October 7, 2014

Michael Babich, PhD
Jay Howell, PhD
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

Re: Comments on CHAP Report on Phthalates

Dear Drs. Babich and Howell,

We respectfully provide comments on the Chronic Hazard Advisory Panel's (CHAP) Report on Phthalates. The attached report summarizes our comments. Briefly, we commend the CHAP for utilizing human biomonitoring data for assessing exposures to phthalates amongst pregnant women and children. However, the CHAP assessment is based on outdated biomonitoring data. Using biomonitoring data collected more recently (2009-2010 versus the 2005-2006 timeframe utilized by the CHAP) indicates that exposures to DEHP have declined significantly, to the point where hazard index (HI) no longer exceeds 1 for the phthalates of interest. Likewise, one of the approaches used to derive a relative potency for DINP is flawed and superfluous. If the CPSC were to conduct a risk assessment using our recommended changes, the overall conclusion of potential risks to public health will be significantly lower than previously estimated and may no longer support recommendations for further bans on phthalates.

We welcome any questions you may have about our comments.

Respectfully,

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Comments on Chronic Hazard Advisory Panel Report on Phthalates

Prepared for

ExxonMobil Biomedical Sciences, Inc.

October 7, 2014

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Executive Summary

Summit Toxicology, L.L.P. was asked by ExxonMobil Biomedical Sciences, Inc. to review specific portions of the Chronic Hazard Advisory Panel's (CHAP's) report on exposures to phthalates (USCPSC, 2014 – hereafter referred to as the CHAP report), with emphasis on (1) how the CHAP assessed exposures to phthalates via use of human biomonitoring (HBM) data; and (2) how the CHAP developed relative potencies for DINP for estrogenic effects.

Newer Biomonitoring Data Yield Far Lower Hazard Indexes and Hazard Quotients
We commend the CHAP for using HBM data to assess exposures to phthalates in pregnant women and children. However, there are some problems with how this approach was utilized. First, the CHAP relied on outdated biomonitoring data on phthalates (NHANES 2005-2006 collection cycle). More recent (reflecting exposure from 2009-2010 time period) biomonitoring data are available for the various phthalates through the National Health and Nutrition Examination Survey (NHANES; http://wwwn.cdc.gov/nchs/nhanes/search/nhanes09_10.aspx). [1]

Analysis of the 2009-2010 collection cycle indicate significantly lower exposures to DEHP and slightly higher exposures to DINP compared to the exposures calculated by the CHAP using data from the 2005-2006 collection cycle. As a result, the Hazard Quotients (HQs) for DEHP have reduced substantially (less than 1) and those of DINP have increased slightly, but still extremely low (HQ < 0.02). The sum of the HQs for DEHP and DINP result in a Hazard Index (HI) that is still dominated by DEHP, but is now below 1. We recommend that the Consumer Product Safety Commission (CPSC) recalculate exposures, HQ and HI values utilizing more recent HBM data.

Case 2 Relative Potency for DINP is Flawed and Superfluous
The relative potencies derived for DINP for Case 2 in their report is flawed and not necessary. Available robust and *in vivo* studies for DEHP and DINP provide far more scientifically defensible approaches for deriving potencies for DINP relative to DEHP. Therefore, we recommend that the Case 2 assessment be removed from the CPSC's rulemaking deliberations.

The following provides more details on these comments and on the new analysis conducted as part of this effort.

Comments on CHAP Exposure Estimates

This report contains comments on the CHAP's method for deriving estimates of daily dose of phthalates from biomonitoring data and their calculations of HQ and HI values for the specific phthalates thought to act by reducing testosterone synthesis.

[1] Data from the 2011-2012 collection cycle were available, but have since been withdrawn because of an error in the weighting factors.

