



Dr. George Borlase  
Assistant Executive Director  
Office of Hazard Identification and Reduction  
U.S. Consumer Product Safety Commission (CPSC)  
4330 East West Highway  
Bethesda, MD 20814

July 29, 2016

Dear Dr. Borlase,

The raw data for the study entitled 'Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats'<sup>1</sup> were made publically available via the U.S. EPA's Integrated Risk Information System (IRIS) Health & Environmental Research Online (HERO) database<sup>2</sup> in February 2016. At the same time Danish EPA with the agreement of Dr. Boberg also provided the raw data directly to the European Council of Plasticisers and Intermediates, in the context of an ongoing discussion on a classification proposal for DINP. We are writing to alert you that upon analysis of these data, we were unable to reproduce a number of the statistical findings in the manuscript. We considered it important to make you aware of these discrepancies given the weight this study was given in the 2014 report by the Chronic Hazard Advisory Panel (CHAP) in its evaluation of DINP. Though DINP was found safe by the CHAP on its own, it was included in the Cumulative Risk Assessment, in part, due to the data presented in Boberg et al. It should be noted that these discrepancies could not have been identified at the time of peer review of the manuscript, during discussions of the data between the CHAP members, nor during the open comment period for the Federal Registry Notice on the draft rule (79 FR 78324, Dec 30<sup>th</sup> 2014 – March 16<sup>th</sup> 2015) because the raw data to Boberg et al. were not yet available.

Using the statistical methods as originally reported in Boberg et al. (2011) we analyzed the raw data that were provided for the following endpoints: 1) testosterone, 2) nipple retention, 3) sperm motility, 4) sperm/g cauda, 5) percent progressive sperm and 6) anogenital distance (AGD/AGDi) measurements. We were unable to reproduce the reported statistical significance ( $P < 0.05$ ) for four of these six parameters as published, i.e. parameters 3, 4, 5 and 6. Additionally, we were unable to replicate some of the descriptive statistics reported in the manuscript and noted a discrepancy of the reported control data with the respective OECD guidance<sup>3</sup> on the evaluation of sperm motility.

In an effort to reconcile these noted discrepancies, we contacted Boberg et al. in May of 2016. The authors acknowledged that modifications to the publication were necessary to facilitate reproducibility and have shared

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<sup>1</sup> J. Boberg, S. Christianson, M. Axelstad, T.S.Kledal, A. M. Vinggaard, M. Dalgaard, C.Nellemann, U. Hass. Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats. *Reprod Toxicol*, 31 (2011), pp. 200-209.

<sup>2</sup> Supplemental Boberg data for HERO ID 806135 from email communication. EPA-Hq-ORD-2014-0637. <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2014-0637-0014>. Last accessed July 2016

<sup>3</sup> Guidance document on mammalian reproductive toxicity testing and assessment (2008), series on testing and assessment. Number 43 Number 43, ENV/JM/MONO(2008)16

with us a Corrigendum to their methods description which they have since submitted to Reproductive Toxicology. While we appreciate the efforts made by the authors in the Corrigendum to address our observations, we have recently issued a correspondence to the editor requesting clarification and corrections beyond those addressed in the Corrigendum. It is our view that the methodological modifications made in the Corrigendum only partially address the discordance of statistical outcomes we identified; and raise some additional deficiencies regarding the thoroughness and transparency of the methods and the influence of irregular approaches in the statistical analysis on the representation of results. In summary, ECPIs view is that several of the results need to be changed to reflect the correct original statistical methods, rather than as is being proposed by Boberg et al that the statistical methods are changed to reflect the results. With respect to the CPSCs work on DINP these discrepancies are noteworthy as the ECPI analysis of the data indicates the findings from Boberg et al. were more consistent with the findings of Clewell et al., where the authors concluded no evidence of Rat Phthalate Syndrome were identified. This is of importance as the ability “to disrupt male sexual differentiation” which “culminates in what has been described as the phthalate syndrome” was the CHAP’s basis for inclusion of DINP in the cumulative risk assessment.

We understand the Corrigendum to Boberg et al. (2011)<sup>1</sup> will be published shortly in Reproductive Toxicology, and expect our letter to the editor to also be published in due course. We encourage the science staff to perform an independent assessment of the analyses using the raw data provided in HERO database. Please evaluate the impact of these data on initial conclusions and consider this information as you deem appropriate during the science staff’s preparation of recommendations on final rule making for DINP. We welcome any questions you may have regarding this communication and are willing and able to share the results of the reanalysis with your science staff for comparison and discussion.

Sincerely,

Michela Mastrantonio  
The European Council for Plasticisers and Intermediates

**About EPCI:** The European Council for Plasticisers and Intermediates is a Brussels-based trade association representing the common interests of European manufacturers of plasticisers, alcohols and acids. Member companies are BASF, Deza, Evonik, ExxonMobil, Lanxess and Perstorp. ECPI is a sector group of Cefic, the European Chemical Industry Council, which represents the interests of the European chemical industry. Some of the member companies of ECPI are producers of DINP.