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Subject: Comments on the July 2014 report -
Chronic Hazard Advisory Panel On Phthalates And Phthalate Alternatives

To: U.S. Consumer Product Safety Commission

I am pleased to provide comments on the recently released report form the Chronic Hazard Advisory Panel (CHAP) that summarizes their findings and conclusions related to the effects of phthalates and phthalate alternatives for use in children's toys and child care articles.

Several concerns have been identified in my review of this report that raise questions about the reliability of the CHAP conclusions and the applicability of their recommendation to permanently ban the use of diisononyl phthalate (DINP) in children's toys and child care articles. First, the assessment performed is only a screening level evaluation and should not be used as the basis for making regulatory decisions. A screening level assessment is conservative, preliminary and incomplete assessment that is performed to identify next steps – it is not a definitive conclusion. Second, the male reproductive effects that are the focus of the risk assessment are combined irrespective of the severity of toxicity observed for various phthalates. The issue with combining significant toxic effects seen with some phthalate with transient/reversible effects seen with other phthalates in the same risk assessment is that it mischaracterizes relative differences in toxicity. Also, the specific mechanisms of action for phthalate toxicity and the

specific toxicological response are caused by one or all three independent mechanisms of action. The CHAP has defined all three of these under a general term of anti-androgenicity. These must be evaluated independently to assess potential cumulative risk. Consequently, it overstates the potential risks for phthalates, such as DINP, that have not been demonstrated to produce significant toxicity at low doses relevant to human exposures. Third, in the exposure assessment based on biomonitoring data, CHAP ignored the more current surveys that show that overall exposure to phthalates is declining. In addition, the risk estimates were calculated using 99th percentile estimates of exposure which are not considered reliable by the CDC. The reason why these 99th percentile values are not reliable is because the sample size being analyzed is so small that this estimate may be based on the data from only one individual. Finally, the cumulative risk assessment is driven by the exposure to diethylhexyl phthalate (DEHP) which is currently banned from use in children's toys and child care products. Therefore, the conclusions of this assessment should not be relied on to assess risks of phthalate exposure from children's toys and child care products. When the risks from DEHP are excluded, no significant risk is associated with DINP exposure.

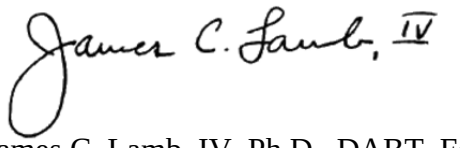
In conclusion, there are no significant risks from exposure to phthalates in children's toys or child-care products and the recommendation that the interim ban for DINP be made permanent is not supported by the evidence.

I submit these comments based upon my extensive experience as a board certified toxicologist who has worked on the hazard evaluation and risk assessment of chemicals, including phthalates for most of my career. After I received my Ph.D. in Pathology in 1975, I worked at the National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA), and as a private consultant in toxicology. I am certified by the American Board of Toxicology (ABT) and the Academy of Toxicological Sciences (ATS); I have served as President of both of these organizations. In 2011, I received the MidAtlantic Chapter of the Society of Toxicology's Ambassador of Toxicology award which recognized my "contributions to the international recognition of the science of toxicology." I have served on committees and in leadership positions in various specialty sections for the Society of Toxicology. I have also served on three committees for the National Research Council/ National Academy of Sciences on risk

assessment and endocrine toxicity. I am currently the Director of the Center for Toxicology and Mechanistic Biology and Principal Scientist at Exponent, Inc.

This critique represents my professional opinion on these issues. It was supported by funding from ExxonMobil Biomedical Sciences Inc. This work was based information in the CHAP (2014) report and select scientific publications cited in the attached critique.

