July 17, 2014

Robert S. Adler, Acting Chairman
U.S. Consumer Product Safety Commission
4330 East-West Highway
Bethesda, MD 20814

Dear Mr. Adler:

On behalf of the Chronic Hazard Advisory Panel on phthalates and phthalate alternatives, we are pleased to transmit the Panel's report.

In preparing its report, the Panel reviewed all of the available toxicity data on phthalates and six phthalate alternatives. Total exposure to phthalates was estimated from high quality biomonitoring studies in humans, including pregnant women (i.e., fetal exposure) and infants. Exposure to phthalates was independently estimated for individual sources of exposure including, but not limited to, diet, personal care products, toys, and child care articles. The Panel estimated the potential risks to consumers for phthalates both in isolation and in combination with other phthalates.

Although phthalates may cause a wide range of toxicities, the Panel concluded that the most sensitive and most extensively studied is male developmental toxicity in the rat. Specifically, exposing pregnant female rats to certain phthalates (not all phthalates) results in abnormalities of the developing male reproductive tract. The populations of greatest concern are the fetus (or pregnant females), infants, and children. Overall, the epidemiological data suggest that phthalate exposure during gestation may contribute to similar effects in human. The Panel also concluded that humans are simultaneously exposed to multiple phthalates. With the exception of di(2-ethylhexyl) phthalate (DEHP), the risks from individual phthalates are low. Considering the combined effects of multiple phthalates, however, roughly 10 percent of pregnant women and 5 percent of infants have exposures exceeding acceptable levels. The Panel further concluded that most phthalate exposure comes from diet and personal care products, which are outside the jurisdiction of the U.S. Consumer Product Safety Commission (CPSC). However, exposures from the use of children's toys and child care articles, while relatively small, contribute to the overall risk.

Based on its examination, the Panel recommends to CPSC that certain phthalates which cause male developmental toxicity be added to the list of permanently banned phthalates, including diisobutyl phthalate (DIBP), di-n-pentyl phthalate (DPENP), di-n-hexyl phthalate (DHEXP), and dicyclohexyl phthalate (DCHP). Diisooctyl phthalate (DIOP), which may cause male developmental effects, should be placed under an interim ban until additional data are available. One of the phthalates currently under an interim ban, diisononyl phthalate (DINP), should be permanently banned. The other interim ban phthalates, di-n-octyl phthalate (DnOP) and diisodecyl phthalate (DIDP) do not appear to cause male developmental effects and may be removed from the interim ban. The available information on some phthalates and phthalates

alternatives is limited. Thus, the Panel recommends that the CPSC and other U.S. agencies obtain the necessary exposure and hazard data to assess the potential health risks of these compounds.

The CHAP has reviewed and evaluated the comments provided by the TERA-coordinated peer review of the draft report of the Chronic Hazard Advisory Panel on Phthalates and Phthalate alternatives. Overall the panel appreciated the time and effort made by the reviewers to read the report, and the thoroughness of their comments on the main document and the Appendices. Many of their comments were directed toward the need for more research, data, and eventually their use in analysis and modeling (e.g., pharmacokinetics; see comment no. 2.1.1.4). Unfortunately, the completion or the detailed description of such efforts were not within the charge of the CHAP, and could only be reflected in our overall recommendations and recommendations for individual compounds. In the draft, our recommendations were presented within the individual chapters, but to achieve the needs for early presentation of such information these are being presented in the executive summary we have written for the report.

Individual comments provided by each of the four reviewers were evaluated in a closed session completed by the CHAP between January 29 and 31, 2014. Those pertaining to the Charge of the CHAP and those requiring better presentation and explanation have been addressed in constructing the revised version of the report. The changes included correcting errors and omissions, and the changes were inserted on individual pages within the Chapters of the report.

As mentioned above, the draft did not include an executive summary. It is now at the beginning of the report, and includes short statements on our recommendations, the results from our evaluation of the literature, and information on the uncertainties associated with the toxicology, internal and external exposure characterization, the hazard evaluation and risk assessment.

There were comments made by the reviewers that required either clarifying individual statements or the addition of text to individual paragraphs to fill in information gaps. These have been added directly to the document and the places noted in the following:

Pages 11-13. The Introduction and Strategy section (2.1) was revised by outlining the subpopulations of concern, addressing which written materials were reviewed by the CHAP, and inserting activities undertaken by the CHAP to reduce information bias. The issue of systematic review was also added, with the CHAP concluding that the project was not amenable to systematic review methodology because of the many different data streams that needed to be reviewed (comments 2.5.1.4, 2.6.1.2, 2.8.1.4).

Page 13-15. The section on Selection of Toxicity Endpoints and Life Cycle Stages (2.2) was rewritten to address comments regarding phthalate-induced carcinogenesis and PPARα. The CHAP states that carcinogenesis may be relevant for certain phthalates, but that considerable data gaps existed for other phthalates and the relevance of the underlying modes of action in humans. The CHAP concluded that the most sensitive and extensively studied toxicity endpoint was male developmental toxicity (comments 2.3.1.1, 2.3.6.1, 2.8.1.1).

