

April 9, 2018

Mary S. Wolfe, Ph.D
NIEHS/NIH
P.O. Box 12233, MD K2-03
Research Triangle Park, NC 27709

Re: Draft NTP Research Report on the CLARITY-BPA Core Study

Dear Dr. Wolfe,

The Endocrine Society appreciates the opportunity to comment on the Draft National Toxicology Program (NTP) Research Report on the CLARITY-BPA Core Study. Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization dedicated to the study of hormones and clinical practice of endocrinology. Our members are among the world's leading experts on the subject of endocrine-disrupting chemicals (EDCs), including scientists investigating the health effects and underlying mechanisms of endocrine disruption due to bisphenols such as bisphenol-A (BPA).

We support the goals of the CLARITY-BPA project, specifically to integrate results from the latest academic studies investigating sensitive endpoints with guideline-compliant studies supported by the Food and Drug Administration (FDA). However, we have significant concerns with the conclusions of the interim Research Report and we strongly urge the FDA and other stakeholders to avoid drawing conclusions regarding the safety of BPA based only on the results presented in the Core Study. Some technical elements of the report deserve very close scrutiny during peer review.

Use of historical rather than concurrent controls as comparators to experimental groups. A statistically significant increase in mammary adenocarcinomas was observed in female offspring exposed to 2.5 µg BPA/kg/day from gestation through the perinatal period. Yet, this result was dismissed in the report by drawing comparisons to historical controls, where rates of adenocarcinoma were much higher than in the controls run in the CLARITY-BPA project. This dismissal of significant results via the use of historical control data runs counter to guidance from the Historical Control Working Group, which suggests that concurrent controls are the most relevant comparator for determining treatment-related effects¹. Historical controls suffer from limitations due to lack of blinding and other potentially confounding effects related to timing, setting, and

¹ C. Keenan, S. Elmore, S. Francke-Carroll, R. Kemp, R. Kerlin, S. Peddada, J. Pletcher, M. Rinke, S.P. Schmidt, I. Taylor, D.C. Wolf. Best practices for use of historical control data of proliferative rodent lesions. *Toxicol Pathol* 37(5) (2009) 679-93.



environmental chemical exposures. Because background exposures to BPA have not been provided for the historical control group, they are likely to be an inappropriate comparator.

Methodology for monitoring of estrous cyclicity. Monitoring was conducted differently compared to standard academic laboratory practice. The methods utilized may have contributed to a detrimental effect on statistical power, precluding the identification of significant effects. We anticipate that there will be challenges integrating the estrous cycle data with the grantee studies that require precise cycle staging unless more details regarding the timing of cyclicity assessments are provided.

Statistical approach and consideration for non-monotonicity. We are concerned that the lack of a conventional dose-response curve resulted in a bias against the significance of effects observed at low-doses across the endpoints investigated, such as body weight. Effects that are seen at the lowest dose range cannot be discarded out of hand and statistical analysis must take into account the fact that relevant effects might be seen at the 2.5 μ g dose but not seen at higher doses. We note that the statistically significant increase of mammary adenocarcinomas observed in the 2.5 μ g BPA/kg/day dose group in females exposed gestationally until PND 21 is consistent with numerous findings across the academic scientific literature. Effects at this low dose are expected based on hormone biology and well-established principles of endocrinology². Furthermore, some effects seen at low doses, such as a significant increase in prostatic lymphocyte infiltration in males from the 2.5 μ g BPA/kg/day group compared to controls at 1 year should be recognized, especially because chronic prostatic inflammation in men can contribute to benign prostatic hyperplasia and prostate carcinogenesis.

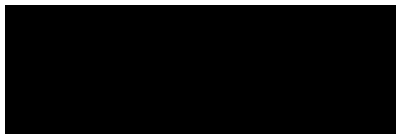
The Endocrine Society previously expressed disappointment with the statement by the FDA asserting that the results of the Core Report support previous determinations that BPA is safe for use in food containers and packaging. It is highly premature to draw any conclusions based only on the Core Report, which only includes one arm of the CLARITY-BPA project and has not been peer-reviewed. As we note above, some of the endpoints in the Core Study do provide evidence of harm from BPA, particularly at the low-dose range. Furthermore, the Core Study did not investigate important highly-sensitive endpoints, such as effects on the brain and ovary, that are necessary to assess before making an informed determination on safety. Indeed, the point of the CLARITY-BPA study was to integrate guideline-compliant studies with other more sensitive and appropriate endpoints frequently used in academic studies.

² Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ, Vom Saal FS. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. *Endocrinology*. 2012 Sep;153(9):4097-110



In conclusion, we strongly recommend that the participants at the peer review meeting carefully examine technical elements such as the use of historical controls, monitoring of estrous cycling, and the statistical approaches used to arrive at the findings described in the report. Endocrinologists with expertise in hormonal systems affected by BPA should be included in the peer review panel. The Endocrine Society looks forward to the final CLARITY-BPA report, including the integration of academic researchers' studies of BPA's effects on additional relevant endpoints. To avoid further public misinterpretation of the potential hazards associated with BPA, it is imperative that the NTP, FDA, and other stakeholders avoid issuing summary judgments about the safety of BPA until all the grantee data are assembled and analyzed together with the Core Study. 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,



Susan Mandel, MD, MPH
President
Endocrine Society