- Based on the CHAP analysis of the NHANES data from the 2005-6 collection cycle, DEHP dominated the HQ (the phthalate with the next highest HQ is almost 1/100th of DEHP). In a situation like this, there is no reason for doing a cumulative risk assessment, especially when the other contributors combined contribute less than 1% of the HQ of DEHP.
- The CHAP used a creatinine excretion rate of 23 mg Cr/kg-day to convert the data from the SFF study to get from creatinine adjusted urinary concentration to daily intake. This value does not appear to be accurate. The 2009-2010 collection cycle of the NHANES has data that allows calculation of creatinine excretion rate for all populations. Analysis of these data suggest that the creatinine excretion rate for pregnant women is 14.6 mg Cr/kg-day. Therefore, the results reported by the CHAP in which a value of 23 mg Cr/kg-day was used are biased high by a factor of 1.5 (23/15) for all analytes and all percentiles.
- Relying on upper percentiles for spot samples is not a realistic representation for upper percentiles on longer-term (chronic or sub-chronic) exposures. As the CHAP has noted, there is substantial evidence that intra-individual variability in spot samples is quite large. The study of Preau et al. (2010) for instance, shows that the variability in concentrations of MEHHP (a metabolite of DEHP) varies by almost four orders of magnitude within an individual across seven days and that range of concentrations of MEHHP in spot samples are almost identical across 8 individuals (Figure 1). The objective of the CHAP analysis is to assess longer-term (preferably life-time) average exposures across the US population. Using a distribution of spot samples across a large sample size likely does not provide an accurate reflection of the variability in longer-term average exposures. In fact, use of a 95th percentile from the distribution of spot samples vastly over-estimates the range of longer-term exposures. The study of Preau et al (2010) is instructive for assessing this issue and provides the means to calculate the range (or ratio of 95th to 50th percentile of the distribution) of urinary concentrations of MEHHP from all spot samples and 24-hour averages and 7-day averages amongst individuals. For example, the ratio of 95th to 50th percentile of MEHHP amongst spot samples was 16.6, amongst all 24-hour composites was 8.2 (almost half the variation as compared to spot samples), and for 7-day averages across individuals, the ratio of the maximum (maximum 7-day average concentration of MEHHP amongst the individuals) to the mean of the individuals was 2.2 (this study did not have enough participants to reliably calculate a 95th percentile on 7-day average concentrations of MEHHP). By utilizing the 95th and 50th percentiles of the distribution of spot samples from the NHANES data, the CHAP is implying that the 95th percentile represents an 'upper end of exposures' amongst the population. Based on the small sample size from the Preau et al study and using the CHAP logic, one would falsely conclude that the 'upper end of exposures' amongst the Preau study population was greater than 16 times the mean exposure of the population. Instead, use of the 7-day average data would indicate that the person with the 'upper end of exposures' is only 2.2 times the mean of the population (Table 1). Extending this out to even longer averaging times would likely reduce this ratio even further. Therefore, use of a 95th percentile of spot urinary concentration of phthalate metabolites by the CHAP is unrealistic and likely to be a vast over-estimation of longer-term exposures. The CHAP should recognize this issue and indicate that the use of the 95th percentile will drastically over estimate the range of longer-term exposures to phthalates.

Figure 1: Variability in spot urine concentrations of MEHHP in 8 volunteers in every void over a one week timeframe. 24-hour and 7-day average concentrations are also provided.

Table 1: Summary statistics for concentrations (ng/ml) in spot samples, 24-hr composite samples, and multi-day composites for MEHHP from the serial urinary collection study of Preau et al. (2010).

	N	% >LOD (LOD, ng/ml)	Mean	SD	GM	GSD	p5	p25	p50	p75	p90	p95	min	max
Spot	328	>95	85.9	188.7	22.9	5.5	1.5	7.9	22.3	72.5	210.5	370.6	0.2	1630
24-hr composites	44		72.8	85.3	37.8	3.3	6.5	13.5	33.4	119.6	173.6	278.6	4.5	371.2
7-day average	8		59.1	51.1									7.1	132.3

- DEHP levels have reduced significantly since the 2005-6 timeframe that is the basis of the CHAP assessment (see Figure 2). Since the hazard quotients (HQs) calculated by the CHAP were vastly dominated by the hazard indices (HIs) for DEHP, significant reductions in DEHP exposures over this time frame would suggest that the HQs for the key phthalates included in the CHAP's cumulative assessment are significantly outdated and my no longer indicate a HQ greater than 1.

