April 15, 2015

Office of the Secretary
Consumer Product Safety Commission
Room 820, 4330 East West Highway
Bethesda, MD 20814

Comments submitted through: www.regulations.gov

Re: Consumer Product Safety Commission, Docket No. CPSC–2014–0033; Proposed Rulemaking for the Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates

Dear Sir or Madam:

On December 30, 2014, the Consumer Product Safety Commission (CPSC) announced a notice of proposed rulemaking for the Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates; Docket No. CPSC–2014–0033.[1] The American Chemistry Council's Center for Advancing Risk Assessment Science and Policy (ARASP) provides the enclosed comments on the CPSC's regulatory proposal. ARASP is a coalition of twenty-two independent groups that promote consistent and transparent risk assessment approaches. ARASP also fosters activities for the adoption of policies and practices that assure the best available and most relevant science is used as the foundation for assessing potential risks from chemical exposures.

The CPSC's regulatory proposal, the underlying data and the methodology used to develop the Chronic Hazard Advisory Panel (CHAP) report, which provides the basis for the regulatory proposal, have significant limitations. Furthermore, the scientific analyses and cumulative risk approach have not been developed in a transparent or systematic manner. Given the important and potential influential impact of the CHAP assessment and the CPSC regulatory proposal, the CPSC should review and revise its proposal to: (1) include an improved and rigorous evaluation of the methods used to assess the risk of phthalate exposures and (2) confirm that the exposure data used is relevant and appropriate to inform the CHAP assessment.

[1] 79 Fed. Reg. 78324 (Dec. 30, 2014). http://www.gpo.gov/fdsys/pkg/FR-2014-12-30/pdf/2014-29967.pdf

Thank you in advance for your consideration of ARASP's comments. If you have questions or need clarification, please contact me at 202-249-7000 or kimberly_wise@americanchemistry.com.

Sincerely,

Kimberly Wise, Ph.D.
American Chemistry Council (ACC)
Senior Director, Chemical Products and Technology
On behalf of ARASP

ARASP members:
Acrylonitrile Group
American Cleaning Institute
American Composites Manufacturers Association
American Forest and Paper Association
American Petroleum Institute
CropLife America
Halogenated Solvents Industry Alliance
Nickel Producers Environmental Research Association
Styrene Information and Research Center
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ACC Chlorine Chemistry Division
ACC Ethylene Oxide Panel
ACC Formaldehyde Panel
ACC Hexavalent Chromium Panel
ACC High Phthalates Panel
ACC Hydrocarbon Solvents Panel
ACC Olefins Panel
ACC Oxo Process
ACC Propylene Oxide/Propylene Glycol Panel
ACC Health, Products, and Science Policy Committee
ACC Silicones Environmental, Health and Safety Center of North America
ACC Vinyl Chloride Health Committee

Attachment: ARASP Comments on CPSC Regulatory Proposal; Docket No. CPSC–2014–0033

Comments

To

The Consumer Product Safety Commission

On

Docket No. CPSC–2014–0033
Proposed Rulemaking for the Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates

Submitted by

ACC's Center for Advancing Risk Assessment Science and Policy

April 15, 2015

INTRODUCTION

Several reports over the past few years have highlighted the importance of understanding the accumulation of risks from multiple environmental stressors. Additionally, regulatory agencies are exploring strategies to move beyond single chemical assessments and to focus, in part, on the effects of chemical exposures occurring simultaneously. The Chronic Hazard Advisory Panel (CHAP) for the Consumer Product Safety Commission (CPSC) released their assessment on phthalates and phthalate alternatives on July 18, 2014.[2] The CHAP was specifically charged with evaluating the risk to children from exposure to phthalates and phthalate alternatives, including diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP), in toys and child care articles. Additionally, the CHAP was to evaluate cumulative risk from exposure to multiple phthalates.

The CHAP's July 2014 report recommends that CPSC take four actions: (1) make permanent the interim ban on DINP; (2) impose a permanent ban on diisobutyl phthalate (DIBP), di-n-pentyl phthalate (DPENP), di-n-hexyl phthalate (DHEXP) and dicyclohexyl phthalate (DCHP); (3) impose an interim ban on diisooctyl phthalate (DIOP); and (4) lift the interim ban on di-n-octyl phthalate (DNOP) and DIDP. On December 30, 2014, CPSC published a notice of proposed rulemaking in the Federal Register implementing the CHAP's recommendations.[3]

The American Chemistry Council (ACC) Center for Advancing Risk Assessment Science and Policy (ARASP)[4] is committed to promoting the development and application of up-to-date, science-based methods for conducting risk assessments. ARASP reviews chemical assessment documents and methodologies to ensure that they are scientifically sound. In this regard ARASP has reviewed the CHAP Report and the CPSC's regulatory proposal for phthalates because it would be one of the first federal actions regulating the use of a chemical on the basis of cumulative risk in this manner. As described in detail below, the CPSC's regulatory proposal, the underlying data and the methodology used to develop the CHAP Report, which provides the basis for the regulatory proposal, have significant limitations. Furthermore, the scientific

[2] Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (CHAP Report). http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf.

