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OF THE
UNITED STATES OF AMERICA

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April 10, 2015

VIA ELECTRONIC FILING

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

RE: Docket No. CPSC-2014-0033: Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates; Federal Register Vol. 80, No. 54 (Friday, March 20, 2015); and Request for Correction Under the Information Quality Act Regarding "Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives"

Dear Sir or Madam:

The U.S. Chamber of Commerce is pleased to present these comments in response to the above-referenced notice of proposed rulemaking (NPRM).[1] The Chamber is also seeking correction, under the Information Quality Act (IQA)[2] and guidelines thereunder issued by the Office of Management & Budget (OMB)[3] and the U.S. Consumer Product Safety Commission,[4] of the above referenced report (CHAP Report).[5]

Because both OMB and the Commission take the position that the notice and comment process serves as the administrative correction mechanism for IQA correction requests involving documents disseminated in connection with a rulemaking,[6] these rulemaking comments also

[1] 79 Fed. Reg. 78324 (Dec. 30, 2014).

[2] Pub. L. 106–554, § 515, 44 U.S.C. § 3516 note.

[3] 67 Fed. Reg. 8452 (Feb. 22, 2002).

[4] http://www.cpsc.gov/Research--Statistics/Information-Quality-Guidelines

[5] http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf.

[6] *See* Memorandum for President's Management Council from John Graham entitled *Agency Final Information Quality Guidelines* (Sept. 5, 2002), attachment at 1, available at http://www.whitehouse.gov/sites/default/files/omb/assets/omb/inforeg/pmcmemo.pdf; CPSC IQA Guidelines, *supra*

serve as the Chamber's request for correction under the IQA. To avoid any question of procedural compliance, this document has also been submitted to by email to cpsc-os@cpsc.gov, as instructed in the CPSC's IQA Guidelines.

This submission focuses exclusively on the treatment of diisononyl phthalate (DINP) in the proposed rule and the CHAP Report. As we demonstrate below, the CHAP report violates the requirements of both the Consumer Product Safety Improvement Act (CPSIA) and the IQA guidelines issued by both OMB and the CPSC, which do not differ in relevant part (IQA Guidelines). As the proposed rule treatment of DINP is required by law to be "based on" the CHAP Report, unless that report is fundamentally reworked to comply with the CPSIA and IQA, any final rule by the CPSC that finalizes the interim ban on DINP necessarily must be arbitrary and capricious and otherwise contrary to both the CPSIA and the IQA. To be clear, the relief the Chamber seeks is two-fold:

- We seek correction of the CHAP Report, separate and apart from the phthalates rulemaking, because the Report has had and will continue to have independent and negative affects on the Chamber's members. This correction should take place within 90 days.[7]

- We also seek a final phthalates rule that is based on, and consistent with, a CHAP Report that meets the obligations of the CPSIA and the IQA.

Part I of these comments explains the Chamber's interest in this rulemaking. Part II summarizes the relevant requirements of the CPSIA and the IQA and their application to this rulemaking. Part III identifies the most substantial methodological flaws of the CHAP Report, and explains in each case how those failings constitute violations of the CPSIA and the IQA.

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note 4 ("Persons questioning the quality of information disseminated in . . . documents referenced or relied upon in [notices of proposed rulemaking], must submit comments as directed in the Federal Register or other notices requesting public comment on the given document.").

[7] *See* CPSC IQA Guidelines ("In cases where the agency disseminates a study, analysis, or other information prior to the final agency action or information product, requests for correction will be considered prior to the final agency action or information product in those cases where the agency has determined that an earlier response would not unduly delay issuance of the agency action or information product and the complainant has shown a reasonable likelihood of suffering actual harm from the agency's dissemination if the agency does not resolve the complaint prior to the final agency action or information product.").

I. The Chamber Has an Interest in the Subject of Phthalates Rulemaking and Is an Affected Party Under the IQA Guidelines

The Chamber is the world's largest business federation, representing the interests of more than three million businesses and organizations of every size, sector, and region. The Chamber's broad membership base includes large and small companies, trade associations, and chambers of commerce.

The Chamber's member companies include those engaged in the manufacture and sale of children's toys and child care articles products that, prior to the interim ban, contained DINP. Other Chamber members formerly manufactured DINP for use in such products. And of greatest importance, the Phthalates rulemaking – and the CHAP Report – both have had and will have an impact on the use (and hence manufacture) of DINP for any purpose whatsoever. State legislatures and agencies, and companies sensitive to consumer demands, already have been influenced by the rulemaking and the report, and will be even more profoundly influenced if the rule is finalized as proposed. Indeed, while the Commission has proposed to end the ban on di-*n*-octyl phthalate and diisodecyl phthalate (DNOP and DIDP), a ban on DINP – the high molecular weight phthalate directly between them – can be expected to color the public's views of the two permitted phthalates as well. Thus, the rulemaking and the report will have an impact far out of proportion to the universe of products and applications they address, and will affect the full range of Chamber members who manufacture or use phthalates or products containing them. Accordingly, the Chamber has a real interest in the phthalates rulemaking and is an affected person in the terms of the IQA Guidelines.

The Chamber's main point of contact for this RFC is:

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II. Relevant Law and Its Application to the CHAP Report and This Rulemaking

A. The CPSIA

The portion of the CPSIA that governs this rulemaking, Section 108, did two things. First, effective early 2009, it permanently banned the use in children's toys or child care articles of three phthalates: di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), or benzyl butyl phthalate (BBP).[8] Second, at the same time, it imposed an interim ban on use in the same products of DnOP, DINP and DIDP.[9] In the interim, the Commission was instructed to establish a new CHAP "to study the effects on children's health of all phthalates and phthalate alternatives as used in children's toys and child care articles."[10] The Commission was then required, "based on" the report of this CHAP, to determine by rule whether to maintain that interim ban in effect (and to determine, after "evaluat[ing] the findings and recommendations of the [CHAP]" whether to declare any other phthalates to be banned hazardous products).[11]

Section 108(b)(2)(B) specifies in great detail what the phthalates CHAP should do and how it should do it. Language that will prove crucial to this rulemaking is italicized below:

> The panel shall, within 18 months after its appointment under subparagraph (A), complete an examination of the full range of phthalates that are used in products for children and shall-
>
> (i) examine all of the potential health effects (including endocrine disrupting effects) of the full range of phthalates;
> (ii) consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates;
> (iii) examine *the likely levels* of children's, pregnant women's, and others' exposure to phthalates, *based on a reasonable estimation* of normal and foreseeable use and abuse of such products;
> (iv) consider the cumulative effect of total exposure to phthalates, both from children's products and from other sources, such as personal care products;
> (v) *review all relevant data, including the most recent, best-available, peer-reviewed, scientific studies of these phthalates and phthalate alternatives that employ objective data collection practices or employ other objective methods;*
> (vi) consider the health effects of phthalates not only from ingestion but also as a result of dermal, hand-to-mouth, or other exposure;
> (vii) consider the level at which there is a *reasonable certainty* of no harm to children, pregnant women, or other susceptible individuals and their offspring,

[8] 15 U.S.C. § 2057c(a)
[9] *Id.* § 2057c(b)(1).
[10] *Id.* § 2057c(b)(2)(A).
[11] *Id.* § 2057c(b)(3).

> *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; and
> (viii) *consider possible similar health effects of phthalate alternatives used in children's toys and child care articles.*[12]

As will be shown in Part III below, the CHAP violated these italicized mandates – and so a rule "based on them" would be arbitrary and capricious and contrary to law.

B. The IQA

1. In General

Congress enacted the IQA to "ensur[e,] and maximiz[e,] the quality, objectivity, utility and integrity of information . . . disseminated by Federal agencies" like the Commission.[13] To accomplish these goals, it required the OMB to issue government-wide implementing guidance.[14] It also instructed each agency to issue its own guidelines, which have two functions: (i) to apply the OMB Guidelines to the agency's particular circumstances, and (ii) to "establish administrative mechanisms allowing affected persons to seek *and obtain* correction of information . . . disseminated by the agency that does not comply with the [OMB] guidelines . . . ."[15]

OMB's Guidelines require all disseminations to meet "a basic standard of quality . . . appropriate to the nature and timeliness of the information . . . ."[16] They define "quality" in terms of objectivity, utility and integrity.[17] "Objectivity" is centrally relevant in cases of scientific health assessments such as the CHAP Report. Objectivity has significant consequences both for the substance of such information and the way it is presented, as discussed below. "Utility" is also important, as it refers to the usefulness of the information to its intended users, including the public.[18]

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[12] *Id.* § 2057c(b)(2)(B).

[13] Pub. L. No. 106-554, § 515(a).

[14] *See* 67 Fed. Reg. 8452.

[15] Pub. L. No. 106-554, § 515(b)(2)(B) (emphasis added).

[16] 67 Fed. Reg. at 8458.

[17] *Id*. at 8459; *cf*. 44 U.S.C. § 3504(e)(1)(B) (2006).

[18] *Id*.

2. Objectivity

From a substantive perspective, "objectivity" means that information must be *accurate, reliable* and *unbiased*.[19] Scientific information must be generated using sound statistical and research methods.[20] "Influential" information regarding risks to health, safety or the environment must be based on requirements, drawn from the Safe Drinking Water Act (SDWA), to use "*the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices*; and . . . data collected by accepted methods or best available methods . . . ."[21]

From the perspective of presentation, "objectivity" means that information must be presented in an *accurate, clear, complete* and *unbiased* manner, which includes presentation in the proper context.[22] Influential information regarding risks to health, safety or the environment must additionally meet requirement drawn from the SDWA; i.e., it must be *comprehensive,* informative and understandable, and must specify, among other things:

- each population affected by any estimate of risk
- the *expected risk or central estimate of risk* for the specific populations affected;
- each *appropriate* upper-bound or lower-bound estimate of risk;
- each *significant uncertainty identified in the risk assessment and studies that would assist in resolving the same*; and
- *peer-reviewed studies known to the author that* support, are directly relevant to, or *fail to support estimates and methodologies used to reconcile inconsistencies in data*.[23]

3. The CHAP Report Is Subject to the IQA

The CHAP Report is clearly subject to IQA requirements. We are mindful that some stakeholders have argued that, because the CHAP is an independent advisory committee, its report was not subject to the OMB Peer Review Bulletin.[24] Whether or not this position is correct as a general matter, whenever the Commission adopts the recommendations of a third party author of information in a way that at least "reasonably suggests that the agency agrees

[19] 67 Fed. Reg. at 8549 (emphasis added).

