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Chris Wallace
Global Regulatory Affairs Manager
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September 16, 2016

Dr. George Borlase (via e-mail**:** GBorlase@cpsc.gov)
Assistant Executive Director
Office of Hazard Identification and Reduction
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

Dear Dr. Borlase,

We had the pleasure of meeting with several of the Commissioners and their staffs on July 14 to discuss the phthalate rulemaking activity. Our discussions focused on three main topics: 1) data from Boberg et al. concerning DINP anti-androgenicity; 2) relevance of phthalate induced anti-androgenic effects for human risk assessment; and 3) use of the Study for Future Families (SFF) database.

A copy of our thank-you letter to Chairman Kaye which contains the various handouts we discussed is attached to this letter for reference. We would like to highlight several key messages from the discussions.

First, we understand that you received a letter from the European Council for Plasticisers and Intermediates (ECPI) regarding discrepancies identified in a report published by Dr. J Boberg et al. that was relied on by the Chronic Hazard Advisory Panel (CHAP). The ECPI analysis indicates that applying the appropriate statistics to the Boberg et al. raw data produces results that are in fact more consistent with the reported results of Clewell et al., which concluded there was no evidence of Rat Phthalate Syndrome for rats exposed to DINP.

Second, in-utero (fetal) anti-androgenic potential of phthalates was the focus for the CHAP assessment. Of note, however, the latest data indicate humans are less sensitive, and potentially non-responsive, to phthalate-induced in-utero anti-androgenic effects. These newest data have been evaluated by EPA staff scientists, and the initial conclusions by EPA staff scientists concur with those of the researchers, that humans are less sensitive to in-utero effects of phthalates than are rats.

Third, published exposure values for pregnant women in The Infant Development and Environment Study (TIDES) show trends similar to the NHANES data incorporated into your staff's data reanalysis, including greatly reduced exposures to DEHP. These trends can be applied to the infant SFF data to estimate current infant HI values, which are well below one in all cases. Thus, the CPSC can feel confident in making a decision to lift the ban on DINP.

In addition, we would like to highlight related issues that are more technically nuanced than were discussed with the Commissioners. These topics have been touched on previously, but given the potential importance for the final assessment we wanted to bring them back to your attention. Of primary relevance, the CHAP's reference to individual risk levels (i.e., percentage of individuals with HI > 1) is inappropriate and scientifically inaccurate, given that the exposure data are spot samples and phthalate levels for an individual can vary greatly from hour to hour. Figures 1-3 illustrate that the 95th percentile of the population's risk levels is protective of all individuals. This point is further demonstrated by the data and figures contained in the Summit Toxicology comments that were submitted as Appendix A of the American Chemistry Council's comments to the docket (Docket ID #CPSC-2014-033-0111). We strongly urge that references to individual risk be omitted from any final documentation as it can be confusing and potentially create an inaccurate understanding or unfounded angst.

Finally, though case studies have merit and can bring forward interesting scientific questions, the end goal of a risk assessment is to increase certainty in a final prediction. Incorporating all three case studies into any final recommendation artificially increases uncertainty in the risk assessment. This is because Case 1 is based on a publication using outdated hazard information, and Case 2 is based on a model that does not accurately predict the in-vivo situation. Though we have differences of scientific opinion for some of the bases for Case 3, this was the Case developed using the points of departure selected by the CHAP after their review of the recent data. Thus, Case 3 is the most appropriate of the three cases to use as a basis for recommendations.

We appreciate the willingness of your office to consider these important issues, and we are happy to provide any additional information that would assist the CPSC science staff as you progress through the rulemaking process. We also remain available to meet with the science staff if you would like to discuss any of these issues in more detail.

If you have any questions, please do not hesitate to contact Dr. Jennifer Foreman at 908-335-3298.

Sincerely,

CWW:jrh
Attachments

c – w/attachments:
Patricia Adkins, CPSC (PAdkins@cpsc.gov)
Dr. Alice Thaler, CPSC (AThaler@cpsc.gov)
Dr. Michael Babich, CPSC (MBabich@cpsc.gov)
Elissa Sterry, ExxonMobil Chemical Company
Dr. Jennifer Foreman, ExxonMobil Biomedical Sciences Inc.

