The contents of this document will be discussed at the Commission Meeting scheduled for October 11, 2017.

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MD 20814

This document has been electronically approved and signed.

DATE: September 13, 2017

THIS MATTER IS NOT SCHEDULED FOR A BALLOT VOTE.
A DECISIONAL MEETING FOR THIS MATTER IS SCHEDULED ON: October 18, 2017

TO: The Commission
Alberta E. Mills, Acting Secretary

THROUGH: Patricia H. Adkins, Executive Director
Mary T. Boyle, General Counsel

FROM: Patricia M. Pollitzer, Assistant General Counsel
David M. DiMatteo, Attorney, OGC

SUBJECT: Final Rule: *Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates*

Staff is forwarding to the Commission a briefing package recommending that the Commission issue a final rule for the "Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates" under section 108 of the Consumer Product Safety Improvement Act of 2008. The Office of the General Counsel is providing for the Commission's consideration the attached draft rule for publication in the *Federal Register*.

Please indicate your vote on the following options:

I. Approve publication of the attached document in the *Federal Register*, as drafted.

_____ _____
(Signature) (Date)

II. Approve publication of the attached document in the *Federal Register*, with changes. (Please specify.)

_____

_____

_____

_____

_____ _____

(Signature) (Date)

III. Do not approve publication of the attached document in the *Federal Register*.

_____ _____

(Signature) (Date)

IV. Take other action. (Please specify.)

_____

_____

_____

_____

_____ _____

(Signature) (Date)

Attachment: Draft *Federal Register* Notice of Final Rule: *Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates*

[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION
16 CFR Part 1307

[Docket No. CPSC-2014- 0033]

Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates

AGENCY: Consumer Product Safety Commission.

ACTION: Final rule.

SUMMARY: The United States Consumer Product Safety Commission (Commission or CPSC) issues this final rule prohibiting children's toys and child care articles that contain concentrations of more than 0.1 percent of diisononyl phthalate (DINP), diisobutyl phthalate (DIBP), di-*n*-pentyl phthalate (DPENP), di-*n*-hexyl phthalate (DHEXP), and dicyclohexyl phthalate (DCHP). Section 108 of the Consumer Product Safety Improvement Act of 2008 (CPSIA) established permanent and interim prohibitions on the sale of certain consumer products containing specific phthalates. That provision also directed the CPSC to convene a Chronic Hazard Advisory Panel (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 and to provide recommendations to the Commission regarding whether any phthalates or phthalate alternatives, other than those already permanently prohibited, should be prohibited. The CPSIA requires the Commission to promulgate a final rule after receiving the final CHAP report. This rule fulfills that requirement.

DATES: The rule will become effective on [INSERT DATE 180 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER.]

FOR FURTHER INFORMATION CONTACT: For information related to the phthalates prohibitions, contact: Carol L. Afflerbach, Compliance Officer, Office of Compliance and Field

Operations, Consumer Product Safety Commission, 4330 East West Highway, Bethesda, MD 20814-4408; telephone: 301-504-7529; email: cafflerbach@cpsc.gov.

SUPPLEMENTARY INFORMATION:

Outline. The information in this preamble is organized as follows:

I. Background

A. Consumer Product Safety Improvement Act

1. Statutory Prohibitions

Section 108 of the Consumer Product Safety Improvement Act of 2008 (CPSIA) establishes requirements concerning phthalates. Section 108(a) of the CPSIA permanently prohibits the manufacture for sale, offer for sale, distribution in commerce, or importation into the United States of any "children's toy or child care article" that contains concentrations of more than 0.1 percent of di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), or butyl benzyl phthalate (BBP). 15 U.S.C. 2057c(a). In addition, section 108(b)(1) prohibits on an

interim basis (*i.e.*, until the Commission promulgates a final rule), the manufacture for sale, offer for sale, distribution in commerce, or importation into the United States of "any children's toy that can be placed in a child's mouth" or "child care article" containing concentrations of more than 0.1 percent of diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), or di-*n*-octyl phthalate (DNOP). *Id*. 2057c(b)(1). The CPSIA provides the following definitions:

- "children's toy" is "a consumer product designed or intended by the manufacturer for a child 12 years of age or younger for use by the child when the child plays."
- "child care article" is "a consumer product designed or intended by the manufacturer to facilitate sleep or the feeding of children age 3 and younger, or to help such children with sucking or teething."
- A "toy can be place in a child's mouth if any part of the toy can actually be brought to the mouth and kept in the mouth by a child so that it can be sucked and chewed. If the children's product can only be licked, it is not regarded as able to be placed in the mouth. If a toy or part of a toy in one dimension is smaller than 5 centimeters, it can be placed in the mouth."

Id. 2057c(g). These statutory prohibitions became effective in February 2009. The interim prohibitions remain in effect until the Commission issues a final rule determining whether to make the interim prohibitions permanent. *Id*. 2057c(b)(1).

2. Chronic Hazard Advisory Panel

The CPSIA directs the CPSC to convene a Chronic Hazard Advisory Panel (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." *Id*. 2057c(b)(2). A "phthalate alternative" is "any common substitute to a phthalate, alternative material to a phthalate, or alternative plasticizer."

Id. 2057c(g). The CHAP is to recommend to the Commission whether any phthalates or phthalate alternatives other than those permanently prohibited should be declared banned hazardous substances. *Id*. 2057c(b)(2)(C).

3. Rulemaking

The CPSIA requires the Commission to promulgate a final rule, pursuant to section 553 of the Administrative Procedure Act (APA), not later than 180 days after the Commission receives the final CHAP report. The Commission must "determine, based on such report, whether to continue in effect the [interim] prohibition . . . , in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety . . . ." 15 U.S.C. 2057c(b)(3)(A). Additionally, the Commission must "evaluate the findings and recommendations of the Chronic Hazard Advisory Panel and declare any children's product containing any phthalates to be a banned hazardous product under section 8 of the Consumer Product Safety Act (15 U.S.C. 2057), as the Commission determines necessary to protect the health of children." *Id*. (b)(3)(B).

B. The Proposed Rule

On December 30, 2014, the Commission published a notice of proposed rulemaking (NPR) in the *Federal Register*. 79 FR 78324. The preamble to the NPR summarized the CHAP report, explaining the CHAP's review of potential health effects of phthalates in animals and humans, the CHAP's assessment of human exposure to phthalates, the CHAP's assessment of risk (both cumulative and in isolation) of various phthalates, and the CHAP's recommendations to the Commission. The preamble to the NPR then provided CPSC staff's assessment of the CHAP report and stated the Commission's description of the proposed rule and its explanation of the rationale for the proposal.

The NPR generally followed the recommendations of the CHAP report. As explained further in section III of this preamble, the CHAP focused on certain phthalates' effect on male reproductive development. After reviewing relevant studies, the CHAP found that certain phthalates (which the CHAP called active or antiandrogenic) cause adverse effects on the developing male reproductive tract. The CHAP determined that these phthalates act in a cumulative fashion. The CHAP concluded that DINP is an active (antiandrogenic) phthalate. Based on the cumulative risk assessment conducted by the CHAP, the Commission determined that ''to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety,'' the Commission proposed to permanently prohibit children's toys and child care articles containing concentrations of more than 0.1 percent of DINP. The Commission proposed making the interim prohibition concerning DINP permanent because the Commission concluded that allowing the use of DINP in children's toys and child care articles would further increase the cumulative risk to male reproductive development. Although the interim prohibition applies to children's toys that can be placed in a child's mouth and child care articles, the NPR proposed permanently prohibiting DINP in all children's toys and child care articles. 79 FR at 78334-35.

The Commission proposed lifting the interim prohibitions regarding DIDP and DNOP. The Commission agreed with the CHAP that DIDP and DNOP are not antiandrogenic, and therefore, they do not contribute to the cumulative risk from antiandrogenic phthalates. The CHAP determined that neither phthalate poses a risk in isolation. Therefore, the Commission concluded that continuing the prohibitions regarding DIDP and DNOP is not necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety. *Id*. at 78334-78336.

In addition, the Commission determined that DIBP, DPENP, DHEXP, and DCHP are associated with adverse effects on male reproductive development and contribute to the cumulative risk from antiandrogenic phthalates. The Commission agreed with the CHAP's recommendation and proposed to prohibit children's toys and child care articles containing concentrations of more than 0.1 percent of DIBP, DPENP, DHEXP, and DCHP. 79 FR at 78326-38. The Commission proposed that the rule would take effect 180 days after publication of a final rule in the *Federal Register*. *Id*. at 78339.

C. Additional NHANES Analysis

As explained further in section III.C.2 of this preamble, the CHAP based its analysis, in part, on human biomonitoring data from the Centers for Disease Control and Prevention's (CDC) National Health and Nutrition Examination Survey (NHANES). The CHAP analyzed data from NHANES' 2005/2006 data cycle. That data set had a larger number of pregnant women than is usual for NHANES data sets. Since publication of the NPR, CPSC staff has reviewed and analyzed the NHANES data cycles released by the CDC after the 2005/2006 data cycle. CPSC staff issued a report in June 2015 concerning the NHANES data sets that had been released up to that point: ''Estimated Phthalate Exposure and Risk to Pregnant Women and Women of Reproductive Age as Assessed Using Four NHANES Biomonitoring Data Sets (2005/2006, 2007/2008, 2009/2010, 2011/2012)." *See* https://www.cpsc.gov/s3fs-public/NHANES-Biomonitoring-analysis-for-Commission.pdf . The June 2015 staff analysis reviewed the 2005/2006 NHANES data set to replicate the CHAP's methodology and reviewed the subsequent NHANES data sets through 2011/2012. Staff's analysis used women of reproductive age (WORA; 15-45 year of age) as the population of interest, because NHANES data sets after 2005/2006 did not have sufficient numbers of pregnant women to be statistically relevant. The

Commission published a notice of availability in the *Federal Register* seeking comment on the CPSC staff document. 80 FR 35939 (June 23, 2015).