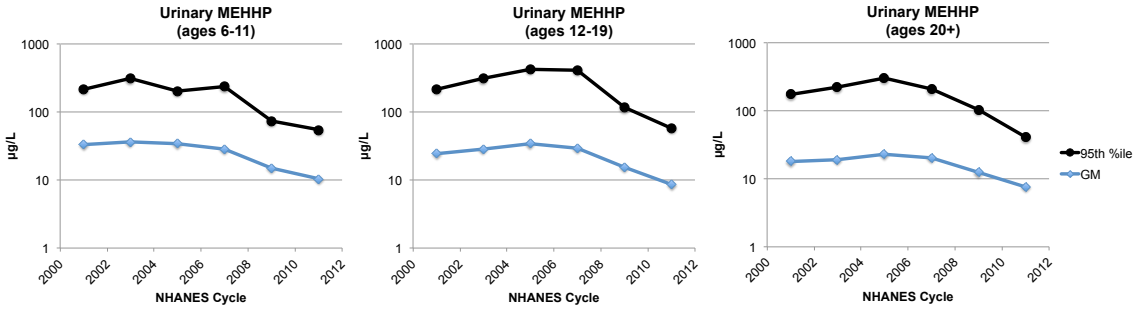

Figure 2: Trend in DEHP exposures (MEHHP in urine) from 2001 to 2011.

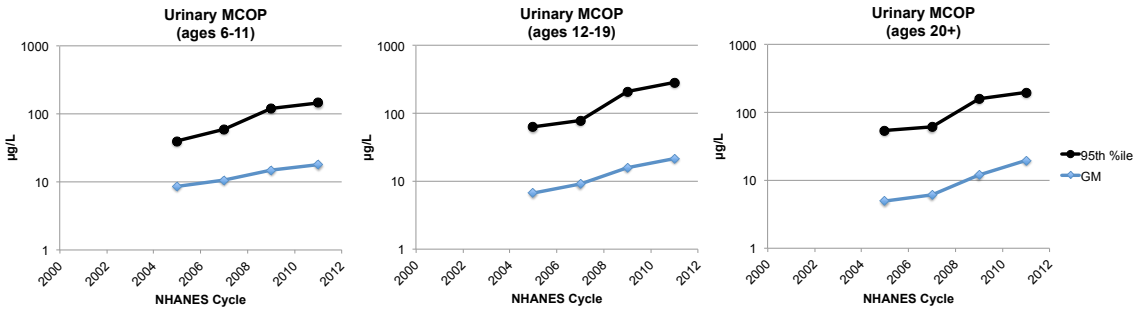

Figure 3: Trend in DINP exposures (MCOP in urine) from 2005 - 2011.

Comments on Point of Departure for Hazard Assessment in Case 2 Presented by the CHAP for DINP

In the CHAP's hazard assessment, 3 cases were used for calculating hazard quotients. Case 2 was based on relative potency assumptions across phthalates. DEHP was selected as the index chemical, with known *in vivo* evidence of antiandrogenicity in experimental animals and a NOAEL of 5 mg/kg-day.
DINP was assumed to be 2.3 times less potent than DEHP based on the *in vivo* ED50 values of Hannas et al. (2011). This approach results in an calculated NOAEL of 11.5 mg/kg-day for DINP (5 mg/kg-day x 2.3). An overall uncertainty factor of 100 was selected to account for inter-species extrapolation (factor of 10) and inter-individual variation (factor of 10). Comments of USCPSC's Case 2 approach for DINP are summarized below.