[20] *Id.*

[21] *Id.* (emphasis added); *see also* 42 U.S.C. § 300g-1(b)(3)(A) (2006).

[22] *Id.* at 8459 (emphasis added).

[23] *Id.* (emphasis added); *see also* 42 U.S.C. § 300g-1(b)(3)(B).

[24] *See, e.g.*, Letter from the American Academy of Pediatrics et al. to Jeffrey Zients (April 23, 2013). The Commission appears to have avoided taking a position on the matter. *See* responses to additional questions for the record at 34-37, attached to letter from Inez Tenenbaum to Mary Bono Black (Nov. 9, 2012).

with the information, this appearance of having the information represent agency views makes agency dissemination of the information subject to th[e IQA] guidelines."[25] The Commission's IQA Guidelines express the same conclusion: "Although third-party sources may not be directly subject to OMB's information quality guidelines, when used by CPSC to develop information products, this information must follow CPSC's information quality guidelines."[26] Indeed, since the CPSIA requires the Commission's decision regarding the interim ban on DINP to be "based on" the CHAP Report,[27] it cannot be otherwise.

4. The CHAP Report Is "Influential"

Phthalates are used in innumerable products throughout the economy – wherever flexible vinyl is used, essentially. As noted above, the outcome of this rulemaking will extend beyond the subject phthalates and uses, and will affect uses of all phthalates throughout the U.S. economy (and abroad). Also, this rulemaking represents the first time a federal agency has tried to examine, characterize and quantify the combined adverse effects on human health or ecologic resources from multiple chemical stressors. Such a cumulative approach to risk characterization will strongly affect the approach of other federal agencies. The CHAP Report thus "has a clear and substantial impact on important public policies or private sector decisions" – the OMB standard for being "influential."[28]

5. The CHAP Report Is Not Insulated From Attack Under the IQA Because It Was Peer Reviewed

OMB's IQA Guidelines provide that, "[i]f data and analytic results have been subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable objectivity. However, this presumption is rebuttable based on a persuasive showing by the petitioner in a particular instance."[29] The Chamber anticipates that the Commission may feel that the CHAP Report can be presumed to meet the IQA's objectivity standard because the CHAP arranged for a peer review of its report. That would be a mistake, however.

The text of the Guidelines quoted above goes on to say that, [i]f agency peer review is employed to help satisfy the objectivity standard, the review process employed shall meet the general criteria for competent and credible peer review recommended by [a 2001 OMB

[25] 67 Fed. Reg. at 8454.
[26] *See supra* note 4.
[27] 15 U.S.C. § 2057c(b)(3)(A).
[28] 67 Fed. Reg. at 8460.
[29] Id. at 8459.

memorandum; including that] peer reviews be conducted in an open and rigorous manner."[30] The CHAP's peer review certainly does not meet that requirement; as it was conducted secretly. (Indeed, the CHAP's only non-public meeting was with the peer reviewers.[31]) Until recently, we did not know who the four peer reviewers were. Neither the CHAP nor the CPSC have released the charge to the peer reviewers, the draft report that they reviewed, or their report(s). Nor do we know what, if any changes to the report the CHAP made in response to the review.

The 2001 OMB memo was superseded in 2005 by OMB's Peer Review Bulletin, but its requirements are only more stringent than the 2001 memo. They specifically require that the charge to the reviewers and their report be made available on the agency's website, and that the agency discuss its response to the reviewers' comments in the preamble to any related rulemaking.[32] The CHAP' report qualifies as a "highly influential" scientific assessment, since its cumulative risk assessment is undeniably "novel, controversial, or precedent-setting"; peer reviews of such assessments require public comment whenever feasible and appropriate, and require disclosure of the reviewers identities and the agency's response to the reviewers.[33] Obviously, there has been a great degree of public interest in the CHAP Report, and the CPSC has already allowed the CHAP to exceed the deadline for its report by over two years. It was feasible and appropriate to have allowed public comment as part of the peer review process.

As can be seen, the CHAP's private peer review fell far short of the minimum required by OMB guidance, and so it does not deserve a presumption of objectivity under the IQA Guidelines.

6. The CHAP Report's IQA Deficiencies Will Invalidate the Phthalates Rulemaking If Not Corrected

A fundamental admonition of the OMB Guidelines is that "[a]gencies shall treat information quality as integral to every step of an agency's development of information, including creation, collection, maintenance, and dissemination."[34] The point of this requirement is not merely that agencies get it right the first time, so they do not have to face the delays and costs of a correction request after the fact; rather, OMB's instruction recognizes the persistent or cumulative effect of an initial failure of information quality: if an agency begins with information that is inaccurate, unreliable, biased or incomplete, those failings will infect subsequent "information products" that the agency develops based on the original information.

[30] *Id*.
[31] *See* 79 Fed. Reg. 78325 n.1.
[32] 70 Fed. Reg. 2675 (Jan. 14, 2005).
[33] *Id*. at 2675-76.
[34] 67 Fed. Reg. at 8459.

Applied to the present case, this means if the CHAP Report is seriously flawed, any Commission rulemaking that depends on it will be similarly flawed. And a cursory review of the proposed rule demonstrates that it is premised virtually entirely on the CHAP Report. Again, this outcome is effectively mandated by the fact that the Commission's decision regarding the interim ban on DINP must be "based on" the CHAP Report.

The D.C. Circuit has held that OMB's IQA guidelines are "binding" on agencies and subject to *Chevron* deference.[35] The court has also found that the IQA Guidelines can serve a substantive role, "reinforcing" comparable requirements of the statute authorizing a rulemaking.[36] In this rulemaking, the CHAP Report violates the objectivity requirements of the IQA for many of the same reasons that it also violates the CPSIA – and for this reason as well, a final rule required to be based on it would be arbitrary and capricious and contrary to law.

Finally, putting aside the validity of any Commission rulemaking, the CHAP Report has been disseminated by the Commission in violation of the OMB and Commission IQA Guidelines, and must be corrected or withdrawn. The report has existence separate from the rulemaking, and left uncorrected will continue to do so, causing harm to the Chamber's members who are involved in the phthalates value chain. As noted at the outset, this document constitutes a request for correction under the IQA Guidelines, and the Commission must respond to its specific requests by correcting the CHAP Report.

III. The CHAP Report's Analysis of DINP Suffers From Serious Methodological Flaws That Violate the CSPIA and the IQA Guidelines

At numerous steps in its analysis of DINP, the CHAP made decisions regarding scientific methodology that contravened the mandates of the CPSIA and the IQA Guidelines. These choices require the CHAP Report to be corrected under the Guidelines. CPSC staff and the Commission itself adopted the CHAP's flawed analysis wholesale. That action requires the Commission to revisit its proposed ban of DINP if it wishes its final rule to be legally sustainable under the CPSIA and the IQA. The CHAP's methodological errors are summarized below roughly in order of how glaring they are. In each case, we explain how those mistakes violate the CPSIA and the IQA.

[35] Prime Time Int'l Co. v. Vilsack, 599 F.3d 678, 685 (D.C. Cir. 2010).

[36] *See* Mississippi v. EPA, 723 F.3d 246, 258 (D.C. Cir. 2013) (describing as a "fair characterization" the argument that the IQA and the Clean Air Act "impose safeguards to ensure accuracy" in EPA's establishment of National Ambient Air Quality Standards).

A. The CHAP Ignored the Most Recent Data on Women's Exposure to Phthalates

Risk equals hazard times exposure, and thus the extent to which populations of interest are actually exposed to phthalates is a fundamental element of determining the risks that they pose. The CHAP estimated exposure in two ways: (i) human bio-monitoring data showing concentrations of phthalate metabolites in urine); and (ii) a variety of "exposure scenarios" that the CHAP modeled using data on phthalates levels in products and environmental media, migration rates and product use information. Bio- monitoring data for pregnant women and women of childbearing age was based principally on information collected by the U.S. Department of Health and Human Services' Centers for Disease Control and Prevention (CDC) via its National Human Health and Nutrition Survey (NHANES). As between the two approaches (i.e., biomonitoring vs. exposure scenarios), Commission staff declared that it:

> [c]onsiders biomonitoring to provide the best available estimates of total exposure because biomonitoring is based on empirical measurements in individuals. Furthermore, the NHANES study is a large statistically representative sample. In contrast, the alternative approach, scenario-based estimates, are subject to a number of assumptions and uncertainties. (CHAP, 2014, Appendix E). The method for estimating exposure from biomonitoring data has been in use since 2000 and was developed by an industry scientist. (David, 2000). The CHAP devoted considerable effort to discussing potential errors and bias in this methodology, having invited two experts (Stahlhut and Lorber) to address this issue at the December 2010 meeting. As discussed in the CHAP report, any errors in this methodology are relatively small and are unbiased (CHAP 2014, pp. 73–75).[37]

The Chamber agrees that the NHANES database provides the superior means for estimating women's exposure to phthalates. Unfortunately, the CHAP relied exclusively on data from the 2005-2006 NHANES survey; data collected before the prohibitions imposed by the CPSIA went into effect – even though two later rounds of NHANES data were available to the CHAP, data which showed dramatic decreases in phthalates exposure.

