# Independent Expert Peer Review of the Final CHAP Report on Phthalates and Phthalate Alternatives

**SEPTEMBER 7, 2014**

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# 1.0 Overview

The U.S. Consumer Product Safety Commission (CPSC) convened a Chronic Hazard Advisory Panel (CHAP) to study the potential effects on children's health of phthalates and phthalate alternatives as used in children's toys and childcare articles. The CHAP Phthalates Panel has been engaged in this effort since the spring of 2010. CPSC released the final CHAP report on July 18, 2014. ToxStrategies, Inc. (ToxStrategies) was retained by the American Chemistry Council (ACC) High Phthalates Panel to manage and coordinate an independent peer review of the final CHAP report by a team of highly respected and internationally-recognized subject matter experts. This effort was undertaken to ensure that a scientifically robust review of the report was performed by independent scientists with recognized expertise in the key subject areas covered in the CHAP report. All aspects of the peer review process were managed by ToxStrategies, including selection of the experts, contracting with the experts, communication with the experts, evaluation of potential conflicts of interest, development of general guidelines for preparation of comments (in lieu of charge questions), distribution of the CHAP report and CPSC-funded peer review of the report, collection of each expert's written comments, and compilation of all comments into the current single report. Neither ACC nor members of the ACC High Phthalates Panel had any contact or communication with the subject matter experts engaged to perform the independent peer review of the CHAP report. The opinions expressed by each peer reviewer are solely their own and do not represent the opinions of their employers or other affiliations, ToxStrategies, or the ACC.

# 2.0 Expert Peer Review

## *2.1 Initial Identification of Potential Peer Reviewers*

Potential subject matter experts were initially identified and considered by ToxStrategies staff based on their expertise in subject area(s) anticipated to be pertinent to the CHAP report and prior experience with phthalates. A preliminary teleconference was held between ToxStrategies and each potential expert to discuss their specific expertise in the subject matter of interest, as well as to ascertain their interest and availability to participate upon release of the final CHAP report at some future date. As part of this exercise, a conflict of interest check was performed for all parties involved (ToxStrategies, ACC, and the experts).

Following this preliminary conference call, ToxStrategies selected experts to review each of the potential subject areas anticipated to be included in the CHAP report. ToxStrategies periodically communicated via E-mail with each expert during the time between the initial contact and the release of the final CHAP report, in order to ensure continued interest and availability.

### *2.2 Selected Peer Reviewers*

ToxStrategies reviewed the final CHAP report in detail immediately following its release to the public. Based on this review, the key subject areas for independent peer review were identified and determined by ToxStrategies to be: 1) Reproductive and Developmental Toxicity/Endocrine/Human Relevance, 2) Epidemiology, 3) Exposure, and 4) Cumulative Risk. The experts previously identified for these subject areas were subsequently contacted to confirm both their interest and availability to participate in the independent peer of the CHAP report.

The specific experts ultimately selected to perform the independent peer review of each of the subject areas of interest are identified in Table 1. As noted above, the peer reviewers are highly respected and internationally recognized experts in the designated subject areas. The curriculum vitae for each peer reviewer demonstrate their unique qualifications in their particular subject matter and are provided in Appendix C.

**Table 1. List of Expert Peer Reviewers and Subject Area**

| Expert | Affiliation | Subject Area |
|---|---|---|
| Christopher J. Borgert, Ph.D. | Applied Pharmacology and Toxicology, Inc. | Cumulative Risk |
| Kathryn Clark, Ph.D., P.Eng. | BEC Technologies, Inc. | Exposure |
| Warren G. Foster, Ph.D. | Department of Obstetrics & Gynecology<br><br>McMaster University | Reproductive and Developmental Toxicity/Endocrine/ Human Relevance |
| Bette Meek, Ph.D. | McLaughlin Centre for Population Health Risk Assessment<br><br>University of Ottawa | Cumulative Risk |
| Douglas L. Weed, M.D., M.P.H., Ph.D. | DLW Consulting Services, LLC | Epidemiology |
| Raphael J. Witorsch, Ph.D. | School of Medicine, Medical College of Virginia<br><br>Virginia Commonwealth University | Reproductive and Developmental Toxicity/Endocrine/ Human Relevance |

### *2.3 Peer Review Process*

General guidelines for performing the technical peer review were drafted by ToxStrategies and shared with each of the subject matter experts prior to their beginning their independent peer review. General guidelines were used in lieu of specific charge questions so as not to limit the scope or viewpoints of the peer reviewers. Further, the guidelines were purposefully general in nature in order to allow the experts to perform a wholly independent and comprehensive review of the CHAP report relevant to their subject area. In brief, peer reviewers were charged with conducting a thorough technical review based on all pertinent information (including all data evaluated by the CHAP) and using the weight-of-evidence to develop relevant comments on the designated subject area(s). The guidelines for review as provided to each expert are included in Appendix A (Guidance for Conducting Independent Expert Review of CHAP Final Report on Phthalates and Phthalate Alternatives).

