

June 19, 2019

United States Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460

On behalf of the Endocrine Society, thank you for the opportunity to comment on the prioritization process for chemicals under section 6(b) of 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 welcome the inclusion of several chemicals with endocrine effects on the list of High-Priority Candidates.

Of the chemicals listed for consideration as high-priority candidates, several have specific hazards associated with the endocrine system as described in the Endocrine Society's Second Scientific Statement on EDCs¹. These hazards are summarized below, with references to the original published research. As EPA finalizes the list of high-priority candidates for detailed review, we urge the agency to carefully consider hazards associated with endocrine disruption in decisions regarding prioritization and subsequent risk evaluation. We assert that a systematic review process that fully incorporates academic peer-reviewed literature and more sensitive endocrine-specific endpoints will better identify hazards at low-doses and with consideration for vulnerable populations.

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

Sincerely



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Phthalates

- Dibutyl phthalate (DBP) is estrogenicⁱⁱ and anti-androgenicⁱⁱⁱ, and has been associated with increased fetal weight^{iv} and epigenetic transgenerational inheritance of adult-onset obesity in animal models^v. DBP has effects on the female and male reproductive system; some of these include alterations in pubertal timing^{viii} and alterations in mammary gland development^{viii}. DBP also has potential effects on thyroid hormone levels^{ix} and dose- and age-dependent effects on neuroendocrine systems^x.
- Benzyl butyl phthalate (BBP) inhibits testosterone production² and has effects on sexual differentiation in male animals^{xi} and mammary gland growth in female animals^{xixiii}.
- Di-ethylhexyl phthalate (DEHP) has a wide range of effects, including DNA modification in male and female gametes^{xivxv}, potentially causing delayed puberty and other reproductive health effects in offspring of exposed animals^{xvixvii}. DEHP also can cause metabolic disorders or obesity through a variety of mechanisms such as changes in metabolism and glucose homeostasis^{xviii}, epigenetic inheritance⁴ or direct promotion of adipogenesis^{xix}. Numerous studies show effects by DEHP on the female reproductive system including interference with steroidogenesis^{xxxxi} and effects on uterine structure and function^{xxixiii}. High-dose DEHP studies in animals showed potential for adverse birth outcomes^{xxivxxv}. DEHP can also disrupt thyroid hormone biology at low doses^{xxvi}.

Flame Retardants

- Tetrabromobisphenol A (TBBPA) is an obesogen^{xxvii} that can act through the disruption of thyroid hormone biology^{xxviii}, thereby altering energy balance in animal models. The National Toxicology Program also reported that TBBPA can induce aggressive uterine cancer in rats, potentially by altering steroid activity^{xxix}.

ⁱ Gore AC, et al., *Endocr Rev.* 2015 Dec;36(6):E1-E150. doi: 10.1210/er.2015-1010. Epub 2015 Nov 6.

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ⁱⁱⁱ 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.

^{iv} 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.

^v 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.



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