Sincerely,



James C. Lamb, IV, Ph.D., DABT, Fellow ATS
Principal Scientist and Center Director

cc:
Mary Ann Danello, Associate Executive Director, Directorate for Health Services
Robert Jay Howell, Deputy Directory for Safety Operations

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Comments on the Summary by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives

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Prepared for

U.S. Consumer Product Safety Commission
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INTRODUCTION

In mid-July 2014, the Chronic Hazard Advisory Panel (CHAP) released their report to the U.S. Consumer Products Safety Commission (CPSC) on Phthalates and Phthalate Alternatives. The CHAP report presents the panel's findings regarding the potential health effects and exposure of phthalates and their alternatives from children's toys and child-care products. One of the ultimate objectives of this report was to identify a level to which people could be exposed that in combination with the use of safety factors would provide confidence that there would be no harm to the public, including sensitive subpopulations, such as pregnant women and children. In addition, CHAP was to provide a recommendation regarding the existing and interim bans on phthalates and whether any additional phthalates or substitutes should be banned.

The CHAP report attempted to address many of the objectives outlined by the CPSC and covered many of the key issues related to the potential health effects of phthalates. However, a number of limitations and errors have been identified with the report that call into question the conclusions reached by the CHAP. Several significant concerns have been identified, which are described in greater detail below, and include:

- The methodology used in the CHAP report is not a systematic review, nor is it a weight-of-the-evidence review. This report can best be characterized as a hazard assessment with a screening level cumulative risk assessment to estimate margins of exposures. This approach to the evaluation of the potential risks from phthalate exposure is very conservative and likely overestimates the true risks.
- The focus of the CHAP review was on male reproductive toxicity and the cumulative risk assessment was based on a presumed anti-androgenic effect. In the derivation of potency estimates for anti-androgenicity (PEAA), CHAP relied on a range of effects without consideration of the type and severity of toxicity. In some cases, the effects relied on are neither permanent nor adverse. Furthermore, no consideration was given to the phthalates evaluated in the cumulative risk assessment as to whether or not they are attributable to the same mechanism of action.
- Three different scenarios (described by CHAP as Case 1 – 3) were developed to derive PEAAs for use in the cumulative risk assessment. These cases are misleading and do not represent independent evaluations of male reproductive toxicity – two of the three cases are based on the same original research study. In addition, there are some issues with the documentation and selection of the POD and the relative potency for DINP
- The quantification of exposure in the cumulative risk assessment is based on biomonitoring data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) survey and the Study for Future Families (SFF). These studies, as used in the cumulative risk assessment, do not appear to reflect the declines in certain phthalate exposures (which are greatest for DEHP) that have occurred in the last several years. It is important to note that the number of subjects in these sub-populations is small and consequently there is increased uncertainty in the estimation of the upper exposure limits; in particular, the estimates of the 99th percentile for the NHANES data are not considered reliable.
- The cumulative risk assessment results are predominately driven entirely by DEHP and when DEHP is excluded from the risk assessment, no significant risks remain. Because DEHP is not present in

children's toys or child-care products, it is not appropriate to consider exposures to DEHP in the regulation of phthalates in these products. The very low risks of phthalates in children's toys is artificially inflated by adding the low risk estimates for rest of the phthalates to the high and erroneous estimates for DEHP, which do not even come from children's toys or child-care products.

These shortcomings challenge the applicability of the cumulative risk assessment and the conclusions reached by the CHAP for any regulatory decisions on the various bans and use of phthalates in children's toys and child-care products.

CONCERNS WITH METHODOLOGY

The CHAP report is not a weight-of-evidence (WOE) review. Although in the recommendations for each phthalate, there is a sub-section titled "Weight of Evidence," these sections are limited to a discussion of the various NOAELs and LOAELs. The summary provided can only be characterized as hazard identification because it fails to consider differences in dose-response for the various effects. It cannot be considered a WOE review of the health effects of phthalates because it does not consider the data collectively and integrate the evidence to reach conclusions related to the question at hand. An integration of the data should involve consideration of issues beyond the dose at which an effect was observed, such as, the potential for an effect threshold, and the clear definition of mechanism of action, including differences in metabolism. In the case of phthalates, the CHAP only selected the lowest doses that were associated with an effect and did not consider the severity of the effect and whether or not these effects were even adverse (this issue is discussed in the next section in greater detail). In addition, there is little discussion of the species differences that have been identified for phthalates. Kay et al. (2014) suggest that rat studies may be less relevant to humans and that the marmoset may be a better model of the true effects in humans. Although CHAP acknowledges species differences and elected to rely on the most sensitive species, this approach compounds the conservatism in estimating cumulative risks. All of the points of departure (POD) used in the cumulative risk assessment are based on rat studies, which may be overestimating risks. Given the reliance on the rat data, which are thought to be less relevant to human health, consideration should be given to modification of the uncertainty factor applied to account for interspecies differences.

