ENDOCRINE SOCIETY
Hormone Science to Health

October 15, 2018

Dear Members of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF),

The Endocrine Society appreciates the opportunity to participate in the public call for data relevant to the re-evaluation of Bisphenol A (BPA) Tolerable Daily Intake (TDI). 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. The Endocrine Society's 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 the Society's members are the world's leading experts on the health effects of endocrine-disrupting chemicals (EDCs) including BPA.

Upon review of the final protocol for the re-evaluation of BPA, we are extremely concerned that the review will not take into account data published prior to 2013. As we stated in our earlier response to the hazard assessment protocol, important data for critical endpoints will be omitted from the re-evaluation unless a systematic review of all the relevant literature is conducted[1]. For example, important data from studies on mammary gland effects of BPA were previously disregarded by EFSA due to the use of subcutaneous exposures (via osmotic pumps), but these same data would now need to be evaluated based on the criteria provided in the new protocol. This is likely the case for other endpoints, including the endocrine pancreas.

In the appendix to this letter, we submit references to scientific articles about the effects of BPA published in peer-reviewed journals. We encourage the European Food Safety Agency to consider these and other studies in the evaluation of BPA. Please note that these papers do not represent the entirety of relevant data and knowledge on BPA, and we encourage EFSA to transparently and systematically evaluate sources of peer-reviewed scientific literature for additional data on the health impacts of BPA exposure.

Thank you for considering our comments. If you have any questions, or if we can be of any additional help in your efforts, please reach out to Joseph Laakso, Director of Science Policy, at jlaakso@endocrine.org

Sincerely,

Angel Nadal, PhD
Chair, EDC Advisory Group
Endocrine Society

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[1] Endocrine Society Comments on EFSA Revised BPA Review Protocol. August 24, 2017. https://www.endocrine.org/-/media/endosociety/files/advocacy-and-outreach/society-letters/2017/20170824-efsa-bpa-protocol-comments.pdf?la=en Accessed September 19, 2018

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APPENDIX: Selected publications on the effects of BPA.

Richard W Stahlhut, John Peterson Myers, Julia A Taylor, Angel Nadal, Jonathan A Dyer, Frederick S vom Saal; Experimental BPA Exposure and Glucose-Stimulated Insulin Response in Adult Men and Women, Journal of the Endocrine Society, https://doi.org/10.1210/js.2018-00151

Li Q, Lawrence CR, Nowak RA, Flaws JA, Bagchi MK, Bagchi IC. 2018. Bisphenol A and Phthalates Modulate Peritoneal Macrophage Function in Female Mice Involving SYMD2-H3K36 Dimethylation. Endocrinology. May 1; 159(5):2216-2228.

Drobná Z, Henriksen AD, Wolstenholme JT, Montiel C, Lambeth PS, Shang S, Harris EP, Zhou C, Flaws JA, Adli M, Rissman EF. Transgenerational Effects of Bisphenol A on Gene Expression and DNA Methylation of Imprinted Genes in Brain. Endocrinology. 2018 Jan 1;159(1):132-144.

Eckstrum KS, Edwards W, Banerjee A, Wang W, Flaws JA, Katzenellenbogen JA, Kim SH, Raetzman LT. Effects of Exposure to the Endocrine-Disrupting Chemical Bisphenol A During Critical Windows of Murine Pituitary Development. Endocrinology. 2018 Jan 1;159(1):119-131.

Mahalingam S, Ther L, Gao L, Wang W, Ziv-Gal A, Flaws JA. The effects of in utero bisphenol A exposure on ovarian follicle numbers and steroidogenesis in the F1 and F2 generations of mice. Reprod Toxicol. 2017 Dec;74:150-157.

Olson MR, Su R, Flaws JA, Fazleabas AT. Bisphenol A impairs decidualization of human uterine stromal fibroblasts. Reprod Toxicol. 2017 Oct;73:339-344.

Patel S, Brehm E, Gao L, Rattan S, Ziv-Gal A, Flaws JA. Bisphenol A Exposure, Ovarian Follicle Numbers, and Female Sex Steroid Hormone Levels: Results From a CLARITY-BPA Study. Endocrinology. 2017 Jun 1;158(6):1727-1738

Ziv-Gal A, Flaws JA. Evidence for bisphenol A-induced female infertility: a review (2007-2016). Fertil Steril. 2016 Sep 15;106(4):827-56.

Li Q, Davila J, Kannan A, Flaws JA, Bagchi MK, Bagchi IC. Chronic Exposure to Bisphenol A Affects Uterine Function During Early Pregnancy in Mice. Endocrinology. 2016 May;157(5):1764-74

Berger A, Ziv-Gal A, Cudiamat J, Wang W, Zhou C, Flaws JA. The effects of in utero bisphenol A exposure on the ovaries in multiple generations of mice. Reprod Toxicol. 2016 Apr;60:39-52

Heindel JJ, Newbold RR, Bucher JR, Camacho L, Delclos KB, Lewis SM, Vanlandingham M, Churchwell MI, Twaddle NC, McLellen M, Chidambaram M, Bryant M, Woodling K, Gamboa da Costa G, Ferguson SA, Flaws J, Howard PC, Walker NJ, Zoeller RT, Fostel J, Favaro C, Schug TT. NIEHS/FDA CLARITY-BPA research program update. Reprod Toxicol. 2015 Dec;58:33-44.