According to the NPRM, "[t]he staff notes that the CHAP used the latest data available at the time the CHAP performed its analysis."[38] But this statement is false: the CHAP Report itself states that "[t]he stopping point for CHAP analysis and interpretation was information available

[37] 79 Fed. Reg. 78333.
[38] *Id*.

by the end of 2012."[39] By that point, two more rounds of NHANES survey data were available, for 2007-2008 and 2009-2010. (The CDC website indicates that the 2009-2010 data were posted there in September 2012.[40])

As more fully discussed in Part III.B below, this omission has devastating effects on the CHAP's analysis, particularly its cumulative risk analysis. Figure 1 below shows the dramatic decreases that have taken place since 2006 in a measurements of a principal metabolite of DEHP, the phthalate that, staff recognized, "dominates"[41] the cumulative risk analysis.

Figure 1. Significant Downward Exposure Trend in DEHP Metabolite Levels Using Mono(2-ethyl-5-carboxypentyl Phthalate (2E/5C) as an Example (95th Percentile)[42]

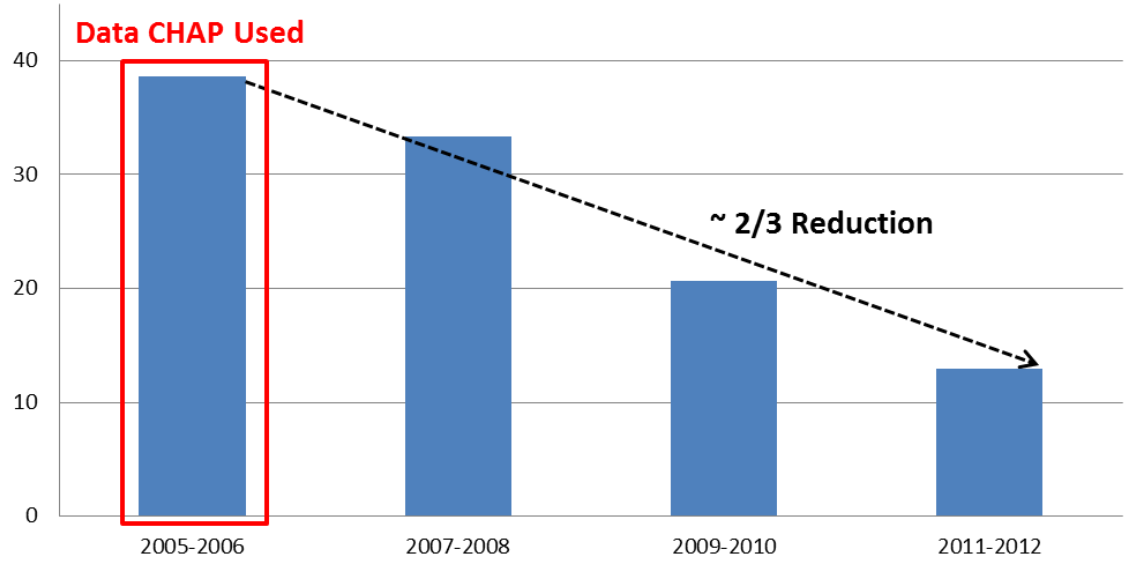


Figure 2 shows that this is not a selective portrait; all four DEHP metabolites monitored by NHANES have fallen over this period.

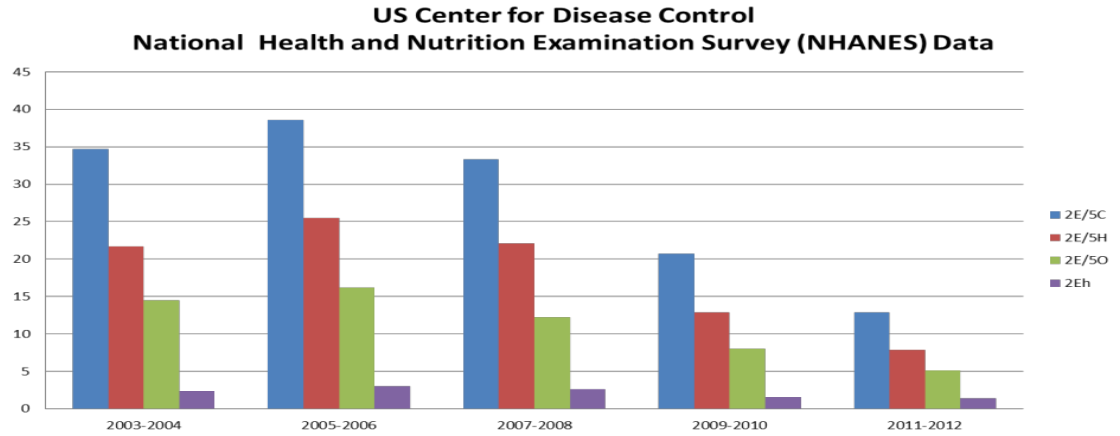
[39] CHAP Report at 12. The CHAP report even cites some publications dated 2013; e.g., Clewell 2013a and 2013b. *Id*. at 147.

[40] See http://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Laboratory&CycleBeginYear=2009.

[41] 79 Fed. Reg. 78328.

[42] Source: ExxonMobil Biomedical Sciences, Inc., ANALYSIS OF THE REPORT TO THE U.S. CPSC BY THE CHAP ON PHTHALATES AND PHTHALATE ALTERNATIVES (Sept. 2014), at iii.

Figure 2. DEHP Urinary Metabolite Data From NHANES[43]



The CHAP Report nowhere explains this omission, simply stating in an appendix that the reliance on 2005-2006 NHANES data is "[a] limitation of the analyses presented here." It notes that, "[s]ince these data were collected, the [CPSIA] restricted some of the uses of the five phthalates evaluated." It then declares, counterfactually, that "[t]he impact on exposure is unknown and not accounted for in the calculation of the HI."[44]

Even more troubling, particularly for purposes of the phthalates rulemaking, is the staff's rather cursory discussion of the omission of the more recent NHANES data. The staff – which also has the 2011-2012 data that the CHAP did not – acknowledges that "[t]he CDC report shows that exposure to DBP, BBP, and DEHP [the three permanently banned phthalates] is declining." But it merely adds that it "has not assessed the effect of changing phthalate exposures on the [hazard index]."[45]

The CPSIA directs the CHAP to "review all relevant data, including the *most recent*, best available . . . scientific studies . . . that employ objective data collection practices . . . ."[46] The NHANES surveys are the paradigm examples of scientific studies that employ objective data collection practices, and they are the best available measurements of phthalate exposures and exposure trends in the United States. The most recent NHANES surveys available to the CHAP within its self-imposed "stopping point" covered 2007-2008 and 2009-2010. The CHAP used neither. The Commission and its staff also have the NHANES data for 2011-2012. They similarly have ignored all three of these surveys. It is hard to imagine a more direct or consequential violation of the CPSIA.

[43] Source: EMBSI comments at 7.
[44] CHAP Report, App. D, at 41.
[45] 79 Fed. Reg. 78333.
[46] 15 U.S.C. § 2057c(b)(2)(B)(v) (emphasis added).

OMB's "binding" IQA Guidelines similarly require agencies, when disseminating influential scientific information, to "use the best available . . . science and supporting studies conducted in accordance with sound and objective scientific practices,"[47] and require in all cases of scientific information that "analytic results shall be developed[] using sound statistical and research methods."[48] That means that the CHAP was required to address the 2007-2008 and 2009-2010 NHANES surveys. The IQA Guidelines also require that information must always be presented in a "complete and unbiased manner,"[49] and agencies must "ensure that the presentation of information on [risk] effects is comprehensive . . . ."[50] The CHAP Report's omission of that later data made its presentation of risk necessarily incomplete. The CPSC must therefore correct the CHAP Report to address all NHANES survey data currently available to it regarding women's phthalates exposures, and cannot base a final rule on it until it does so.

B. The CHAP's Cumulative Risk Assessment Depends on Its Unrealistic Inclusion of Permanently Banned Phthalates; DINP Makes No Meaningful Contribution to the Calculated Risk

1. DEHP Dominates the CHAP's Cumulative Risk Assessment; The Addition of DINP Is Irrelevant

As just noted, the CHAP's cumulative risk assessment was dominated by phthalates that have been permanently banned since 2009 from children's toys and child care articles. The CHAP Report makes this point quite openly in discussing hazard indices calculated from biomonitoring data:

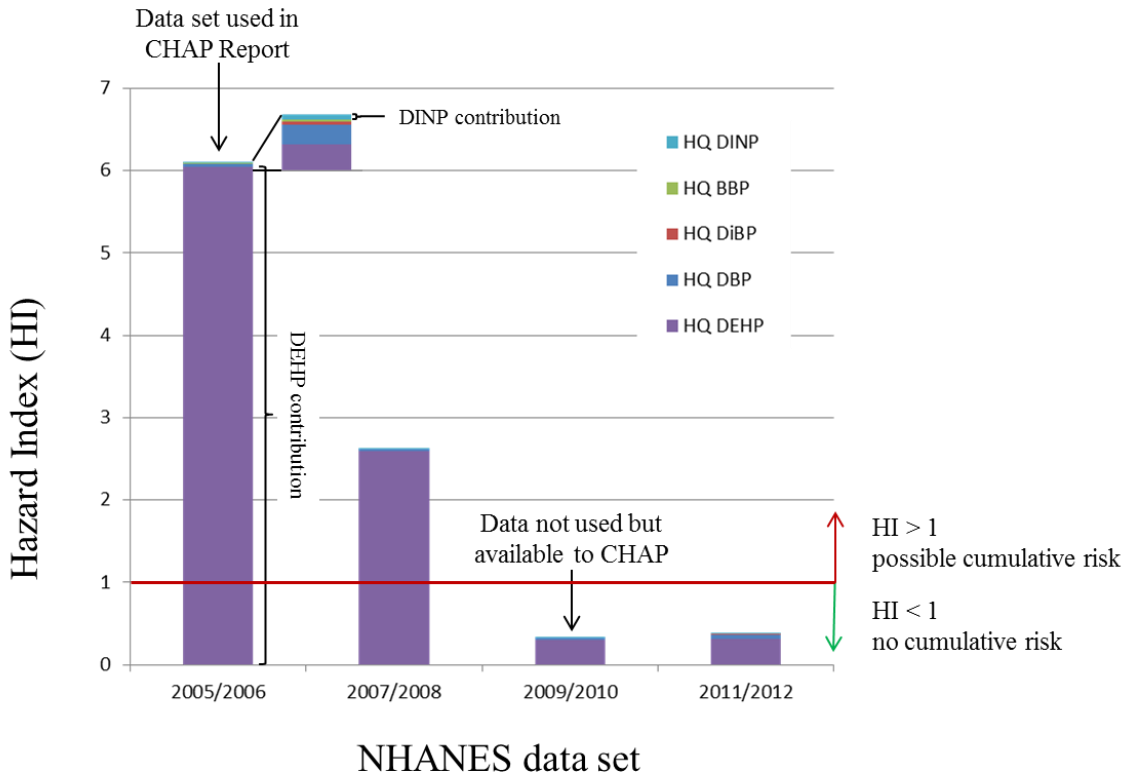
> The primary contributor(s) to the HI can be identified by evaluating the hazard quotients that comprise the HI. Clearly, the hazard quotient for DEHP dominates the calculation of the HI, as expected, with high exposure levels and one of the lowest PEAAs. The rank contribution of the five phthalates to risk was calculated using the median 95th percentile across the cases for pregnant women in NHANES and SFF (Sathyanarayana *et al.*, 2008a; 2008b) women (prenatal and postnatal combined) and infants:
>
> NHANES women (2005–2006): DEHP > DBP >DINP ~DIBP >BBP
> SFF women: DEHP >BBP >DBP > DIBP > DINP
> SFF infants: DEHP > DBP > BBP > DINP ~DIBP