In the CHAP report, it is stated that they could not apply a systematic review methodology (p.12), which was attributed to the "nature of the subject matter and the charge questions." However, it is unclear why a systematic review could not be applied to the elements related to the collection and review of data: "examine all of the potential health effects (including endocrine disrupting effects) of the full range of phthalates" and "examine the likely levels of children's, pregnant women's, and others' exposure to phthalates." Use of a systematic review methodology would have provided increased confidence that the data reviewed and conclusions reached were based on consideration of all the data as defined by the parameters of the review. In the existing review it is unclear what literature search strategies were employed. It is claimed that "to avoid bias," new information and opinions were obtained through public comments and presentations. Although this is a useful approach for obtaining new research data it does not preclude the need for an independent assessment of the scope, relevance and reliability of evidence available.

CHAP states it was guided by quality criteria and analyzed all studies in the public domain relying on the criteria developed by the Organization for Economic Cooperation and Development (OECD 2007). This guidance is for assessing the quality of data on high production volume chemicals in the preparation of "Screening Information Data Sets" or SIDS. SIDSs are used to make initial hazard assessments and assess the need for additional testing data. While these quality criteria are useful for assessing the reliability, relevance, and adequacy of the data, it does not address other quality issues such as reproducibility, bias, and confounding. Use of these guidelines results in only limited review of data quality. This level of review is not sufficient to assess the data quality of studies that would be used in evaluating causal relationship or the risks associated with a specific hazard.

CHAP conducted a cumulative risk assessment to evaluate the combined risk of several phthalates. However, this cumulative risk assessment can only be described as a screening level risk assessment. A screening level risk assessment is typically used to assess if a potential problem exists and is not the basis for taking regulatory action (EPA 1989). If a potential problem is identified in a screening risk assessment, additional refinements of exposure or toxicity can be conducted to better understand the potential risks to the population. It is important to note that no significant risks were associated with DIBP, DBP, BBP, or DINP – even in the screening level assessment – therefore, no further refinements would be required. In particular, these results do not support the retention of the interim ban on DINP. Only DEHP exposure in the screening level cumulative risk assessment indicates a potential for concern. In addition, the CHAP cumulative risk assessment incorporates multiple conservative elements that should be re-examined before regulatory decisions are based on these preliminary risk estimates. The most important factors that need to be addressed are discussed in the following sections: reliance on a POD based on toxicological observations that are transitory and not necessarily adverse, the inappropriate use of relative potency for certain phthalates, the reliance on exposure data that overstates current exposures, and the calculation of upper bound estimates of exposure (99^{th} percentiles) that are not supported by the datasets. In addition, the inclusion of DEHP in the cumulative risk assessment may be appropriate to evaluate overall exposure to phthalates, but it is not relevant to the assessment of phthalates in children's toys and child-care products.