- The study of Hannas et al. (2011) has flaws and limitations, which preclude its application to estimating the relative potency of DINP with any degree of -confidence. Hannas et al. (2011) assessed the impact of DEHP and DINP on 3 endpoints in SD rats: testosterone production, StAR gene expression, and CYP11a gene expression.
    - *Flaw*: Unfortunately, the authors obtained SD rats from different labs for DEHP (Charles River) and DINP (Harlan). Control values for testosterone production are significantly different for these two rat suppliers (5.36+/-0.15 ng/testis for Charles River; 7.00+/-0.36 for Harlan). Differences between rat suppliers could not be assessed for the other two labs since the data were expressed in terms of percent control value. Furthermore, the shapes of the dose-response curves obtained for DEHP and DINP are very different (Figure 3), with curves for DEHP exhibiting highly nonlinear behavior, while those for DINP are fairly linear in behavior. The difference in behavior may reflect differences in the two rat populations, or may serve to indicate a fundamental difference in the underlying MOA for the observed effects.

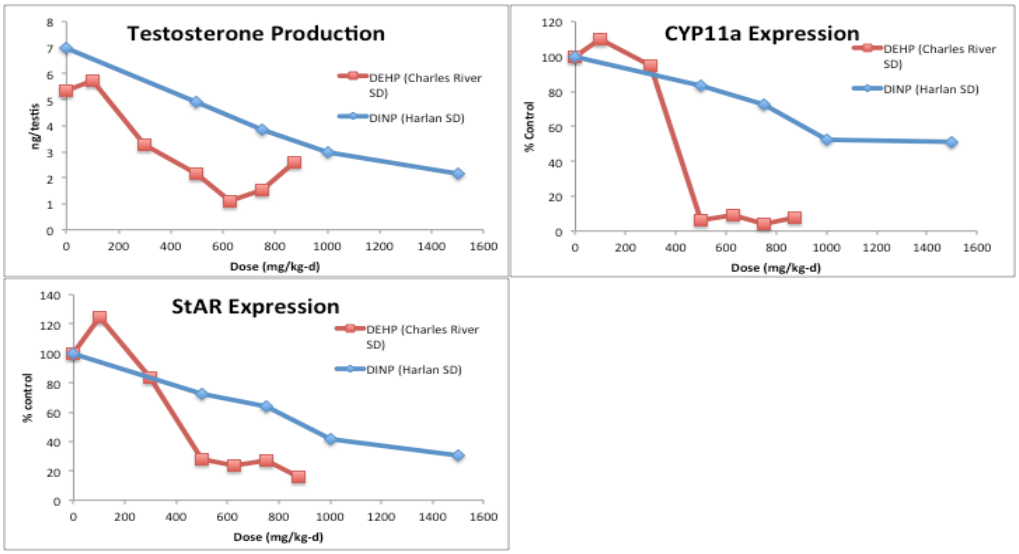

Figure 4: Dose-response curves for DEHP and DINP in SD rats (Hannas et al., 2011)

- *Flaw*: Because the shapes of the dose-response curves for DEHP and DINP appear sufficiently different, global regression modeling (as performed by Hannas et al. 2011) may not be appropriate. Furthermore, because the curves appear fundamentally different, reliance on relative ED50 values may not reflect the relative potency of DINP at low doses (e.g., ED01, ED05).
- *Limitation*: The dose-response data are based on small groups of rats (n=3 to 9 per group). Groups of 10 or more animals are generally preferred for assessing dose-response relationships.
- *Limitation*: In this study, the NOAEL for DEHP effect on testosterone is 100 mg/kg-day, a dose that is 20x higher than the POD identified by the CHAP for DEHP (5 mg/kg-day). Based on the lack of dose-response concordance the relationship between the POD for DEHP and the data set used to estimate relative potency is unclear.

Based upon these considerations we recommend that USCPSC reconsider using the Hannas et al. 2011 study as the basis for estimating relative potency.

- A relative potency approach is not needed for DINP since sufficient data are available from *in vivo* studies. The developmental effects of DINP have been well characterized in rats (Clewell et al., 2013a,b; Hannas et al., 2011a,b; Boberg et al., 2011; Gray et al., 2000; Waterman et al., 1999, 2000). The relative potency approach is usually reserved for situations in which sufficient dose-response data are not available for the chemical of interest. The USCPSC's reliance upon a relative potency approach for Case 2 therefore reflects a step backwards with respect to risk assessment methodology, and does not make the best use of toxicity information available for DINP. We recommend that USCPSC reconsider including Case 2 for DINP, and instead rely upon the results of either Case 1 or 3 since they are better supported by the available information.