[47] 67 Fed. Reg. 8457.
[48] Id. at 8459.
[49] Id.
[50] Id. at 8457.

> In all cases, DEHP and DBP contributed strongly to the HI while DIBP and DINP contributed considerably less.[51]

Comments on the CHAP Report prepared by ExxonMobil Biomedical Sciences, Inc. (EMBSI) illustrate the same phenomenon, in a graph that shows the CHAP's cumulative risk assessment for pregnant women and the results of the same assessment run with more recent NHANES data.

Figure 3. CHAP Cumulative Risk Assessment for Pregnant Women Based on NHANES Data From 2005 to 2012[52]



This graph shows dramatically how, absent DEHP, the cumulative risk assessment would never show a HI >1. It also shows the vanishingly small contribution that DINP makes to the calculated risk.

The CHAP proceeded similarly in its scenario-based exposure estimates, assuming that DEHP, DBP and BBP would be present in children's toys and child care articles even though they have been banned permanently from those uses: "Although certain phthalates are currently banned in toys and child care articles, we estimated exposures that hypothetically would occur if

[51] CHAP Report at 65.

[52] Source: EMBSI comments at iv.

phthalates were allowed in these products." This hypothetical would require Congress to repeal the permanent ban – something that the Commission, at least, must realize is a preposterous scenario.

Granted, DEHP, DBP and BBP have only been banned from children's toys and child care articles, but in fact, as the NHANES data show, they are rapidly disappearing from the marketplace altogether, due to multiple adverse actions being taken against them under REACH[53] and snowballing product deselection in the marketplace. Yet the CHAP never attempted to model that possibility, even "hypothetically." More distressing, Commission staff adopted the same policy: "The [2011-2012] CDC report shows that exposure to DBP, BBP, and DEHP is declining . . . . Staff has not assessed the effect of changing phthalate exposures on the HI."[54]

Why have the CHAP and the staff both refused to consider what the cumulative risk assessment might look like if DEHP were omitted, or even if current levels of DEHP were used? The inevitable conclusion is that, absent DEHP, the cumulative risk assessment would not show a risk of concern.

As can be seen from Figure 3, the contribution of DINP to the estimated risk is miniscule – calculated by EMBSI at <1%. The Chamber recognizes that the CHAP's risk assessment showed that DINP could account for as much as 8% of the risk to women and 15% of the risk to children.[55] Indeed, using 2011-2012 data, DINP now accounts for close to 50% of the risk to children under Case 3 of the CHAP's analysis – but that is 50% of a HI of 0.25, still well below the level that should trigger concern.[56] Moreover, as explained below, the Case 3 overstates risks in multiple ways, so the real risk is likely far less.

Kathryn Clark, a peer-reviewer retained by ToxStrategies to review the CHAP Report, made the same point:

> The CHAP report recommends that the interim ban on the use of diisononyl phthalate (DINP) in children's toys and child care articles at levels greater than 0.1% be made permanent. The basis for this recommendation is not clear; according to the CHAP report (Table E1-20), exposure to toys and child care articles represents only 0.1% of total exposure to DINP for pregnant women so a ban would not be expected to alter exposure of pregnant women. For infants

[53] See, e,g., http://www.bureauveritas.com/wps/wcm/connect/7848128049da1f5e9c169e4f5d28a257/Bulletin_12B-101.pdf?MOD=AJPERES.

[54] 79 Fed. Reg. 78333.

[55] *Id*. at 78328.

[56] EMBSI comments at 10.

> (Table E1-21) exposure to toys and child care articles represents 30% of total exposure to DINP; however, this percentage was calculated in the scenario-based assessment, which over-estimates total exposure to DINP by a factor of six (Table 2.14) and, therefore, it is highly uncertain what effect a ban on DINP in toys and child care articles would have.[57]

Under the Commission's approach to conventional, single-chemical risk assessment, a chemical is regarded as "safe" if its margin of exposure (MOE) is ≥100 or greater based on a no observed adverse effect level (NOAEL) or ≥1,000 otherwise.[58] In a cumulative risk assessment, however, the Commission has taken the position that it makes no difference what MOE a chemical has: so long as it can lead to the same adverse endpoint, it "contributes to the cumulative risk."[59]

First, this position begs the questions of whether DINP is in fact antiandrogenic, or antiandrogenic at the levels seen in humans. The former issue – i.e., the questionable relevance to humans of the animal data – is discussed in Part III.E below. The latter issue is addressed by one expert peer reviewing the CHAP report:

> While there is evidence for additive effects at the high doses used by Howdeshell and co-workers (2007) there is no evidence that the same will hold true at concentrations representative of human exposure documented in contemporary biomonitoring studies (Kamrin, 2009). Indeed, typical exposures for most phthalates considered may be too low to by many orders of magnitude to produce the adverse effects described in this report. . . . While there is evidence of additive effects in rats at high concentration it is unclear how these results translate to humans with much lower exposures, more complex exposures, and with generally less sensitivity to the adverse effects under consideration. Based on these considerations it is suggested that the authors consider a more detailed discussion of the issues relating to additive effects. Furthermore, on the basis of these considerations it is suggested that the conclusions and recommendations in the report are overly conservative and inadequately justified as written.[60]

In other words, while the Commission's approach may make sense where individual chemicals make some meaningful contribution to the cumulative risk, in this case, the inclusion of DINP is not necessary in order to provide "a reasonable certainty of no harm." The Commission notes that the MOE for DINP's antiandrogenic effects, based on the CHAP's "hypothetical" NOAEL, is between 830-15,000.[61] As discussed in Part III.D, these MOEs should be more than tripled,

[57] ToxStrategies, INDEPENDENT EXPERT PEER REVIEW OF THE FINAL CHAP REPORT ON PHTHALATES AND PHTHALATE ALTERNATIVES (2014), at 10.

[58] 79 Fed. Reg. 78333.

[59] *Id.* at 78334.

[60] *Id.* at 64.

[61] *Id.*

based on the CHAP's more appropriate, "conservative" NOAEL, to between 2,800 and 65,000 or more. And an expert peer reviewer concluded that the real MOE is between 3,600-125,000.[62] At these levels, whatever "contribution" DINP may be making to male reproductive effects in humans is so minor as to be meaningless and unlikely to make any difference in the real world.[63]

The bottom line is that, whether using 2005-2006 or more recent exposure data, any additional risk contributed by DINP is trivial, and is certainly swamped by the uncertainty of the assessment. In even simpler terms, there is no difference in estimated risk whether one includes DINP or not.

The CHAP also faces a problem of inconsistency: it included DINP in its cumulative risk assessment because it concluded that it is antiandrogenic, notwithstanding how miniscule its marginal contribution must be to that risk. Yet one of the phthalate alternatives that the CHAP examined, TOTM, has been found to have reproductive effects on male rats in two studies: one found that mid- and high-dose males had reduced numbers of spermatocytes and spermatids in the testes (NOAELrepro=100 mg/kg-day), and another found a statistically significant increase in the number of high-dose male offspring with retained areolar regions (NOAEL = 1050 mg/kg-day).[64] And neither the CHAP, the staff nor the Commission included TOTM in the cumulative risk assessment, or proposed a ban or other restriction on TOTM. Under the principle that justified inclusion of DINP in the cumulative risk assessment, TOTM warrants inclusion – and a permanent ban on its use in children's toys and child care articles. Either that or the Commission should recognize that chemicals exhibiting such ambiguous evidence of anti-androgenicity and such enormous margins of exposure (the CHAP did not calculate an MOE for TOTM) should be omitted from a cumulative risk assessment of phthalates for reproductive endpoints – as EPA scientists have done.[65]

The distinctive value of cumulative exposure (and risk) assessment is in circumstances where (i) exposure to any single substance is below levels of concern, but (ii) exposures to multiple chemicals with the same mechanism of action (or that affect the same endpoint) *do* rise to levels of concern.[66] In the circumstances evaluated by the CHAP and this rulemaking,

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[62] ToxStrategies report at pdf pages 66-67 (comments of Warren Foster, Ph.D.).

[63] The peer review comments of Christopher Borgert expand on the unreality of the CHAP's estimated reproductive risks given their lack of any clinical validation. *See* ToxStrategies report at pdf pages 19-20.

[64] CHAP Report at 140.