The cumulative risk assessment undertaken by CHAP is based upon a very non-specific and inappropriate definition of the mechanism of action for phthalates. The CHAP has confused the general term mode of action with the more specific term mechanism of action. The mode of action of anti-androgenicity is not well-defined. The mechanism of action is quite specific and more likely to be subjected to cumulative risk assessment. The CHAP also did not evaluate the target response specifically, so that adding the risks together is likely erroneous because the different target organ adverse effects have unique mechanisms of action. There are at least three independent mechanisms of action for phthalates and phthalate alternatives. Each phthalate must be evaluated for potential activity by each mechanism if a cumulative risk assessment is done, because each phthalate can act differently via each mechanism. Hypospadias and infertility are adverse effects that are caused through a mechanism of action that is distinct from the mechanism of action for impaired gubernaculum development and cryptorchidism. Both of those two mechanisms of action are distinct from the mechanism of action for impaired testis development and tumors. These mechanisms need to be treated independently in a cumulative risk assessment, not under a broad umbrella of anti-androgenicity. DEHP has the ability to affect all three mechanisms of action in a dose-dependent manner.

The phthalate alternative TOTM affects none. It has not been reported that DINP can affect any of these mechanisms of toxicity. The CHAP has made the unsupported assumption that the mechanisms are the same, although studies show that they are not.

The CHAP report can, at best, be described as a collective hazard analysis of phthalates with a screening level cumulative risk assessment. However, due to the high exposures to DEHP, the overall hazard index only reflects the risk for DEHP and does not provide substantive risk information on the other phthalates. It is inappropriate to reach conclusions for the phthalates used in toys based on the information for DEHP, which is not used in toys or child-care products. Furthermore, this analysis and risk assessment does not address several key factors for understanding the relevance of these data to human health, such as the mechanism of action of the various phthalates, potential thresholds, and dose-response. In addition, additional refinements to the cumulative risk assessment would better represent current human exposures.

MALE REPRODUCTIVE TOXICITY DATA RELIED ON FOR CUMULATIVE RISK ASSESSMENT

Despite the charge to the CHAP, that all potential health effects (including endocrine disruption) of the full range of phthalates were to be examined, the report focused on male rat reproductive effects only. The rationale for this limitation in the review was that male developmental toxicity in the rat was "the most sensitive and most extensively studied endpoint." However, as noted in the CHAP report (2014), liver toxicity is considered the most sensitive toxic endpoint for DINP with a NOAEL of 12 mg/kg/day, which is lower than the NOAEL of 50 mg/kg/day based on the observation of multinucleated gonocytes (MNGs) characterized as anti-androgenic toxicity.

Consequently, the CHAP reviewed the male reproductive and developmental toxicity on the various phthalates and developed a cumulative risk assessment based upon a proposed anti-androgenic mechanism of action for specific phthalates. The "phthalate syndrome" includes various effects that are clearly adverse, including malformations of accessory sex organs and cryptorchidism. Such effects have been observed with some phthalates such as DEHP, DBP and BBP (but not DINP) and can be characterized as a high dose effect.

Other changes in male offspring have been seen at lower doses, such as increased nipple retention, decreased anogenital distance, and delayed preputial separation, which can be considered as biomarkers of the "phthalate syndrome." Although there may be some debate among reproductive toxicologists as to the adverse nature of these observations, it may be reasonable to rely on them for the purposes of risk assessment and regulatory decision making, but it should be recognized that these effects do not represent the same degree of toxic severity. Anti-androgenic activity seems to play a role in "phthalate syndrome," but is not a sufficient description of the mechanism of action to conduct a cumulative risk assessment or combine disparate observations.

There are also transient, non-adverse effects on other endpoints related to anti-androgenicity, such as reduced fetal testosterone production, Leydig cell aggregation and the induction of multinucleated giant cells. These types of findings are adaptive changes and cannot be considered as the same degree of severity as adverse effects associated with the "phthalate syndrome" or even biomarkers. CHAP has conducted a cumulative risk assessment that includes a combination of biomarkers and non-adverse effects, confusing the potential toxic potency of the various phthalates.