In December 2016, the CDC released the NHANES 2013/14 data cycle. CPSC staff prepared a document with staff's analysis of the NHANES 2013/14 data cycle titled, ''Estimated Phthalate Exposure and Risk to Women of Reproductive Age as Assessed Using 2013/2014 NHANES Biomonitoring Data.'' *See* https://www.cpsc.gov/s3fs-public/Estimated%20Phthalate%20Exposure%20and%20Risk%20to%20Women%20of%20Reproductive%20Age%20as%20Assessed%20Using%202013%202014%20NHANES%20Biomonitoring%20Data.pdf. The Commission published a notice of availability in the *Federal Register* seeking comments on CPSC staff's February 2017 analysis of the NHANES 2013/14 data cycle. 82 FR 11348 (February 22, 2017).

D. Public Comments

The NPR, which published in the *Federal Register* on December 30, 2014, requested comments by March 16, 2015. 79 FR 78324 (Dec. 30, 2014). The Commission extended the comment period for an additional 30 days to April 15, 2015. 80 FR 14880 (March 20, 2015). Additionally, the Commission requested comments on each of the staff's analyses of more recent NHANES data. 80 FR 35939 (June 23, 2015); 82 FR 11348 (February 22, 2017). The Commission received 91 comments on the NPR and an additional 18 comments on CPSC staff's reports on more recent NHANES data cycles. The comments are available on *regulations.gov* under the docket: CPSC-2014-0033. Throughout this preamble, we discuss significant issues raised by these comments and CPSC's responses to those issues. As part of the briefing package that CPSC staff prepared for the Commission's consideration of this final rule, staff developed a more detailed summary of the public comments and staff's responses. These may be found at

Tab B of the staff's briefing package: [Insert link] At the end of each comment summary in this preamble, we provide, in parentheses, the number of the relevant and more detailed comment/response in Tab B of the staff's briefing package.

E. Final Rule

The Commission has considered the CHAP report, CPSC staff's analyses, and comments submitted on the NPR and staff's reports concerning later NHANES data cycles. CPSC staff prepared a briefing package for the Commission that provides staff's analysis of these materials and gives staff's recommendations for the final rule. Staff's briefing package is available at: [Insert link]. Based on consideration of these materials, the Commission issues this final rule, which is substantially the same as the proposed rule.

In the interest of clarity, the final rule restates the CPSIA's permanent prohibition on the manufacture for sale, offer for sale, distribution in commerce, or importation into the United States of any children's toys and child care articles that contain concentrations of more than 0.1 percent of DEHP, DIBP, or BBP.

The final rule continues the interim prohibition concerning DINP and expands that restriction to prohibit all children's toys (not just those that can be place in a child's mouth) and child care articles that contain concentrations of more than 0.1 percent of DINP. After reviewing the information presented by the CHAP, CPSC staff, and commenters, the Commission concludes that continuing the interim prohibition regarding DINP will ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety. The Commission also determines that expanding the prohibition regarding DINP to cover all children's toys, not just those that can be placed in a child's mouth, is necessary to protect the health of children.

The final rule also prohibits children's toys and child care articles that contain concentrations of more than 0.1 percent of DIBP, DPENP, DHEXP, and DCHP. After reviewing the information presented by the CHAP, CPSC staff, and commenters, the Commission concludes that this restriction on the four additional phthalates is necessary to protect the health of children.

The final rule adds a paragraph, not in the proposed rule, that repeats the statutory provision stating that the phthalates prohibitions apply to plasticized component parts of children's toys and child care articles, or other component parts of those products that are made of materials that may contain phthalates. *See* 15 U.S.C. 2057c(c). This addition does not make any substantive change, but it provides clarity by placing this statutory language in the regulation.

As was proposed, the final rule will take effect 180 days after publication in the *Federal Register* and will apply to products manufactured or imported on or after that date. The Commission's rationale for the final rule is explained in the following sections of this preamble.

II. Legal Authority

A. Summary of Legal Authority

Section 108 of the CPSIA provides the legal authority for this rule. As directed by section 108(b)(2), the Commission convened a CHAP to study the effects on children's health of phthalates and phthalate alternatives. The CPSIA directs the CHAP to examine "the full range of phthalates that are used in products for children," and to consider numerous issues specified in the statute (discussed further in section III.A of this preamble). As required by section 108(b)(2)(C), the CHAP prepared a report for the Commission that included recommendations to

the Commission concerning any phthalates not already subject to the permanent prohibition or phthalate alternatives that should be prohibited. 15 U.S.C. 2057c(b)(2)(C).

The CPSIA further directs that, within 180 days of receiving the CHAP's report, the Commission shall promulgate a final rule in accordance with section 553 of the APA. The Commission must "determine, based on such report, whether to continue in effect the [interim] prohibition . . . , in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." *Id*. 2057c(b)(3)(A). Additionally, the Commission must "evaluate the findings and recommendations of the Chronic Hazard Advisory Panel and declare any children's product containing any phthalates to be a banned hazardous product under section 8 of the Consumer Product Safety Act (15 U.S.C. 2057), as the Commission determines necessary to protect the health of children." *Id*. 2057c (b)(3)(B).

A violation of the permanent or interim prohibitions or any rule the Commission subsequently issues under section 108(b)(3) "shall be treated as a violation of section 19(a)(1) of the Consumer Product Safety Act." *Id*. 2057c (e). Additionally, section 108(f), concerning preemption, states that the permanent and interim prohibitions and the Commission's phthalates rule "shall be considered consumer product safety standards under the Consumer Product Safety Act." *Id*. 2057c (f).

Section 108 of the CPSIA sets out the criteria for the Commission's determinations in this rulemaking. Regarding phthalates subject to the interim prohibition, the Commission is to determine, based on the CHAP report, whether their continued regulation is needed "to ensure a reasonable certainty of no harm … with an adequate margin of safety." Regarding other children's products and other phthalates, the Commission is to evaluate the CHAP report and determine whether additional restrictions are "necessary to protect the health of children." 15

U.S.C. 2057c(b)(3). Congress required the Commission to use these criteria for the phthalates rulemaking.

B. Comments Regarding Legal Authority

Comments raised various issues concerning the Commission's legal authority for this rulemaking. These comments focused primarily on: the CPSIA's requirements for the CHAP, the CPSIA's requirements for the rulemaking, relevance of (and compliance with) the Information Quality Act (IQA), and compliance with requirements of the Administrative Procedure Act (APA). This section summarizes and responds to key issues raised by comments related to the Commission's legal authority. Tab B of staff's briefing package provides a more detailed discussion of the comments and responses. [Insert link]

1. The Information Quality Act

Comment: IQA Applicability: Several commenters asserted that the CHAP report and the phthalates rulemaking must comply with the Office of Management and Budget's (OMB's) Guidelines issued under the IQA and CPSC's guidelines. The commenters stated that the OMB's IQA Guidelines require that agencies' disseminations meet a basic standard of quality for objectivity, utility and integrity, and that these requirements apply to the CHAP report and to CPSC's rulemaking. The commenters also asserted that the CHAP report is "influential" under the IQA Guidelines because it meets the OMB standard for influential, *i.e.*, has "a clear and substantial impact on important public policies or private sector decisions."

Response: The IQA, Public Law 106-554, required OMB to draft guidelines regarding "the quality, objectivity, utility, and integrity of information … disseminated by Federal agencies" and required each agency to issue its own guidelines. OMB issued "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integration of Information

Disseminated by Federal Agencies" (OMB Guidelines), 67 FR 8452. The CPSC issued its Information Quality Guidelines (CPSC Guidelines) in October 2002, which substantially follow OMB's Guidelines.[1] As provided in CPSC's Guidelines, we are responding to comments on the NPR to address a commenter's request for correction under the IQA.

OMB's Guidelines apply to federal agencies that are subject to the Paperwork Reduction Act (PRA), 42 U.S.C. chapter 35. 67 FR 8453. This includes the CPSC. Both OMB's and CPSC's Guidelines apply to information that the agency "disseminates." OMB's Guidelines define the term "dissemination" to mean "agency initiated or sponsored distribution of information to the public," with several exclusions. Under OMB's Guidelines, if an agency releases information prepared by an outside party, but the agency then distributes the information "in a manner that reasonably suggests that the agency agrees with the information, this appearance of having the information represent agency views makes agency dissemination of the information subject to the guidelines." 67 FR 8454. As the commenters noted, the CHAP report was not prepared by CPSC but by a third party. However, in the NPR, CPSC based its recommendations on the CHAP report as required by section 108 of the CPSIA. Thus, we agree that OMB's and CPSC's Guidelines apply to the CHAP report.

As discussed in the following comments/responses, OMB's Guidelines require agencies to adopt a basic standard of information quality that includes "objectivity, utility, and integrity." OMB's Guidelines define "influential" as:

> "Influential", when used in the phrase "influential scientific, financial, or statistical information", means that the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions. Each

[1] CPSC Information Quality Guidelines. Available at: https://www.cpsc.gov/en/Research--Statistics/Information-Quality-Guidelines/.

> agency is authorized to define "influential" in ways appropriate for it given the nature and multiplicity of issues for which the agency is responsible.

67 FR 8460. The definition of "influential" places significant emphasis on the agency's discretion to determine what information is influential. The OMB Guidelines state that influential information is held to a higher standard and must have a high degree of transparency. Even if the CHAP report is considered "influential," it met the OMB Guidelines' provisions for such documents. As explained throughout this document, the CHAP was transparent about its data sources and processes. See the following comments and responses. (Comments 8.1 and 8.2).

Comment: Objectivity of CHAP report. Commenters asserted that the CHAP Report (and by extension, the rulemaking) does not meet the IQA Guidelines' standard of "objectivity." In addition, the commenters argued that, because the CHAP Report is influential information regarding risks to health, safety, or the environment, it "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 . . . .' " (Comment 8.3).

Response: The OMB Guidelines state: "'Objectivity' includes whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner." 67 FR 8459. According to the OMB Guidelines, this involves presenting the information within a proper context and identifying the sources of the information. *Id*. The OMB Guidelines further state: "In addition, 'objectivity' involves a focus on ensuring accurate, reliable, and unbiased information." In a scientific context, this means "using sound statistical and research methods." *Id*.