Figure 1

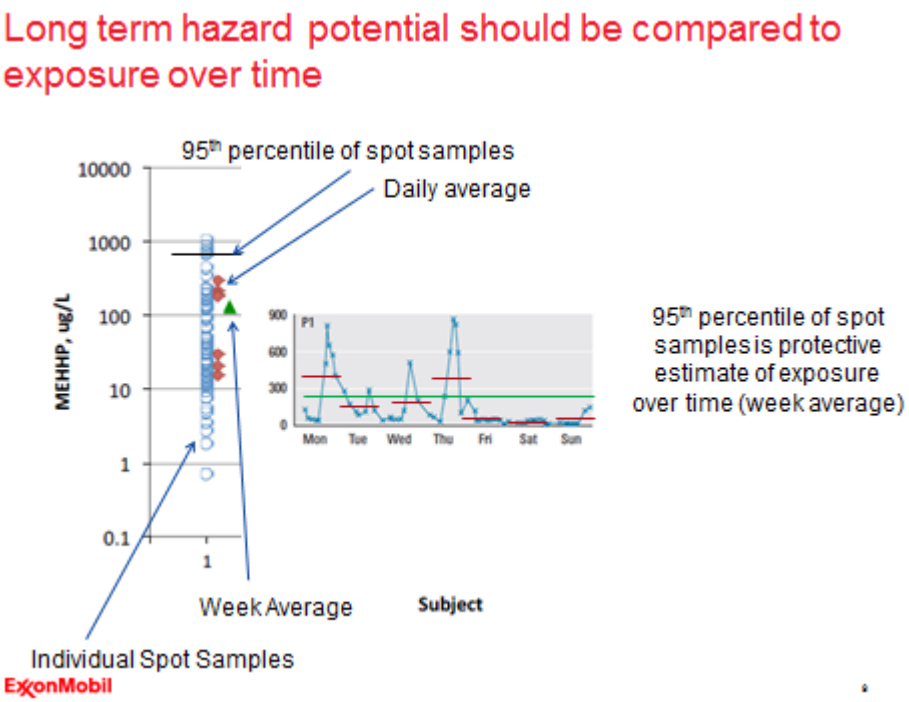


Figure 2

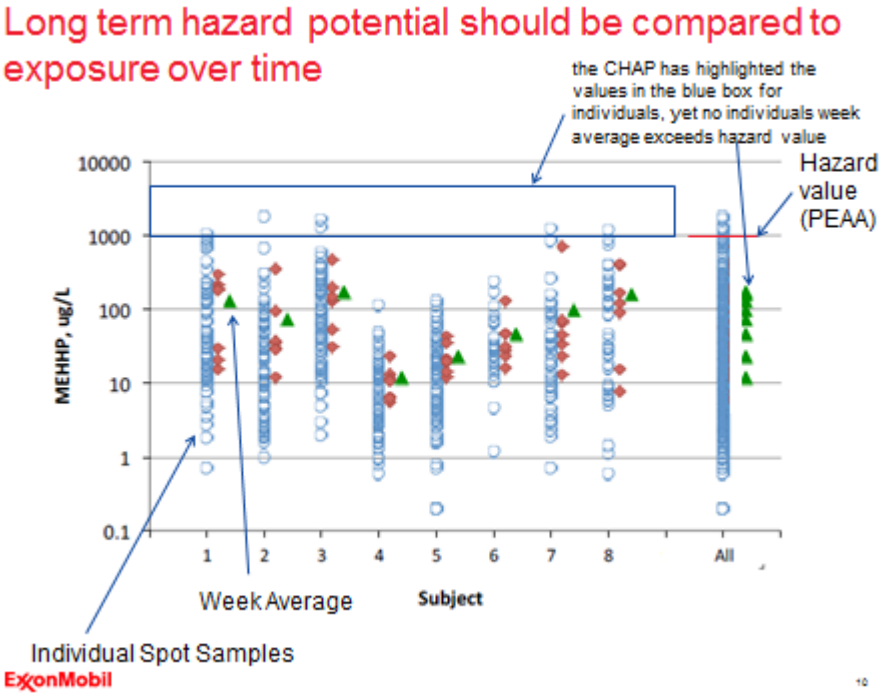
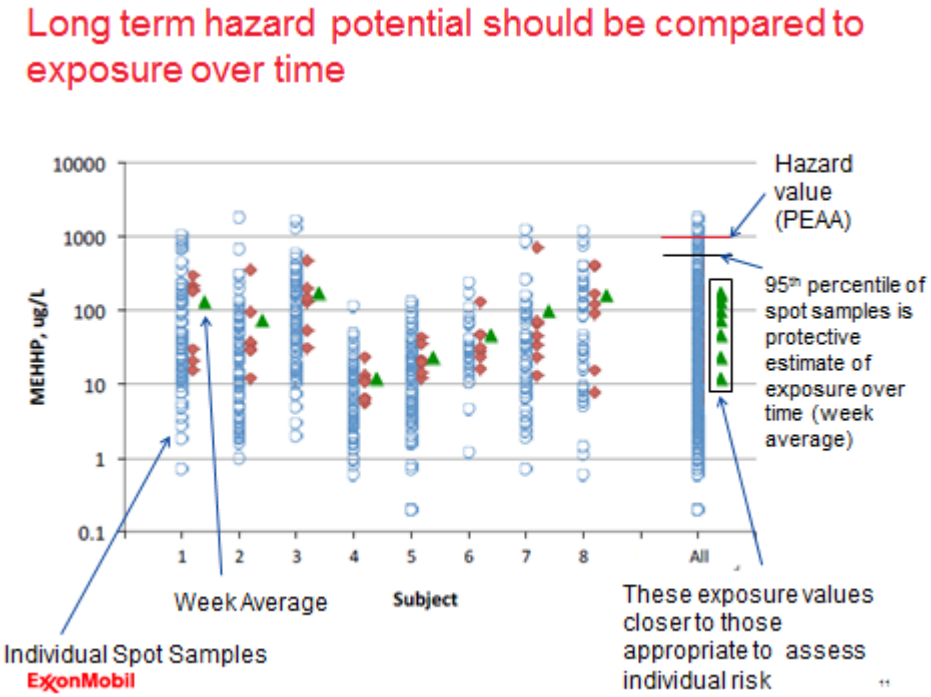


Figure 3


Long term hazard potential should be compared to exposure over time
10000
1000
100
10
1
0.1
MEHHP, ug/L
1
2
3
4
5
6
7
8
All
Subject
Hazard value (PEAA)
95th percentile of spot samples is protective estimate of exposure over time (week average)
Week Average
Individual Spot Samples
These exposure values closer to those appropriate to assess individual risk
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Elissa Sterry
Vice President
Intermediates

August 31, 2016

Chairman Elliot Kaye (via e-mail**:** EKaye@cpsc.gov)
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

Dear Chairman Kaye,

We are sorry that we were not able to meet with you in person on July 14, but we appreciate being able to meet with your staff to discuss the phthalate rulemaking activity. Please find attached the summary handout we discussed, as well as copies of several graphs that we reviewed with your staff and with other Commissioners. We also wish to provide further information on three pertinent issues from these discussions: 1) data from Boberg et al. concerning DINP anti-androgenicity; 2) relevance of anti-androgenic effects for human risk assessment; and 3) use of the Study for Future Families (SFF) database.