In particular, the adverse effects associated with the "phthalate syndrome" have not been observed with DINP, even at dose levels as high as 750 mg/mg/day (Clewell et al. 2013). The DINP transitory, non-adverse responses are neither permanent nor adverse, so the no observed effect level (NOEL) for these endpoints was set at 50 mg/kg/day (Clewell et al. 2013). The endpoints associated with the adverse effects have not been observed in studies on DINP. The reliance on the induction of MNGs and the mode of action of anti-androgenicity to set the POD for DINP is misleading. Anti-androgenicity is a general mode of action, not a mechanism of action. MNGs are a reversible and non-adverse effect that should not be relied upon in the cumulative risk assessment in combination with other phthalates with PODs based on more significant toxicity. Instead, the NOAEL for similar biomarker changes (i.e., increased nipple retention, decreased anogenital distance) is 600 mg/kg/day (LOEL = 750 mg/kg/day for nipple retention; LOEL = 900 mg/kg/day for a decrease in anogenital distance) and should have been used in Case 3 of the cumulative risk assessment (Boberg et al. 2011).

The CHAP cumulative risk assessment inappropriately combined toxicity POD values for the phthalates ignoring the differences in potency and the distinction between adverse and non-adverse effects. Furthermore, the cumulative risk assessment relies on anti-androgenicity as a general mode of action, but fails to show that these effects are the result of the same mechanism of action. Even if two compounds induce the same effect, but they are the result of changes in two different biochemical pathways, they cannot be considered additive responses for a cumulative risk assessment.

POINTS OF DEPARTURE AND DERIVATION OF POTENCY ESTIMATES FOR ANTI-ANDROGENICITY

Several concerns have been identified in the selection of the PODs and derivation of potency estimates for anti-androgenicity. CHAP developed three scenarios or cases to calculate a hazard quotient (HQ) for each phthalate and a hazard index (HI) for the sum of the five phthalates in the cumulative risk assessment. The "Cases" were chosen to evaluate the impact of the assumptions used in the selection of the PODs and the derived PEAAs. However, the selection of these cases is misleading because they do not represent independent research, but rather the selection of different PODs. In some of the cases, the PODs include a mixture of biomarkers and non-adverse effects, which as described above is inappropriate. In addition, some errors were identified in the selection of specific NOAEL or LOAEL values.

Case 1 and 2 are both primarily based on the research of Howdeshell et al. (2008). Although the citation provided for each case in the CHAP report differs (Kortenkamp and Faust 2010, Hannas et al. 2011a, b), the original citation for the data being relied on is Howdeshell et al. (2008). In both cases, for all phthalates except DINP, the explicit endpoint being evaluated was a reduction in fetal testosterone.

In Case 1, the POD for BBP, DBP and DIBP is based on a benchmark dose (BMD) value for decreased fetal testosterone calculated by NRC (2008) and the POD for DINP is based on a LOEL for nipple retention (Grey et al. 2000). As noted above, changes in fetal testosterone can only be considered as transient, non-adverse effects and should not be combined with other biomarkers or true adverse effects. It should further be noted that changes in fetal testosterone are not directly related to the induction of more severe changes in the male reproductive tract. Furthermore, CHAP failed to show a common mechanism of action for these testosterone changes to support the combination of these phthalates in a cumulative risk assessment.

In Case 2, the POD for these compounds is based on the relative to potency to DEHP based on the effective dose which inhibited fetal testosterone production by 50% (ED_{50}). It is more appropriate to compare relative potency at well-established low doses that at a high dose, such as an ED_{50}. Selection of the relative potency based on the median response (ED_{50}) is not relevant for predicting low dose effects. In fact, looking at Figure 1 in Howdeshell et al. (2008), at the lowest dose administered for BBP (100 mg/kg/day) fetal testosterone levels were higher than the controls. Although the CHAP selected a 2.3-fold relative potency for DINP, it is worth noting that this value is significantly lower than the estimate for general anti-androgenicity by Gray et al. (2000) who stated: "DINP was about 10- to -20-fold less potent than BBP or DEHP." .

