ENDOCRINE SOCIETY
Hormone Science to Health

June 04. 2020

Risk Assessment Division
Office of Pollution Prevention and Toxics,
United States Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460

Re: EPA-HQ-OPPT-2019-0131; EPA-HQ-OPPT-2018-0503; EPA-HQ-OPPT-2018-0501; EPA-HQ-OPPT-2018-0433; EPA-HQ-OPPT-2018-0434; EPA-HQ-OPPT-2018-0504

On behalf of the Endocrine Society, thank you for the opportunity to comment on the draft scope documents for high-priority chemicals for risk evaluation under the Toxic Substances Control Act (TSCA). 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 interference with hormonal systems by manufactured chemicals, called endocrine disrupting chemicals (EDCs). We were encouraged by the inclusion of several phthalates with endocrine effects on the list of High-Priority Candidates; however, the draft scopes do not adequately describe how EPA will evaluate hazards associated with exposure to these chemicals. In our comments, we identify several improvements to the scoping documents that will allow EPA to conduct a more thorough examination of the endocrine-related effects of these chemicals.

Hazard Selection Process Should be More Transparent

We are concerned that EPA has already selected a subset of human health hazards for further evaluation without describing the process used to arrive at this decision. For instance, EPA has selected reproductive and developmental effects and cancer as hazards for DEHP, but DEHP has also been reported to cause metabolic disorders and effects on thyroid hormone biology. During the prioritization process, we submitted a list of effects for several phthalates based on information in the Endocrine Society's Second Scientific Statement on EDCs, this information is included in the appendix to this letter and **we ask EPA to more fully describe the process by which hazards were included or excluded for each chemical under review**. In the actual risk assessment, hazard evaluation should bear more consideration than exposure since exposures can change through time due to unexpected uses, changes throughout the product lifecycle and new uses.

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EPA Should Adopt A Cumulative Assessment Strategy, Incorporating Aggregate Exposure Estimates for Phthalates

Humans are exposed to a complex mixture of phthalates on a regular basis, creating challenges in the attribution of specific effects to specific chemicals. However, substantial peer-reviewed evidence has emerged in recent years demonstrating that chemicals within this class contribute to common adverse health outcomes through cumulative or mixture effects. Although data gaps may exist at the level of individual chemicals, the lack of data for an individual chemical within the class does not indicate a lack of hazard. **We therefore strongly encourage EPA to adopt a cumulative and/or read across risk assessment for the high-priority phthalates encompassing an expanded list of health endpoints**. Where peer-reviewed studies show evidence of hazard for a particular endpoint, this information should inform data gaps across the assessment group. Likewise, EPA should consider aggregate exposure from all sources when conducting risk assessments for phthalates in order to avoid underestimating the actual risk from phthalate exposure.

EPA Must Clarify and Improve Systematic Review Approach

Throughout the scoping documents there exist references to additional details pending the development of the systematic review protocol. Without a detailed systematic review protocol or analysis plan, it is extremely difficult to evaluate the draft scoping documents as presented. Transparency in EPA's methodology is necessary, given our concerns about EPA's draft systematic review approach as described in the Endocrine Society comments to docket EPA-HQ-OPPT-2018-0210 on the Application of Systematic Review in TSCA Evaluations[i]. Due to the health effects of phthalates described in the peer-reviewed literature, it is imperative that the evaluation of study quality evaluate GLP and non-GLP studies in the same way and that this be made explicit.

To improve transparency and ensure that stakeholders can make informed comments on EPA's approach, **we request that EPA publish the systematic review protocols and analysis plans as soon as possible, and then reopen the draft scoping documents for further comment**. There exist several useful examples of systematic review approaches that could inform EPA's approach, including the Navigation Guide[ii] and SYRINA framework for EDCs[iii]. To further improve transparency and standardization across EPA reviews, EPA could also adopt the IRIS program's systematic review procedures as these have already been reviewed and recommended by the National Academy of Sciences.

EPA Should Consider the Entire Product Lifecycle and Legacy Uses

Given the widespread prevalence of phthalates and their variety of uses in consumer products and manufacturing, **EPA should comprehensively assess product lifecycle and uses as part of an aggregate exposure approach.** This should include legacy use, associated disposal, and legacy disposal. Uses should also consider disproportionate exposures to sensitive populations such as low-income communities that obtain items second-hand and in a state that may be more likely to degrade

and increase exposures or contain chemicals that are now phased out for legacy uses. Consistent with the need to protect children and pregnant women, **EPA's approach to assessing occupational exposure and children's exposure via hand/mouth activity from second hand or legacy uses should be described in detail**.