1) We are attaching a copy of a letter that the European Council for Plasticisers and Intermediates (ECPI) recently sent to the CPSC Science Staff to alert them to discrepancies between the raw data and the results in a report published by Dr. J. Boberg et al. That report was important to the CHAP's inclusion of DINP as a "Rat Phthalate Syndrome" (anti-androgenic) substance. The ECPI analysis indicates the Boberg et al. data in fact are more consistent with the data of Clewell et al., ***which concluded there was no evidence of Rat Phthalate Syndrome for rats exposed to DINP***.

2) In-utero (fetal) anti-androgenic potential was the focus for the CHAP assessment. Of note, however, the latest data indicate humans are less sensitive, and potentially non-responsive, to phthalate-induced in-utero anti-androgenic effects. Initial data indicating this was reviewed by the CHAP, which determined the research needed to be progressed before incorporating it into a human health risk assessment. Since that time, the concerns highlighted by the CHAP have been addressed, and the newest data have been evaluated by EPA staff scientists. ***The initial conclusions by EPA staff scientists concur with those of the researchers, that humans are less sensitive to in-utero effects of phthalates than are rats.***

3) The SFF database was used by the CHAP, in addition to the CDC's National Health and Nutrition Examination Survey (NHANES), to evaluate exposures in infants and pregnant women. NHANES data has been sufficient to address exposures in pregnant women, but data for recent infant exposures in the US has not been made publicly available. Nevertheless, the CPSC can feel confident in making a decision to lift the ban on DINP. First, the risk estimates in the CHAP report are based on risks from in-utero exposures, the most sensitive time window for "Rat Phthalate Syndrome." ***Those in-utero exposures are measured in terms of the pregnant mother exposures – data for which NHANES is sufficient.*** Second, the SFF data are from a time period prior to the steep decline in use of DEHP. ***Yet, despite using this old data with higher DEHP levels, the CHAP's Case 3 HI was only 0.55 at the 95th percentile.*** Case 3 is the most appropriate for regulatory decisions as the CHAP based it on their own independent review of the datasets. And third, there is an updated version of the SFF database being developed, called The Infant Development and Environment Study (TIDES). ***Published exposure values for pregnant women in TIDES show trends similar to the NHANES data, including greatly reduced exposure to DEHP. These trends can be applied to the infant SFF data to estimate current infant HI values, which HIs are well below one in all cases.***

We appreciate the willingness of your office to discuss these important issues, and we are happy to provide any additional information that would assist the CPSC as the agency proceeds in the rulemaking process.

If you have any questions, please do not hesitate to contact me at 832-625-4062.

Sincerely,

EPS:jrh
Attachments

c – w/attachments:
Jana Fong-Swamidoss (JFSwamidoss@cpsc.gov)
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Jonathan Midgett (JMidgett@cpsc.gov)
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CPSC Phthalates Rule Overview for DINP/DIDP

July 2016

Background

- In 2008 Congress passed the Consumer Product Safety Improvement Act (CPSIA).
  - Three phthalates (DBP, BBP, DEHP) were permanently banned from children's toys.
  - Three phthalates (DINP, DIDP, DnOP) were banned on an interim basis from mouthable children's toys and childcare articles.
  - CPSC appointed a Chronic Hazard Advisory Panel (CHAP) to evaluate the safety of the three interim-banned phthalates as well as the safety of other phthalates and phthalate alternatives.

CHAP Report

- The CHAP evaluated each phthalate and phthalate alternative individually using a margin-of-exposure (MOE) method.
  - DINP and DIDP were confirmed to be safe individually.
- The CHAP evaluated several phthalates having data indicating anti-androgenic effects on a cumulative basis using a hazard index (HI) methodology.
  - This approach was unprecedented in a product regulatory context, and the CHAP called the approach "novel".
  - The analysis included the three permanently-banned phthalates (DBP, BBP, DEHP) plus DINP and DIBP.
    - DINP should not have been included in this grouping since its effects, as observed in laboratory animals, are minimal, temporary and reversible.
  - The analysis utilized the CDC's National Health and Nutrition Examination Survey (NHANES) data from 2005-2006, a period prior to the CPSIA ban and other regulatory restrictions, mainly in Europe, taking effect on DEHP.
    - Note that NHANES data sets from 2007-2008 and 2009-2010were also available for the CHAP to use during their analysis.
  - The analysis found an HI greater than 1, driven almost exclusively by the hazard quotient (HQ) for DEHP. The HI thus suggested the cumulative risk from the combined phthalates could be a concern.
- The CHAP issued its final report in July 2014.
  - Based on the MOE analysis and lack of anti-androgenic effects, the CHAP recommended lifting the interim ban on DIDP.
  - Based on the cumulative risk analysis, the CHAP recommended making the interim ban on DINP permanent.
    - In other words, a chemical which itself was found to be safe was found to have an unacceptable risk only when combined with other now-banned chemicals.
- Based on the CHAP report, the CPSC voted in December 2014 to proceed with rulemaking by a vote of 3-2. The proposed rule incorporated the CHAP's recommendations.