Additionally, in Case 2, no reference is provided for the POD of 5 mg/kg/day for DEHP. Using relative potency estimates and this value, the PODs were established for BBP, DBP and DIBP. In the absence of other information, it is presumed that the POD for DEHP in this case is the same as in Case 3. In Case 3, the effects associated with the NOAEL include: delayed preputial separation, an increase in total reproductive tract abnormalities, and decreased spermatocytes/spermatids[1]. It is not appropriate to rely on a NOAEL for one effect to predict the relative potency because if the effects are independent, the ratio of the two doses does not represent the same mechanism or action. Given the fact that a NOEL of 100 mg/kg/day for fetal testosterone exists there is no rationale for relying on the dose associated with a different effect to evaluate the relative potency for changes in fetal testosterone (Hannas et al 2011a, Table 1).

In Case 1, for DINP the POD is the LOAEL for retained nipples from Gray et al. (2000). This LOAEL has been superseded by Boberg et al. (2011) that identified a NOAEL of 600 mg/kg/day for nipple retention. If retained nipples are determined to be the most appropriate POD for DINP, then the NOAEL could be used and the uncertainty factor of 500 modified to reflect the use of a NOAEL instead of a LOAEL. However, the reliance on nipple retention as a POD is clearly different from the changes in fetal testosterone that were the basis for the POD for all of the other phthalates (especially if one relies on the BMD value for DEHP) and should not be combined. Boberg et al. (2011) also evaluated changes in fetal testosterone and these data would be more appropriate to rely on for a POD as they represent the same toxic endpoint and potential mode of action, but not necessarily the same mechanism of action. Fetal testosterone on PND 90 was decreased in a dose-related manner, but was not statistically significant; therefore, the DINP NOEL would be 900 mg/kg/day for changes in fetal testosterone (Boberg et al. 2011).

In Case 2, the CHAP used a relative potency factor that assumes that the toxicity of DINP was 2.3 times less than DEHP based upon kinetics. That factor is derived from studies of the diester, not the active monoester that was measured in the NHANES human biomonitoring study. This factor was not based upon adverse effects because DINP has not been shown to cause the collection of adverse effects described as the "phthalate syndrome." As noted above, Gray et al. (2000) estimated that the potency of DINP was 10- to 20-fold less than DEHP based on anti-androgenic effects (e.g., nipple retention). Clewell and colleagues (2013) evaluated the relative potency by considering not only pharmacokinetics, but also pharmacodynamics. Based on this work, the relative potency difference would be 4- to 7-fold for the non-adverse effects related

[1] Although a decrease in spermatocytes and spermatids were presented as one of the developmental endpoints on Table 2.1, this was not confirmed as reported in the studies cited.

to the induction of multinucleated giant cells. Thus, the use of a relative potency of 2.3 does not reflect the available data and over-estimates the potential toxicity of DINP.

Case 3 is based on the lowest LOAELs and associated NOAELs and NOELs identified in the report irrespective of the type of toxicity associated with these doses. As stated previously, it is not appropriate to combine toxicity of varying severity without consideration of the mechanism of action. There is a clear lack of consistency in the most sensitive effect for individual phthalates; in some cases it is a reduction in anogentital distance and in other increase nipple retention. It is not clear that these differences are compatible with each other for assessing a dose-response and relative potency. The endpoints relied on for Case 3 includes both biomarkers and transient, non-adverse effects. In particular, adverse effects have not been demonstrated for DINP and it is not appropriate to sum the non-adverse and adverse effects. In any event, the value used for DINP (50 mg/kg) based on nipple retention is incorrect as in the cited reference (Boberg et al., 2011), the NOEL is 600 mg/kg.

There are insufficient data to support the use of these three scenarios to derive HQs and HIs. Case 1 and 2 rely on the same original research and are redundant. The POD for DEHP as presented in Case 1 is incorrect; it is recommended that the BMD value for DEHP be used as it derived from the same research and represents similar toxic effects. Case 3 relies on a combination of effects as the PODs and the CHAP failed to demonstrate that these effects can be linked to a common mechanism of action. Therefore, the inclusion of these different endpoints may overstate the potential risk from cumulative exposure.