In addition to providing each subject matter expert with the general guidelines for performing the peer review, each peer reviewer was also provided with the following prior to initiating work: 1) Subcontractor consulting and confidentiality agreement with ToxStrategies, Inc., 2) Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel On Phthalates and Phthalate Alternatives[1], and 3) Peer Review of the CHAP Draft Report on Phthalates and Phthalate Substances, submitted to the CPSC by Toxicology Excellence for Risk Assessment[2].

ToxStrategies subsequently contracted directly with each peer reviewer (listed in Section 2.2). Depending on the date of execution of the contract, each peer reviewer was given approximately 2-3 weeks to perform the review and provide written comments to ToxStrategies. Each reviewer was tasked with following the guidelines in Appendix A as provided. However, due to existing time constraints, Drs. Borgert and Meek followed the guidelines to the extent possible with the focus of their reviews being limited to the methodological aspects of the approach used and, as such, their review did not necessarily encompass a full technical review of all data evaluated by the CHAP.

Each expert submitted his or her comments electronically to ToxStrategies in PDF format. The independent comments submitted by each subject matter expert are provided in their entirety in Appendix B as originally authored by each peer reviewer without modification. In addition, key findings/conclusions noted by each subject matter expert are summarized in Section 3.0 below.

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[1] Accessed from: https://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/The-Consumer-Product-Safety-Improvement-Act/Phthalates/Chronic-Hazard-Advisory-Panel-CHAP-on-Phthalates/\

[2] *Ibid.*

# 3.0 Key Findings of Independent Peer Review

Each subject matter expert was asked to highlight his or her key findings as an outcome of their independent technical review of the CHAP report; the key findings/conclusions identified by the six experts are quoted below organized by subject area. As noted above, the independent comments submitted by each subject matter expert are provided in their entirety in Appendix B.

## *3.1 Reproductive and Developmental Toxicity/Endocrine/ Human Relevance*

**Reviewer: Warren Foster, Ph.D.**
**Key Findings:**
*Although the authors have done a very good job of managing a very rich data set and preparing a very well written document, several weaknesses with the report need attention. From this review three main points are as follows:*

- *The epidemiological evidence linking phthalate exposure to decreased circulating testosterone concentrations, even in young boys, and developmental abnormalities of the male reproductive tract are thought to be weak.*

- *While the animal literature provides a plethora of studies documenting the characteristics of the rat phthalate syndrome, the relevance of these findings to human health remain questionable. Specifically, differences in cross species sensitivity to the effects of phthalates, the high concentrations of phthalates needed to induce effects in rats, potential confounding from xenoestrogens in the diet, data gaps in understanding of the relevant mechanisms of phthalate action, and the relatively low concentrations of phthalate metabolites measured in human urine.*

- *The assumption of additive effects appears to have weighed heavily in the authors consideration of risk. However, as discussed by others, there is concern about the potential for phthalates to act in an additive manner when present [in] concentrations well below those used in animal studies to demonstrate an additive effect. Moreover, potential for additive effects when divergent mechanism or modes of action are operable raises concerns about the soundness of using the potential for an additive effect in risk assessment and generating the conclusions presented in the CHAP report.*

*Taken together, human exposures to phthalates remains low with MOEs that are many times above the concentrations needed to induce adverse effects in rats. Hence, there should be confidence in existing regulatory decisions and the recommendations presented in the CHAP report are viewed as overly cautious.*

**Reviewer: Raphael J. Witorsch, Ph.D.**
**Key Findings:**
*While the CHAP is commended for a very scholarly and in depth review of the literature pertaining to the adverse effects [of] prenatal pththalate exposure on the development male reproductive system, this reviewer noted three issues that deserved further discussion.*

- *First of all, this reviewer seems more optimistic than the CHAP about the utility of the rat as a model for risk assessment of exposure to phthalates both individually and as mixtures.*

- *Secondly, the weight of evidence indicates that the rat is more sensitive to the effects of phthalate than the mouse and possibly than primates, as well.*

- *Finally, in contrast to the opinion expressed by CHAP, the epidemiologic data associating maternal phthalate levels in body fluids with decreased AGD in human male offspring are inconclusive.*

### *3.2 Epidemiology*

**Reviewer: Douglas L. Weed, M.D., M.P.H., Ph.D.**
**Key Findings:**
*The following represent key findings of my review of the CHAP report to the U.S. Consumer Product Safety Commission on phthalates. These findings are made with particular emphasis on epidemiology and, more broadly, an emphasis on the methodological approach taken by the CHAP committee.*

