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United States Food and Drug Administration  
5100 Paint Branch Pkwy.,  
College Park, MD 20740

RE: Docket No. FDA-2016-F-1253

July 14, 2016

Dear Dr. Randolph and Dr. Keefe,

The Endocrine Society appreciates the opportunity to provide comments on the food additive petition to amend and/or revoke specific regulations regarding specified ortho-phthalates in food contact materials. 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. Our membership of over 18,000 includes researchers who are making significant contributions to the advancement of knowledge in toxicology, especially in the field of endocrine-disrupting chemicals (EDCs), a class of chemicals that includes phthalates.

Although we do not take a position on specific regulatory actions that should be taken by the FDA in response to the petitioners' claims, new evidence accumulated over the past 5 years strongly implicates phthalates in a range of human health impacts, and these impacts incur significant costs on society. Furthermore, current policy governing EDCs might not take into consideration the full body of research into EDCs. In our comments we highlight recent research from Endocrine Society members that we ask the FDA to consider as you develop your response to the petition on ortho-phthalates.

**Information on Phthalates from the Endocrine Society's Second Scientific Statement on EDCs**

On September 28, 2015, the Endocrine Society released an update to the breakthrough 2009 Scientific Statement on EDCs. The updated statement examined the state of scientific evidence on EDCs and risks posed to human health due to exposures to EDCs in topic areas for which the evidence was strongest. This comprehensive assessment of the scientific literature concluded that recent research has led "to a much fuller understanding of the endocrine principles by which EDCs act, including nonmonotonic dose-responses, low-dose effects, and developmental vulnerability." In the studies reviewed within the Scientific Statement, phthalates were linked to obesity and diabetes, female and male reproductive health concerns, hormone-sensitive breast cancer, thyroid disruption, and neurodevelopmental effects<sup>1</sup>. A copy of the Scientific Statement has been appended to this letter, and uploaded to the docket via regulations.gov. We encourage the FDA to review and consider the information contained in this scientific statement when evaluating the claims of the petitioners.

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<sup>1</sup> Gore, AC et al., "EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals." *Endocr Rev.* 2015 Dec; 36(6): E1-E150.



## Significant Costs Associated with Phthalate Exposure

Due to the links between EDCs and harms to human health, attention has focused on the economic costs associated with improper regulation of EDCs. A series of studies published last year in *The Journal of Clinical Endocrinology & Metabolism* found that health problems associated with EDC exposures cost the European Union more than €157 billion each year in healthcare expenses and lost productivity<sup>2</sup>. Of these costs, approximately €26 billion can be attributed to phthalates and chemicals in plastics and cans. These costs represent real harms to human health; for example, up to 145,000 attributable cases of endometriosis are associated with exposure to phthalates, representing costs of up to €1.25 billion<sup>3,4</sup>.

**In summary, we assert that new evidence accumulated over the past 5 years strongly implicates phthalates in a range of human health impacts, and that these impacts incur significant costs on society.** It is also worth noting that all phthalates that have been examined for reproductive and endocrine effects have been found to pose endocrine-related risks. A large number of the ortho-phthalates included in the petition have no published safety data, leading to concern within the scientific community about possible endocrine effects of these compounds. All of the ortho-phthalates share a common functional group and similar metabolic pathways, so they are likely to have similar endocrine effects. Because the phthalates are commonly used in food packaging and handling equipment, one of the greatest sources of exposure to humans is through food. A number of papers have demonstrated that processed foods and fast foods significantly increase phthalate exposures in humans, particularly in children, females, lower socio-economic groups, and non-hispanic blacks<sup>5,6,7</sup>. As discussed in this petition, infant formula and baby foods

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<sup>2</sup> Trasande L. et al., “Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union.” *J Clin Endocrinol Metab*, April 2015, 100(4):1245–1255.

<sup>3</sup> Hunt PA. et al., “Female Reproductive Disorders, Diseases, and Costs of Exposure to Endocrine Disrupting Chemicals in the European Union.” *J Clin Endocrinol Metab*, April 2016, 101(4):1562–1570.

<sup>4</sup> Buck Louis, GM. Et al., “Bisphenol A and Phthalates and Endometriosis, The ENDO Study.” *Fertil Steril*. 2013 Jul; 100(1): 162–169.e2.

<sup>5</sup> Zota, AR, Phillips, CA, and Mitro, SD. “Recent Fast Food Consumption and Bisphenol A and Phthalates Exposures among the U.S. Population in NHANES, 2003-2010.” *Environ Health Perspect*. 2016 Advanced publication: DOI:10.1289/ehp.1510803

<sup>6</sup> Cao XL. “Phthalate esters in foods: sources, occurrence, and analytical methods.” *Compr Rev Food Sci Food Saf* 2010 9:21-43.

<sup>7</sup> Rudel RA, et al. “Food packaging and bisphenol A and bis (2-ethylhexyl) phthalate exposure: findings from a dietary intervention.” *Environ Health Perspect* 2011 119:914-920.



have been shown to contain high concentrations of various ortho-phthalates,<sup>8,9</sup> which puts children at a high risk of exposure during critical developmental stages.

We ask that the FDA consider these and other relevant research findings in your evaluation of regulations for the use of ortho-phthalates in food contact materials. Thank you for considering our comments. If we can be of any further assistance in your efforts, please reach out to Joseph Laakso, PhD, Associate Director of Science Policy at [jlaakso@endocrine.org](mailto:jlaakso@endocrine.org).

Sincerely,

Henry Kronenberg, MD  
President  
Endocrine Society

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<sup>8</sup> Cirillo, T. et al. "Exposure to Di-2-Ethylhexyl Phthalate, Di-N-Butyl Phthalate and Bisphenol A through Infant Formulas." *Journal of Agriculture and Food Chemistry* 2015 63:3303-3310 .

<sup>9</sup> Arnold Schechter et al. "Phthalate Concentrations and Dietary Exposure from Food Purchased in New York State." *Environ Health Perspectives* 2013 121:473–479.