In conclusion, we urge EPA to improve the draft scoping documents for the remining high-priority chemicals. Following the inclusion of additional information on EPA's systematic review approach, the draft scoping documents should be republished for an additional 45-day comment period. Thank you for considering the Endocrine Society's comments. If we can be of any further assistance, please contact Joseph Laakso, PhD, Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

Gary D. Hammer, MD, PhD
President
Endocrine Society

Appendix: Health Hazards Summarized in the Endocrine Society's Second Scientific Statement on EDCs.

- Dibutyl phthalate (DBP) is estrogenic[iv] and anti-androgenic[v], and has been associated with increased fetal weight[vi] and epigenetic transgenerational inheritance of adult-onset obesity in animal models[vii]. DBP has effects on the female and male reproductive system; some of these include alterations in pubertal timing[viiiix] and alterations in mammary gland development[x]. DBP also has potential effects on thyroid hormone levels[xi] and dose- and age-dependent effects on neuroendocrine systems[xii].

- Benzyl butyl phthalate (BBP) inhibits testosterone production[2] and has effects on sexual differentiation in male animals[xiii] and mammary gland growth in female animals[xivxv].

- Di-ethylhexyl phthalate (DEHP) has a wide range of effects, including DNA modification in male and female gametes[xvixvii], potentially causing delayed puberty and other reproductive health effects in offspring of exposed animals[xviiixix]. DEHP also can cause metabolic disorders or obesity through a variety of mechanisms such as changes in metabolism and glucose homeostasis[xx], epigenetic inheritance[4] or direct promotion of adipogenesis[xxi]. Numerous studies show effects by DEHP on the female reproductive system including

interference with steroidogenesis[xxiixxiii] and effects on uterine structure and function[xxivxxv]. High-dose DEHP studies in animals showed potential for adverse birth outcomes[xxvixxvii]. DEHP can also disrupt thyroid hormone biology at low doses[xxviii].

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[i] https://www.endocrine.org/-/media/endocrine/files/advocacy/society-letters/2018/20180816-endocrine-society-comments-on-guiding-principles-to-apply-systematic-review-in-tsca.pdf

[ii] Tracey J. Woodruff, Patrice Sutton. The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes. Environ Health Perspect. 2014 Oct; 122(10): 1007–1014. Published online 2014 Jun 25. doi: 10.1289/ehp.1307175

[iii] L. Vandenberg et al., A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals. Environ Health. 2016; 15: 74. Published online 2016 Jul 14. doi: 10.1186/s12940-016-0156-6.

[iv] Jobling S, Reynolds T, White R, Parker MG, Sumpter JP. A variety of environmentally persistent chemicals, including some phthalate plasticizers, are weakly estrogenic. Environ Health Perspect . 1995;103:582–587.

[v] Axelstad M, Christiansen S, Boberg J, et al. . Mixtures of endocrine-disrupting contaminants induce adverse developmental effects in preweaning rats. Reproduction . 2014;147:489–501.

[vi] Guerra MT, Scarano WR, de Toledo FC, Franci JA, Kempinas Wde G. Reproductive development and function of female rats exposed to di-eta-butyl-phthalate (DBP) in utero and during lactation. Reprod Toxicol . 2010;29:99–105.

[vii] Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PLoS One . 2013;8:e55387.

[viii] Hu J, Du G, Zhang W, et al. . Short-term neonatal/prepubertal exposure of dibutyl phthalate (DBP) advanced pubertal timing and affected hypothalamic kisspeptin/GPR54 expression differently in female rats. Toxicology . 2013;314:65–75.

[ix] Craig ZR, Hannon PR, Wang W, Ziv-Gal A, Flaws JA. Di-n-butyl phthalate disrupts the expression of genes involved in cell cycle and apoptotic pathways in mouse ovarian antral follicles. Biol Reprod . 2013;88:23.

[x] Lee KY, Shibutani M, Takagi H, et al. . Diverse developmental toxicity of di-n-butyl phthalate in both sexes of rat offspring after maternal exposure during the period from late gestation through lactation. Toxicology . 2004;203:221–238.

[xi] O'Connor JC, Frame SR, Ladics GS. Evaluation of a 15-day screening assay using intact male rats for identifying antiandrogens. Toxicol Sci . 2002;69:92–108.