- *The CHAP report is not a systematic review of the available scientific evidence and, as such, is of questionable reliability and validity, lacking in the objectivity and transparency generally recognized as critical by the scientific community. The credibility of the recommendations in this report are therefore questionable, given that they are not "evidence-based" as the co-chair of the committee, Dr. Hauser, recognized and mentioned in a separate review published in the peer-reviewed literature (Braun et al., 2013).*

  *Indeed, the CHAP committee specifically rejected the need for a systematic review (see CHAP Report, p. 12). This unfortunate decision on the part of the CHAP committee puts the credibility of their entire project at risk. Their argument—that interpreting different streams of evidence is not amenable to the systematic review methodology—is at best an indication that they are unaware of the well established need for a systematic approach, and at worst, scientific nonsense. The systematic review methodology is clearly the best approach to be used in the situation in which there is evidence from different disciplines.*

- *The CHAP report misrepresents the results of some (but not all) of the available epidemiological evidence, ignoring or downplaying negative results and emphasizing*

*positive (i.e. apparently harmful) results. Theirs is not a critical and balanced review of the epidemiological evidence. That evidence, which I have examined in detail, is inconsistent and, in some instances, shows that exposure to phthalates may be good for children. I am not advocating that exposure to phthalates be encouraged. I am pointing out that the CHAP report is biased with respect to the findings of the epidemiological evidence.*

- *The CHAP report fails to justify their recommendations to reduce exposure to phthalates. It cannot be justified by the available epidemiological evidence. The CHAP committee fails to point out that there are no studies documenting a reduction in developmental outcomes or neurodevelopmental outcomes in children after a reduction in exposure to phthalates. No effort is made on the part of the CHAP Committee to grade the strength of the evidence or the recommendations made, despite the fact that the Committee reviewed literature that provides a process for grading the quality of evidence and the quality of recommendations.*

- *The CHAP report fails to mention much less discuss a relatively large number of published reviews and several epidemiological studies on the topic of phthalates and human health including children's health. The missed epidemiological studies provide evidence of null ("no association") results. In addition, the fact that many of these reviews disagree with the CHAP report's assessment of the epidemiology (and of the use of animal models to represent adverse health events in humans) is important and should have been addressed in the CHAP Report.*

### *3.3 Exposure*

**Reviewer: Kathryn Clark, Ph.D., P.Eng.**
**Key Findings:**

- *In general, the approach employed was sound and included comparisons of human exposure to phthalate esters from biomonitoring data with exposures estimated from a range of sources including consumer products, diet, and environmental media.*

- *My concerns with the report are in how the results of the exposure assessment are used to respond to the questions posed to the CHAP, deficiencies in the methodology and available data for estimation of exposure to children's toys and child care articles, and also in some assumptions used in the calculations and inconsistencies in those assumptions, including receptor characterization and statistical measures.*

- *The CHAP report states that "phthalates cause a wide range of toxicities in experimental animals but the one considered of greatest concern for purposes of this report is a syndrome indicative of androgen insufficiency in fetal life, what is referred to in rats as the phthalate syndrome, caused by exposure of pregnant dams to certain phthalates". Review of the toxicity evaluation is beyond the scope of my review; however, from a high level review point, it is unclear how recommendations can be made with respect to children's toys and child care articles when the toxicity*

*endpoint is for non-users of those products (i.e., pregnant women, fetuses, and neonates).*

- *The CHAP report (Table E1-20) indicates that there is no exposure of pregnant women to phthalates contained in child care articles and that the highest potential exposure from dermal contact with toys is for DNOP (comprising 4.7% of total exposure to DNOP), followed by 0.5% for DEHP, and 0.1% for DINP. These estimated exposures are based on a scenario-based assessment described in the CHAP report as "highly uncertain" (p.E1-46) and are "hypothetical because these PEs currently are not allowed in toys" (p.E1-35).*

- *The CHAP report recommends that the interim ban on the use of diisononyl phthalate (DINP) in children's toys and child care articles at levels greater than 0.1% be made permanent. The basis for this recommendation is not clear; according to the CHAP report (Table E1-20), exposure to toys and child care articles represents only 0.1% of total exposure to DINP for pregnant women so a ban would not be expected to alter exposure of pregnant women. For infants (Table E1-21) exposure to toys and child care articles represents 30% of total exposure to DINP; however, this percentage was calculated in the scenario-based assessment, which over-estimates total exposure to DINP by a factor of six (Table 2.14) and, therefore, it is highly uncertain what effect a ban on DINP in toys and child care articles would have.*

