rigorous, transparent, and avoid COI.

The Endocrine Society agrees that NAMs should be implemented after they have established scientific relevance and reliability, and only when there is sufficient confidence in the ability of the NAM to accurately predict consequences of exposures. It is extremely important that criteria for reliability and confidence include a performance comparison to existing testing strategies in the same chemical domain of applicability, and against assays with the highest levels of sensitivity, to be consistent with the need to provide information of similar or better quality than conventional animal testing. Until performance-validated NAMs have been developed that can confidently cover a wide range of potential exposures and sensitive endpoints, EPA should proceed with the most protective methodologies that result in the broadest possible coverage of potential harms from chemical exposures.

We also are concerned about the potential for conflicts of interest (COI) by industry participation in the development, submission, and review of NAMs. Restrictions on the release of confidential business information (CBI) may prevent full transparency about NAMs, preventing an accurate assessment of confidence, reliability, and relevance. We appreciate that there are cases in which CBI should not be disclosed to the public; however, in the case of scientific reviews to establish validity and build confidence in NAMs it is essential that reviewers have all necessary data and information, including CBI, to properly evaluate the approach. When industry-sponsored assays

[1] https://www.endocrine.org/-/media/endosociety/files/advocacy-and-outreach/society-letters/2018/20180122-endocrine-society-comments-on-pre-prioritization-process.pdf?la=en Accessed April 20, 2018.

are proposed, it will be particularly important to allow maximal transparency for 3rd party reviewers, including academic scientists, to reduce bias. In all cases, COI-free independent scientists familiar with a broad range of endpoints and pathways should be engaged in reviews of NAMs to evaluate against existing practices.

Near-, Mid- and Long-Term Objectives Should Include Academic Research

The Endocrine Society has consistently argued for greater involvement of scientists with expertise in endocrinology and hormonal systems in regulatory decision-making involving EDCs. Independent scientists, including academic researchers, can and should be part of the collaborative process to identify new NAMs for further development as described in Chapter 7 of the Strategic Plan. The involvement of independent scientists should also be required throughout the implementation phase of the Plan, including the evaluation, validation, and further development of NAMs.

One area where academic scientists can play a critical role is in the development and eventual utilization of adverse outcome pathways (AOPs) as a component of integrated approaches to testing and assessment (IATAs). To date, AOPs have not demonstrated utility as decision-making tools in a regulatory context, nor have they been adequately validated as predictive models for adverse effects. However, we recognize the potential for AOPs to accelerate regulatory decision-making for classes of chemicals with similar features. Academic science, including research on animals, is essential to build the foundational knowledge on which AOPs are based. It will therefore be important for EPA to involve academic scientists in the development and review of AOPs to ensure that AOPs are interpreted and applied correctly.

Finally, we acknowledge the need for additional research and development activities for NAMs, including high-throughput systems for hazard assessment, screening, and prioritization. We would add that computational approaches to predict fate, transport, and persistence of chemicals in the environment require substantial further research and development to demonstrate their reliability and value, evidenced by the continued harms to human health and the environment presented by perfluoronated compounds with exceptionally long half-lives. Compounds with such demonstrated capacity to bioaccumulate should not be missed. Building testing and assessment strategies for complicated hormonal systems will require multidisciplinary approaches involving teams of scientists. Future testing strategies will need to consider a variety of susceptible subpopulations, including developmental stages, genetic diversity, geographic location, and other variables; sex-specific effects will also need to be carefully considered. As an overarching goal, increased coverage of hormonal pathways beyond ER and AR need to be prioritized.

Systematic Review Should be Used to Evaluate NAMs

We are concerned with the proposed use of Weight of Evidence (WoE) evaluations for the evaluation and implementation of NAMS. The Strategic Plan should seek to ensure that all available scientific evidence is evaluated, to the extent possible, against the same standards during chemical assessments and reviews. As an organizing principle, the Endocrine Society strongly supports the use of systematic review to promote objectivity and transparency in scientific reviews. Features of systematic reviews lead to more reproducible results than earlier WoE methods; in other contexts, EPA has used a term "weight of scientific evidence" that is defined in a way that is consistent with established systematic review methodologies. We strongly recommend that the Strategic Plan implement a systematic review methodology that is clearly and transparently defined in processes to evaluate and make decisions regarding the implementation of NAMs. Application of systematic review methodologies would align EPA with directives issued by the National Academy of Science to improve consistency of reviews across the agency, also concluding that WoE was not a meaningful term, nor a rigorous approach[2][3].

Timeframes and Goals Should be Realistic

While the use of NAMs may accelerate the pace of regulatory decision-making, we are concerned that the timelines in the plan are clearly unrealistic, given the need to develop and validate assays for complicated areas like reproduction and development. Some areas such as fetal development and neurological impairment may require vertebrate animal testing for the foreseeable future, and the strategic plan should include realistic goals and manageable expectations. A scientifically rigorous approach that is protective of human and ecological health should take precedence over an accelerated timeframe for implementing NAMs[4].

Summary of Recommendations

We appreciate that screening the universe of chemicals under the toxic substances control act is a challenging task. By incorporating the recommendations below, the EPA will be able to implement

---

[2] National Academies of Sciences, Engineering, and Medicine. 2017. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, DC: The National Academies Press. https://doi.org/10.17226/24758.

[3] Druwe, I., M. Taylor, A. Persad, K. Thayer, AND JaniceS Lee. Implementation of Systematic Review Tools in IRIS. OpenTox, Durham, North Carolina, July 12 - 13, 2017.

[4] National Academies of Sciences, Engineering, and Medicine. 2017. Using 21st Century Science to Improve Risk-Related Evaluations. Washington, DC: The National Academies Press. https://doi.org/10.17226/24635.

more effective NAMs for the protection of human and ecological health from harms due to chemical exposures, including EDCs.

- NAMs should undergo a performance comparison to existing testing strategies, including highly-sensitive endpoints for endocrine effects.
- EPA should use the most protective testing strategies that generate information on a broad range of endpoints, including disease-focused endpoints.
- CBI should be disclosed to scientific reviewers of NAMs.
- NAMs must account for effects on hormone biology and endocrine pathways, incorporating principles of endocrinology[5].
- Independent scientists, including endocrine scientists, should be involved in review and implementation of NAMs to ensure coverage of hormonal systems.
- AOPs should undergo rigorous scientific review and demonstrate utility before use in the context of IATAs.
- Review processes should use systematic review methodologies, instead of WOE.
- Long-term research objectives should reflect the need to evaluate various sources of susceptibility and cover all hormonal pathways.
- Conflict of interest should be minimized or avoided entirely; industry-developed NAMs should be reviewed and evaluated by independent scientists free from COI.

Thank you for considering our comments. If we can be of any assistance, please do not hesitate to contact Joseph Laakso, PhD, Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

Susan Mandel

Susan Mandel, MD, MPH
President, Endocrine Society

[5] Zoeller, RT, et al., Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. Endocrinology. 2012 Sep;153(9):4097-110. doi: 10.1210/en.2012-1422.