Zhou C, Wang W, Peretz J, Flaws JA. Bisphenol A exposure inhibits germ cell nest breakdown by reducing apoptosis in cultured neonatal mouse ovaries. Reprod Toxicol. 2015 Nov;57:87-99.

Ziv-Gal A, Wang W, Zhou C, Flaws JA. The effects of in utero bisphenol A exposure on reproductive capacity in several generations of mice. Toxicol Appl Pharmacol. 2015 May 1;284(3):354-62.

Strakovsky RS, Wang H, Engeseth NJ, Flaws JA, Helferich WG, Pan YX, Lezmi S. Developmental bisphenol A (BPA) exposure leads to sex-specific modification of hepatic gene expression and epigenome at birth that may exacerbate high-fat diet-induced hepatic steatosis. Toxicol Appl Pharmacol. 2015 Apr 15;284(2):101-12.

Peretz J, Vrooman L, Ricke WA, Hunt PA, Ehrlich S, Hauser R, Padmanabhan V, Taylor HS, Swan SH, VandeVoort CA, Flaws JA. Bisphenol a and reproductive health: update of experimental and human evidence, 2007-2013. Environ Health Perspect. 2014 Aug;122(8):775-86.

Wang W, Hafner KS, Flaws JA. In utero bisphenol A exposure disrupts germ cell nest breakdown and reduces fertility with age in the mouse. Toxicol Appl Pharmacol. 2014 Apr 15;276(2):157-64.

Peretz J, Neese SL, Flaws JA. Mouse strain does not influence the overall effects of bisphenol a-induced toxicity in adult antral follicles. Biol Reprod. 2013 Nov 7;89(5):108.

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Peretz J, Flaws JA. Bisphenol A down-regulates rate-limiting Cyp11a1 to acutely inhibit steroidogenesis in cultured mouse antral follicles. Toxicol Appl Pharmacol. 2013 Sep 1;271(2):249-56.

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Brannick KE, Craig ZR, Himes AD, Peretz JR, Wang W, Flaws JA, Raetzman LT. Prenatal exposure to low doses of bisphenol A increases pituitary proliferation and gonadotroph number in female mice offspring at birth. Biol Reprod. 2012 Oct 11;87(4):82.

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Ehrlich S, Williams PL, Missmer SA, Flaws JA, Berry KF, Calafat AM, Ye X, Petrozza JC, Wright D, Hauser R. Urinary bisphenol A concentrations and implantation failure among women undergoing in vitro fertilization. Environ Health Perspect. 2012 Jul;120(7):978-83.

Peretz J, Gupta RK, Singh J, Hernández-Ochoa I, Flaws JA. Bisphenol A impairs follicle growth, inhibits steroidogenesis, and downregulates rate-limiting enzymes in the estradiol biosynthesis pathway. Toxicol Sci. 2011 Jan;119(1):209-17.

Tucker DK, Hayes Bouknight S, Brar SS, Kissling GE, Fenton SE. 2018. Evaluation of prenatal exposure to bisphenol analogues on development and long-term health of the mammary gland in female mice. Environ Health Perspect 126:087003.

Prins GS, Ye SH, Birch L, Zhang X, Cheong A, Lin H, et al. 2017. Prostate cancer risk and DNA methylation signatures in aging rats following developmental bpa exposure: A dose-response analysis. Environ Health Perspect 125:077007.

Hass U, Christiansen S, Boberg J, Rasmussen MG, Mandrup K. 2016. Low-dose effect of developmental bisphenol a exposure on sperm count and behaviour in rats. 4:594-607.

Mandrup K, Boberg J, Isling LK, Christiansen S, Hass U. 2016. Low-dose effects of bisphenol a on mammary gland development in rats. Andrology 4:673-683.

Tremblay-Franco M, Cabaton NJ, Canlet C, Gautier R, Schaeberle CM, Jourdan F, et al. 2015. Dynamic metabolic disruption in rats perinatally exposed to low doses of bisphenol-a. PLoS One 10:e0141698.

Christiansen S, Axelstad M, Boberg J, Vinggaard AM, Pedersen GA, Hass U. 2014. Low-dose effects of bisphenol a on early sexual development in male and female rats. Reproduction 147:477-

Wadia PR, Cabaton NJ, Borrero MD, Rubin BS, Sonnenschein C, Shioda T, et al. 2013. Low-dose bpa exposure alters the mesenchymal and epithelial transcriptomes of the mouse fetal mammary gland. PLoS ONE 8:e63902.

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Murray TJ, Maffini MV, Ucci AA, Sonnenschein C, Soto AM. 2007. Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol a exposure. Reprod Toxicol 23:383-390.

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Markey CM, Luque EH, Munoz De Toro M, Sonnenschein C, Soto AM. 2001. In utero exposure to bisphenol a alters the development and tissue organization of the mouse mammary gland. Biol Reprod 65:1215-1223.

Papers on BPA replacement chemicals:

Kolla S, Morcos M, Martin B, Vandenberg LN. 2018. Low dose bisphenol S or ethinyl estradiol exposure during the perinatal period alter female mouse mammary development. *Reproductive Toxicology. 78: 50-59.*

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Catanese MC, Vandenberg LN. 2017. Bisphenol S (BPS) alters maternal behavior and brain in mice exposed during pregnancy and lactation and their daughters. Endocrinology. 158(3): 516-530.

Kim B, Colon E, Chawla S, Vandenberg LN, Suvorov A. 2015. Endocrine disruptors alter social behaviors and indirectly influence social hierarchies via changes in body weight. Environmental Health.14:64.