[3] 79 Fed. Reg. 78324 (Dec. 30, 2014). http://www.gpo.gov/fdsys/pkg/FR-2014-12-30/pdf/2014-29967.pdf

[4] ARASP is a coalition of twenty-two organizations focused on promoting the development and application of up-to-date, scientifically sound methods for conducting chemical assessments. ARASP members are Acrylonitrile Group, American Cleaning Institute, American Composites Manufacturers Association, American Forest and Paper Association, American Petroleum Institute, CropLife America, Halogenated Solvents Industry Alliance, Nickel Producers Environmental Research Association, Styrene Information and Research Center, Wood Preservative Science Council, ACC Chlorine Chemistry Division, ACC Ethylene Oxide Panel, ACC Formaldehyde Panel, ACC Hexavalent Chromium Panel, ACC High Phthalates Panel, ACC Hydrocarbon Solvents Panel, ACC Olefins Panel, ACC Oxo Process, ACC Propylene Oxide/Propylene Glycol Panel, ACC Health, Products, and Science Policy Committee, ACC Silicones Environmental, Health and Safety Center of North America and ACC Vinyl Chloride Health Committee.

analyses and cumulative risk approach have not been developed in a transparent or systematic manner. Given the important and potential influential impact of the CHAP assessment and the CPSC regulatory proposal, the CPSC should review and revise its proposal to: (1) include an improved and rigorous evaluation of the methods used to assess the risk of phthalate exposures and (2) confirm that the exposure data used is relevant and appropriate to inform CHAP assessment.

COMMENTS

I. The CHAP Assessment Suffers from a Highly Flawed Problem Formulation Step

It has long been recognized that the key to developing a major risk assessment is to make appropriate early judgments regarding the purpose, scope and technical approaches that will be used in the assessment.[5] In 1997, the U.S. Environmental Protection Agency's (EPA's) Science Policy Council issued a policy statement on cumulative risk assessment. This policy addresses the first step in the overall assessment process (i.e., problem formulation).[6] EPA recently affirmed the importance of problem formulation in its 2014 Framework for Human Health Risk Assessment to Inform Decision Making.[7] Among the many important pieces of planning, scoping, and problem formulation is the need to ensure the assessment is designed to be "fit for purpose." While no clear problem formulation is contained in the CHAP Report, or in Appendix D, the Cumulative Risk Assessment (CRA), our understanding is that the goal of the CHAP CRA was to evaluate the potential health effects of specified phthalates, in combination, to inform decision making. In particular, to understand if a mixture of phthalates when present in combination may exceed a specified threshold of concern.

In this case, the threshold of concern was a hazard index (HI) of greater than one. The CHAP states, "[i]n all cases, DEHP and DBP contributed strongly to the HI while DIBP and DINP contributed considerably less."[8] In fact, using the 2005-2006 NHANES data, the CHAP calculates that at the 95th and 99th percentiles, the Hazard Quotient (HQ)[9] for DEHP exceeds one for all cases.[10] DEHP has been permanently banned in children's toys and child care articles at levels greater than 0.1% for several years and recent U.S. biomonitoring data illustrate that exposure to DEHP has decreased significantly. The CHAP nevertheless recommends banning DINP, stating "This recommendation is made because DINP does induce antiandrogenic effects in animals, although with lesser potency than other active phthalates, and therefore can

[5] See EPA, Planning a Human Health Risk Assessment. http://www.epa.gov/risk_assessment/planning-hhra.htm.
[6] See EPA. 2000. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533.
[7] http://www2.epa.gov/sites/production/files/2014-12/documents/hhra-framework-final-2014.pdf.
[8] CHAP Report, p. 65.
[9] When looking at just one compound, a hazard quotient (HQ) is used. When summing impacts of multiple chemicals, it is referred to as a hazard index (HI).
[10] CHAP Report, Table 2.16, p. 67.

contribute to the cumulative risk from other antiandrogenic phthalates."[11] However, the CRA shows that the DINP HQ levels are well below one.

If the CHAP had conducted a rigorous problem formulation, it would have determined that if it included a phthalate for which it calculated an HQ greater than one, the CRA would necessarily result in an exceedance of the HI, regardless of the HQ of any other phthalate. The CRA should be improved by including a clear problem formulation step that takes into account what is known about current exposures and calculated risks from individual phthalates. For example, if the CHAP were to evaluate only phthalates that have not been banned, or as discussed below, used more recent data, there may be no exceedances of the HI.