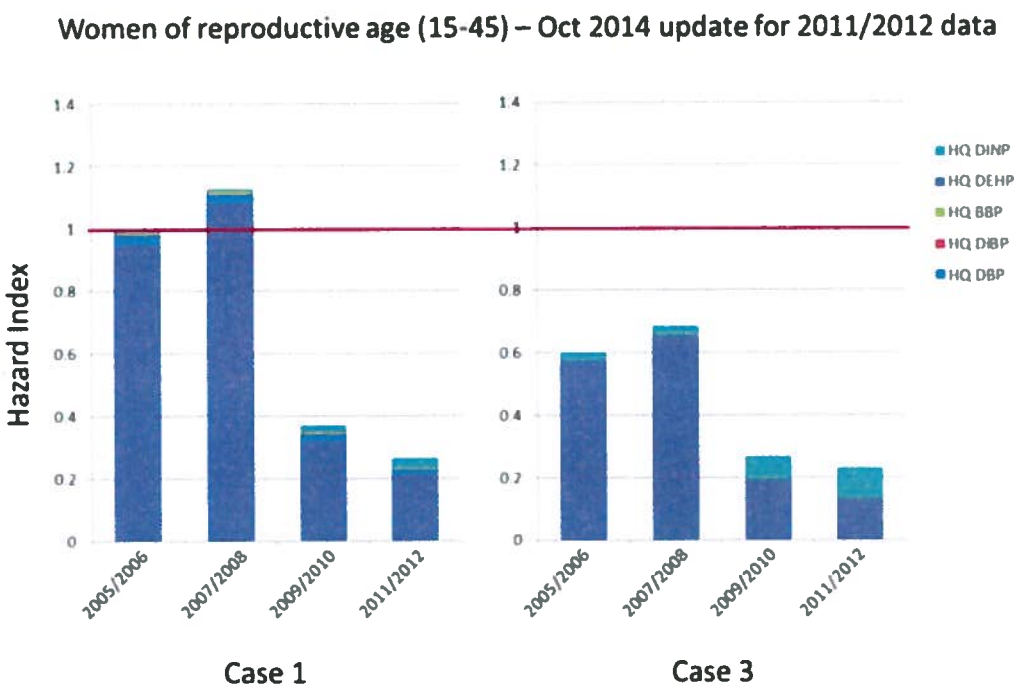
NEW INFORMATION: Errors within Boberg et al (2011)

- The Boberg et al. (2011) study was used as a reference by the CHAP for their analysis of anti-androgenic effects of DINP. This study evaluated the effects of DINP during fetal development.
- The US EPA recently made publicly available the raw data from this study. Two statisticians from ECPI member companies were unable to duplicate the analytical results for four of six parameters presented by Boberg et al. using the raw data and methods described in the publication.
- When contacted about this discrepancy, Boberg et al. acknowledged that modifications to the publication were necessary to facilitate reproducibility, and has submitted a written correction to the journal.
- Significant questions remain about the adequacy of the written correction, particularly the appropriateness of the statistical analyses and the explanation for the change of statistical method for AGD.

CPSC Science Staff Reanalysis

- The CPSC Science Staff re-analyzed the cumulative risk using the most recent NHANES datasets.
  - The reanalysis results were made public in June 2015.
  - The updated analysis considered NHANES datasets from 2007-2008, 2009-2010, and 2011-2012.
  - Although there was an upward trend in DEHP exposure between 2005/6 and 2007/8, the reanalysis confirms that the cumulative risk from the considered phthalates has significantly declined over time due to the reduction of DEHP, DBP, and BBP use in commerce.
  - The analysis further confirms that DINP exposure has increased over time as it has frequently been used as a replacement for DEHP. However, since DINP is less potent than DEHP, the overall HI has dropped well below the threshold for concern. See the graph below for details.
    - Note that both the CHAP and the CPSC Science Staff considered three different "cases" for analyzing the NHANES data. Since Case 2 was based on modeled data to derive a no effect level that is lower than that given by actual study data on DINP, it is scientifically invalid to use Case 2 and therefore it is excluded from the graph below.
    - To the extent DEHP is further replaced by DINP, the HI will drop yet lower.

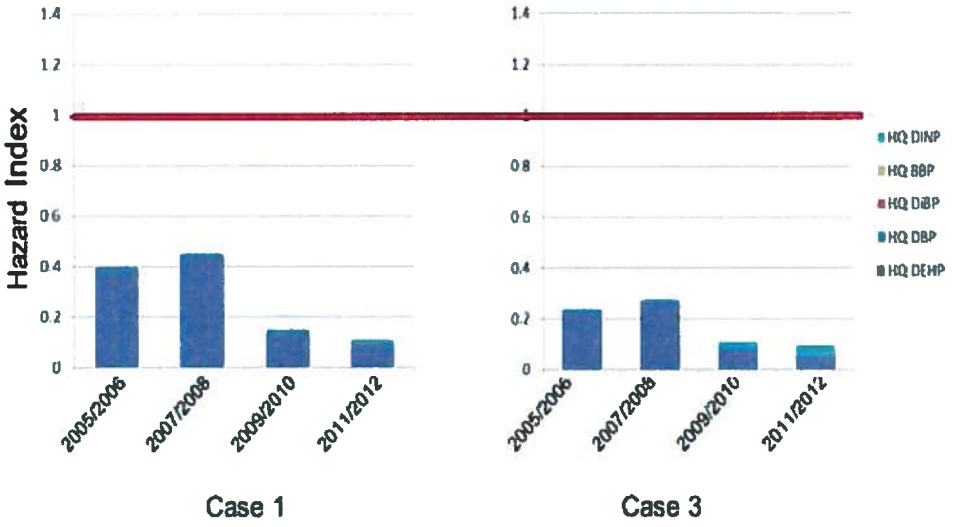
Graphical Representation of Reanalysis Results (ex. Scientifically Invalid Case 2)