The CHAP report met the "objectivity" standard enunciated in the OMB Guidelines. The fact that the commenters might have conducted the analysis differently does not mean that the CHAP's analysis was not "objective." The CHAP report clearly set forth its data sources and noted that to assess studies, it used the criteria of reliability, relevance, and adequacy established by the Organisation for Economic Cooperation and Development. CHAP report at pp. 13-14. The CHAP held open meetings during the process of developing its analysis, inviting experts to present their latest research findings and taking submissions of a large volume of written material. The CHAP members were selected in accordance with section 28 of the CPSA through a process to ensure their independence from bias (*e.g.*, nominated by National Academy of Sciences; free from compensation by or substantial financial interest in a manufacturer, distributor or retailer of a consumer product; not employed by the federal government, with certain scientific/research related exceptions). The CHAP explained its choices, such as the decision to focus on the effects on male reproductive development, and the CHAP noted that this approach was consistent with a National Research Council (NRC) report.[2] Similarly, the CHAP explained its decision to conduct a cumulative risk assessment and explained the methodology that it used which, again, was consistent with one of the methods discussed in the NRC report.

For an analysis of risks to human health, safety, and the environment that an agency disseminates, OMB's Guidelines direct agencies to "adapt or adopt" the information quality principles of the SDWA. 67 FR 8460. The SDWA directs agencies to use: "(i) the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data)."

[2] NRC (2008).

Id. at 8457. The SDWA direction is very similar to the charge to the CHAP in section 108, which states, among other things, that the CHAP is to "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." 15 U.S.C. 2057c(b)(2)(B)(v). As our discussion in section III of this preamble demonstrates, the CHAP report met this direction.

Comment: IQA deficiencies as basis to invalidate rule. A commenter asserted that the CHAP report had numerous methodological flaws that violated the IQA and that these deficiencies would invalidate the phthalates rulemaking unless they are corrected because the proposed rule was premised almost entirely on the CHAP report. The commenter further asserted that OMB's IQA Guidelines are "binding" on agencies. (Comment 8.4).

Response: Elsewhere in this document and in Tab B of staff's briefing package, staff responds to the specific methodological "flaws" the commenter identifies. Regarding the legal point, we note that OMB's Guidelines are not legally enforceable requirements – guidelines, which are essentially interpretive rules, by their nature do not establish binding requirements. *See, e.g., U.S. Iowa League of Cities v. EPA*, 711 F.3d 844, 873 (8th Cir., 2013) ("interpretive rules do not have the force of law"). Notably, the IQA directed OMB to "issue guidelines . . . that provide policy and procedural guidance to Federal agencies." The IQA did not direct OMB or agencies to undertake substantive legislative rulemaking. Consolidated Appropriations Act of 2001, Pub. L. 06-554, 515 (codified at 44 U.S.C. 3516 Note). OMB's Guidelines repeatedly stress their flexibility, noting that they are not intended to be "prescriptive, 'one-size-fits-all'" and that OMB intends for agencies to "apply them in a common-sense and workable manner." 67 FR at 8452-53. The IQA established a binding requirement that OMB issue guidelines and

that each agency that is subject to the PRA must issue its own guidelines, but the guidelines themselves do not bind agencies. Courts that have examined the question of the legal status of the IQA have found that the IQA (and thus necessarily, OMB's guidelines) "creates no legal rights in any third parties." *Salt Inst. v. Leavitt*, 440 F.3d 156, 159 (4th Cir. 2006). *See Mississippi Comm. on Environmental Quality v. EPA*, 790 F.3d 138 (D.C. Cir. 2015) (dismissing argument that IQA created a legal requirement for EPA to use "best available science and supporting studies").

2. CPSIA Requirements for the CHAP

Comment: Review of all relevant data. Several commenters noted that the CPSIA directed the CHAP to "review all relevant data, including the most recent, best available . . . scientific studies . . . that employ objective data collection practices." A commenter asserted that the CHAP's "selective use and systematic mischaracterization of the data" did not meet this requirement. Commenters argued that the CHAP's reliance on the 2005/2006 NHANES data set, rather than later data sets that were available to the CHAP before the CHAP's stopping point (2007/2008, 2009/2010 and 2011/2012 data sets), violated the CPSIA's direction to review "all relevant data" and to include "the most recent" studies. The commenters asserted that the CHAP's failure to rely on later data sets is particularly important because, due to the drop in DEHP exposures, there has been a significant decline in total risk. One commenter asserted that the CHAP had ignored 32 relevant publications on phthalates. Other commenters stated that the CHAP's analysis "represents the cutting edge and most current and best available science," a significant improvement over methodologies currently used for government review of chemical risk that considered one chemical at a time. (Comments 7.8, 8.17, and 10.2).

Response: The CHAP used 2005/2006 NHANES data on pregnant women to assess phthalate exposure as part of the CHAP's cumulative risk analysis, to satisfy the CPSIA's charge to "examine the likely levels of children's, pregnant women's, and others' exposure to phthalates . . ." 15 U.S.C. 2057c(b)(2)(B)(iii). This data set was the most recent data on pregnant women available at the time the CHAP completed its analysis in July 2012, CHAP report at p. 31, and it was the last data set to include a larger sample of pregnant women. CPSC staff subsequently analyzed NHANES WORA data from 2007/2008 through 2013/2014 using the CHAP's analytical methodology.

The CHAP considered new scientific information published up to the end of 2012, and used standard and acceptable methods for study review, conducting an unbiased literature search and publication identification and in-depth review and reporting of the most important publications. Specifically, the CHAP included many elements of systematic review methods in its work. The CHAP used a defined literature search strategy and limited the search to studies published through 2012. The CHAP considered the quality, relevance, and weight of evidence (WOE) of individual studies. The CHAP described criteria for evaluating published studies, CHAP report at pp. 19–23, and the CHAP ensured that all studies and data were publicly available. The CHAP also described the criteria used to formulate its recommendations on individual phthalates and phthalate alternatives. *Id* at p. 79. The CHAP criteria included review of animal and human data, weight of evidence, study replication, human exposure, hazard, and risk. *Id.* at pp. 82–142. The CHAP conducted a thorough review of a large body of literature on a complex environmental health question using appropriate methods.

All current scientific publications and NHANES data sets have been analyzed by the CHAP and CPSC staff in preparation for the final rule. This fulfills the CPSIA's directive to review "all relevant data" and to include "the most recent" studies.

Regarding the assertion that the CHAP ignored 32 relevant publications, CPSC staff reviewed this claim. The CHAP cited approximately 250 articles using a systematic approach to select the most relevant and informative articles. Five of the 32 articles the commenter identified are not relevant because they considered effects that are not relevant to the CHAP's focus on male reproductive development (*e.g.*, onset of puberty in girls, estrogenic effects); they measured exposure, but not health effects; or did not accurately reflect exposure. The other 27 articles were review articles (which are considered secondary sources), several of which covered broad topics such as environmental chemicals. Staff's more detailed assessment of these publications is provided in the response to comment 7.8 at Tab B of the staff's briefing package.

Comment: Foreseeable use and likely exposure. Several commenters noted that 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." Commenters asserted that the CHAP failed to meet this requirement because the CHAP ignored the more recent data that shows a significant drop in DEHP exposure and the CHAP included permanent prohibitions involving phthalates in the analysis. (Comment 8.18).

Response: As explained, the 2005/2006 NHANES dataset that the CHAP used was the most recent data on pregnant women available at the time the CHAP completed its analysis in July 2012, CHAP report at p. 31, and included a larger sample of pregnant women. CPSC staff has since analyzed more recent NHANES data using the same methodology used by the CHAP

and using WORA as a surrogate for pregnant women because an insufficient number of pregnant women were sampled in the later data sets. The final rule considers the most recent NHANES data, as well as the CHAP report.

In accordance with the CPSIA's direction to the CHAP, the CHAP's cumulative risk analysis estimated phthalate exposure from all phthalates and all sources, not only toys and child care articles. Because the CPSIA prohibition covers only children's toys and child care articles, exposures to DEHP, DBP, and BBP still occur from other sources. Thus, the CHAP and subsequent staff analyses provide a robust assessment of the "likely levels" of current exposures to phthalates.

Comment: CPSIA direction to CHAP to conduct a cumulative risk assessment. One commenter stated that the CPSIA did not require the CHAP to conduct a cumulative risk assessment; the CHAP could have considered cumulative effects in a more general (qualitative) way. Other commenters asserted that a cumulative risk assessment was well within the CPSIA's direction to the CHAP, noting that the CPSIA provided a clear mandate to "review the toxicity of phthalates cumulatively" and to consider "the exposure to all sources of these chemicals." One comment from a group of commenters stated Congress specifically required the cumulative risk analysis. (Comment 8.19).

Response: Several provisions in section 108(b)(2) called on the CHAP to consider cumulative effects of phthalates. Specifically, the statute directed the 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";
- "consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates"; and

- "consider the cumulative effects of total exposure to phthalates, both from children's products and from other sources, such as personal care products."

Thus, the CPSIA required the CHAP to use some method to evaluate the health effects of multiple phthalates from multiple products. The statute did not specify that the only way to do this was through a cumulative risk assessment. However, nothing in the statute prohibited the CHAP from conducting a cumulative risk assessment. As explained in the CHAP report, and in the NPR, based on the CHAP's knowledge and expertise, the CHAP decided that a cumulative risk assessment was the most appropriate method to fulfill the direction given to the CHAP. Furthermore, the CHAP used a cumulative risk assessment approach that was consistent with recommendations from a National Academy of Sciences committee that was convened specifically to consider methods for assessing the cumulative risks from phthalates. Thus, the CHAP used its judgment and provided an explanation for its reasonable choice.

Comment: Applicability of the Federal Hazardous Substances Act. A commenter argued that the CPSIA required the CHAP to present its analysis in terms of the criteria stated in the FHSA, and the commenter asserted that the CHAP failed to do so. Similarly, a commenter asserted that the CHAP's risk assessment improperly included consideration of exposures to substances that are excluded from the FHSA's definition of "hazardous substance," such as foods and drugs. 15 U.S.C. 1261(f)(2). (Comments 8.27 through 8.29).