II. The CHAP Finding is Based on Precautionary Judgments Not Sound Science

Due to the CHAP's flawed problem formulation, the CRA approach, if widely applied, could result in unjustified regulatory action for any compound that showed any level of antiandrogenic effects. This could include foods, such as licorice, and other naturally occurring compounds. This approach, based on a flawed problem formulation, is overly precautionary as the CRA does not show whether there is any additional risk from a weakly antiandrogenic compound, such as DINP, that impacts risks from exposure to other phthalates. CPSC should provide a rigorous scientific assessment to evaluate whether prohibition of weakly antiandrogenic compounds, such as DINP, results in any public health benefits. As discussed by Borgert et al. (2013),[12] thresholds govern endocrine activity, and even though activities of substances may be observed in certain endocrine assays, substances with low potencies are likely not to be biologically active at environmentally relevant exposure levels *in vivo*. In an evaluation of endocrine related endpoints, it has been recommended that potency cutoff values be developed, and substances with activity values lower than these cutoff values be deprioritized; calculation of metrics such as the HQ for substances would not be scientifically meaningful (Becker et al., 2015).[13]

III. Regulations Must be Based on Relevant and Current High Quality Data

Exposure levels to phthalates have been changing, due in part to restrictions required by the 2008 Consumer Product Safety Improvement Act (CPSIA). These changes in exposure levels have been reflected in biomonitoring studies conducted in the U.S.[14] In light of these changing levels, it is unclear why the CHAP relied on NHANES survey data from 2005-2006, when NHANES

[11] CHAP Report, p. 7.
[12] Borgert CJ, Baker SP, Matthews JC. 2013. Potency matters: thresholds govern endocrine activity. Regul Toxicol Pharmacol 67: 83-88.
[13] Becker RA, Friedman KP, Simon TW, Marty MS, Patlewicz G, Rowlands JC. 2015. An exposure:activity profiling method for interpreting high-throughput screening data for estrogenic activity-Proof of concept. Regul Toxicol Pharmacol 71: 398-408.
[14] See for example Zota AR, Calafat AM, Woodruff TJ. 2014. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001-2010. Environ Health Perspect 122(3): 235-241.

survey data from 2009-2010 were available for consideration. The CHAP Report is not based on the most recently available biomonitoring data and this is a significant shortcoming of the assessment. To inform regulation, any CRA must rely upon and be informed by the most recently available high quality data. At present, the NHANES 2009-2010 and 2011-2012 data releases are available and CPSC should conduct an updated CRA using these data, in conjunction with a more appropriate problem formulation step.

In addition, the CHAP report relies on NHANES data from a subset of pregnant women. This sample, in 2005-2006, included 130 pregnant women. This sample size is of concern when evaluating the upper percentiles of the distribution (e.g., above the 95th percentile). The Centers for Disease Control and Prevention (CDC) Analytic Guidelines, which accompany the NHANES survey, state that "the statistical reliability of an estimate depends on the sample size on which it is based, the design effect and relative standard error (RSE) of the estimate, the reliability of the estimated standard error, and whether the estimate of interest is a rare event or an extreme proportion."[15] In addition to other necessary parameters, including the need to evaluate the RSE, the guidelines note that a sample size of 150 persons is necessary in order to confidently evaluate the 95th percentile. The CPSC rulemaking should be relying on stable estimates that are developed with confidence, consistent with CDC guidance. High end estimates developed by the CHAP should be reevaluated and considered to be highly uncertain when the statistical analyses are not consistent with CDC recommendations for data use and evaluation.

IV. Relevance of Hazard Endpoints to the Population of Concern Must be Considered

The CHAP Report focuses on a variety of molecular endpoints in a pathway that may lead to reproductive dysgenesis[16]— if potency is sufficient, high exposures can overcome homeostatic mechanisms during specific windows of susceptibility in fetal development. A focus on this pathway would be appropriate if the CPSC were considering regulatory actions that would decrease risks to the developing fetus, which is likely the most sensitive population of concern. However, the regulatory actions CPSC is considering relate to children's toys and child care articles; these regulatory actions are designed to protect children. The endpoints in the CRA, however, are focused on fetal development; endpoints which are not relevant once an infant is born. Children that mouth toys have reproductive systems developed beyond the window of susceptibility for the endpoints used in the CRA (suppression of fetal testosterone synthesis, retained nipples and malformations in offspring) and thus these endpoints are not relevant. To understand the conservatism in the CHAP approach, and to inform a regulation of children's toys, it would be most useful for the CPSC to conduct a CRA that evaluates endpoints that are relevant to children. While the fetus may still be a susceptible population, the toxicological effects considered in the CHAP CRA are not directly relevant to children.

[15] CDC Analytic Guidelines, available at http://www.cdc.gov/nchs/data/series/sr_02/sr02_161.pdf.
[16] See CHAP Report, p. 14.