[65] Christensen, K., Makris, S., and Lorber, M. 2014. Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessments. Regulatory Toxicology and Pharmacology 69:380-389.

[66] *See* National Research Council, PHTHALATES AND CUMULATIVE RISK ASSESSMENT: THE TASKS AHEAD (2008) at 8 ("Where single-chemical risk assessments might yield the verdict 'absence of risk,' dose addition might yield the opposite conclusion.").

however, only one phthalate ever posed a risk of concern in isolation: DEHP. Now, none pose such risk, whether in isolation or when exposures are cumulated.

2. Legal Analysis of Cumulative Risk Assessment

a. CPSIA

The CPSIA required the CHAP to "examine the *likely levels* of children's, pregnant women's, and others' exposure to phthalates, based on *a reasonable estimation* of normal and foreseeable use and abuse of such products."[67] This requirement can and should be read together with the immediately following directive to "consider the cumulative effect of total exposure to phthalates . . . ."[68] The import of these two clauses, read together, is that the CHAP – and by extension the Commission – have to base their assessment of risks from cumulative exposures on exposure levels that are "likely" and based on reasonable estimations. Ignoring actual exposure data from the last three rounds of NHANES surveys that show a dramatic, monotonic drop in DEHP exposure does not produce "likely" estimates of current or possible future cumulative exposures, and is unrealistic. Assuming "hypothetically," for purposes of scenario-based assessments, that Congress would repeal its permanent ban on DEHP, DBP and BBP is also "unrealistic" and does not predict "likely levels" of exposure.

The CPSIA also directs the CHAP to "consider the level at which there is a reasonable certainty of no harm to . . . susceptible individuals . . ., considering the best available science, and using sufficient safety factors to account for uncertainties regarding exposure and susceptibility of . . . potentially susceptible individuals."[69] The CHAP violates this direction in two ways:

- First, there is no uncertainty regarding the levels of DEHP exposure shown in the NHANES data, despite the CHAP's and staff's apparent efforts to create it. More generally, Congress' inclusion of the phrase "best available science" in the very same clause can only mean that the CHAP's job is, first, to describe what the best available science evidence is, and, then, to add safety factors sufficient to account for what the science does not tell us. Congress cannot have intended for the CHAP to hide data in order to be protective.
- Second, the CHAP was to "consider the level at which there is a reasonable certainty of no harm" to susceptible individuals (and the CPSC is to regulate to "ensure" such

[67] 15 U.S.C. § 2057c(b)(2)(B)(iii).
[68] *Id.* § 2057c(b)(2)(B)(iv).
[69] *Id.* § 2057c(b)(2)(B)(vii).

certainty "with an adequate margin of safety").[70] As shown above, the lowest MOE for DINP for any population examined by the CHAP is at least 2,800 and quite likely one or two orders of magnitude greater. This is well above the 100-1,000 margin that the Commission regards as adequate. Including DINP in the cumulative risk assessment is more than is necessary to provide a "reasonable certainty of no harm . . . with an adequate margin of safety" – or, put another way, it provides a more-than-adequate margin of safety.

The CHAP Report and the NPRM thus violate the CPSIA. Also, by inconsistently including DINP but excluding TOTM from regulation, the CPSC would be acting arbitrarily and capriciously.

b. IQA

Similarly, the IQA Guidelines require that, in order to be objective, information must be "accurate, reliable, and unbiased." To have utility, it must be "useful[]." The 2006-2007 NHANES data is not a reliable indicator of phthalate exposures now, and its use produces inaccurate results. "Hypothetically" including banned phthalates in exposure scenarios does not produce reliable or accurate results. These practices bias the cumulative risk estimates toward showing risk where it no longer exists. Such an assessment is not useful for making decisions under a statute that calls for decisions to be made on the basis of "likely levels of . . . exposure." The CHAP Report thus needs to be corrected, so that it relies on current NHANES data and does not assume the repeal of any part of the CPSIA. Until then, a final rule based on it would be arbitrary, capricious and contrary to law.

C. The CHAP Did Not Systematically Select or Evaluate Studies and Improperly Emphasized Adverse Findings

The CHAP and the staff emphasize the NRC's 2008 report on assessing the cumulative risks of phthalates, but neglect to cite another NRC report that emphasizes the importance of adopting a systematic approach to selecting and evaluating studies and, in particular, clearly articulating a rationale for selecting studies on which toxicity criteria are based.[71]

Without a systematic approach, studies are chosen arbitrarily at best and intentionally at worst (*i.e.*, only those that best support a particular position), resulting in a biased picture of the issue and leading reviewers to draw incorrect and/or incomplete conclusions. The CHAP Report

[70] *Id.* §§ 2057c(b)(2)(B)(vii), (3)(A).
[71] NRC, REVIEW OF THE ENVIRONMENTAL PROTECTION AGENCY'S DRAFT IRIS ASSESSMENT OF FORMALDEHYDE (2011).

does a very poor job in this regard.

1. Study Selection

The CHAP Report explicitly rejected a systematic approach:

> The CHAP considered the systematic review process (Guyatt *et al.*, 2011; Higgins *et al.*, 2011; Woodruff and Sutton, 2011). Because of the nature of the subject matter and the charge questions, which involve different streams of evidence and information, the CHAP concluded that its review was not amenable to the systematic review methodology.

The Chamber cannot understand this explanation. The systematic review process is amenable to handling "different streams of evidence and information" – as one peer reviewer pointed out, "[t]he systematic review methodology is clearly the best approach to be used in the situation in which there is evidence from different disciplines."[72]

The CHAP added that, "[t]o avoid bias, the CHAP obtained new information and opinions about the availability of other information through public comment and presentations." An after-the-fact "notice and comment" process is no substitute, however, for implementing an explicit, objectively-expressed framework – especially since the CHAP failed to cite published work even after it was provided to them.[73]

The CHAP's enumeration of study selection criteria focuses solely on study design (e.g., number of dose levels, number of animals) and does not include consideration of model relevance or database consistency.[74]

The CHAP says: "In cases in which peer-reviewed data were not available, the CHAP made decisions on a case-by-case basis as to whether non-peer-reviewed data would be used in making recommendations to the CPSC."[75] The report contains no further explanation of what considerations might have come into play in such decisions, leaving open the possibility that, consciously or unconsciously, the CHAP chose studies that supported its members' biases.

[72] ToxStrategies report at 8 (comments of Douglas Weed). Weed's more detailed comments address explain how the CHAP could have conducted a systematic review; *see id*. at pdf pages 80-86.
[73] *Id*. at 25.
[74] *See* CHAP Report, App. A, Table A-3.
[75] *Id*. at 5.

2. Evidence Integration

As for which studies would be used to reach conclusions about the existence or severity of a hazard, when faced with conflicting animal studies, the CHAP said it followed the "conservative approach [of] rely[ing] on [a] study reporting adverse effects unless there are compelling reasons to exclude the study, *i.e.,* considerations such as quality, design, execution or interpretation.[76] This approach is the antithesis of a weight of evidence approach, one the staff say they employed.[77]

One peer reviewer, who conducted a systematic review of human studies of the possible effects of phthalates on male reproductive development, discusses at length the failure of the CHAP Report to evaluate the human evidence completely or fairly:

> The CHAP report misrepresents the results of some (but not all) of the available epidemiological evidence, ignoring or downplaying negative results and emphasizing positive (i.e. apparently harmful) results. Theirs is not a critical and balanced review of the epidemiological evidence. That evidence, which I have examined in detail, is inconsistent . . . . [T]he CHAP report is biased with respect to the findings of the epidemiological evidence.
>
> The CHAP report fails to mention much less discuss a relatively large number of published reviews and several epidemiological studies on the topic of phthalates and human health including children's health. The missed epidemiological studies provide evidence of null ("no association") results. In addition, the fact that many of these reviews disagree with the CHAP report's assessment of the epidemiology (and of the use of animal models to represent adverse health events in humans) is important and should have been addressed in the CHAP Report.[78]

Another reviewer expressed the same conclusion:

> The CHAP report failed to consider published literature at odds with its selected cumulative risk theory and methodology, thereby undermining the scientific credibility and reliability of its cumulative risk predictions and recommendations based on them.[79]

[76] *Id.* at 20-21.

[77] *See* 79 Fed. Reg. 78333

[78] ToxStrategies report at 8-9 (comments of Douglas Weed). Weed's more detailed comments explain the CHAP's mischaracterizations of the studies they do discuss (pdf pp. 90-99) and summarizes the studies they do not cite (pdf pp. 99-106).

[79] *Id.* at 11 (comments of Christopher Borgert).

As did another:

> 1. The CHAP report relies heavily on the purported relationship between phthalate exposure and reduced AGD in young boys (Swan et al., 2005; Swan, 2008). However, the report fails to critically assess the reported link between phthalate exposure and reductions in AGD. Specifically, only four epidemiological studies are available in the literature and previous reviews have acknowledged the limited consistency of results for individual phthalates. While the present report recognizes the lack of consistency in the findings, it fails to discuss the lack of agreement between the U.S. studies in which many of the same subjects were included in the second study (Swan et al., 2005; Swan, 2008). Furthermore, there is no discussion of the potential for type I error inflation and detection of spurious associations arising from multiple independent comparisons. Consequently, the link between phthalate exposure and reduced AGD is less convincing than suggested by the authors of this report. Moreover, the same evidence has been considered to be only modest by others (Kay et al., 2014). Thus, it is suggested that the authors consider a more developed discussion of the dependence on the use of AGD as the critical marker of adverse effect and the overall strength or weakness of the data should also be acknowledged in the report. It is further suggested that the uncertainty in the association should be reflected in the risk assessment and conclusions reached.
>
> 2. Further to the points raised above, it is noted that several reports have raised the issue that AGD and AGI are not linked with any adverse clinical health outcome and thus lack of clinical relevance has been considered by others (McEwen, Jr. and Renner, 2006; Weiss, 2006) to be a weakness with these outcomes. This point should be discussed in the report. Several authors have made the point that these markers are linked with diminished reproductive health in males (Eisenberg et al., 2012b; Eisenberg et al., 2012a; Eisenberg et al., 2011; Mendiola et al., 2011b) and the strengths and weaknesses of this data should be discussed given the weight AGD and AGI are given in this report.[80]

And another:

> According to the CHAP report, the literature suggests that prenatal exposure to phthalates is associated with a decrease in anogenital distance (AGD) in human male offspring, evidence consistent with the existence of "phthalate syndrome" in humans. Their conclusion is based upon data from four epidemiologic studies (Swan et al., 2005; Swan, 2008; Huang et al., 2009; Suzuki et al., 2012) which report occasional inverse statistically significant relationships between phthalate metabolites in body fluids (maternal urine or amniotic fluid) and a measurement of AGD in mother-son cohorts. Recently, a fifth paper not mentioned in the

[80] *Id*. at pdf p. 63 (comments of Warren Foster).