Response: The commenter bases its argument that the CHAP should have followed FHSA criteria on a phrase in CPSIA section 108 that also appears in the FHSA. However, neither section 108 nor the legislative history of that provision mentions the FHSA. Rather, section 108(b)(2)(B) provides detailed direction to the CHAP about the criteria that the CHAP is to consider in its examination. Moreover, section 108(f) states clearly that the statutory

prohibitions and the Commission's future phthalates rule "shall be considered consumer product safety standards under the Consumer Product Safety Act." It is not logical that Congress would expect the CHAP to apply FHSA criteria (without mentioning that statute) to provide a report to the Commission for a rule that is to be treated as a rule under the CPSA. In fact, section 108 established a unique procedure for phthalates, making it clear that Congress did not intend for the Commission to undertake rulemaking under the FHSA. The CHAP and the Commission followed the specific process and criteria set forth in section 108. The direction to the CHAP explicitly requires the CHAP to consider phthalates that are in products outside the CPSC's jurisdiction, directing the CHAP to consider effects "both from children's products and from other sources, such as personal care products." 15 U.S.C. 2057c(b)(2)(B)(iv). Many personal care products are considered cosmetics and are under the jurisdiction of the U.S. Food and Drug Administration (FDA). Congress thus intended for the CHAP's examination to be broader than just products under CPSC's authority, even though CPSC's rulemaking applies only to products under CPSC's jurisdiction.

3. CPSIA's Requirements for the Rulemaking

Comment: Commission's role regarding the CHAP report. Comments questioned the Commission's reliance on the CHAP report in the NPR. Commenters asserted that the Commission cannot merely codify or "rigidly adhere" to the CHAP report without applying the Commission's own judgment. To do so, they argued, would raise serious Constitutional questions by vesting government powers in a private entity and would also conflict with the CPSIA and sections 28 and 31 of the CPSA (*e.g.*, the word "advisory" in the CHAP). Another commenter stated that CPSC acted appropriately on the CHAP report, noting that "CPSC made

its own decision, issued its own proposed rule, and solicited public comment from industry and others on its proposed rule." (Comment 8.20).

Response: Section 108(b)(3) of the CPSIA requires that the Commission's rule concerning the interim prohibition be "based on" the CHAP report and requires the Commission to evaluate the findings and recommendations of the CHAP to determine whether to prohibit any other children's products containing any other phthalates. We agree that the statutory language does not require rigid adherence to the CHAP report and that the Commission cannot simply "rubber-stamp" the CHAP's recommendations. Rather, the CHAP report is advisory, and the Commission must use its judgment to decide on appropriate regulatory action in accordance with the specific criteria stated in section 108(b)(3)(A) and (B) and must consider public comments that the Commission received. This is exactly the process the Commission followed. The NPR summarized the CHAP report, including the CHAP's recommendations. 79 FR 78326-78330. The NPR presented CPSC staff's evaluation of the CHAP report and the Commission's assessment of the CHAP's recommendations. *Id*. 78330–78338. Additionally, CPSC staff reviewed more recent NHANES data and conducted an analysis of the CHAP's evaluation of exposure data. Staff reviewed and considered the comments submitted in response to the NPR and the NHANES data analysis to develop recommendations to the Commission. All of this information provides the basis for the Commission's decision on the final rule.

Comment: Meaning of "reasonable certainty of no harm." Several commenters addressed the meaning of the phrase "reasonable certainty of no harm." Some commenters asserted that the standard must be interpreted in the context of CPSC's other statutes and case law. In this view, the phrase essentially means "reasonably necessary to prevent or reduce an unreasonable risk of injury," as would be required for a consumer product safety rule the

Commission issues under sections 7, 8 and 9 of the CPSA. Commenters also discussed the level of certainty required for a "reasonable certainty of no harm." One commenter noted that the FDA uses a similar standard for food additives. One commenter stated that in the NPR, the CPSC has applied the standard essentially to require absolute certainty. In contrast, another commenter emphasized that the CPSIA calls for ensuring a "'reasonable certainty of *no* harm' (emphasis added)." (Comments 8.14, 8.22, 8.23, and 8.25).

Response: The requirements stated in section 108(b)(3) of the CPSIA, rather than sections 7, 8 and 9 of the CPSA, apply to this rulemaking. For the Commission to issue a consumer product safety rule under sections 7, 8 and 9 of the CPSA, the Commission must determine that the product presents an unreasonable risk of injury and that a rule is necessary to reduce or prevent the unreasonable risk. The term "unreasonable risk" does not appear anywhere in the criteria stated in section 108(b)(3) that the Commission is to use to determine appropriate phthalate regulations. Nothing in the legislative history of section 108 indicates that Congress intended the Commission to make "unreasonable risk" determinations. Nor is there any indication that Congress intended that the case law related to the Commission's rules issued under sections 7, 8 and 9 of the CPSA would apply to the phthalates rulemaking.

We are aware of two other statutory schemes that use somewhat similar language. The Food Quality Protection Act (FPQA) uses a similar phrase regarding tolerance levels for pesticide residue on food. That provision requires the U.S. Environmental Protection Agency (EPA) to "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue." 21 U.S.C. 346a(b)(2)(A)(ii)(I). Under the Federal Food, Drug, and Cosmetic Act (FDCA), food additives must be "safe." 21 U.S.C. 348. FDA has issued regulations that define "safe or safety" to mean

"that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions or use." In a very general sense, CPSC's approach on phthalates is consistent with FDA and EPA in that CPSC's evaluation is based on expert scientific opinion (the CHAP), takes into account the cumulative effect of the substance at issue (phthalates), and provides appropriate safety factors (*e.g.*, for inter- and intra-species uncertainties). However, because the pesticide tolerance and food additive schemes differ significantly from the CPSIA's phthalates provision, FDA's and EPA's approaches do not provide CPSC with more specific guidance on "reasonable certainty of no harm."

Regarding the level of certainty required, the language "ensure a reasonable certainty of no harm . . . with an adequate margin of safety" calls for a highly protective standard, but not 100 percent certainty of no harm. Congress required "a reasonable certainty of no harm," not an absolute certainty of no harm.

4. The APA's Requirements

Comment: Data and the CPSC's obligation under the APA. Some commenters argued that the Commission's reliance on certain data violated the APA. One commenter asserted that the NPR's reliance on "decade-old data" is not reasonable, and therefore, violates the APA. Some commenters stated that because the NPR "rests on outdated data," CPSC should withdraw the NPR, conduct a reanalysis with current exposure data, and re-propose the rule with a new comment period. In comments on CPSC staff's analysis of recent NHANES data, a commenter asserted that under the APA, "the Commission has an obligation to disregard the CHAP's report to the extent it is incorrect, unreasonable, inconsistent with existing CPSC policy, practice, regulations or governing statutes, or is based on data that is outdated or of poor quality." The commenter set out the minimum requirements of informal rulemaking: adequate

notice, sufficient opportunity for public to comment, and a final rule that is not arbitrary and capricious. (Comments 8.12 and 8.13).

Response: The NPR's reliance on the CHAP report and the data the CHAP used did not violate the APA. Rather, the Commission followed the CPSIA's direction to base the rulemaking on the CHAP report. As commenters requested, staff subsequently considered updated exposure data. As the CPSIA requires, the Commission's proposal regarding the interim prohibition was "based on the CHAP report," and in addition, the Commission evaluated the CHAP report to determine whether to prohibit any children's products containing any other phthalates. Additionally, as required by the CPSIA, the Commission followed the notice and comment procedures of the APA. For the final rule staff considered more recent exposure data than the CHAP used. Several commenters asked the Commission to do this additional work. Staff conducted two analyses of more recent NHANES biomonitoring data sets, posted reports of staff analyses on the CPSC website, and the Commission requested public comment on each analysis. 80 FR 35938 (June 23, 2015) and 82 FR 11348 (February 22, 2017). We agree that under section 553 of the APA, the Commission must evaluate the CHAP report along with comments submitted in response to the proposed rule and engage in reasoned decision making to issue a final rule. This is the approach the agency has taken. The Commission provided adequate notice in the NPR (describing the CHAP report, providing staff's evaluation of the CHAP report and explanation of, and reasons for, the proposed rule); provided sufficient opportunity for the public to comment (even extending the comment period and obtaining comment on the two staff reanalysis documents); and the Commission explains its reasoning for the final rule in this preamble and supporting documents.

Comment: Restriction involving DINP and compliance with APA: A commenter asserted that continuing the interim prohibition involving DINP is arbitrary and capricious (in violation of the APA) because:

- there is a reasonable certainty of no harm without such a prohibition (due to permanent prohibition involving DEHP);
- DINP contributes only a small fraction to overall risk;
- the endpoint of antiandrogenicity is likely inappropriate;
- it is questionable that DINP should be included in a cumulative risk assessment;
- it is questionable that a cumulative risk assessment provides a reasonable basis for a regulatory decision;
- DEHP levels have dropped so that the Hazard Index (HI) is now well below one; and
- even using the 2005/2006 NHANES data, the contribution of DINP to the overall HI is minimal and the major source of exposures is diet - children's products account for only a small fraction of overall HI.

In contrast, another commenter stated that the CHAP's recommendation and the Commission's proposal to permanently prohibit children's toys and child care articles containing more than 0.1 percent of DINP are justified. The commenter stated that data indicating that DINP is a potential health risk have gotten stronger since release of the CHAP report. (Comment 8.16).

Response: In general, the APA requires that agencies' rulemaking be based on reasoned decision making. Staff's briefing package explains the reasons for staff's recommendations, satisfying this threshold requirement. The specific issues the commenter raised about regulation

of DINP and the apparent reductions over time in exposure to DEHP are addressed in detail in section IV.D.1.a. of this preamble.