V. The CHAP Assessment Approach is Overly Simplistic and Lacks Scientific Rigor

Cumulative exposures are the norm – humans are exposed to a number of natural and man-made chemicals simultaneously and continuously every day. As a result of these exposures, measureable concentrations of a number of chemicals may occur in urine, circulating blood, and tissues. Human biomonitoring data have shown that multiple substances can be detected in an individual. However, this finding should not necessarily lead to undue concern. The presence of a substance that has adverse effects at some level does not imply that the presence of that chemical will lead to adverse effects at all levels. Simultaneous exposures to low levels of natural or environmental chemicals do not imply that potential risks would be summed. In fact, at low levels of exposures, exposures below the threshold of toxicity for a substance, the normal metabolic and repair capabilities of the body effectively protect against toxicity.[17] Under the independent action assumption for chemicals that act through independent pathways, even when multiple stressors are involved, so long as exposure to each component of a mixture occurs at its safe dose or below, no toxicological effects of the mixture would be expected. Scientific literature supports independent action at low exposure levels.[18] In contrast, summing scenario-derived exposure estimates is likely to over-predict exposures because: a) each estimate is generally a conservative value and b) personal contact to multiple sources is likely to occur over an extended time period rather than all at the same time. Basing cumulative assessments on multiple assumptions creates a situation where conservative default assumptions could be compounded, resulting in a significant over-estimation of risk. It is critical that sufficient data and robust models be available to inform a cumulative risk assessment.

Interactions among chemicals in causing toxic effects can be complex. The potential for certain phthalates to affect testosterone levels is just such a complex case. However, the CHAP uses simple dose additivity with relative potency among phthalates and an HI approach, where each agent's dose is expressed as an HQ – a fraction of that needed to produce a standard level of effect if acting alone. These fractions are then added up across agents to see if the total exceeds 1.0. The HI approach also assumes the chemical interactions are additive in nature. The existence of additivity at doses in the range of human exposure levels is theoretical and work by Borgert et al. (2012) suggests that at these levels additivity does not apply.[19] In addition the work on phthalates by Howdeshell et al. (2008) acknowledges that use of the dose addition

[17] See for example Rhomberg LR et al. 2011. Linear low-dose extrapolation for noncancer health effects is the exception, not the rule. Crit Rev Toxicol 41: 1-19

[18] See for example EPA. 2000. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. http://www.epa.gov/raf/publications/pdfs/CHEM_MIX_08_2001.PDF; and Borgert CJ, Sargent EV, Casella G, Dietrich DR, McCarty LS, Golden RJ. 2012. The human relevant potency threshold: reducing uncertainty by human calibration of cumulative risk assessments. Regul Toxicol Pharmacol 62: 313-328.

[19] Borgert CJ, Sargent EV, Casella G, Dietrich DR, McCarty LS, Golden RJ. 2012. The human relevant potency threshold: reducing uncertainty by human calibration of cumulative risk assessments. Regul Toxicol Pharmacol 62: 313-328.

model needs to be verified due to violated assumptions, great uncertainty, and poor model fit.[20] The CHAP assessment does not address the work of Borgert et al. or sufficiently address concerns raised by Howdeshell et al. on the dose additivity of phthalates. This deficit creates substantial uncertainty for the basis of the CRA and further erodes its basis for regulatory actions.

In addition, the use of fractions of effect doses (the HQs) for different agents implies that the dose-response curves among agents are parallel. For phthalates, the basis for this assumption is limited and can have substantial consequences for the validity of the computed HI. If dose-response curves are not parallel, they will likely intersect at some point and the rank order of potency of the chemicals would switch. In other words, phthalate 1 can be more potent than phthalate 2 at high doses, but less potent than phthalate 2 at low doses. This is illustrated in Figure 1. The dose addition model that underlies the HI approach used in the CRA assumes the relative potency of phthalates in a mixture is the same regardless of dose.[21] Thus, to achieve the same response, the dose of phthalate 1 must be a linear proportion of phthalate 2, and the dose-response curves must be parallel. If the maximum response differs among chemicals or endpoints, relative potencies observed at high doses may differ from relative potencies at low doses. As shown in Figure 2, phthalate 1 is almost twice as potent as phthalate 3 at the ED50, but the NOAELs of the phthalates are almost the same.

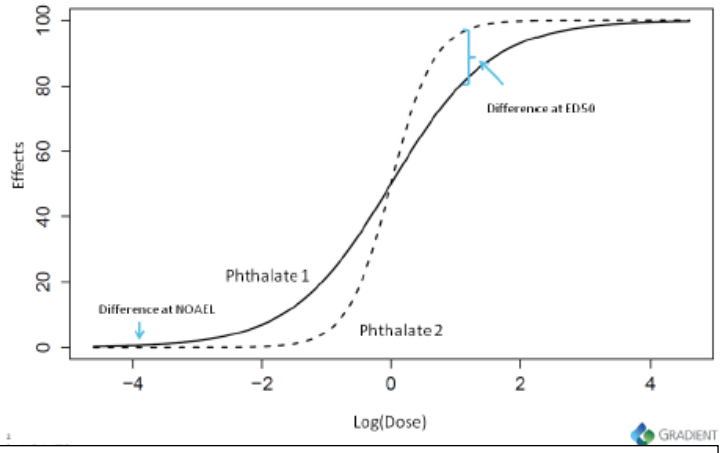

Figure 1- Illustration of non-parallel dose response curves. Calculations and graphic provided by Gradient.