NEW INFORMATION: EPA IRIS Preliminary Conclusion

- EPA's Integrated Risk Information System (IRIS) staff is evaluating DBP.
  - Dr. Xavier Arzuaga, the IRIS assessment manager for DBP, presented data at two scientific meetings in December 2015. In both meetings he presented his interpretation of the data for the in-progress IRIS assessment of DBP, which suggests rats are more sensitive than humans to the anti-androgenic effects of DBP during fetal development.
  - The higher rat sensitivity has important implications since humans were assumed to be more than twice as sensitive as rats to the anti-androgenic effects of phthalates (including DBP) in the CHAP and CPSC assessments.
  - If the anti-androgenic effect in rats is determined to have little or no relevance for humans, the resulting hazard indices would be yet lower than those calculated by the CPSC science staff. See, for example, the graph below, showing hazard indices where the sensitivity of rats and humans to anti-androgenic effects is assumed to be equivalent.

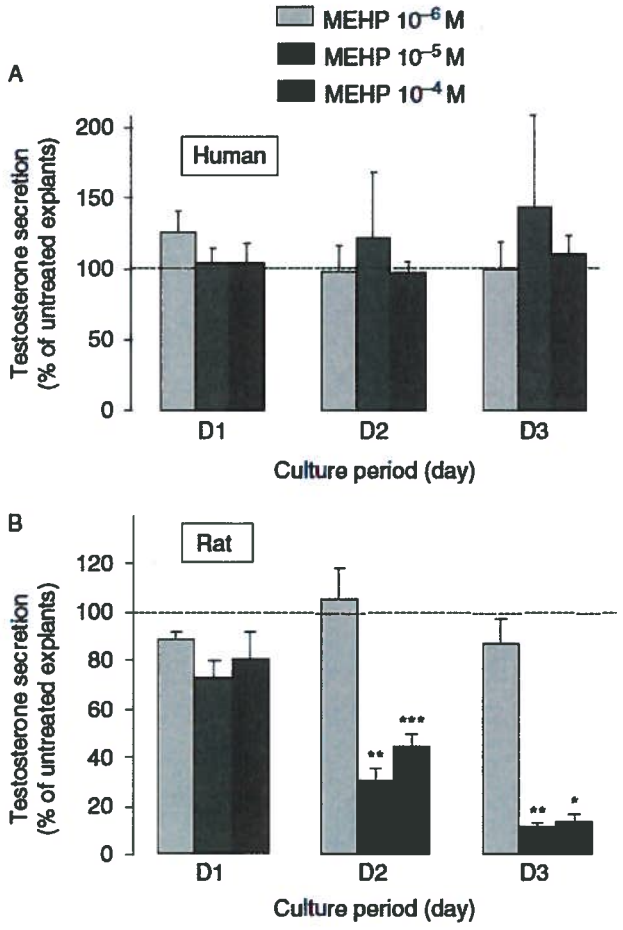
Graphical Representation of Reanalysis Results, Adjusted for EPA IRIS Preliminary Conclusions



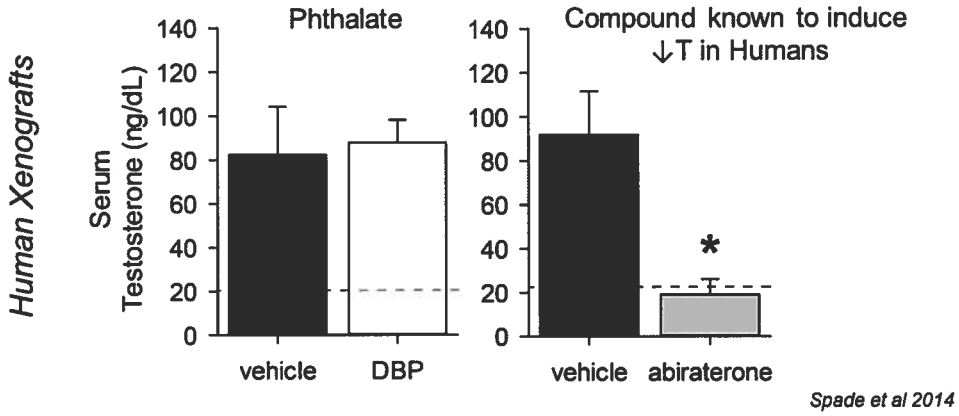
Conclusions

- DINP and DIDP are both safe individually as confirmed by the MOE analysis.
- The cumulative risk from the combined anti-androgenic phthalates has decreased over time, largely due to the reduction of DEHP exposure. It is now well below the threshold for concern.
- The cumulative risk hazard index is even lower when the preliminary IRIS conclusions are considered.
- Thus the interim bans for both DINP and DIDP can confidently be lifted.