III. The CHAP

A. CPSIA Direction

The CPSIA directed the Commission to convene a 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." 15 U.S.C. 2057c (b)(2). The statute provides very specific direction to the CHAP regarding its work. The CHAP must:

> complete an examination of the full range of phthalates that are used in products for children and shall—
>
> - examine all of the potential health effects (including endocrine disrupting effects) of the full range of phthalates;
> - consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates;
> - 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;
> - consider the cumulative effect of total exposure to phthalates, both from children's products and from other sources, such as personal care products;
> - 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;

- consider the health effects of phthalates not only from ingestion but also as a result of dermal, hand-to-mouth, or other exposure;
- consider the level at which there is a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals and their offspring, considering the best available science, and using sufficient safety factors to account for uncertainties regarding exposure and susceptibility of children, pregnant women, and other potentially susceptible individuals; and
- consider possible similar health effects of phthalate alternatives used in children's toys and child care articles.

Id. 2057c(b)(2)(B). In its final report, the CHAP is required to recommend to the Commission whether any "phthalates (or combinations of phthalates)" in addition to those permanently prohibited, including the phthalates covered by the interim prohibition or phthalate alternatives, should be declared banned hazardous substances. *Id*. 2057c(b)(2)(C).

B. The CHAP's Process

The CHAP's process was open and transparent. The CHAP met in public session (and webcast) seven times and met via teleconference (also open to the public) six times.[3] A record of the CHAP's public meetings, including video recordings and information submitted to the CHAP, as well as the final CHAP report, are available on the CPSC website.[4]

[3] The CHAP met in one closed meeting as part of the peer review process, January 28-29, 2015.
[4] http://www.cpsc.gov/chap.

At a meeting on July 26-28, 2010, the CHAP heard testimony from the public, including testimony from federal agency representatives, who discussed federal activities on phthalates. The CHAP also invited experts to present their latest research findings at the meeting in July 2010 and during subsequent meetings. Members of the public who presented testimony to the CHAP at the July 2010 meeting included manufacturers of phthalates and phthalate substitutes, as well as representatives of non-governmental organizations. In addition to oral testimony, the manufacturers and other interested parties submitted an extensive volume of toxicity and other information to the CHAP and the CPSC staff. All submissions given to CPSC staff were provided to the CHAP.

Although the CPSIA did not require peer review of the CHAP's work, at the CHAP's request, four independent scientists peer reviewed the draft CHAP report. CPSC staff applied the same criteria for selecting the peer reviewers as is required for the CHAP members.[5] The CHAP report was due to the Commission on April 13, 2012. The CHAP submitted the final report to the Commission on July 18, 2014.

C. The CHAP Report

1. Health Effects

The CHAP reviewed all of the potential health effects of phthalates. The CHAP explained that, although phthalates cause a wide range of toxicities, the CHAP focused on male reproductive developmental effects (MRDE) in part because this is the most sensitive and extensively studied endpoint for phthalates. The CHAP noted that this focus was consistent with

[5] Peer reviewers were nominated by the National Academy of Sciences. Peer reviewers did not receive compensation from, nor did they have a substantial financial interest in, any of the manufacturers of the products under consideration. In addition, the peer reviewers were not employed by the federal government, except the National Institutes of Health, the National Toxicology Program, or the National Center for Toxicological Research.

a 2008 report from the National Research Council.[6] The CHAP systematically reviewed literature on phthalate developmental and reproductive toxicology. CHAP report, at pp. 1-2 and 12-13. The CHAP found that "[s]tudies conducted over the past 20 years have shown that phthalates produce a syndrome of abnormalities in male offspring when administered to pregnant rats during the later stages of pregnancy." *Id.* at p. 15. The CHAP explained its approach to selection of data so that its analysis would be based on the most appropriate and reliable toxicological data. *Id.* at pp. 19-22. The CHAP stated that this collection of interrelated abnormalities, known as the "rat phthalate syndrome," is characterized by various effects on the male reproductive system: malformations of the testes, prostate, and penis (hypospadias); undescended testes; reduced anogenital distance (AGD), and retention of nipples.[7] Male pups also have reduced fertility as adults. The CHAP noted that only certain phthalates produce these abnormalities, phthalates with certain structural characteristics (three to seven, or eight, carbon atoms in the backbone of the alkyl side chain). The CHAP referred to these phthalates as "active" or "antiandrogenic" phthalates. *Id.* at pp. 15-16.

The CHAP noted that, although there is a great deal of information on phthalate syndrome in rats, there is relatively little on the phthalate syndrome in other animal species. The CHAP reviewed the existing data-exposing species, such as rabbits, mice, and marmosets, to phthalates. The CHAP concluded that these studies with animals other than rats show that most animals tested are more resistant to phthalates than rats, but due to the limitations on these studies (*e.g.*, small number of animals exposed, only one phthalate, only one dose, high

[6] NRC recommended, for example, that it is appropriate to perform a phthalate cumulative risk assessment for MRDE (phthalate syndrome); the cumulative risk assessment should consider all endpoints associated with MRDE or, alternatively, one sensitive endpoint such as reductions in testosterone. NRC also recommended using dose addition, a hazard index approach, assuming that mixture effects occur at low-doses, and including other (non-phthalate) antiandrogens.

[7] Nipple retention does not normally occur in rodents, as it does in humans.

experimental variation), the CHAP found that "studies in rats currently offer the best available data for assessing human risk." *Id*. at p. 18.

The CHAP reviewed, and discussed in its report, studies examining the mechanism by which phthalates produce adverse effects. The CHAP concluded that the phthalate syndrome effects are largely due to the suppression of testosterone production, as well as reduced expression of the insulin-like hormone 3 gene. *Id.* at pp. 18-19.

In addition to studies on animals, the CHAP also reviewed studies on the effect that exposure to phthalates has on human health (epidemiological studies). The CHAP noted that rat phthalate syndrome resembles testicular dysgenesis syndrome (TDS) in humans. TDS includes poor semen quality, reduced fertility, testicular cancer, undescended testes, and hypospadias.[8] CHAP report at p. 2. The CHAP concluded that studies provide human data linking prenatal exposure to phthalates with certain effects on male reproductive development (such as reduced anogenital distance,[9] reduced sperm quality and infertility in male infants). In addition, the CHAP discussed studies that found associations between prenatal or neonatal exposure to phthalates and reductions in mental and psychomotor development and increases in attention deficits and behavioral symptoms in children. *Id.* pp. 27-33; Appendix C.

2. *Exposure*

The CHAP assessed human exposure to phthalates by two different, but complementary, methods: human biomonitoring (HBM) and exposure-scenario analysis. HBM relies on measurements of phthalate metabolites in human urine to estimate exposure to phthalates. *Id.* at pp. 34-48; Appendix D. The CHAP used two data sources for HBM: NHANES and the Study for Future Families (SFF). NHANES is conducted by the CDC, and measures phthalates and

[8] A malformation of the penis.
[9] Distance between the anus and genitals, which is greater in males than in females.

other chemicals in human urine and blood in a statistically representative sample of thousands of U.S. residents. The CHAP used data from NHANES to estimate phthalate exposures in pregnant women and women of reproductive age (WORA). Because NHANES does not measure phthalate metabolites in children younger than 6 years old, the CHAP used measurements from the SFF to obtain exposure estimates for infants. SFF is a study of mother-child pairs, funded by the National Institutes of Health (NIH) and the EPA. The CHAP used this HBM data to derive daily intake (DI) estimates to use in its risk assessment calculations. The CHAP used the 2005/2006 NHANES data cycle in its analysis. The SFF data are from 1999 to 2005. From the HBM data, the CHAP concluded that "exposure to phthalates in the United States (as worldwide) is omnipresent. The U.S. population is co-exposed to many phthalates simultaneously." *Id.* at p. 37. The CHAP also noted that, because the data indicate that sources and routes of exposure among high- and low-molecular weight phthalates are similar, it is highly likely that substitution of one phthalate will lead to increased exposure to another similar phthalate. *Id*.

The HBM data do not measure the sources of people's exposure to phthalates. For this, the CHAP used a scenario-based exposure assessment. *Id*. at pp. 49-60; Appendix E. The CHAP used estimations of phthalate concentrations in various sources to predict exposures to subpopulations (pregnant women/WORA, infants, toddlers, and children). For the scenario-based exposure assessment, the CHAP estimated the DINP exposure that would occur if DINP were allowed in toys and child care articles. The CHAP found that for most phthalates, food, rather than children's toys or child care articles, is the primary source of exposure for women and children. The CHAP examined exposures to various phthalates from these sources. The CHAP found that infants, toddlers, and children were primarily exposed to DINP, DEHP, and

DIDP. For infants, exposure to DINP was primarily from diet, but exposure was also due to DINP in teethers and toys. *Id.* at pp. 50-51.

3. Phthalates Risk Assessment

a. Cumulative Risk Assessment

In accordance with the CPSIA's direction, the CHAP considered health effects of phthalates "in combination with other phthalates." 15 U.S.C. 2057c(b)(2)(B)(ii). The CHAP found, based on published studies, that active phthalates act in an additive fashion. That is, exposures to multiple phthalates at lower doses act in concert to produce the same effect as a higher dose of a single phthalate. The CHAP stated: "Experimental data on combination of effects of phthalates from multiple studies (*e.g.*, Howdeshell *et al.* (2008)) provide strong evidence that dose addition can produce good approximations of mixture effects when the effects of all components are known." *Id*. at p. 61. The CHAP also noted that, in addition to phthalates, other chemicals, including certain pesticides and preservatives, add to the male reproductive effects of phthalates. CHAP report at pp. 26-27. Due to the additive effects of certain phthalates, the CHAP determined that it is appropriate to conduct a cumulative risk analysis to assess the antiandrogenic phthalates the CHAP identified. *Id.*

For its cumulative risk assessment, the CHAP used a Hazard Index (HI) approach which, the CHAP noted, is widely used in cumulative risk assessments of chemical mixtures. *Id.* To determine the HI, one first calculates the hazard quotient (HQ) for each chemical and then adds the HQs together. The "HQ" is generally defined as the ratio of the potential exposure to a substance and the level at which no adverse effects are expected. If the HQ is less than one, the expectation is that no adverse effects will result from exposure; but if the HQ is greater than one, adverse effects are possible. Rather than use acceptable daily intakes (ADI) or reference doses

(RfDs) as the denominator of HQs, the CHAP used "potency estimates for antiandrogenicity" (PEAAs). The PEAA is an estimate of the level of exposure at which the risk of antiandrogenic effects is considered negligible. The CHAP estimated a PEAA for each phthalate by dividing the MRDE "antiandrogenic" point of departure (POD; toxicity endpoint) by an uncertainty factor (UF). The CHAP used three sets of PEAAs (the CHAP refers to these as Cases) to evaluate the impact of assumptions in calculating the HI. *Id*. at pp. 61-65.