[20] Howdeshell KL, Wilson VS, Furr J, Lambright CR, Rider CV, Blystone CR, Hotchkiss AK, Gray LE Jr. 2008. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicol Sci 105(1): 153-165.
[21] Putzrath RM. 1997. Estimating relative potency for receptor-mediated toxicity: Reevaluating the toxicity equivalence factor (TEF) model. Regul Toxicol Pharmacol 25: 68-78.

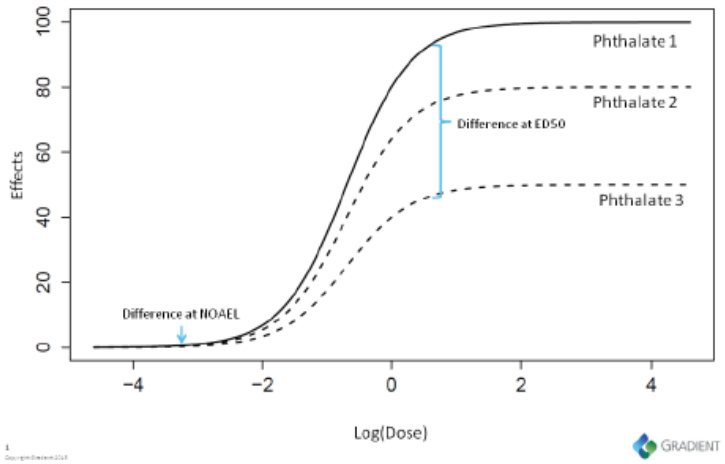

Figure 2 - Illustration of non-parallel dose response curves with different maximum responses. Calculations and graphic provided by Gradient.

This point is of particular importance to the CHAP's Case 2 for derivation of PEAAs. The estimations of the relevant potencies are derived from Hannas et al. (2011).[22] As can be seen in Figure 7 of Hannas et al., the dose response curves for DIBP, DEHP and DINP intersect; therefore these phthalates should not be analyzed using a dose addition model. Relative potencies at the ED50 are likely to underestimate relative potencies at a NOAEL dose. As with all extrapolations, relatively small discrepancies at one response level are likely to extrapolate to much larger discrepancies at responses distant from the point of the original calculation.[23] This is the case for the potencies calculated by Hannas et al., which estimate a 2.3 fold difference between DEHP and DINP whereas relative potencies calculated by Gray et al. (2000) based on *in vivo* considerations put relative potencies in the range of 10-20 fold.[24] Hannas et al. did not evaluate DBP and BBP. Hence, the CHAP's basis for assuming they are equipotent is not clear. The relative potencies obtained from ED50 values should not be applied to NOAELs. As we can see, the basis for invoking parallelism is quite limited, and violations of this assumption can have significant consequences for the validity of the computed HI.

In conclusion, as pointed out by the World Health Organization's International Programme on Chemical Safety (WHO/IPCS) this HI approach is best considered as a screening level or Tier 1

[22] Hannas BR, Lambright CS, Furr J, Howdeshell KL, Wilson VS, Gray LE Jr. 2011. Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. Toxicol Sci 123(1): 206-216.
[23] Putzrath RM. 1997. Estimating relative potency for receptor-mediated toxicity: Reevaluating the toxicity equivalence factor (TEF) model. Regul Toxicol Pharmacol 25: 68-78.
[24] Gray L, Ostby J, Furr J, Price M, Veeramacheneni D, and Parks, L. 2000. Perinatal exposure to phthalates DEHP, BBP and DINP but not DEP, DMP or DOTP alters sexual differentiation of the male rat. Toxicol Sci 58: 350-365.

approach.[25] It should not be considered as a method that leads to a true estimate of potential risk to humans or wildlife. If an HI exceeds one, an adverse effect should not be presumed. Instead, the assessment should proceed to the next tier. Such an iterative approach is key. Prior to making any regulatory decisions, CPSC should conduct a more refined assessment that goes beyond the screening level and does not inappropriately assume that dose response curves for the different phthalates are parallel.

VI. There are Significant Uncertainties Created by Combining Endpoints

The CHAP acknowledges challenges and shortcomings in the methods used, however these issues are dismissed rather than analyzed for their potential impact on the assessment. For example, the method used combines different endpoints into a so-called "phthalate syndrome" and suggests that effect levels for one endpoint can be compared to those for another. The methodology also uses dose levels corresponding to different effect measures (e.g., no adverse effect levels, low adverse effect levels and benchmark dose model levels, with uncertainty factors of varying magnitude) as indices of potency and presumes that each can be compared across endpoints and effects measured can be used to gauge relative potencies. To understand the impact of these assumptions and uncertainties embedded in these approaches, alternative plausible assumptions should be evaluated to enable a transparent, side by side comparison. In addition, in order to rely on a risk assessment for regulatory decision making, decision makers and stakeholders must be able to fully understand the impacts of assumptions and uncertainties in the risk assessment. Unfortunately, the CHAP recognizes the shortcomings and then dismisses them without further evaluation.

