ENDOCRINE SOCIETY
Hormone Science to Health

August 24, 2017

Dear Members of the EFSA Unit on Food Ingredients and Packaging,

The Endocrine Society appreciates the opportunity to participate in the public consultation on the draft Bisphenol A (BPA) hazard assessment protocol. 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.

This guidance is a significant improvement over prior evaluations of BPA proposed or completed by the European Food Safety Authority (EFSA). We are particularly impressed with the transparent and systematic methodology to evaluate the literature, grounded in knowledge from clinical and environmental health. However, there are important issues that the Endocrine Society recommends addressing prior to finalizing the protocol. Our detailed comments are provided in the web-based form; to summarize, we recommend:

- Replacing "breastfed" in line 190 to include infants exposed through e.g., consumer products.
- Removing the classification scheme in Table 1.
- Cautiously interpret 'toxicokinetic' studies that are unable to know or control BPA levels.
- Cautiously interpret (or avoid interpreting) extrapolations from toxicokinetic studies to biomonitoring studies.
- Review important literature prior to 2013 for many endpoints.
- Assess the activity of BPA when co-exposure occurs with endogenous hormones.
- Include cross-sectional study designs in the inclusionary criteria.
- Identify sources of funding in studies, to reduce risk of bias.
- Ensure that expert judgment includes scientists with expertise in hormonal systems and endocrinology in all steps, but particularly the completion of table 10.
- Clarify the term "sufficient number of animals" and provide additional explanation throughout section 9.

Thank you for considering the Endocrine Society's comments. If we can be of further assistance, please do not hesitate to contact Joseph Laakso, PhD, Associate Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

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Detailed Comments

Section 2.2 – Target population

Infants may be exposed through consumer products, in addition to breastfeeding. We therefore recommend that the term "breastfed" be removed in line 190 to be replaced by a more inclusive statement.

Section 2.4 – Endpoints relevant to the hazard assessment

The revised BPA protocol should be implemented without extensive reference to previous evaluations, which had serious flaws. Specifically, the classification scheme in table 1 using the phrases "likely", "as likely as not", and "unlikely" should be discarded. This classification, as it stands, may create bias or predispose judgment in the evaluation of effects through the revised protocol.

Section 2.5 – Identification of the hazard assessment sub-questions

For the evaluation of toxicokinetic data in animals and humans, it is important to acknowledge the following issues:

- First, for a study to be considered a toxicokinetic study, actual administered doses must be known; thus, providing individuals with canned foods and measuring their BPA levels (in serum or urine) is an important 'intervention' study, but it is not a toxicokinetic study, because the amount administered is not known or controlled. We recommend that EFSA note studies in the literature that self-identify as 'toxicokinetic' studies that do not meet these criteria.
- Second, it must be acknowledged that toxicokinetic studies examine individuals (animals or humans) administered BPA via a single route of exposure, yet EFSA's own work has shown that humans encounter BPA via multiple routes of exposure. Thus, extrapolations from toxicokinetic studies to biomonitoring studies (designed to evaluate exposures) must be done with caution – or perhaps not at all.

Section 3.1 Time span of evidence search

The prior reviews of the literature conducted by EFSA did not use the same criteria to evaluate and weigh data. For some endpoints (mammary gland proliferation, neurodevelopment, metabolic effects), important data published prior to 2013 exist, therefore the entirety of the literature must

be examined under this new protocol. For example, the evaluation of BPA and the mammary gland has been given a high preference by EFSA, and much of the data showing low dose effects of BPA on the mammary gland pre-dates 2013. Many of these studies were previously disregarded by EFSA due to the use of subcutaneous exposures (via osmotic pumps) but 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. A partial list of important references pre-dating 2013 is provided as a separate annex.

Section 4.2.4.3 – Mode of action studies

We note that BPA will not be assessed as part of a mixture in the context of this protocol, limiting the ability to reflect real-world exposures. The activity of BPA should be assessed when co-exposure occurs with endogenous hormones. This should also be reflected in Table 5.

Section 4.2.5 – Inclusion/exclusion criteria for human, animal and MoA studies

The prior reviews of the literature conducted by EFSA did not use the same criteria to evaluate and weigh data. Thus, it does not make sense for this new protocol to exclude data published prior to 2013, as described in table 3 (see our recommendation for Section 3.1). We also recommend inclusion of cross-sectional study designs.

Section 5.1 – Data extraction

The source of funding for a study is an important potential component of risk of bias where there may exist conflicts of interest. We recommend that the source of funding be recorded for all studies.

Section 7.3 – Quality appraisal of animal studies

The use of the SciRAP criteria is a great improvement. However, Table 10 cannot be completed without expert judgement about what should be considered a 'sensitive' model and a 'sensitive' endpoint. The CD-Sprague Dawley rat, for example, can be administered high doses of ethinyl estradiol (1 µg/rat, approximately 3.3 µg/kg, a dose 6-times higher than what is typically prescribed to women for birth control) without any obvious effects. Scientists with expertise in endocrinology and detailed knowledge of hormonal systems will be essential for accurate completion of Table 10.

Also, it is unclear what is meant by "a sufficient number of animals". Clarification should be provided so that academic studies are not disadvantaged in assessments.