The CHAP calculated the HI per woman and infant, using the NHANES data on pregnant women (representing exposure to the fetus) and the SFF data on children. The CHAP found that roughly 10 percent of pregnant women in the U.S. population have HI values that exceed 1.0 (pregnant women had median HIs of about 0.1 (0.09 to 0.14), while the 95th percentile HIs were about 5, depending on which set of PEAAs was used. The CHAP found that 4-5 percent of infants have HI values that exceed 1.0 (infants had median HIs about 0.2, while the 95th percentiles were between 0.5 and 1.0). *Id.* at p. 65 and Table 2.16. Based on this cumulative risk assessment, the CHAP recommended that phthalates that induce antiandrogenic effects (DINP, DIDP, DPENP, DHEXP, and DCHP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1 percent. *Id.* at pp. 7-8.

Regarding the HQs for the individual phthalates, the CHAP found that DEHP dominated, "with high exposure levels and one of the lowest PEAAs." *Id*. at p. 65. HQ values were similar for three phthalates (DBP, BBP, and DINP), while DIBP had the smallest HQs. *Id*.

b. Risks in Isolation

In accordance with the CPSIA's direction, the CHAP also considered the risks of phthalates in isolation. 15 U.S.C. 2057c(b)(2)(B)(ii). The CHAP used a margin of exposure (MOE) approach to assess the risks in isolation. CHAP report at p. 69. The MOE is the "no

observed adverse effect level" (NOAEL) of the most sensitive endpoint in animal studies divided by the estimated exposure in humans. Higher MOEs indicate lower risks. Generally, MOEs greater than 100 to 1,000 are adequate to protect public health. *Id.* The CHAP found that, with the exception of DEHP, for all phthalates that it evaluated in isolation, the MOEs were within acceptable ranges. *Id*. at pp. 82-121.

4. CHAP's Recommendations to the Commission

a. *Phthalates Subject to the Interim Prohibition*

Diisononyl phthalate (DINP)

The CHAP recommended that the Commission permanently prohibit the use of DINP in children's toys and child care articles at levels greater than 0.1 percent. The CHAP explained that, although DINP is less potent than other active phthalates, it induces antiandrogenic effects in animals, and therefore, DINP can contribute to the cumulative risk from other antiandrogenic phthalates. *Id.* at pp. 95-99.

The CHAP explained that studies exposing rats to DINP during the critical period of fetal development showed effects on male reproductive development. The CHAP stated: "Five such studies have shown that DINP exposure in rats during the perinatal period is associated with increased incidence of male pups with areolae and other malformations of androgen-dependent organs and testes (Gray *et al.,* 2000), reduced testis weights before puberty (Matsutomi *et al.*, 2003), reduced AGD (Lee *et al.*, 2006), increased incidence of multinucleated gonocytes, increased nipple retention, decreased sperm mobility, decreased male AGD, and decreased testicular testosterone (Boberg *et al.*, (2011)), and reduced fetal testicular testosterone production and decreased StAR and Cyp11a mRNA levels (Adamson *et al.*,2009; Hannas *et al*., 2011b)." *Id*. at pp. 96-97.

The CHAP report discussed the CHAP's determination of a NOAEL for DINP. *Id.* at pp. 97-98. The CHAP stated:

> Taken together, the data from Boberg *et al*. (2011), Hannas *et al*. (2011b), and Clewell *et al*. (2013a; 2013b) indicate that the developmental NOAEL, based on 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. However, the CHAP also wants to point out that a simple extrapolation based upon relative potencies (as described in Hannas *et al*., 2011b) with 2.3-fold lesser potency of DINP than DEHP (in terms of fetal testicular T reduction) would lead to a NOAEL of 11.5mg/kg-d for DINP. This scenario is reflected in case 2 of the HI approach.

Id. at p. 98. Regarding exposure, the CHAP observed: "DINP has been used in children's toys and child care articles in the past." *Id.* The CHAP noted that metabolites of DINP have been detected in urine samples in NHANES surveys. *Id.*

Considering risk in isolation (following the MOE approach), the CHAP found MOEs that are generally considered adequate for public health. For male developmental effects, in infants (using the SFF study) the CHAP stated that the total exposure ranged from 640 to 42,000, using 95th percentile estimates of exposure. For pregnant women (using NHANES data), the CHAP stated that the MOE for total DINP exposure ranged from 1000 to 68,000. The CHAP stated: "Typically, MOEs exceeding 100-1000 are considered adequate for public health; however, the cumulative risk of DINP with other antiandrogens should also be considered." *Id.* at p. 99. The CHAP also considered the effects of DINP on the liver, and it found that the MOEs were within an acceptable range.

In making its recommendation to the CPSC concerning DINP, the CHAP stated: "The CHAP recommends that the interim ban on the use of DINP in children's toys and child care articles at levels greater than 0.1% be made permanent. This recommendation is made because DINP does induce antiandrogenic effects in animals, although at levels below that for

other active phthalates, and therefore can contribute to the cumulative risk from other antiandrogenic phthalates." *Id.*

Di-*n*-octyl phthalate (DNOP)

The CHAP reviewed data on DNOP. *Id.* at pp. 91-95. The CHAP found that, although DNOP is a potential developmental toxicant (causing supernumerary ribs) and a potential systemic toxicant (causing adverse effects on the liver, thyroid, immune system and kidney), "DNOP does not appear to possess antiandrogenic potential." The CHAP estimated that MOEs for DNOP for infants and toddlers ranged from 2,300 to 8,200. The CHAP concluded: "because the MOE in humans are likely to be very high, the CHAP does not find compelling data to justify maintaining the current interim ban on the use of DNOP in children's toys and child care articles." The CHAP recommended that the Commission lift the interim prohibition with regard to DNOP, but also recommended that "agencies responsible for dealing with DNOP exposures from food and child care products conduct the necessary risk assessments with a view to supporting risk management steps." *Id.* at p. 95.

Diisodecyl phthalate (DIDP)

The CHAP reviewed data on DIDP. *Id.* at pp. 100-105. The CHAP found that, although DIDP is a potential developmental toxicant (causing supernumerary ribs) and a potential systemic toxicant (causing adverse effects on the liver and kidney), "DIDP does not appear to possess antiandrogenic potential." The CHAP estimated the MOEs for DIDP range from 2,500 to 10,000 for median intakes and from 586 to 33,000 for 9th percentile intakes. *Id.* at p. 104. The CHAP found that DIDP's MOEs in humans are likely to be relatively high. The CHAP stated: "The CHAP does not find compelling data to justify maintaining the current interim ban on the use of DIDP in children's toys and child care articles." The CHAP recommended that the

Commission lift the interim prohibition with regard to DIDP, but suggested that "agencies responsible for dealing with DIDP exposures from food and child care products conduct the necessary risk assessments with a view to supporting risk management steps." *Id.* at pp. 104-105.

b**.** *Other Phthalates*

Due to their adverse effect on male reproductive development (and thus their contribution to the cumulative risk from other antiandrogenic phthalates), the CHAP recommended that the Commission permanently prohibit the use of four additional phthalates at levels greater than 0.1 percent in children's toys and child care articles.

Diisobutyl phthalate (DIBP)

The CHAP found that DIBP is similar in toxicity to DBP, one of the phthalates subject to the CPSIA's permanent prohibition. The CHAP reviewed studies that found that exposure to DIBP had effects on male reproductive development. The CHAP stated: "Six studies in which rats were exposed to DIBP by gavage during late gestation showed that this phthalate reduced AGD in male pups, decreased testicular testosterone production, increased nipple retention, increased the incidence of male fetuses with undescended testes, increased the incidence of hypospadias, and reduced the expression of P450scc, ins13, genes related to steroidogenesis, and StAR protein (Saillenfait *et al.*, 2006; Borch *et al*., 2006a; Boberg *et al*., 2008; Howdeshell *et al*., 2008; Saillenfait *et al*., 2008; Hannas *et al.*, 2011b)." *Id.* at p. 110.

Regarding exposure, the CHAP noted that DIBP has been detected in some toys during routine CPSC compliance testing. The CHAP stated: "DIBP is too volatile to be used in PVC but is a component in nail polish, personal care products, lubricants, printing inks, and many

other products." *Id*. at 111. Metabolites of DIBP have been detected in human urine in NHANES surveys and in Germany.

Assessing risk, the CHAP found: "The margins of exposure (95th percentile total DIBP exposure) for pregnant women in the NHANES study ranged from 5,000 to 125,000. For infants in the SFF study, the MOE (95th percentile total DIBP exposure) ranged from 3,600 to 89,000." *Id.* Although these MOEs are within an acceptable range, the CHAP stated that the cumulative risk should be considered. *Id*. Explaining its recommendation concerning DIBP, the CHAP stated:

> Current exposures to DIBP alone do not indicate a high level of concern. DIBP is not widely used in toys and child care articles. However, CPSC has recently detected DIBP in some children's toys. Furthermore, the toxicological profile of DIBP is very similar to that of DBP, and DIBP exposure contributes to the cumulative risk from other antiandrogenic phthalates. The CHAP recommends that DIBP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1%.

Id. at pp. 111-112.