VII. The Relevance of Rat Data to Humans Should be More Fully Explored

The majority of the available toxicity data for phthalates is from animals, specifically rats. There are potential issues in species differences between rats and humans and the impacts can be both qualitative and quantitative. For instance, DEHP metabolism differs between rats vs. primates. Urinary excretion products in primates consist primarily of glucuronide conjugates of DEHP requiring at most a single round of oxidative metabolism. In contrast, urinary excretion products in rats consist of diacids requiring three to six rounds of oxidative metabolism, and no glucuronide metabolites.[26]

[25] See WHO (World Health Organization) 2009. Harmonization Project Document 7; Assessment of Combined Exposures to Multiple Chemicals: Report of a WHO/IPCS International Workshop on Aggregate/Cumulative Risk Assessment; WHO: Geneva, Switzerland. http://www.who.int/ipcs/methods/harmonization/areas/aggregate/en/; and Meek ME et al. 2011. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regul Toxicol Pharmacol 60: S1-S14. http://www.sciencedirect.com/science/article/pii/S0273230011000638.
[26] Albro PW, Corbett JT, Schroeder JL, Jordan S, Matthews HB. 1982. Pharmacokinetics, interactions with macromolecules and species differences in metabolism of DEHP. Environ Health Perspect 45: 19-25.

Rats appear to absorb a larger fraction of ingested phthalates than humans; once absorbed, the ingested phthalates may be metabolized differently in rats and humans. As a result, the effective tissue concentrations from a given ingestion level may vary between rats and humans. Kessler et al. (2004) find that, in pregnant animals exposed to 30 mg/kg-day DEHP via oral administration, the normalized area under the curve was 2.6-fold greater for rats compared to marmosets,[27] and compared to humans, rats appear to absorb a higher percentage of orally administered phthalates.[28] Williams and Blanchfield (1974) report that 90-97% of ^{14}C-activity from DEHP-^{14}C is recovered in urine from rats following dietary administration of DEHP-^{14}C.[29] In contrast, approximately 47% of deuterated DEHP is recovered as primary and secondary metabolites in urine following oral exposure in humans.[30]

Unfortunately, the CHAP does not account for these potential differences in species metabolism and impacts on effective tissue concentrations when comparing daily intakes for humans to effect levels established in rats. To inform regulatory decisions, a more thorough evaluation should be required.

Additionally, recent work by leading experts in the field, Dr. Richard Sharpe and Dr. Kim Boekelheide, question the relevance of the antiandrogenic endpoints to human risk assessment.[31,32,33] These works demonstrate that human testis are refractory to the antiandrogenic effects seen in rats. The results of Boekelheide and Sharpe are strengthened by recent data produced by independent laboratories using a different model system. Habert el al. (2014) demonstrate no effect on testosterone after treatment with an antiandrogenic phthalate in an *in vitro* system[34] and Lambrot et al. (2009) show similar results in a separate *in vitro* system.[35]

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[27] Kessler W, Numtip W, Grote K, Csanády GA, Chahoud I, Filser JG. 2004. Blood burden of di(2-ethylhexyl) phthalate and its primary metabolite mono(2-ethylhexyl) phthalate in pregnant and nonpregnant rats and marmosets. Toxicol Appl Pharmacol 195(2): 142-153.

[28] Agency for Toxic Substances and Disease Registry (ATSDR). 2002. Toxicological Profile for Di(2-ethylhexyl)phthalate. http://www.atsdr.cdc.gov/toxprofiles/tp9.pdf.

[29] Williams DT, Blanchfield BJ. 1974. Retention, excretion and metabolism of di-(2-ethylhexyl) phthalate administered orally to the rat. Bull Environ Contam Toxicol 11(4): 371-378.

[30] Anderson WA, Castle L, Hird S, Jeffery J, Scotter MJ. 2011. A twenty-volunteer study using deuterium labelling to determine the kinetics and fractional excretion of primary and secondary urinary metabolites of di-2-ethylhexylphthalate and di-iso-nonylphthalate. Food Chem Toxicol 49(9): 2022-2029.

[31] Heger NE, Hall SJ, Sandrof MA, McDonnell EV, Hensley JB, McDowell EN, Boekelheide K. 2012. Human fetal testis xenografts are resistant to phthalate-induced endocrine disruption. Environ Health Perspect 120(8): 1137-1143.

[32] Johnson KJ, Heger NE, and Boekelheide K. 2012. Of mice and men (and rats): phthalate-induced fetal testis endocrine disruption is species-dependent. Toxicol Sci 129(2): 235-248.