> CHAP report has been published that has examined this issue, that of Bustamante-Montes et al. (2013) which employed a mother-son cohort from Mexico. A close scrutiny of these studies indicates that the data do not support the conclusion of the CHAP report. While statistically significant negative associations between the concentration of a particular phthalate monoester and an estimate of AGD are evident, they occur sporadically, are in some cases toxicologically irrelevant, and are very inconsistent from one study to the next, even internally inconsistent in the case of different publications from the same laboratory.
>
> One important shortcoming of this particular database is the marked methodological differences from study to study. Among these methodological disparities are the particular times when phthalate levels are estimated in the mother, when AGD are measured in offspring, and the method by which AGD was measured. The variation in AGD measurement among these studies is particularly noteworthy. . . .
>
> On the basis of occasional sporadic statistically significant associations, some of which are toxicologically insignificant, as well as severe methodologic inadequacies, it would appear that occasional associations are artifactual and, at best, inconclusive. Certainly the weight of evidence does not support a causal relationship between phthalate exposure during gestation and decreased AGD in human offspring.[81]

3. Legal Analysis of Study Selection and Evaluation

The CPSIA plainly requires the CHAP to "review all of the relevant data"[82] – not just the studies that suit its biases. It is impossible to square the selective use and systematic mischaracterization of the data described above with the CPSIA's mandate. The IQA Guidelines are even more prescriptive in relevant part, requiring analyses disseminated by federal agencies to be developed "using sound research methods" and to "be[] presented in a . . . clear, complete, and unbiased manner."[83] In presenting risks to health, agencies must "specify . . . peer-reviewed studies known to the [agency] that support, are directly relevant to, or fail to support any estimate of [risk] effects and the methodology used to reconcile inconsistencies in the scientific data."[84] The CHAP Report does not do so. The Commission must correct it as described above.

[81] *Id.* at pdf pp. 130-32 (comments of Raphael Witorsch).
[82] *Id.* § 2057c(b)(2)(B)(v).
[83] 67 Fed. Reg. 8459.
[84] Id. at 8457.

D. The CHAP Derived Erroneously Low Potency Estimates for DINP, Resulting in an Erroneously Low Lower Bound for Margin of Exposure Estimation

1. Problems With Derivation of Potency Estimates

In its dose/response calculation for DINP, the CHAP used three different "cases" to estimate a No Observed Adverse Effect Level (NOAEL).[85] In the first two of these cases, however, the CHAP failed to follow good toxicological practice. The Chamber also believes the third case is overly conservative.

In Case 1, the CHAP relied on a cumulative risk assessment conducted by Kortenkamp & Faust 2010, which calculated a potency estimate of 1500 µg/kg/day, based on a point of departure derived from Gray et al. 2000. Gray observed nipple retention in male rats at the single dose given there, 750 mg/kg/day. Kortenkamp & Faust then divided 750 by a safety factor of 500 (10 for animal to human extrapolation, 10 for intraspecies sensitivity, and 5 because of the uncertainty created by starting with a Lowest Observed Adverse Effect Level (LOAEL) rather than a NOAEL), yielding a point of departure of 1.5 mg/kg/day. However, as the CHAP itself noted in Case 3, several studies had been published since 2010 that were superior to Gray et al. in two respects: (i) they were more robust[86]; and (ii) they included doses at which no effects were observed, thus eliminating the need to rely on a LOAEL (and its attendant uncertainty). As discussed in Case 3, the CHAP concluded that these newer studies justified a "conservative" NOAEL of 50 mg/gk/day. Thus, there was no reason for the CHAP even to consider a point of departure based on Gray et al. or Kortenkamp & Faust's analysis of it.

In Case 2, the CHAP relied on Hannas et al. 2011b. Hannas found only a LOAEL for DINP, of 300 mg/kg/day. But it did find a NOAEL for DEHP of 5 mg/kg/day, and it also concluded that DEHP is 2.3 times more active than DINP, based on testosterone production in male rat fetuses in *in vitro* (i.e., tissue growing in glassware) conditions. The CHAP thus conducted "a simple extrapolation" to conclude that the NOAEL for DINP should be 11.5 mg/kg/day, resulting in a potency estimate of 115 µg/kg/day (11,500 divided by 100). There are two objections to this approach:

- First, this type of potency adjustment – extrapolating to one substance conclusions based on data from another – is only appropriate when there is limited data for the former

[85] The CHAP Report discusses the three cases at 64, though most of that discussion (and most of the quotations above) are drawn from a more detailed discussion at 95-98.

[86] For example, Boberg 2011 used four doses plus control, exposed animals during the developmentally-sensitive period (post-natal day 17) and used a relatively high number of dams (16). *See* CHAP Report at 97.

substance. That is not the case for DINP, which has a large set of substance-specific data to draw from. Available, robust *in vivo* studies for DINP provide scientifically defensible points of departure and should be used.

- Second, the CHAP should have noted that Gray et al. 2000 had previously estimated, based on *in vivo* conditions (i.e., live animals), that DEHP is actually 10-20 times more active than DINP. (The Hannas data actually exhibit a consistent "factor of 20" difference in potency between DEHP and DINP, according to "a crude extrapolation" conducted by the CHAP.) If one were to make a DEHP-to-DINP adjustment, a potency estimate based on Gray et al. would be more reliable, and would have been between 50-100 mg/kg/day. That results in a potency estimate of 500-1000 µg/kg/day.

Thus, Case 2 was also based on bad scientific methodology and should similarly be disregarded.

In Case 3, the CHAP conducted its own de novo review of the literature. It relied on three studies:

- Boberg 2011 – The study's authors said their NOAEL was at 300 mg/kg/day. Claiming to see reduced testosterone production at that level, the CHAP concluded that the "real" NOAEL must have been below 300.
- Hannas 2011b – As noted, Hannas found only a LOAEL for DINP, of 500 mg/kg/day, but the CHAP concluded that its "crude extrapolation of [Hannas'] dose-response data . . . suggests that the NOAEL is approximately 100 mg/kg/day . . . ."
- Clewell 2013a – This very robust study found a NOAEL of 50 mg/kg/day based on mononucleated gonocytes (MNGs), an endpoint that the CHAP regards as anti-androgenic.

The CHAP Report opined that, "[t]aken together, the data from Boberg *et al.* (2011), Hannas *et al.* (2011b), and Clewell *et al.* (2013a; 2013b) indicate that the developmental NOAEL, based upon antiandrogenic endpoints (nipple retention, fetal testosterone production, and MNGs), is between 50 and 300 mg/kg-day. Taking a conservative approach, the CHAP assigns the NOAEL for DINP at 50 mg/kg-day." This produces a potency estimate of 500 µg/kg/day.

As just explained, the lowest no effect level actually observed in a DINP study discussed by the CHAP was 50 mg/kg/day, based on MNGs seen in Clewell. The Chamber agrees that this is a NOEL – that is, a no observed effect level. There leaves two important questions, however: 1) Are MNGs an endpoint relevant to anti-androgenicity?; and 2) Is the finding a NO*A*EL – that is, is the observed effect *adverse*? We think it is questionable that MNGs are anti-androgenic,

since it has been established that MNGs occur in tests with animals that are not sensitive to the anti-androgenic effects of phthalates.[87] We also think that it is questionable that they are adverse, since MNGs are eliminated within two weeks of birth and are not associated with a reduction in any reproductive outcome in adults. Rather, they seem to be simply a nonandrogenic mediated biomarker of exposure. Animals in whom they are seen engage in normal reproductive behavior and produce normal young. *See* Part III.E below. Thus, using 50 mg/kg/day as the point of departure for estimating the potency of DINP is indeed highly conservative.

2. Effect on Margins of Exposure

At the conclusion of the discussion of DINP in the recommendations section, the CHAP report said:

> In infants in the SFF study, the MOE for total exposure ranged from 640 to 42,000 using 95th percentile estimates of exposure. For pregnant women, the MOE for total DINP exposure ranged from 4,500 to 68,000. Typically, MOEs exceeding 100-1000 are considered adequate for public health; however, the cumulative risk of DINP with other anti-androgens should also be considered.[88]

Relying on the CHAP's 50 mg/kg/day point of departure – which, as just seen, is highly conservative – instead of its hypothetical 11.5 mg/kg/day value would raise the lower bounds of these ranges by more than a factor of four; i.e., from 640 to 2,800 and from 1,000 to 4,500 – in each case, well above the 1,000 margin that serves as the more conservative threshold of adequacy. Other MOEs calculated in the CHAP report would be similarly increased.

3. Legal Analysis

The CPSIA requires that the CHAP "consider the level at which there is a reasonable certainty of no harm . . . considering the best available science, and using sufficient safety factors to account for uncertainties regarding exposure and susceptibility of . . . potentially sensitive individuals.[89] For its part, the IQA requires information to be accurate, reliable and unbiased, and for analytical results to be developed using sound methods. The foregoing analysis makes clear that:

[87] *See, e.g.*, Johnson, K. J., Heger, N. E., and Boekelheide, K. (2012). Of mice and men (and rats): phthalate-induced fetal testis endocrine disruption is species-dependent. Toxicological Sciences, 129(2), 235-248.