Di-*n*-pentyl phthalate (DPENP)

Although DPENP is not widely used, the CHAP found that it is the most potent phthalate with respect to developmental toxicity. According to the CHAP, two studies (Howdeshell *et al.* (2008) and Hannas *et al*. (2011a)) found that DPENP exposure reduced fetal testicular testosterone production, StAR Cyp11a, and ins13 gene expression, and increased nipple retention. *Id*. at p. 112. The CHAP stated that DPENP is not currently found in children's toys or child care articles and is not widely found in the environment. *Id.* at p. 113. In its recommendation, the CHAP stated: "The CHAP recommends that DPENP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1%. The toxicological profile of DPENP is very similar to that of the other antiandrogenic phthalates, and DPENP exposure contributes to the cumulative risk." *Id.*

Di-*n*-hexyl phthalate (DHEXP)

According to the CHAP, a National Toxicology Program review of DHEXP in 2003 reported that based on the limited data available at that time, DHEXP is a developmental toxicant at high doses (9900 mg/kg-d), but the data were not adequate to determine an NOAEL or LOAEL. The CHAP stated that since then, "one developmental toxicity study has reported that DHEXP exposure reduced the AGD in male pups in a dose-related fashion and increased the incidence of male fetuses with undescended testes (Saillenfait *et al.,* 2009a)." *Id*. at p. 114. The CHAP report stated: "Saillenfait *et al*. observed reproductive tract malformations, including hypospadias, undeveloped testes, and undescended testes, in young adult male rats exposed prenatally to doses of 125 mg/kg-d DHEXP or greater (Saillenfait *et al*., 2009b)." *Id.* at p. 115.

The CHAP stated that DHEXP is currently not found in children's toys or child care articles and is not widely found in the environment. It is primarily used in the manufacture of PVC and screen printing inks and is also used "as a partial replacement for DEHP." *Id.* at p. 116.

Regarding risk, the CHAP stated: "DHEXP is believed to induce developmental effects similar to those induced by other active phthalates. Due to low exposure, current risk levels are believed to be low." *Id*. The CHAP recommended that DHEXP be permanently banned from use in children's toys and child care articles at levels greater than 0.1 %. The CHAP stated: "The toxicological profile of DHEXP is very similar to that of the other antiandrogenic phthalates, and DHEXP exposure contributes to the cumulative risk." *Id.*

Dicyclohexyl phthalate (DCHP)

The CHAP found that studies on DCHP showed effects on male reproductive development. The CHAP report states: "Two studies in rats exposed to DCHP by gavage during

late gestation showed that this phthalate prolonged preputial separation, reduced AGD, increased nipple retention, and increased hypospadias in male offspring (Sallenfait *et al*, 2009a; Yamasaki *et al.*, 2009). One study in rats exposed to DCHP in the diet showed that DCHP decreased the AGD and increased nipple retention in F1 males (Hoshino *et al*., 2005)." *Id*. at 116-117. The CHAP stated that DCHP is currently not found in children's toys or child care articles and is not widely found in the environment. FDA has approved it "for use in the manufacture of various articles associated with food handling and contact." DCHP is also a component of hot melt adhesives. *Id*. at 117. The CHAP stated: "DCHP induces developmental effects similar to other active phthalates. Due to low exposure, current risk levels are believed to be low." The CHAP recommended that DCHP be permanently banned from use in children's toys and child care articles at levels greater than 0.1 %. *Id.* at p. 118.

c. Phthalate Alternatives

The CPSIA also directed the CHAP to consider health effects of phthalate alternatives and to include in its report to the Commission recommendations for any phthalate alternatives that should be banned. 15 U.S.C. 2057c(b)(2)(B)(viii) and 2057c(b)(2)(C). The CPSIA defines "phthalate alternative" as "any common substitute to a phthalate, alternative material to a phthalate, or alternative plasticizer." *Id.* 2057c(g)(2)(A). Accordingly, the CHAP also reviewed phthalate alternatives. CHAP report at pp. 121-142. The CHAP did not recommend banning any phthalate alternatives. We also note that the Commission's rulemaking authority under section 108 of the CPSIA does not extend to phthalate alternatives. 15 U.S.C. 2057c(b)(3).

D. Comments Regarding the CHAP

Comments concerning the substance of the CHAP's analysis are discussed in section IV of this preamble. This section covers comments concerning the CHAP's process.

1. Peer Review

Comment: Applicability of OMB Peer Review Bulletin. Commenters asserted that the CHAP report was subject to OMB's peer review bulletin, that it qualifies as a "highly influential" scientific assessment, and that it should be subject to a peer review that comports with the highest standards for transparency, openness, and objectivity, as outlined in the OMB's peer review bulletin. (Comments 8.6 and 8.7).

Response: The OMB's bulletin, *Final Information Quality Bulletin for Peer Review* (70 FR 2664 (Jan. 14, 2005)) (OMB Bulletin), requires "to the extent permitted by law," that agencies conduct peer review on all influential scientific information that the agency intends to disseminate. The OMB Bulletin defines "influential scientific information" as "scientific information the agency reasonably can determine will have or does have a clear and substantial impact on important public policies or private sector decisions." *Id*. at 2675. We believe that the CHAP report could be considered "influential" under this definition. According to the OMB Bulletin, "dissemination" means "agency initiated or sponsored distribution of information to the public." *Id*. at 2674. The preamble to the OMB Bulletin notes that the OMB Bulletin "does not directly cover information supplied by third parties (*e.g*., studies by private consultants, companies and private, non-profit organizations, or research institutions such as universities). However, if an agency plans to disseminate information supplied by a third party (*e.g*., using this information as the basis for an agency's factual determination that a particular behavior causes a disease), the requirements of the OMB Bulletin apply, if the dissemination is 'influential.'" *Id.* at 26676. Although the CHAP report was written by a third party, we believe that by relying on the CHAP report in support of the NPR, the Commission disseminated the CHAP report.

Under the Bulletin, additional requirements apply to "highly influential scientific assessments," which the Bulletin defines as a scientific assessment that:

(1) could have a potential impact of more than $500 million in any year, or

(2) is novel, controversial, or precedent-setting or has significant interagency interest.

One might consider the CHAP report to be a "novel, controversial, or precedent-setting" report that it could be of "significant interagency interest" because, as the CHAP report indicates, many of the products that contain phthalates (*e.g.*, food and cosmetics) fall under other agencies' jurisdiction.

Comment: Compliance with OMB Peer Review Bulletin. Some commenters asserted that the CHAP failed to adhere to the OMB Bulletin requirements for the peer review of a highly influential scientific assessment. In contrast, other commenters supported the peer review process used for the CHAP report, stating that the peer review was part of an open and transparent process. (Comment 8.7).

Response: The peer review process used for the draft CHAP report complied with the additional requirements for highly influential scientific assessments. For example, as noted by some commenters, the peer review of the draft report was conducted by four independent scientists, using the same criteria for selecting the peer reviewers (by nomination of the National Academy of Sciences) required for selecting the CHAP members. The peer reviewers were not employed by manufacturers of the products under consideration or by the federal government, except the National Institutes of Health, the National Toxicology Program, or the National Center for Toxicological Research.

Additionally, the CPSC made public: the identity of the peer reviewers, the charge to the peer reviewers, the draft report that was reviewed, and the peer reviewers' comments. CPSC

posted all of the information on the CPSC website at the same time the final CHAP report was released to the public; and the information is available on the CPSC's website, in accordance with the additional requirements for a highly influential scientific assessment.[10] Thus, the public would have ample opportunity to see the concerns reviewers raised and how the CHAP addressed the concerns.

Finally, regarding public comment, as discussed in the next response, the peer review process used by CPSC complied with the OMB Bulletin.

Comment: Peer review and public comment. Commenters asserted that as a "highly influential" assessment, the CHAP report should have been subject to an open public comment period, as set forth in the OMB Bulletin. Commenters asserted that the Bulletin establishes strict minimum requirements for the peer review of highly influential scientific assessments, including a requirement that an agency "make the draft scientific assessment available to the public for comment at the same time it is submitted for peer review . . . and sponsor a public meeting where oral presentations on scientific issues can be made to the peer reviewers by interested members of the public." Commenters asserted that this would have allowed for comment on flaws in the CHAP's analysis. (Comment 8.8).

Response: The OMB Bulletin states: "The selection of an appropriate peer review mechanism for scientific information is left to the agency's discretion." *Id*. at 2665. It also advises: "[a]gencies are directed to choose a peer review mechanism that is adequate, giving due consideration to the novelty and complexity of the science to be reviewed, the relevance of the information to decision making, the extent of prior peer reviews, and the expected benefits and costs of additional review." *Id.* at 2668. We also note that CPSC staff consulted with OMB staff

[10] *See* https://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/The-Consumer-Product-Safety-Improvement-Act/Phthalates/Chronic-Hazard-Advisory-Panel-CHAP-on-Phthalates/.

before finalizing the peer review plan for the CHAP report, as recommended by the OMB Bulletin.

Although the OMB Bulletin uses the term "requirements," the document emphasizes the intent to allow agencies flexibility in determining appropriate methods of peer review, *id*. at 2665, and the OMB Bulletin is a guidance document. The OMB Bulletin states that it "is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity." *Id*. at 2677. *See Family Farm Alliance v. Salazar*, 749 F. Supp. 2d 1083 (E.D. Cal. 2010) (finding that a claim that the U.S. Fish and Wildlife Service had not conducted appropriate peer review was not judicially reviewable). Although the draft CHAP report was not provided to the public for comment at the time that the CHAP submitted the report for peer review, the agency was not required to do so, nor was the agency required to sponsor a public meeting on the peer review. CPSC staff and the CHAP members reasonably desired that the report should achieve a high level of quality before it was released to the public. Moreover, as explained in the next response, the CHAP report was developed through a very open public process that provided for public input as the CHAP was developing its report.

2. CHAP's Transparency and Openness

Comment: Transparency and openness of CHAP's process. Several commenters stated generally that the process for the CHAP report was not open and transparent, but had been conducted behind closed doors. Other commenters questioned the transparency of particular aspects of the CHAP report, such as the methods used to review the scientific health evidence and assess cumulative risk. In contrast, other commenters asserted that the CHAP process was a sound and fair process, adding that the process was highly public, and that the CHAP considered

public comments and written submissions (including from industry representatives who charged that the process was not open). (Comments 8.8 and 10.3).