- If a relative potency approach for DINP is desired by USCPSC, then the available *in vivo* studies should be used instead of a flawed study of Hannas et al. (2011) (see comment above). Better estimates of relative potency can be obtained

using NOAELs for effects in similarly conducted studies. Preliminary calculations indicate that the ratio of NOAEL values (DEHP/DINP) are considerable larger than 2.3 used by USCPSC based on the Hannas et al. study. For example, in Wistar rats the ratio of NOAEL values is approximately 100 (300 mg/kg-day/ 3 mg/kg-day) (Boberg et al., 2011; Christiansen et al., 2010). This ratio relies upon NOAEL values obtained using the same test lab (National Food Institute, Technical University of Denmark), method of administration (oil gavage), and rat supplier (Taconic), with both studies including a sufficient number of animals per test group (generally >30). Similarly, in Sprague-Dawley rats the ratio is approximately 10 (50 mg/kg-day/ 5 mg/kg-day) (Clewell et al., 2013; Blystone et al. 2010). This ratio relies upon NOAEL values using the same method of administration (diet) and rat supplier (Charles River), with both studies including a sufficient number of animals per test group (generally >10). However, the Sprague-Dawley ratio relies upon different test labs (Hamner, NIEHS). Benchmark dose methods could be used with these data sets to calculate a more robust ratio of appropriate BMD values (e.g., replace the NOAEL values with BMDSD values).

Alternate Exposure Estimates

- The most current NHANES data that is available is the 2009-10 collection cycle[2]. Starting in 09-10, CDC started collecting total urine void volume and time since last void. This allows calculation of mass excretion rate (ug/kg-hr). This can be extrapolated to 24-hr excretion rate (assuming a constant excretion rate over the 24 hours). The following outlines the methods used for this analysis.

Methods

- Database of HBM Data: NHANES 2009-2010 collection cycle.
- Downloaded data files for phthalates, body measures, urine pregnancy test and urine flow rate.
- Data analyzed using Stata (version 13.1)
- The following phthalate metabolites were analyzed for DEHP exposures;
    - MEHP; mono(2-ethylhexyl) phthalate
    - MEHHP; mono(2-ethyl-5-hydroxyhexyl) phthalate
    - MEOHP; mono(2-ethyl-5-oxohexyl) phthalate
    - MECPP – mono(2-ethyl-5-carboxypentyl) phthalate
- Mono(carboxynonyl) phthalate (MOCP) was the metabolite chosen as a metric of DINP exposures.
- For each analyte, the mass excretion rate (ug/kg-day) was calculated as the concentration (ug/L) times the urine flow rate (L/hr) *24 hrs/day divided by body weight.
- Conversion to DEHP exposures was accomplished by summing the mass excretion rate for each of the DEHP metabolites by individual and dividing by urinary excetion fraction (Fue) of 0.528 of DEHP exposures (urinary excretion fraction on a mass basis – Aylward et al., 2009).

[2] CDC originally released the phthalate results from the 2011-2012 collection cycle, but it has since been retracted because they found an error in the weighting factors.

- Conversion to DINP exposures was accomplished by dividing the mass excretion rate of MCOP for each individual by 0.28 (urinary excretion fraction on a mass basis– Hays et al., 2012).
- All mass excretion rates were adjusted using the weighting factors for the 2009-2010 collection cycle.
- The 50th and 95th percentiles were calculated for pregnant participants. The 50th and 95th percentiles were also calculated for all participants between the ages of 15 and 45 (reproductive age).
- Hazard Index was calculated using the same potency estimates for antiandrogenicity (PEAA's) used by the CHAP for Case 1 and 3. The PEAA's from Case 2 were not utilized (see comments above).

Results

DEHP Exposures

Exposures to DEHP from the 2009-2010 collection appear to have declined by at least a factor of 3 at the 50th percentile compared to the 2005-2006 collection time frame (as calculated by the CHAP) (Table 2). The results for pregnant women (N=25) and men and women of reproductive age (N=1050) are fairly similar from the 2009-2010 collection cycle.