[88] CHAP Report at 99.

[89] 15 U.S.C. § 2057c(b)(2)(B)(vii).

- The best available science – including a series of well-conducted animal studies – interpreted via sound toxicological and risk assessment practice supports a NOAEL for DINP of no less than 50 mg/kg/day. That value is reliable and conservative.
- Relying on a single study, and developing a NOAEL by applying a potency adjustment derived from in vitro measurements, is not a sound method, and produces an unreliable value.
- All the potency estimates properly derived Gray, Boberg, Hannas and Clewell are based on safety factors totaling 100 (and 500 in the case of Gray). Given the relatively low degree of uncertainty remaining in this literature, no additional safety factor needs to be introduced to produce a reasonable certainty of no harm. As noted, the estimation already includes a 10x safety factor to account for differing sensitivities among individuals.

For these reasons, the CHAP Report needs to be corrected to use a point of departure for DINP's potential anti-androgenicity of no less than 50 mg/kg/day.

E. The CHAP Overstated the Human Relevance of Animal Data and Mischaracterized the Limited Human Data

Repeatedly in its discussion of animal data, the CHAP Report recites simply that "[t]he reported animal studies are assumed to be relevant to humans." The field of toxicology has advanced well beyond this 1970s approach to use of animal data – but the CHAP Report ignores these advances. The Report also assumes that human beings are ten more sensitive than rats to the anti-androgenic effects of phthalates. In fact, a wealth of data more strongly supports the conclusion that humans are less sensitive than rats to these effects. This point is made most clearly in the comments of Christopher Borgert, who evaluates the two examples of where human males have been exposed to chemicals that are recognized antiandrogens: finasteride and DES. Borgert's comments summarize the literature on rats and humans exposed to these chemicals, and show in both cases the lesser sensitivity of humans.[90]

[90] ToxStrategies Report at pdf pp. 22-23.

Figure 4. DES Potency Comparison for Male Reproductive Tract Parameters[91]

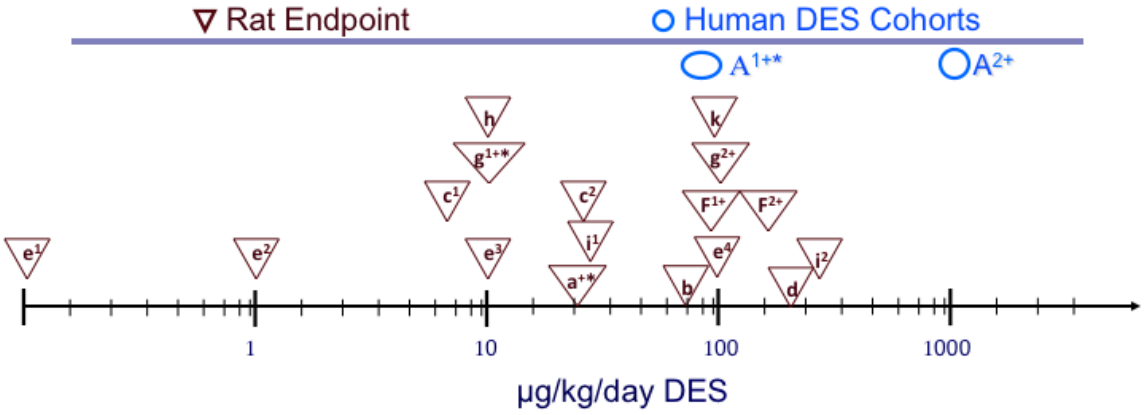
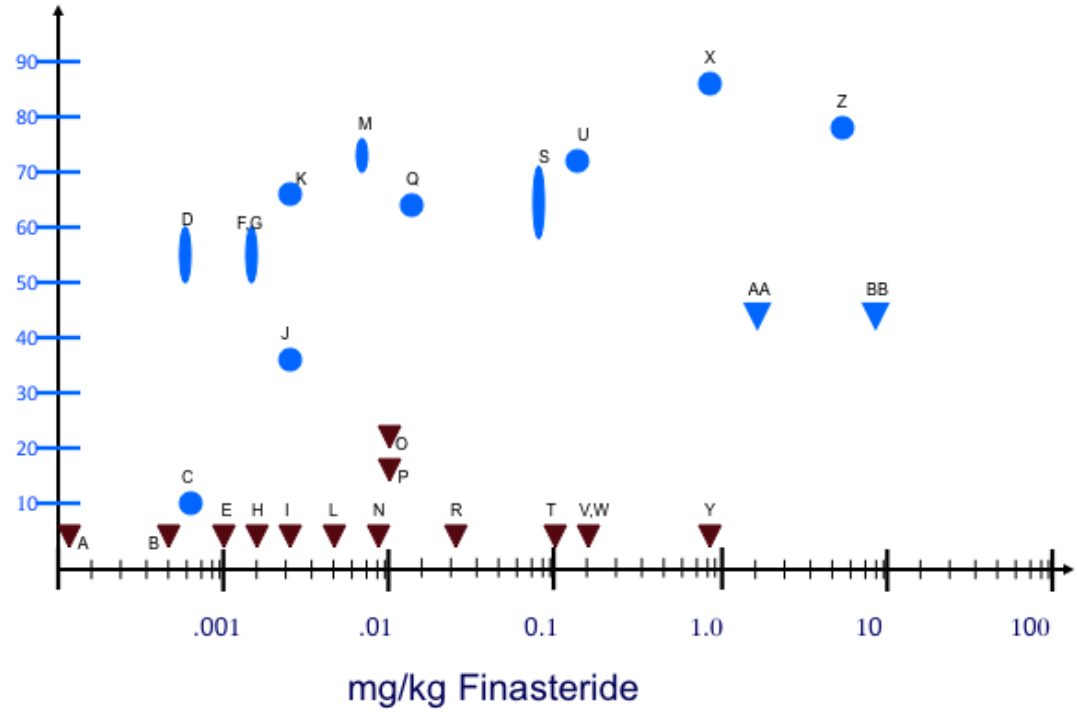


Figure 5. Finasteride Potency Comparision for Human Clinical Suppression of DHT Versus Rat Endpoints[92]

(Human clinical data: ovals; rat experimental data: triangles. Blue points indicate % reduction in DHT.)



[91] Source: Borgert, C.J., Sargent, E.V., Casella, G., Dietrich, D.R., McCarty, L.S., and Golden, R.J. (2012). The human relevant potency threshold: reducing uncertainty by human calibration of cumulative risk assessments. Regul Toxicol Pharmacol 62, 313-328.

[92] Source: Borgert, C.J., Sargent, E.V., Casella, G., Dietrich, D.R., McCarty, L.S., and Golden, R.J. (2012). The human relevant potency threshold: reducing uncertainty by human calibration of cumulative risk assessments. Regul Toxicol Pharmacol 62, 313-328.

There are many reasons, moreover, to question the human relevance of the animal data relied on by the CHAP Report.[93] Put simply, DINP does not cause the same reproductive endpoints as DIBP, DBP, BBP and DEHP. The latter produce the effects typically characterized as "rat phthalate syndrome": hypospadias, cryptorchism, decreased anogenital distance (AGI), nipple retention, changes in androgen-sensitive tissue weight, and infertility.[94] By contrast, in studies with strong statistical power, DINP has not been shown to induce permanent alterations in the male reproductive tract or fertility at doses that are well in excess of 50 mg/kg/day. Gross male reproductive tract malformations, such as cryptorchidism or hypospadias, have not been reported in any studies for DINP. Nor have such studies reported any effects in onset of puberty or male mating behavior. Most important, since it is the fundamentally most important reproductive endpoint, DINP has not been shown to have any effect on fertility.[95] Effects that have been seen (e.g., mononucleated gonocytes) are not related to reduced testosterone synthesis, are transitory, and are not adverse.[96] The CHAP Report's statement to the contrary[97] is contrary to the weight of the evidence.[98]

Moreover, the human relevance of some "rat phthalate syndrome" endpoints is questionable. For example, unlike rats, human males do not lose their nipples, significantly challenging the relevance of nipple retention for use in human hazard assessment or by extension to cumulative risk assessment. Also, the mechanisms for fetal testosterone production are different in rats and people. In rats, the process is heavily dependent on luteinizing hormone (LH); in humans, the process is driven by hCG, a hormone not produced in rats. Rats and humans also have very different steroidal cascades.[99] Recent work has illustrated that the abnormal clustering of Leydig cells and decreased T production seen in rats with developmental exposure to phthalates does not occur in mice and humans.[100]

[93] Also, as noted in Part III.B, it is questionable whether the NRC's assumption of additivity for chemicals that produce the same toxic endpoint, regardless of whether they act by the same mechanism of action, is tenable when doses are as low as seen here (i.e., when margins of exposure are so high).

[94] EMBSI Report at 30.

[95] Id. at 34-42.

[96] Id at 34, 41.

[97] CHAP Report at 96-97.

[98] *See* EMBSI comments at 34 ("There is evidence that [MNGs] are not a consequence of reduced testosterone synthesis. For example mice lack the compliment of antiandrogenic effects demonstrated in rats, yet produce MNGs after phthalate exposure. Additionally, an investigation into the role of androgens in fetal testis development and dysgenesis concluded that the induction of MNGs was mechanistically separated from intra-testicular testosterone reduction (Scott *et al.* 2007). Finally, of importance is that MNGs are not considered adverse as they are eliminated in a p53-dependent manner from the seminiferous epithelium within 1–2 weeks postnatally (Johnson *et al.* 2012).")

[99] *Id.* at 31-33.

[100] *Id*. at 33-34; ToxStrategies Report at pp. 64-65 (comments of Warren Foster).