Section 9 – Relevance and adversity of the effect for human health

This section is extremely vague and relies exclusively on expert judgement. Additional explanation is needed to ensure that a sufficient and transparent justification is provided by experts.

Annex: List of selected pre-2013 references

1. Pancreas/glucose metabolism endpoints

Alonso-Magdalena P., Morimoto S., Ripoll C., Fuentes E., Nadal A., 2006. The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance. Environ Health Perspect. Jan;114(1):106-12.

Alonso-Magdalena P., Vieira E, Soriano S., Menes L., Burks D., Quesada I., Nadal A. 2010. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ Health Perspect. Sep;118(9):1243-50.

Wei J., Lin Y., Li Y., Ying C., Chen J., Song L., Zhou Z., Lv Z., Xia W., Chen X., Xu S. 2011. Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. Endocrinology. Aug;152(8):3049-61.

2. Mode of action

Alonso-Magdalena P., Ropero A.B., Carrera M.P., Cederroth C.R., Baquié M., Gauthier B.R., Nef S., Stefani E., Nadal A. 2008. Pancreatic insulin content regulation by the estrogen receptor ER alpha. PLoS One. Apr 30;3(4):e2069.

Soriano S., Alonso-Magdalena P., García-Arévalo M., Novials A., Muhammed S.J., Salehi A., Gustafsson J.A., Quesada I., Nadal A. 2012. Rapid insulinotropic action of low doses of bisphenol-A on mouse and human islets of Langerhans: role of estrogen receptor β. PLoS One. 7(2):e31109.

3. Mammary gland endpoints

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

Markey, C.M., Coombs, M.A., Sonnenschein, C., Soto, A.M., 2003. Mammalian development in a changing environment: exposure to endocrine disruptors reveals the developmental plasticity of steroid-hormone target organs. Evolution and Development 5, 67-75.

Munoz-de-Toro, M., Markey, C.M., Wadia, P.R., Luque, E.H., Rubin, B.S., Sonnenschein, C., Soto, A.M., 2005. Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. Endocrinology 146, 4138-4147.

Vandenberg, L.N., Maffini, M.V., Wadia, P.R., Sonnenschein, C., Rubin, B.S., Soto, A.M., 2007. Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. Endocrinology 148, 116-127.

Murray, T.J., Maffini, M.V., Ucci, A.A., Sonnenschein, C., Soto, A.M., 2007. Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. Reprod Toxicol 23, 383-390.

Durando, M., Kass, L., Piva, J., Sonnenschein, C., Soto, A.M., Luque, E.H., Munoz-de-Toro, M., 2007. Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. Environ Health Perspect 115, 80-86.

Wadia, P.R., Vandenberg, L.N., Schaeberle, C.M., Rubin, B.S., Sonnenschein, C., Soto, A.M., 2007. Perinatal bisphenol A exposure increases estrogen sensitivity of the mammary gland in diverse mouse strains. Environ Health Perspect 115, 592-598.

Vandenberg, L.N., Maffini, M.V., Schaeberle, C.M., Ucci, A.A., Sonnenschein, C., Rubin, B.S., Soto, A.M., 2008. Perinatal exposure to the xenoestrogen bisphenol-A induces mammary intraductal hyperplasias in adult CD-1 mice. Reprod Toxicol 26, 210-219.

Durando, M., Kass, L., Perdomo, V., Bosquiazzo, V.L., Luque, E.H., Munoz-de-Toro, M., 2011. Prenatal exposure to bisphenol A promotes angiogenesis and alters steroid-mediated responses in the mammary glands of cycling rats. J Steroid Biochem Mol Biol 127, 35-43.

Weber Lozada, K., Keri, R.A., 2011. Bisphenol A Increases Mammary Cancer Risk in Two Distinct Mouse Models of Breast Cancer. Biol Reprod 85, 490-497.

Tharp, A.P., Maffini, M.V., Hunt, P.A., Vandevoort, C.A., Sonnenschein, C., Soto, A.M., 2012. Bisphenol A alters the development of the rhesus monkey mammary gland. Proc Natl Acad Sci U S A 109, 8190-8195.

Kass, L., Altamirano, G.A., Bosquiazzo, V.L., Luque, E.H., Munoz-de-Toro, M., 2012. Perinatal exposure to xenoestrogens impairs mammary gland differentiation and modifies milk composition in Wistar rats. Reprod Toxicol 33, 390-400.

Vandenberg, L.N., Schaeberle, C.M., Rubin, B.S., Sonnenschein, C., Soto, A.M., 2013. The male mammary gland: a target for the xenoestrogen bisphenol A. Reprod Toxicol 37, 15-23.

Acevedo, N., Davis, B., Schaeberle, C.M., Sonnenschein, C., Soto, A.M., 2013. Perinatally administered bisphenol a as a potential mammary gland carcinogen in rats. Environ Health Perspect 121, 1040-1046.

Wadia, P.R., Cabaton, N.J., Borrero, M.D., Rubin, B.S., Sonnenschein, C., Shioda, T., Soto, A.M., 2013. Low-Dose BPA Exposure Alters the Mesenchymal and Epithelial Transcriptomes of the Mouse Fetal Mammary Gland. PLoS ONE 8, e63902.