ENDOCRINE SOCIETY
Hormone Science to Health

Submitted by the Endocrine Society in response to Notice EPA-HQ-OPP-2021-0756-0001 "New Approach Methodologies in the Endocrine Disruptor Screening Program".

March 19, 2023

The Endocrine Society appreciates the opportunity to comment on the white paper "New Approach Methodologies in the Endocrine Disruptor Screening Program." 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. Our membership consists of over 18,000 scientists, physicians, educators, nurses, and students in more than 100 countries. Society members represent all basic, applied and clinical interests in endocrinology. Included among our members are the world's leading experts on the health effects of endocrine-disrupting chemicals (EDCs).

We maintain our position that a fundamental hurdle facing the EPA in the achievement of important public health and ecological goals related to endocrine disruption is the insensitivity of the Endocrine Disruptors Screening Program (EDSP) to properly identify the effects of chemicals on the endocrine system. We remain convinced that EPA should re-envision the EDSP so that the program can more comprehensively evaluate effects of chemicals on hormone actions and fully validate methods using test cases that are consistent with the latest scientific information on chemicals.

Unfortunately, the white paper fails to include a plan with tangible milestones towards that goal. Without concrete steps and implementable actions, EDCs will continue to cause significant adverse health consequences for all populations but in particular for children, pregnant women, and other vulnerable populations; further, EDCs will continue to have disproportionate effects on communities with higher levels of exposure. To improve the EDSP and ensure it reaches its stated goals, we identify several issues that should be addressed in the final white paper.

We remain concerned that EDSP has failed to be fully implemented, and thus has failed to identify EDCs or reduce exposures to EDCs. Ample evidence of human and environmental health harms resulting from exposure to EDCs is documented in findings from myriad peer-reviewed publications and is unclear why the EDSP is unable to employ these studies in their analyses. Public health authorities in the European Union and elsewhere have implemented strategies that have identified individual chemicals as EDCs, yet the EDSP seems incapable of functioning in a way that identifies these – or other - chemicals as EDCs. The whitepaper should be revised specifically to include plans to validate the Agency's approach with case studies comparing the performance of the EDSP against known EDCs such as BPA, DDT and atrazine, and explicitly describe how other relevant

2055 L Street NW
Suite 600
Washington, DC
20036

T. 202.971.3636
F. 202.736.9705

endocrine.org

scientific information (OSRI) will be used to supplement data from EDSP to arrive at regulatory decisions.

Also critically, EPA should utilize their own longstanding definition of an EDC. In 1996, the EPA's own scientists defined an EDC as "An exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes[1]". This definition is similar to the Endocrine Society's definition of an EDC as "an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action."

We are also concerned that some of the assays described in the white paper that have been used to screen the original 18,000 chemicals are no longer available, leaving it unclear how the EDSP will be able to assess chemicals that have entered the market in recent years or will be introduced in the future. Public health protection requires ongoing surveillance of all chemicals in commerce, and thousands of new chemicals are developed every year, including many substitutes for known hazardous chemicals that are structurally similar to and are suspected or demonstrated to have similar effects. Therefore, in addition to re-evaluating older chemicals by incorporating newer and more sensitive assays, EPA should describe how they plan to evaluate new chemicals that have or will enter into commerce. Furthermore, we note that the white paper focuses strictly on assays that are used for screening and priority setting; however, it is important for the public to know more about EPA's vision for understanding and regulating chemical hazard through testing for effects on the endocrine system. The current tier 2 assays are not sensitive to measure many hormone activities of significance to human health outcomes, and we know that NAMs cannot yet assess many generational, delayed and feedback loops. We urge EPA to propose activities beyond prioritization and screening in the final whitepaper to allow the public to better understand how the agency will mitigate public health hazard.

The test methods incorporated into the EDSP should be transparent and available to laboratories outside of the US EPA to demonstrate reproducibility of the methodologies. The portability and reproducibility of the EDSP methods is a critical component of validation and the lack of external validation is inconsistent with scientific best practices. We also urge EPA to provide a transparent reporting of the underlying data used throughout the white paper to allow evaluation of the

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[1] Kavlock RJ, Daston GP, DeRosa C, Fenner-Crisp P, Gray LE, Kaattari S, Lucier G, Luster M, Mac MJ, Maczka C, Miller R, Moore J, Rolland R, Scott G, Sheehan DM, Sinks T, Tilson HA: Research needs for the risk assessment of health and environmental effect of endocrine disruptors: a report of the US EPA-sponsored workshop. Environ Health Perspect 1996, 104:715–740.

performance of the assays. Data on the chemicals referenced in the white paper would be particularly useful, but the white paper should also include more information on how adverse outcome pathways (AOPs) are used and what Key Events (KEs) are being evaluated, and the regulatory status of the AOPs being used in the context of the 18 estrogen-related assays. EPA also should describe in the final white paper whether the KE data shown would be sufficient to trigger regulatory actions – if so, what actions would be considered and if not, what additional evidence would be needed?

Finally, we reiterate that the public looks to the EPA to provide comprehensive screening and regulation of chemicals that interfere with *all* aspects of hormonal signaling. While we understand that EPA is focusing on new approach methodologies (NAMs) to reduce the use of animals in testing, it remains true for the foreseeable future that many aspects of endocrine biology, including thyroid hormone biology, are not currently sufficiently covered by NAMs. Ongoing work by the National Academies of Science, Engineering, and Medicine (NASEM) and the Organization for Economic Cooperation and Development (OECD) are aiming to help agencies like EPA better understand the gaps in coverage by NAMs that currently exist and what areas should be considered for regulatory application. We urge EPA to incorporate the findings, when published, from these and other relevant projects in the final white paper to ensure that this plan is timely and up to date with consensus scientific assessments. In the meantime, and appreciating that NAMs may not provide comprehensive coverage to ensure health safety for citizens, EPA can take steps towards the goal of reducing the use of animals in testing strategies by making better use of peer-reviewed academic publications in regulatory decisions, encouraging transparency in the tests done by chemical manufacturers, and adopting group-based restrictions to chemicals that allow hazard data on one chemical to be applied to chemicals with similar structure and activity.

Thank you for considering the Endocrine Society's comments; if we can be of further assistance, please contact Joe Laakso, PhD, Director of Science Policy at jlaakso@endocrine.org.