Finally, in a very recent publication entitled "Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessments," three EPA scientists excluded DINP from their HI calculations because "the critical effect is not in the reproductive/developmental domain."[101]

Again, the CPSIA requires that the CHAP "consider the level at which there is a reasonable certainty of no harm . . . considering the best available science, and using sufficient safety factors to account for uncertainties . . . susceptibility of . . . potentially sensitive individuals.[102] In this case, the CHAP has introduced two unnecessary safety factors by assuming that (i) rat reproductive endpoints are relevant to humans, and (ii) humans are more sensitive to anti-androgens than are rats. There is science on these issues that addresses these questions, and the best available science answers them. These are not uncertainties that need to be protected against by safety factors, even to provide a reasonable certainty of no harm with an adequate margin of safety. The CHAP has not followed the requirements of the CPSIA.

The IQA requires information to be accurate, reliable and unbiased, and for analytical results to be developed using sound methods.[103] It also requires the CHAP to present "peer-reviewed studies known to [it] that . . . fail to support any estimate of [risk] effects and the methodology used to reconcile inconsistencies in the data."[104] The CHAP Reports's default assumptions that rat phthalate findings are relevant to humans, and that humans are more sensitive than rats to these effects, are not accurate or reliable, are biased toward making "artifactual" effects look actual, and omit discussion of peer-reviewed studies that contradict these assumptions. The CHAP Report must be corrected to present the relevant science more accurately and completely.

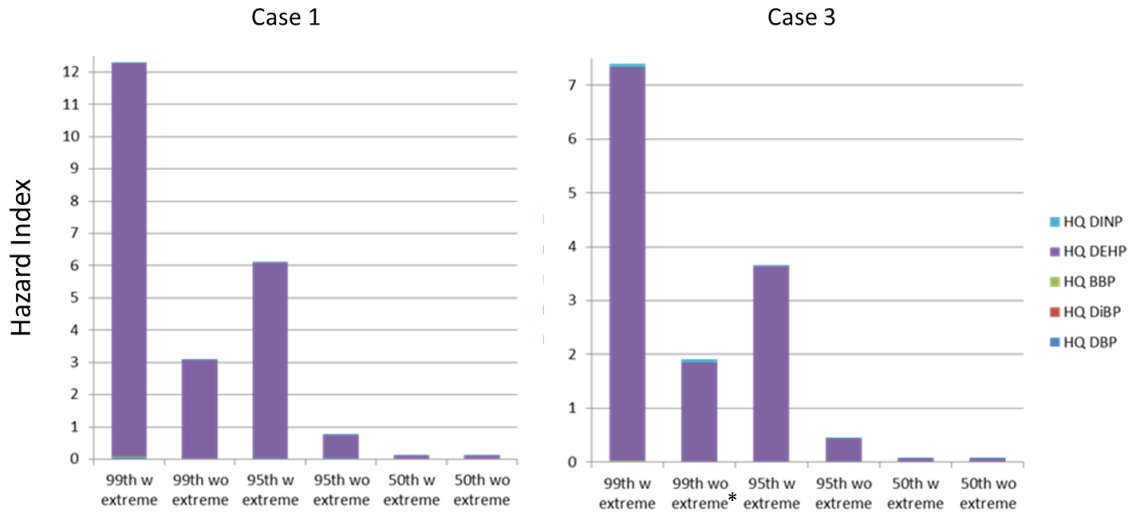
F. The CHAP's Sample Size for Pregnant Women Was Too Small to Yield Reliable Estimates of Risk; The CHAP Should Have Used Data for Women of Child-Bearing Age in Its Cumulative Risk Assessment

In Part III.A, we discussed the CHAP Report's omission of more recent NHANES data to which it had access before its "stopping point." The exposure assessment that the CHAP performed for its cumulative risk assessment suffers from two other momentous flaws that, compounded, produce an HI of 1 where it otherwise would not exist. First, the sample size for pregnant women was too small, and second, the CHAP evaluated the 99th and 95th percentiles of exposure.

[101] Christensen, K., Makris, S., and Lorber, *supra* note 65.
[102] 15 U.S.C. § 2057c(b)(2)(B)(vii).
[103] 67 Fed. Reg. at 8459.
[104] 67 Fed. Reg. at 8457.

The 2005-2006 NHANES survey contained phthalates data for only 130 pregnant women. The statistics for such a small population are highly vulnerable to being skewed by outliers – and that occurred here. The EMBSI comments dramatically illustrate the cumulative risk assessment HIs calculated with and without the *single individual* with the highest exposure for the 99th, 95th and 50th percentiles:

Figure 6. Hazard Indices for Pregnant Women Calculated Both With and Without the Individual With the Highest HI Value (Sample Size of 130 v. 129)



Remarkably, eliminating this one individual drops the HIs for both Case 1 and Case 3 below 1, the level of concern, at the 95th percentile of exposure. This extreme sensitivity to the tails of the distribution demonstrates the inappropriateness of assessing the exposure of pregnant women using the small sample of pregnant women contained in the NHANES data for 2005-2006. In their cumulative risk assessment for phthalates, Kortenkamp and Faust concluded that the most likely explanation for the highest levels of DEHP metabolites that they observed was that their maximally exposed individuals were patients undergoing medical procedures involving phthalate-containing tubing and disposables.[105] That certainly counsels against basing worst-case exposure assessments on such individuals.

Compounding the problem caused by the small sample size for pregnant women, the CHAP generated risk estimates for infants and pregnant women for the cumulative risk assessment by interpolating between the 95th and 99th percentiles of the NHANES data.[106] This was poor risk assessment practice. As several EPA scientists explained recently in discussing how to do cumulative risk assessments for phthalates:

[105] Kortenkamp & Faust 2010.

[106] *See* CHAP Report, App. D, at D-40

> Phthalate metabolites have very short half-lives, on the order of ~5 to 12h. . . . Thus urinary concentrations peak shortly after exposure . . . and urine sampled during this time of peak concentration could lead to artificially high estimates of daily intake. . . . [R]ecent work has demonstrated that on the population level, a group of spot urine samples provides a reasonable approximation of concentrations that would have been observed in a population of full-day urine samples collected from the same population for phthalates. . . .[107]

The EPA scientists accordingly limited their data presentation to the 95th percentile. Similarly in evaluating the risks posed by the different phthalates individually, the CHAP itself relied on 95th percentile estimates of exposure.[108] The CHAP should not have adopted a different practice for its cumulative risk assessment.

The CPSIA requires the CHAP to "examine the likely levels of . . . pregnant women's . . . exposure to phthalates, based on a reasonable estimation . . . ."[109] That does not, however, require the CHAP (or the CPSC) to based that assessment on exposure data involving only pregnant women, no matter small the sample population. More reliable, but equally protective, results could be generated simply by using NHANES data for women of reproductive age – so long as that latter population is representative of the former. The Chamber submits that it is: pregnant women are simply the subset of women of childbearing age who happen to be pregnant at a given time. Neither the CHAP nor the CPSC offer any evidence or argument to the contrary. Rather, they both seem to agree with the Chamber: "Based on NHANES data, pregnant women have median exposures that are roughly similar to those of women of reproductive age. (CHAP 2014, Table 2.7, page 45)."[110] The only difference is that the latter population, being larger, is less sensitive to being skewed by individuals with extreme levels.

Basing risk assessments on exposure assessments that are driven by a single individual does not meet the CPSIA's requirement that the CHAP estimate "likely levels" of pregnant women's exposures. That is especially true given the very short duration of peak urinary concentrations of phthalate metabolites and the representativeness of central tendency metabolite measurements.

The IQA Guidelines require information being disseminated by federal agencies to be "reliable" and "unbiased." They also require the presentation of risk estimates to specify "each appropriate upper-bound . . . estimate of risk."[111] Calculating risk estimates by interpolating

[107] Christensen, K., Makris, S., and Lorber, M, *supra* note 64.
[108] *See, e.g.,* CHAP Report at 99 (discussing DINP).
[109] 15 U.S.C. § 2057c(b)(2)(B)(iii).
[110] 79 Fed. Reg. 78327.
[111] 67 Fed. Reg. at 8457, 8459.

between the 95th and 99th percentiles is not appropriate in the circumstances presented here, and yields unreliable and biased estimates of risk. The CHAP Report must be corrected to rely the more robust NHANES data for women of child-bearing age, rather than pregnant women, and to rely on the 95th percentile of exposure.

IV. Conclusion

For the reasons set forth above, the CPSC must correct the CHAP Report to bring it into compliance with the requirements of the CPSIA and the IQA Guidelines. In particular, it must correct the CHAP Report to:

- Address all NHANES survey data currently available to it regarding the exposure to phthalates of women of childbearing age, including the 2007-2008, 2009-2010 and 2011-2012 NHANES surveys.

- Not assume the repeal of any part of the CPSIA, including the permanent ban on DEHP, BBP and DDP.

- Adopt a systematic approach to selecting and evaluating studies, including:
    - Clearly articulating a rationale for selecting studies on which toxicity criteria are based; and
    - Conducting a critical and unbiased review of the epidemiological evidence, rather than relying on studies reporting adverse effects unless there are compelling reasons to exclude the study. This must include specifying peer-reviewed studies known to the Commission that support, are directly relevant to, or fail to support any estimate of risk and the methodology used to reconcile inconsistencies in the scientific data.

- Use a point of departure for DINP's potential anti-androgenicity of no less than 50 mg/kg/day.

- Present an accurate and complete discussion of the science regarding the human relevance of rat data regarding anti-androgenicity, including:
    - Not adopting default assumptions that rat phthalate findings are relevant to humans or that humans are more sensitive than rats to these effects; and
    - Not omitting discussion of peer-reviewed studies that contradict these assumptions.

- Rely on the more robust NHANES data for women of child-bearing age, rather than pregnant women, and to rely on the 95th percentile of exposure.

The Commission may only issue a final phthalates rule that is based on such a corrected CHAP Report.

Pursuant to IQA Guidelines, the Chamber requests within 90 days the correction sought by this RFC. If the Commission requires more than 90 calendar days, please provide the Chamber notice that more time is required, an explanation, and an estimated decision date. I can be reached at (202) 463-5457 or wkovacs@uschamber.com.

Sincerely,

William L. Kovacs