- The CHAP reviewed two experimental studies with human xenografts. Regarded results of studies as inconclusive due to noted issues:
    - Fetal material obtained at ages which male programming has already occurred
    - High variability
- The science has advanced on the relevance of rat fetal testis effects and related endpoints to human health risk assessment
    - Early data was suggestive that humans were less sensitive or refractory as compared to rats
    - Critiques regarding potential influence of experimental design have since been addressed
        - *Habert et al 2014* conducted explant studies with human tissue from the Male Programming Window. Results indicated no effect of MEHP exposure. Decreases in testosterone secretion were observed in the rat positive control samples.



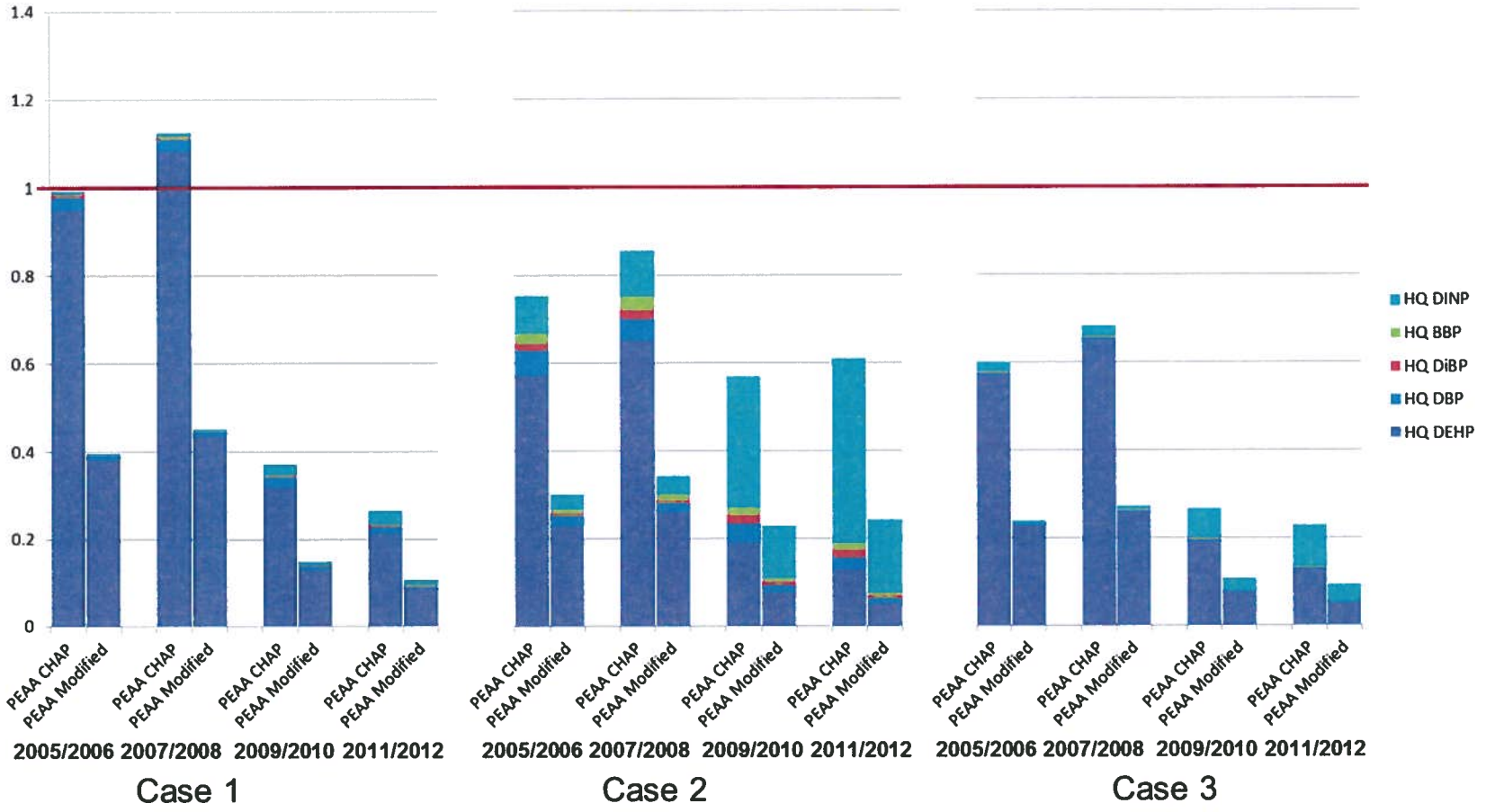
- Additional study by *Spade et al 2014* demonstrated reduction in Testosterone is observed after exposure to a compound known to reduce testosterone in humans. This demonstrates that the model is sensitive enough to pick up compounds with the ability to reduce testosterone in humans addressing the concern that variability in the model who preclude its ability to identify positive effects