### *3.4 Cumulative Risk Methodology*

**Reviewer: Christopher J. Borgert, Ph.D.**
**Key Findings:**
*The Report to the U.S. Consumer Product Safety Commission by the CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES AND PHTHALATE ALTERNATIVES, dated July 2014, suffers a number of scientific deficiencies that limit its utility for evaluating the safety of consumer products. These deficiencies, and potential remedies for them, are summarized below and detailed in the review and cited literature that follows.*

- *The CHAP report failed to test logical extensions of its cumulative risk theory, methodology and conclusions, and thus failed to recognize obvious inconsistencies with human experience and clinical evidence.*

- *The CHAP report failed to account for model uncertainties in extrapolating chemical mixture effects observed at high doses in animal studies to the lower doses potentially received by humans; consequently, the CHAP overstates the accuracy of its cumulative risk methods and conclusions.*

- *The CHAP report failed to compare human versus rodent sensitivity to antiandrogenic effects of chemicals, and as a consequence, appears to have grossly overestimated chemical potencies in assessing potential risks to humans from*

*cumulative exposures to phthalates, phthalate alternatives, and other potential antiandrogens.*

- *The CHAP report failed to consider published literature at odds with its selected cumulative risk theory and methodology, thereby undermining the scientific credibility and reliability of its cumulative risk predictions and recommendations based on them.*

- *Deficiencies in the CHAP report could be remedied by adopting reasonable limitations of potency and dose in applying its cumulative risk assumptions and methods, and reforming its recommendations accordingly.*

**Reviewer: Bette Meek, Ph.D**
**Key Findings:**
*Focus of this review was on methodology for the cumulative assessment, which with few exceptions represents state of the art methodology drawing maximally on multiple sources of relevant data. Principal comments relate to the defensibility of the use of Hazard Indices based on Reference Doses rather than Points of Departure, since this limits transparency and consideration of important aspects of uncertainty and variability not currently addressed in traditionally applied uncertainty factors. It also complicates comparison with the individual exposure data since reference doses are designed to protect populations.*

- *Consideration of uncertainty and variability in the assessment is uneven, being fairly robust for the biomonitoring data but extremely limited for the scenario based exposure and potency estimates.*

- *Sensitivity, though mentioned, is seemingly not analyzed as a basis for weighting of various approaches and/or identification of critical datagaps.*

- *Weight of evidence analysis including consideration of broader biological knowledge as a basis for more robust discussion of potential species differences for bounding of the PODs is not evident and weight of evidence considerations across the available database (beyond those that are study specific) are also not specified.*

# Appendix A

# Guidance Provided to Expert Peer Reviewers

**Guidance for Conducting Independent Expert Review of CHAP Final Report on Phthalates and Phthalate Alternatives**

*1. Objective and overview of the review process*

The overall aim of the technical review is to assess the work carried out, including methodology and conclusions, as reported in the CHAP Final Report on Phthalates and Phthalate Alternatives. The final product of this review will be a written report that consists of a brief executive summary based on the key findings of each reviewer (to be drafted by ToxStrategies, Inc.) with the comments as received from each independent reviewer attached.

Each reviewer's task is to perform an independent expert review of a specified section(s) corresponding to their subject matter area(s) of expertise (other sections should not be reviewed unless necessary to review the assigned section and related conclusions). It is expected that the expert will conduct a thorough technical review based on all pertinent information (including all data evaluated by the CHAP) and use the weight-of-evidence to provide conclusions on the designated subject area(s). Upon execution of a subcontractor agreement with ToxStrategies, Inc., the reviewer should prepare and provide written comments to ToxStrategies, Inc. no later than August 31, 2014. These comments will remain unaltered and will be attached directly to an overall executive summary as described above. For any logistical issues during the review process, each reviewer is expected to follow the terms of their respective contract with ToxStrategies, Inc. (as a subcontract to ACC).

*2. Preparation of written comments*

The reviewer is asked follow these general guidelines when drafting written comments:

- Review all sections of the CHAP Final Report and the Peer Review of the Draft Report specific to your topic area(s) as specified in the Scope section of the Consulting Agreement with ToxStrategies, Inc.
- Provide an independent discussion and opinion of your assessment of:
    - the evaluation of available data for your topic area(s), and
    - whether or not the data for your topic area(s) support the risk assessment, overall conclusions and recommendations of the CHAP Report (if applicable).
- Include discussion on both positive and negative aspects of the analyses related to your topic area(s) in the CHAP Report, as well as recommendations on how to improve the evaluation of your topic(s), if warranted.
- Summarize the conclusions of your assessment, and in doing so, highlight 2-3 key findings.
- Include citations and a reference list as support for your assessment where relevant.
- Use the standard terminology/abbreviations/acronyms listed in the CHAP Final Report.

*Submission of written comments*

The reviewer will provide their written comments electronically as PDF document to ToxStrategies, Inc. by the designated deadline at the contact information provided below:

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