[xii] Hu J, Du G, Zhang W, et al. . Short-term neonatal/prepubertal exposure of dibutyl phthalate (DBP) advanced pubertal timing and affected hypothalamic kisspeptin/GPR54 expression differently in female rats. Toxicology . 2013;314:65–75.

[xiii] Gray LE Jr, Ostby J, Furr J, Price M, Veeramachaneni DN, Parks L. Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol Sci . 2000;58:350–365.
[xiv] Moral R, Santucci-Pereira J, Wang R, Russo IH, Lamartiniere CA, Russo J. In utero exposure to butyl benzyl phthalate induces modifications in the morphology and the gene expression profile of the mammary gland: an experimental study in rats. Environ Health . 2011;10:5.
[xv] Moral R, Wang R, Russo IH, Mailo DA, Lamartiniere CA, Russo J. The plasticizer butyl benzyl phthalate induces genomic changes in rat mammary gland after neonatal/prepubertal exposure. BMC Genom . 2007;8:453.
[xvi] Li L, Zhang T, Qin XS, et al. . Exposure to diethylhexyl phthalate (DEHP) results in a heritable modification of imprint genes DNA methylation in mouse oocytes. Mol Biol Rep . 2014;41:1227–1235.
[xvii] Wu S, Zhu J, Li Y, et al. . Dynamic epigenetic changes involved in testicular toxicity induced by di-2-(ethylhexyl) phthalate in mice. Basic Clin Pharmacol Toxicol . 2010;106:118–123.
[xviii] Zhang T, Li L, Qin XS, et al. . Di-(2-ethylhexyl) phthalate and bisphenol A exposure impairs mouse primordial follicle assembly in vitro. Environ Mol Mutagen . 2014;55:343–353.
[xix] Doyle TJ, Bowman JL, Windell VL, McLean DJ, Kim KH. Transgenerational effects of di-(2-ethylhexyl) phthalate on testicular germ cell associations and spermatogonial stem cells in mice. Biol Reprod . 2013;88:112.
[xx] Lin Y, Wei J, Li Y, et al. . Developmental exposure to di(2-ethylhexyl) phthalate impairs endocrine pancreas and leads to long-term adverse effects on glucose homeostasis in the rat. Am J Physiol Endocrinol Metab . 2011;301:E527–E538.
[xxi] Biemann R, Navarrete Santos A, et al. . Endocrine disrupting chemicals affect the adipogenic differentiation of mesenchymal stem cells in distinct ontogenetic windows. Biochem Biophys Res Commun . 2012;417:747–752.
[xxii] Craig ZR, Hannon PR, Wang W, Ziv-Gal A, Flaws JA. Di-n-butyl phthalate disrupts the expression of genes involved in cell cycle and apoptotic pathways in mouse ovarian antral follicles. Biol Reprod . 2013;88:23.
[xxiii] Gupta RK, Singh JM, Leslie TC, Meachum S, Flaws JA, Yao HH. Di-(2-ethylhexyl) phthalate and mono-(2-ethylhexyl) phthalate inhibit growth and reduce estradiol levels of antral follicles in vitro. Toxicol Appl Pharmacol . 2010;242:224–230.
[xxiv] Wang X, Shang L, Wang J, Wu N, Wang S. Effect of phthalate esters on the secretion of prostaglandins (F2α and E2) and oxytocin in cultured bovine ovarian and endometrial cells. Domest Anim Endocrinol . 2010;39:131–136.
[xxv] Toft G, Jönsson BA, Lindh CH, et al. . Association between pregnancy loss and urinary phthalate levels around the time of conception. Environ Health Perspect . 2012;120:458–463.
[xxvi] Wang X, Shang LX, Zhang Q, Xu XD, Huo XX. Study on the effect of di-(2-ethylhexyl) phthalate on pregnant rats and the protection of zinc against it in pregnancy [in Chinese]. Zhonghua Fu Chan Ke Za Zhi . 2011;46:928–930.
[xxvii] Pocar P, Fiandanese N, Secchi C, et al. . Exposure to di(2-ethyl-hexyl) phthalate (DEHP) in utero and during lactation causes long-term pituitary-gonadal axis disruption in male and female mouse offspring. Endocrinology . 2012;153:937–948.
[xxviii] Ibhazehiebo K, Koibuchi N. Thyroid hormone receptor-mediated transcription is suppressed by low dose phthalate. Niger J Physiol Sci . 2011;26:143–149.