Spade et al 2014

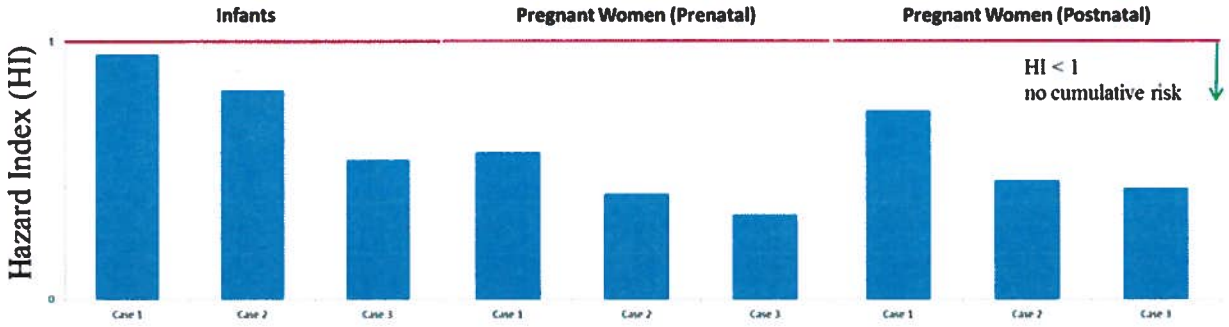
- This data is consistent with a lack of effect observed in Marmosets after in utero exposure (*McKinnell et al 2010*).
- The CHAP assumed that all of the phthalates in the cumulative risk acted via the same mechanism to induce a decrease in testosterone. If that assumption is true the mechanistic relevance to humans of the DEHP and DBP data applies to the other phthalates in the cumulative risk assessment. If that assumption is not true the basis for the cumulative risk assessment is not appropriate.
- EPA is evaluating the science as part of IRIS assessment
    - Anti-androgenic mode of action identified in rats as more sensitive to in-utero anti-androgenic insults of phthalate esters compared to humans

Comparison between humans more sensitive and equal sensitivity



Decline in DEHP similar in an updated version of SFF

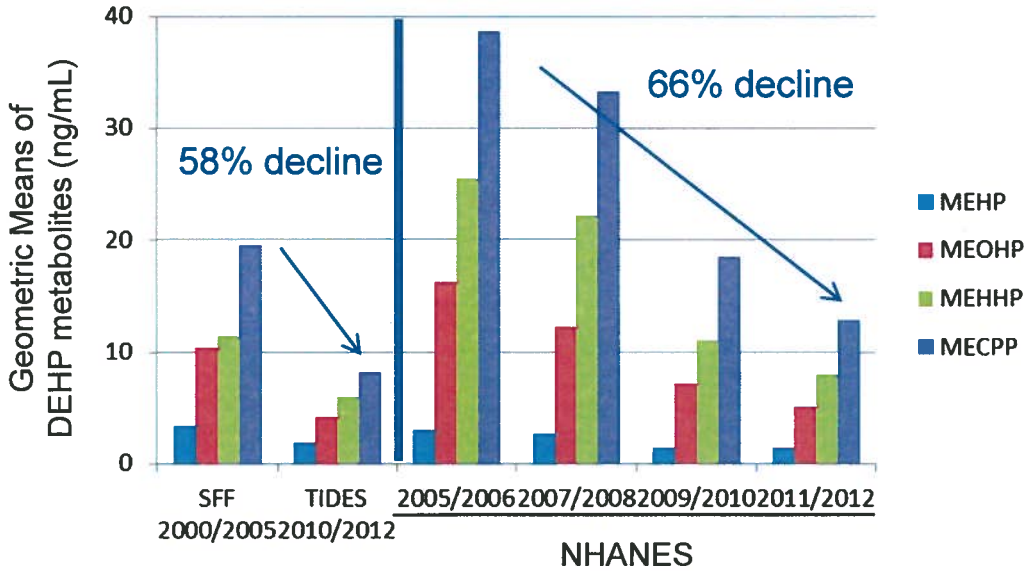
- SFF dataset: included high levels of DEHP (2000-2005); all HI's were < 1 at the 95th percentile



SFF data sets 95th percentile
Table D – 9 CHAP 2014

- DEHP metabolites decline seen in an updated database of pregnant women (2005-2012) matches declines seen in NHANES

The Infant Development and the Environment Study (TIDES) is the latest study by researchers involved with the Study for Future Families (SFF).



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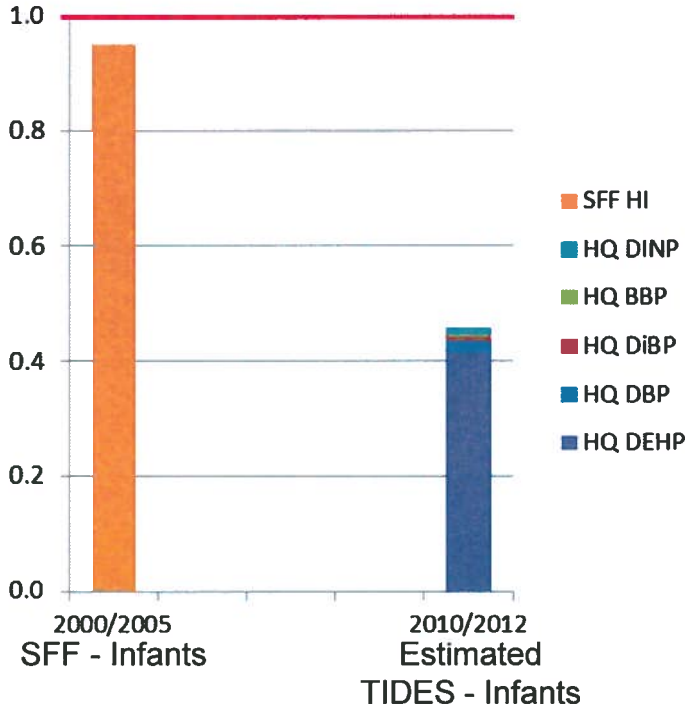
Based on change in metabolite levels in SFF compared to TIDES, one would anticipate infant HI dropping by about 50%

- All populations are showing a similar pattern of metabolite level changes.
- By looking at the percent changes of each phthalate between pregnant women in the SFF database and pregnant women in the TIDES database and applying that to the respective HQ's, an impact estimate can be derived for infants.