EXPOSURE CHARACTERIZATION IN CUMULATIVE RISK ASSESSMENT OF PHTHALATES

Concerns have been identified regarding the exposure characterization and use of the biomonitoring data in the cumulative risk assessment as presented in the CHAP report. First, the biomonitoring data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) survey does not reflect the most current data available, which suggests that certain phthalate metabolite levels are declining. These biomonitoring data were selected to represent sensitive sub-populations, such as pregnant women and children. The distributions of daily intakes for phthalates based on the NHANES and the SFF biomonitoring data are based on small populations and consequently result in highly imprecise estimates at the tail ends of the distribution. The 99^{th} percentile estimates cannot be considered reliable and therefore cannot be used to estimate HQs and the HIs.

The CHAP relied on biomonitoring data for several phthalate metabolites from the 2005-2006 NHANES and the Study for Future Families (SFF) (Sathyanarayana et al. 2008a, 2008b) to estimate exposure in the cumulative risk assessment. Although the CHAP report presents metabolite data for DIDP and DINP from the SFF, the cited publications do not provide any data on the metabolites for these compounds. Use of raw data from study investigators should be relied on with caution as they have not undergone any independent review process. If the data are considered important to provide context where no other data exist, at the very least these data need to be clearly identified as such in the report and should not be utilized in making regulatory decisions.

Overall Urinary Phthalate Metabolite Concentrations Are Declining

The CHAP report relied on the NHANES data from the 2005-2006 sampling period. Since that time, the data from two more surveys have been released and indicate an overall decline in phthalate exposure. According to the most recent tables from Center for Disease Control's (CDC) Fourth National Report on Human Exposure (CDC 2014), most of the individual phthalate metabolites have decreased and collectively phthalate metabolites are declining. Although exposure to some phthalates are increasing, these represent a lower hazard and the risks overall from phthalate exposures are declining.

According to the cumulative risk assessment, DEHP is the largest, if not sole, contributor to the HI. The geometric mean (GM) urinary concentrations of DEHP metabolites have all declined by approximately 50% or two-fold. The decline at the 95th percentile is even greater, with reductions between 69 and 84%. Thus, the calculated HIs for virtually all scenarios would be reduced by two-fold. In addition, the urinary metabolites for DBP and BBP have also declined over this time period, between 37 and 55% (both GM and 95th percentile). Although the metabolites for DIBP and DINP have increased slightly, less than 1-fold and 4-fold, respectively, the margins of exposure for remain sufficiently large such that these increases would not have any impact on the HI.

Number of Samples for Sensitive Sub-Populations are Small and 99th Percentile Values Imprecise

Biomonitoring data for pregnant women from the 2005-2005 NHANES survey were selected for use in the cumulative risk assessment. As a result of sampling design changes, the 2005-2006 dataset is the last survey to conduct oversampling of pregnant women. In the 2005-2006 survey, the oversampling resulted in the collection of urine samples from 130 pregnant women, ages 15 to 41 years old. However, the CHAP report (p. 36) notes that "comparing pregnant women to non-pregnant women in this age range, the exposures were not found to be significantly different." Given the lack of differences in pregnant women and women of reproductive age, it is not clear why the CHAP elected to use the smaller dataset from an older survey. Use of data from all women of reproductive age in this analysis would have been more statistically robust and the use of a smaller dataset raises questions about the reliability of the conclusions.

In addition to the issue of declining phthalate levels over time, as discussed above, the use of the subsample of pregnant women is hampered by the small number of urine spot samples available. This is particularly problematic when evaluating the tail ends of the HQ distribution for the individual phthalates. According to the analytic guidelines for the NHANES survey (CDC 2013) when considering the utility of a sample for analysis, the target is a relative standard of error (RSE) of 30%. To meet this requirement, a minimum sample size of 150 is identified. This is the sample size necessary to estimate a 95th percentile with any precision. To estimate the 99th percentile a much larger sample would be needed to achieve an acceptable relative standard of error. Given the log-normal distribution for DEHP metabolites in the pregnant women data set, it is estimated that a sample size of between 400 and 500 women would be required to achieve the minimum requirements identified by NHANES. Given the

sample size of only 130 pregnant women in the 2005-2006 NHANES with urinary phthalate data, the HQs and HI at the 99th percentile are not reliable and should be excluded.