Table 2. DEHP exposures (ug/kg-day) calculated from NHANES 2009-2010 collection cycle and comparison to results from CHAP report.

Population	N	mean	p50	p95
NHANES 2009-10: Reproductive age females (15-45)	518	2.6	1.1	7.6
NHANES 2009-10: Reproductive age males (15-45)	532	5.0	1.4	17.6
NHANES 2009-10: Pregnant	25	1.3	0.6	9.6
NHANES 2005-6: Pregnant[a]	130		3.5	181.0

a - Values reported by the CHAP in Table 2.7 of their report.

DINP Exposures

Exposures to DINP among pregnant women as characterized using the 2009-2010 NHANES collection cycle appear to have remained consistent as compared to those calculated by the CHAP (NHANES 2005-2006 collection cycle). However, the low N for pregnant women included in the 2009-2010 collection cycle precludes any strong conclusions regarding comparisons between 2009-2010 and 2005-2006 and between pregnant women and men and women of reproductive age within the 2009-2010 collection cycle (TABLE 3).

Table 3. DINP exposures (ug/kg-day) calculated from NHANES 2009-2010 collection cycle and comparison to results from CHAP report.

Population	N	mean	p50	p95
NHANES 2009-10: Reproductive age females (15-45)	518	6.2	2.1	26.0
NHANES 2009-10: Reproductive age males (15-45)	532	8.6	2.7	36.7
NHANES 2009-10: Pregnant	25	3.2	1.2	9.6
NHANES 2005-6: Pregnant[a]	130		1.0	11.1

a - Values reported by the CHAP in Table 2.7 of their report.

Hazard Quotients (HQs)

The HQs calculated using these exposure estimates indicates that the HQs for DEHP have decreased substantially and those of DINP have remained largely the same compared to the calculations of the CHAP (Table 4). These results indicate that the exposures to DEHP no longer exceed the PEAA's and DINP exposures are still far below the PEAA's for DINP.

Table 4: Hazard Quotients (HQs) for DINP and DEHP for pregnant women, women and men of reproductive age for the 2009-10 NHANES collection cycle and for pregnant women from the 2005-6 NHANES collection cycle.

NHANES Cycle	2009-10		2009-10		2009-10		2005-6[a]	
Population	Pregnant Women		Women of reproductive Age		Men of reproductive Age		Pregnant Women	
PEAA Case	1	3	1	3	1	3	1	3
DEHP - 50th	0.020	0.012	0.035	0.021	0.046	0.027	0.117	0.070
DEHP - 95th	0.322	0.193	0.253	0.152	0.588	0.353	6.033	3.620
DINP - 50th	0.001	0.002	0.001	0.004	0.002	0.005	0.001	0.002
DINP - 95th	0.006	0.019	0.017	0.052	0.006	0.019	0.007	0.022

a - all values taken from Table 2.16 from the CHAP report.

Conclusions

The CHAP should redo their analysis using the most recent biomonitoring data for phthalates available from NHANES (either 2009-2010 collection cycle or the 2011-2012 collection cycle once they are released again). Using the most recent biomonitoring data, the conclusion drawn from this analysis of exposures (that are more indicative of current exposures to phthalates) indicates that the HQs for DEHP are no longer above 1 and those for DINP are still far below 1. Considering DINP's lower potency relative to DEHP for reducing testosterone synthesis, direct substitution of DINP for DEHP reduces the overall HI for cumulative phthalate exposure. This would indicate there are no cumulative exposures of concern for these two phthalates under current exposures in the US. Given the HQs for the remaining phthalates included in the CHAP report (DIBP, DBP, BBP) also had extremely low HQs, the overall HI for all of the relevant phthalates is below 1.

Relying on old biomonitoring data (that are indicative of exposures to DEHP before the bans were implemented) and concluding that the US population has a cumulative HI greater than 1 for these select phthalates (that **was** entirely dominated by DEHP) is no longer relevant.

Due to flaws and limitations in the key study used to support the Case 2 calculations for DINP, we recommend that the CHAP either remove or significant revise their approach.

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