[33] Mitchell RT, Childs AJ, Anderson RA, van den Driesche S, Saunders PTK, McKinnell C, ... & Sharpe RM. 2012. Do phthalates affect steroidogenesis by the human fetal testis? Exposure of human fetal testis xenografts to di-n-butyl phthalate. J Clin Endocrinol Metab 97(3): E341-E348.

[34] Habert R, Livera G, and Rouiller-Fabre V. 2014. Man is not a big rat: concerns with traditional human risk assessment of phthalates based on their anti-androgenic effects observed in the rat foetus. Basic Clin Androl 24(1): 14.

Taken together, these are compelling evidence and should be considered in the risk assessment. This could be achieved in different manners, one of which would be modification of the interspecies uncertainty factor to reflect species sensitivity.

VIII. Differences in Points of Departure (POD) Must be Considered

Basic principles of pharmacology dictate that, for comparison of relative potency across phthalates, points of departure should be for the same endpoint, same species, and ideally from the same study. For the Case 1 PODs derived from Kortenkamp and Faust (2010), such basic pharmacological principles were not followed. For example, for DEHP, the POD is a no-observed adverse effect level (NOAEL) for retained nipples from a study by Christiansen et al. (2009)[36]; for DINP, the POD is a lowest observed adverse effect level (LOAEL) for testosterone synthesis from studies by Borch et al. (2004) and Gray et al. (2000, both as cited in Kortenkamp and Faust, 2010); and for DIBP, DBP and BBP, the PODs are BMDLs for reduced testosterone synthesis estimated by NRC (2008)[37] using data from a study by Howdeshell et al. (2008).[38]

Because reduced testosterone synthesis presumably occurs at a lower dose than retained nipples, the PODs from Kortenkamp and Faust could overestimate the relative toxicity of phthalates (other than DEHP) relative to DEHP. Alternatively, the POD for DEHP of 3 mg/kg-day, which is 10-fold lower than the BMDL for reduced testosterone synthesis, could overestimate the relative potency for DEHP. It is not clear why Kortenkamp and Faust used a different endpoint and study for DEHP. In addition, the high uncertainty factors (UFs), as used for DINP, could overestimate potency relative to phthalates with smaller UFs. Although not specified by Kortenkamp and Faust, the UF of 200 presumably is comprised of UFs of 10 each for inter- and intra-species variability, and an additional UF of 2 for study size. BMDLs, which are calculated as the lower 95th percentile confidence limit on a benchmark dose, reflect study design issues such as study size and dose selection. All else being equal, the BMDL for a small study will be lower than the BMDL for a larger study.[39] Hence, application of an additional UF to account for small study size is not necessary, and thus overestimates both the relative and actual toxicity of

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[35] Lambrot R, Muczynski V, Lécureuil C, Angenard G, Coffigny H, Pairault C, Rouiller-Fabre V. 2009. Phthalates impair germ cell development in the human fetal testis in vitro without change in testosterone production. Environ Health Perspect 117(1): 32-37.

[36] Christiansen S, Scholze M, Dalgaard M, Vinggaard AM, Axelstad M, Kortenkamp A, Hass U. 2009. Synergistic disruption of external male sex organ development by a mixture of four antiandrogens. Environ Health Perspect 117(12):1839-1846.

[37] National Research Council (NRC). 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. Committee on the Health Risks of Phthalates, Board on Environmental Studies and Toxicology, Division of Earth and Life Sciences. http://www.nap.edu/catalog/12528.html.

[38] Howdeshell KL, Wilson VS, Furr J, Lambright CR, Rider CV, Blystone CR, Hotchkiss AK, Gray LE Jr. 2008. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicol Sci 105(1):153-165.

[39] US EPA Risk Assessment Forum. 2012. Benchmark Dose Technical Guidance.

DIBP, DBP and BBP. The implications of using these disparate endpoints and PODs should be further examined.

IX. A Better Understanding of Internal Exposures is Critical

Radio-labeled phthalate exposures show that only 40-60% (depending on the phthalate) of an ingested dose is excreted in urine. For oral exposure, hydrolysis largely occurs in the intestine before absorption. Either the primary metabolites (the monoesters), or the secondary metabolites (the oxidized monoesters) all of which are excreted rather quickly, are actually the primary cause of effects.[40] Phthalates are readily metabolized and cleared fairly quickly, thus the rapid clearance means that a spot urine sample, as was done in the human biomonitoring data used to define the patterns and amounts of human exposure, may not provide an accurate picture of exposure scenarios. Day-to-day intra-individual variability is particularly large for DEHP. This is a concern as DEHP comprised the greatest portion of the HI and its exposure values contain the greatest degree of uncertainty, in a direction that over estimates the risk.