The raw data for the SFF study are not available, and therefore, a similar analysis has not been conducted. As noted above, it is particularly problematic for certain phthalate metabolites as these data were not reported (for DINP or DIDP) in the publications on the study. However, it is likely that given small sample sizes, albeit larger than the NHANES data set, that the 99th percentile estimates may be imprecise and not appropriate for establishing HIs.

In this screening assessment, the evaluation of pregnant women may have been useful as a sensitivity analysis to ensure the applied uncertainty factors are protective of these populations. The use of the large dataset of reproductive age women would have provided a more robust analysis. However, given the lack of difference noted in phthalate levels in pregnant women and women of reproductive age, it is not clear that a sensitivity analysis would have been necessary. Finally, if there are no differences in exposure or risk between the general population and the sensitive sub-population, there is no need for additional protection and the use of an uncertainty factor to account for sensitive subpopulations in the derivation of the POD is not warranted. The use of both a sensitive subpopulation to estimate exposure and inclusion of the uncertainty factor to account for sensitive subpopulations is overly-conservative and redundant.

CUMULATIVE RISK ASSESSMENT DRIVEN BY RISKS FROM DEHP

The CHAP report presents a range of HIs for the cumulative risk from five phthalates: DIBP, DBP, BBP, DEHP, and DINP. HIs presented in Table 2.16 of the CHAP report are rounded up, which suggests that other phthalates have some contribution to the overall risk. Based on a sum of the HQ provided, DEHP generally accounts for over 90% of the total risk. Excluding DEHP from the cumulative risk assessment would result in all HIs being less than one – even at the 99th percentile which as mentioned is not a reliable estimate given the small sample sizes.

Specifically, the risk of DINP is trivial compared to DEHP because DEHP acts through all three mechanisms of action while DINP has not been shown to act through any of them. Based on the results of the cumulative risk assessment the risk of DEHP is already unacceptable, so any additional risk, even trivial ones, could not be acceptable according to CHAP. As a result, the inclusion of DEHP in the cumulative risk assessment predicates excess risk for any phthalate which defeats the objective of assessing phthalate exposures from children's toys and childcare products. Given the fact that DEHP is not used in children's toys or child-care products, this screening risk assessment should not be used to regulate these products. The potential risks from the phthalates in children's toys and child-care products have sufficient margins of exposure, even on a conservative cumulative risk basis.

CONCLUSIONS

The CHAP report is a summary of the potential hazards and a screening level cumulative risk assessment of phthalate exposure. The identification of potential hazards and a screening level assessment did not provide a sufficient basis for making regulatory decisions. Other factors including the relevance to humans,

thresholds, dose-response, and the potential mechanism of action for the various phthalates need to be given greater consideration.

Various concerns have been identified above regarding the errors in the selection of PODs, the inappropriate combination of adverse and non-adverse effects for phthalates, lack of evidence for a common mechanism of toxicity, declining exposure to phthalates since 2005-2006, and the limitations in exposure estimates at the tail ends of the distribution. In light of these significant concerns, the results presented and the conclusion reached in the CHAP report cannot be considered reliable.

The inclusion of DEHP in the cumulative risk assessment is particularly troubling and drives the risk assessment, despite the fact that it is not used in toys or other child-care products. Excluding DEHP, refining the cumulative risk assessment to reflect more current phthalate exposure, and use of more appropriate PODs shows that none of the HIs in would be greater than 1.0. In addition, sufficient MOEs exist for individual phthalates to protect public health. Thus, there are no significant risks from exposure to phthalates in children's toys or child-care products and the recommendation that the interim ban for DINP be maintained is not supported by the evidence.

This critique was based information in the CHAP (2014) report and select scientific publications cited in this critique. We reserve the right to revise or update these comments as new information becomes available.

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