Pages 15-16. The Rat Phthalate Syndrome section (2.2.1) was revised by adding citations to the text (comments 2.3.1.1, 2.8.1.1, 2.8.1.2).

Pages 27-28. The Epidemiology section (2.4) was revised by adding discussion on phthalate metabolites in amniotic fluid (comments 2.1.1.1, 2.8.1.1).

Page 36. The Human Biomonitoring Results section (2.5.4) was revised to reflect that sampling weights were used in the calculation of NHANES biomonitoring data (comments 2.1.5.2, 2.1.5.4).

Pages 61-63. The title of section 2.7 "Hazard Index Approach" was changed to "Cumulative Risk Assessment" for clarity. Similarly, the title of section 2.7.1 "Choice of Approach for Quantitative Assessment" was changed to "Choice of Approach for Cumulative Assessment." The text in section 2.7.1 was extensively revised. In particular, a more general narrative of the Hazard Index method was inserted just before the CHAP identified issues with adapting the HI for use in the cumulative risk assessment. After discussing issues associated with using antiandrogenicity endpoints as the basis for the cumulative risk assessment, the CHAP replaced the term Reference Dose (RfD) with a new term, Potency Estimates for Antiandrogenicity (PEAA), to make it clear that these reference values are specific for antiandrogenicity endpoints. The CHAP also asserted that these PEAA should be considered only in the context of the antiandrogenicity-based cumulative assessment and not individual phthalate risk assessments. The CHAP then described an alternate approach, the Point of Departure Index, that was also considered in the assessment. Strengths and weaknesses were discussed in relation to the Hazard Index. The final revised text addressed how three different PEAA sources (Case 1, 2, and 3) were used in conjunction with the Hazard Index approach (comments 2.2.1.1, 2.2.1.2, 2.2.1.3, 2.2.1.4, 2.2.2.1, 2.8.1.2).

Pages 63-64. The section on potency estimates (2.7.2.2) was revised by deleting a portion of the discussion pertaining to points of departure and how they relate to the Hazard Index. The "RfDs" were changed to "PEAAs" to emphasize that they are based on antiandrogenicity (comments 2.2.1.1, 2.2.1.2, 2.2.1.3, 2.2.1.4, 2.2.2.1).

Pages 64-65. The section on Calculation of Hazard Quotients section (2.7.3.1) was clarified by deleting reference to MOEs and revising the summary by replacing RfDs with PEAAs.

Page 79. The Criteria for Recommendations section (5.1) (number 4) was clarified by stipulating that the likely risk to humans was going to be assessed by utilizing MOEs (comment 2.8.1.3).

Pages 80-81. Table 2.17 (Margin of Exposure estimates for pregnant women and infants) was moved from section 2.7.3.1 (page 57 of the Draft report) to section 5.1 and renumbered as Table 5.1. The table was also expanded to include data for infants and for all 20 chemicals (phthalates and phthalate substitutes) (comment 2.8.1.4).

Page 114-115. Data and reproductive/developmental conclusions from Saillenfait *et al.*, 2009b were added to the "Developmental" section (5.4.5.1.1.2) of DHEXP (comments 2.6.1.2, 2.8.1.4).

Page 119. The paragraph on DIOP exposure (section 5.4.7.4) was revised by adding a citation regarding the presence of DIOP in pacifiers and bottle nipples.

Page 129. The recommendation for DEHA (section 5.5.2.6) was edited for clarity (comment 2.6.1.2).

Minor editorial comments, formatting changes in tables (such as standardization of significant digits), and revising references and citations have also been addressed within the report.

Philip E. Mirkes was elected as CHAP Chairman at the first CHAP meeting in April 2010 and served until September 2013. He was unable to continue as Chairman for personal reasons. Paul Lioy and Russ Hauser served as Co-Chairmen from October 2013 to the present. Bernard A. Schwetz was elected Vice-Chairman in April 2010 and served until December 2012. He was unable to continue for health reasons.

The members of the Panel agree with the contents of the report and have indicated their approval below.

Sincerely,

Paul J. Lioy, Co-Chairman
Professor and Vice Chair, Department of Environmental and Occupational Medicine,
RBHS-Robert Wood Johnson Medical School and
Deputy Director of Government Relations and Director of Exposure Science,
Rutgers Environmental and Occupational Health Sciences Institute
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Russ Hauser, Co-Chairman
Professor of Environmental and Occupational Epidemiology,
Department of Environmental Health, Harvard School of Public Health
Boston, MA

Final Report of the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives

Approved:

Paul J. Lioy
Co-Chairman

Russ Hauser
Co-Chairman

Chris Gennings

Holger M. Koch

Andreas Kortenkamp

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