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Case 1

Dr. George Borlase
Assistant Executive Director
Office of Hazard Identification and Reduction
U.S. Consumer Product Safety Commission (CPSC)
4330 East West Highway
Bethesda, MD 20814

July 29, 2016

Dear Dr. Borlase,

The raw data for the study entitled 'Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats'[1] were made publically available via the U.S. EPA's Integrated Risk Information System (IRIS) Health & Environmental Research Online (HERO) database[2] in February 2016. At the same time Danish EPA with the agreement of Dr. Boberg also provided the raw data directly to the European Council of Plasticisers and Intermediates, in the context of an ongoing discussion on a classification proposal for DINP. We are writing to alert you that upon analysis of these data, we were unable to reproduce a number of the statistical findings in the manuscript. We considered it important to make you aware of these discrepancies given the weight this study was given in the 2014 report by the Chronic Hazard Advisory Panel (CHAP) in its evaluation of DINP. Though DINP was found safe by the CHAP on its own, it was included in the Cumulative Risk Assessment, in part, due to the data presented in Boberg et al. It should be noted that these discrepancies could not have been identified at the time of peer review of the manuscript, during discussions of the data between the CHAP members, nor during the open comment period for the Federal Registry Notice on the draft rule (79 FR 78324, Dec 30th 2014 – March 16th 2015) because the raw data to Boberg et al. were not yet available.

Using the statistical methods as originally reported in Boberg et al. (2011) we analyzed the raw data that were provided for the following endpoints: 1) testosterone, 2) nipple retention, 3) sperm motility, 4) sperm/g cauda, 5) percent progressive sperm and 6) anogenital distance (AGD/AGDi) measurements. We were unable to reproduce the reported statistical significance ($P<0.05$) for four of these six parameters as published, i.e. parameters 3, 4, 5 and 6. Additionally, we were unable to replicate some of the descriptive statistics reported in the manuscript and noted a discrepancy of the reported control data with the respective OECD guidance[3] on the evaluation of sperm motility.

In an effort to reconcile these noted discrepancies, we contacted Boberg et al. in May of 2016. The authors acknowledged that modifications to the publication were necessary to facilitate reproducibility and have shared

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[1] J. Boberg, S. Christianson, M. Axelstad, T.S.Kledal, A. M. Vinggaard, M. Dalgaard, C.Nellemann, U. Hass. Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats. Reprod Toxicol, 31 (2011), pp. 200-209.

[2] Supplemental Boberg data for HERO ID 806135 from email communication. EPA-Hq-ORD-2014-0637. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-ORD-2014-0637-0014. Last accessed July 2016

[3] Guidance document on mammalian reproductive toxicity testing and assessment (2008), series on testing and assessment. Number 43 Number 43, ENV/JM/MONO(2008)16

European Council for Plasticisers and Intermediates
COMMITTED TO THE SCIENCE OF SAFETY

with us a Corrigendum to their methods description which they have since submitted to Reproductive Toxicology. While we appreciate the efforts made by the authors in the Corrigendum to address our observations, we have recently issued a correspondence to the editor requesting clarification and corrections beyond those addressed in the Corrigendum. It is our view that the methodological modifications made in the Corrigendum only partially address the discordance of statistical outcomes we identified; and raise some additional deficiencies regarding the thoroughness and transparency of the methods and the influence of irregular approaches in the statistical analysis on the representation of results. In summary, ECPIs view is that several of the results need to be changed to reflect the correct original statistical methods, rather than as is being proposed by Boberg et al that the statistical methods are changed to reflect the results. With respect to the CPSCs work on DINP these discrepancies are noteworthy as the ECPI analysis of the data indicates the findings from Boberg et al. were more consistent with the findings of Clewell et al., where the authors concluded no evidence of Rat Phthalate Syndrome were identified. This is of importance as the ability "to disrupt male sexual differentiation" which "culminates in what has been described as the phthalate syndrome" was the CHAP's basis for inclusion of DINP in the cumulative risk assessment.

We understand the Corrigendum to Boberg et al. (2011)[1] will be published shortly in Reproductive Toxicology, and expect our letter to the editor to also be published in due course. We encourage the science staff to perform an independent assessment of the analyses using the raw data provided in HERO database. Please evaluate the impact of these data on initial conclusions and consider this information as you deem appropriate during the science staff's preparation of recommendations on final rule making for DINP. We welcome any questions you may have regarding this communication and are willing and able to share the results of the reanalysis with your science staff for comparison and discussion.

Sincerely,

Michela Mastrantonio
The European Council for Plasticisers and Intermediates

About EPCI: The European Council for Plasticisers and Intermediates is a Brussels-based trade association representing the common interests of European manufacturers of plasticisers, alcohols and acids. Member companies are BASF, Deza, Evonik, ExxonMobil, Lanxess and Perstorp. ECPI is a sector group of Cefic, the European Chemical Industry Council, which represents the interests of the European chemical industry. Some of the member companies of ECPI are producers of DINP.