In the experimental animal studies used for identifying PODs, developmental effects associated with exposure to phthalates are likely related to exposure averaged over at least several days, rather than a single exposure. Measurement of phthalate metabolites in urine demonstrates substantial intra-individual variability in metabolite levels. The use of the 95th percentile spot urine sample to represent exposure for an individual with a 95th percentile average exposure to phthalates will overestimate the average exposure for that individual. Aylward et al. (2013) point out that substances that have short half-lives in the body are expected to exhibit substantial intra-individual variability in human biomonitoring studies such as NHANES, and upper percentiles are likely not a valid measure of long-term average concentrations for individuals.[41] As such Aylward et al. (2013) indicate use of the central tendency concentration is likely to be more representative of average exposure levels for the general population over a longer time period. The CHAP relies heavily on HI values at percentiles greater than the 95th percentile. The instability and uncertainty associated with these estimates should be closely examined.

There is also uncertainty regarding whether effects are mediated by primary or secondary metabolites, and whether the relative proportion of metabolites differs according to the exposure route. Thus, it may not be appropriate to extrapolate effects across exposure routes.

[40] According to CDC. 2013. Fourth National Report on Human Exposure to Environmental Chemicals. Updated Tables, DEHP toxicity is thought to be mediated by the primary monoester (mono-ethyl hexyl phthalate); according to Koch HM, Bolt HM, Preuss R, Eckstein R, Weisbach V, Angerer J. 2005. Intravenous exposure to di(2-ethylhexyl)phthalate (DEHP): metabolites of DEHP in urine after a voluntary platelet donation. Arch Toxicol 79: 689-693, DEHP toxicity is likely mediated by the secondary oxidized monoesters.

[41] Aylward LL, Kirman CR, Schoeny, R, Portier CJ, Hays SM. 2013. Evaluation of Biomonitoring Data from the CDC National Exposure Report in a Risk Assessment Context: Perspectives across Chemicals. Environ Health Perspect 121(3): 287-294. http://ehp.niehs.nih.gov/1205740/

X. Meeting the Standard of 'Reasonable Certainty of No Harm' Requires a Full Evaluation of Uncertainties and Assumptions

In the rulemaking, the CPSC was required to consider "the level at which there is a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals and their offspring, considering the best available science, and using sufficient safety factors to account for uncertainties regarding exposure and susceptibility of children, pregnant women, and other potentially susceptible individuals." However, many of the uncertainties noted above would likely overestimate potential effects of phthalate exposure. To understand the impact of these assumptions and uncertainties embedded in these approaches, alternative plausible assumptions should have been used to enable a transparent, side by side comparison. In order to rely on a risk assessment for regulatory decision making, decision makers and stakeholders must be able to fully understand the impacts of assumptions and uncertainties in the risk assessment.

XI. The Peer Review Process Lacks Transparency and Must Be Improved to Incorporate Public Comments

The July 2014 CHAP Report has been used as the basis for the CPSC's proposed rule, however, the CHAP Report was not subject to an open and rigorous peer review process with input from the public. Given the potential that other federal agencies may adopt the CPSC's cumulative risk methodology to inform regulatory decision making, a rigorous and open opportunity for stakeholder input on the validity and limitations of the methods, as well as their application for regulatory purposes, should be effectively implemented.

XII. CPSC Should Consider How These Analyses Will Inform Retrospective Review.

To implement President Obama's Executive Order 13563, which requires retrospective review of significant rules,[42] OMB has directed Agencies to promote a culture that makes these reviews feasible and implementable. In doing so, OMB states "To promote that culture, future regulations should be designed and written in ways that facilitate evaluation of their consequences and thus promote retrospective analyses. To the extent consistent with law, agencies should give careful consideration to how best to promote empirical testing of the effects of rules both in advance and retrospectively."[43] OMB further noted that regulations should be designed to measure "actual results."[44]

Consistent with these memorandums, CPSC should explain how the outcomes CPSC intends to impact will be measured and evaluated. Considering that the endpoints evaluated by the CHAP

[42] See http://www.gpo.gov/fdsys/pkg/FR-2011-01-21/pdf/2011-1385.pdf.
[43] OMB Memorandum re Retrospective Analysis of Existing Significant Regulations (Apr. 25, 2011), available at https://www.whitehouse.gov/sites/default/files/omb/memoranda/2011/m11-19.pdf.
[44] See OMB Memorandum re Final Plans for Retrospective Analysis of Existing Rules (June 14, 2011), available at https://www.whitehouse.gov/sites/default/files/omb/memoranda/2011/m11-25.pdf.

focus on effects pre-birth, and the biomonitoring data reflect all exposures, we question how CPSC will evaluate the effectiveness of the proposed regulations. In particular, how will CPSC evaluate the effectiveness of removing certain phthalates from children's toys? The analysis in the CHAP report is too broad to inform this endpoint and CDC has stated clearly that "The presence of an environmental chemical in people's blood or urine does not mean that it will cause effects or disease."[45] CPSC should explicitly address how regulatory impacts will be measured and how effectiveness, consistent with CPSIA goals, will be evaluated.

[45] See CDC. 2009. Fourth National Report on Human Exposure to Environmental Chemicals, available at http://www.cdc.gov/exposurereport/pdf/FourthReport_ExecutiveSummary.pdf.