Response: The CHAP's process for developing its report was open and transparent throughout. The CHAP developed its approach in public during seven public meetings and six public teleconference calls. During these public meetings, the CHAP discussed the methods that the CHAP would use to conduct the cumulative risk assessment. CPSC provided a page on its website to post all CHAP-related information. All of the data submitted to the CHAP, CPSC contractors' reports, and peer-reviewed staff reports used by the CHAP were posted on the CPSC's public website. The CPSC's website also included correspondence submitted to CPSC concerning the CHAP's work. In fact, the CHAP elected not to use industry studies on DINX and DPHP, for the very reason that the manufacturer would not make the toxicology studies available to the public. NHANES data (which the CHAP relied on) are available to the public from the CDC. Once the CHAP transmitted its final report to the Commission, CPSC posted the final report, the draft report that had been submitted for peer review, and peer reviewers' comments. The CHAP considered all subject matter expert comments from the peer review of the CHAP draft report. The initial pages of the CHAP report outlined changes to the CHAP report resulting from the peer reviewers' comments.

3. Weight of Evidence and Completeness of CHAP's Review

Comment: Nature of CHAP's review. Some commenters stated that the CHAP did not, but should have, conducted a systematic review and/or followed a weight of evidence (WOE) approach. Various commenters asserted that the CHAP should have: employed a consistent WOE framework; demonstrated how the CHAP graded, rated, and interpreted the epidemiology

studies; and specified a clear and systematic approach for addressing the uncertainties of the data equally. (Comment 10.1).

Response: The CHAP used the WOE approach in two different manners. First, the CHAP wrote a "Weight of Evidence" section for each recommendation for each phthalate and phthalate alternative. The CHAP also used WOE more broadly when developing overall recommendations for each phthalate or phthalate alternative. The CHAP explicitly stated factors it considered relevant to making its recommendations. CHAP report at p. 79. The CHAP stated, however, that "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." *Id.* p. 12. This does not mean that the CHAP's review was unsystematic and biased. Rather, the CHAP, which began in 2010, did not have all of the systematic review methods that are available today. However, the CHAP incorporated many of the elements that are now included in systematic review methods in their work. (See Response 10.1 of Tab B of staff's briefing package for more detailed response.)

IV. Final Rule and Rationale

This section presents the final rule and explains the Commission's rationale for the rule. The Commission has considered the CHAP report, staff's analysis of the CHAP report, staff's analysis of recent NHANES data, and the public comments submitted in response to the proposed rule and staff's NHANES reports. More specifically, we present the Commission's rationale for the rule by explaining the Commission's consideration of: phthalates' effects on male reproductive development, human exposure to phthalates, assessment of phthalates' cumulative risk and risks in isolation, and assessment of risk for each phthalate that the CHAP considered. In addition, the Commission considered the appropriate concentration limit for the

phthalates restrictions and the appropriate effective date for the rule. In this section, we also discuss phthalate requirements established by international standards and other countries.

A. Hazard: Phthalates' Effect on Male Reproductive Development

1. Summary

In accordance with the CPSIA's direction, the CHAP reviewed all available toxicity data on phthalates. The CHAP determined that the critical endpoint for its analysis was adverse effects on male reproductive development (MRDE) and other adverse effects on male fertility. This focus was consistent with the NRC's 2008 assessment. As noted in the NPR, CPSC staff supports the CHAP's choice to focus on this endpoint because: MRDE in animals is associated with many of the most common phthalates; for most active phthalates, these effects are the most sensitive health effect; and phthalate syndrome in animals resembles testicular dysgenesis syndrome (TDS) in humans. Moreover, phthalates' effects on male reproductive development are well studied. 79 FR 78331-32.

As the CHAP reported, "Studies conducted over the past 20 plus years have shown that phthalates produce a syndrome of reproductive abnormalities in male offspring when administered to pregnant rats during the later stages of pregnancy." CHAP report at p. 15. These effects include: reduced testosterone synthesis, reduced anogenital distance (AGD), nipple retention (normally does not occur in male rats), undescended testes, testicular atrophy, testicular histopathology, multi-nuclear gonocytes (MNGs), reduced production of insulin-like hormone 3 (insl3), underdeveloped gubernacular cords,[11] undescended testes, and genital malformations (hypospadias).[12] Effects may differ depending on the dose. The CHAP noted: "the highest incidence of reproductive tract malformations is observed at higher phthalate dose levels,

[11] Underdeveloped gubernacular cords lead to undescended testes.
[12] Foster (2006); Foster *et al*. (2001); Howdeshell *et al*. (2016); Howdeshell *et al*. (2008).

whereas changes in AGD and nipple/areolae retention are frequently observed at lower phthalate does levels." CHAP report at p. 15. These effects persist into adulthood and lead to reduced or absent reproductive ability. Many, but not all, phthalates cause phthalate syndrome.[13] The CHAP identified five phthalates (DBP, BBP, DINP, DIBP, and DEHP) that cause phthalate syndrome and for which human biomonitoring data were available to assess exposure.

As discussed in the CHAP report, studies have reported similar effects in species other than rats, such as guinea pigs, mice, rabbits, and ferrets.[14] The evidence of phthalate syndrome in mice is even stronger now than when the CHAP developed its analysis.[15] In addition, as the CHAP noted, "there is a rapidly growing body of epidemiological studies on the potential association of exposure to phthalates with human health." CHAP report at 27. For example, the CHAP discussed two human studies linking prenatal phthalate exposure to effects such as reduced AGD in male infants. *Id*. at 28. TDS in humans bears similarities to rat phthalate syndrome. *Id.* at 2. The effects of TDS (*e.g.*, hypospadias, cryptorchidism, testicular cancer, impaired fertility) are observed with regularity in the U.S. population. Phthalates have been proposed as possible contributors to TDS.[16]

2. *Comments Concerning Male Reproductive Developmental Effects*

Several commenters raised issues concerning phthalates' effects on male reproductive development (MRDE). They asserted that studies do not support a determination that phthalates have the same effects on male reproductive development in humans (and other animals) as they do in rats. Commenters also asserted that, even if phthalates have some effect, humans are less

[13] The CHAP referred to phthalates that cause phthalate syndrome as "antiandrogenic," due to the importance of testosterone inhibition in causing phthalate syndrome. Antiandrogenic also serves to distinguish phthalates from other chemicals that act through the androgen receptor, which phthalates do not.
[14] Guinea pigs (Gray *et al*. (1982)), mice, (Gray *et al*. (1982); Moody *et al*. (2013); Ward *et al*. (1998)), rabbits (Higuchi *et al*. (2003)), and ferrets (Lake *et al*. (1976)).
[15] Clewell *et al.* (2011) and Ding *et al.* (2011).
[16] Scott *et al*. (2007); Skakkebaek *et al*. (2001).

sensitive and the CHAP failed to take this into account, especially through appropriate uncertainty factors. Additionally, commenters raised questions about the epidemiology studies the CHAP discussed, *i.e.*, studies concerning phthalates' effects on human populations. Commenters also asserted that, because MRDE would affect the developing fetus, this was not an appropriate endpoint for CPSC's consideration of a regulation on children's toys and child care articles. Commenters raised questions specifically about DINP's association with MRDE. A summary of key comments/responses concerning MRDE appears in this section. Comments/responses concerning DINP, in particular, are provided in section IV.D.1.a. of this preamble.

a. *Animal Studies and Their Relevance to Humans*

Comment: Studies on effects of phthalates on animals other than rats. Several commenters questioned the relevance of studies on rat phthalate syndrome in assessing effects on humans. Commenters asserted that studies involving animals other than rats (*e.g.*, hamsters and marmosets,) indicate that phthalates are not likely to have the same adverse effects in people that they have in rats. Commenters argued that marmosets, being primates and having reproductive organ development that is similar to humans, were more closely related to humans than rats and, therefore, are a better model for estimating human risk. Commenters focused particularly on one study (McKinnell *et al.* (2009)) that reported no observed effects for several relevant endpoints. Some commenters asserted that studies involving mice indicate that humans, who are more similar to mice than rats, are likely less sensitive to phthalates than rats. Commenters also cited xenograft studies (*i.e.*, transplanting human fetal testicular tissue into rats or mice) as supporting the conclusion that exposure to phthalates does not result in MRDE in humans, or at the least, humans are less sensitive than rats. (Comments 1.1 through 1.5).

Response: Phthalate syndrome has been reported to occur in multiple mammalian species, including guinea pigs, mice, rabbits, and ferrets. Although studies indicate that hamsters were resistant to the effects of phthalates due to their slow metabolism to the active metabolite, a study by Gray *et al.* (1982) shows that giving the active metabolite to hamsters causes phthalate syndrome. Regarding mice, the CHAP discussed studies that found some effects in mice (*e.g.*, disruptions in seminiferous cord formation, the appearance of multinucleated gonocytes, and suppression of insulin-like factor 3 (insl3)). CHAP report at p. 6. Some studies published after the CHAP completed its analysis provide additional evidence of phthalate syndrome effects in mice, including reduced testosterone levels, reduced testosterone production, testicular damage, reduced sperm count and quality, reduced AGD, delayed pubertal onset, and increased nipple retention.[17] Thus, there is now even stronger evidence of phthalate syndrome in mice than was available to the CHAP. The CHAP cautioned that differences in methodology could cloud the issue of which species is more sensitive. CHAP report at pp. 17 and 72. Even if mice or other species are less sensitive than rats, it is not possible to make a direct comparison to humans without dose-response information in humans.

Furthermore, the most sensitive species is generally used in assessing risks to humans.[18] The CHAP concluded that rats provide the most sensitive and most extensive studies in male developmental toxicity. CHAP report at pp. 1, 15, 16, 76. Phthalate syndrome in rats resembles the TDS in humans. *Id.* at pp. 2, 75. For these reasons, the CHAP concluded that studies in rats currently offer the best available data for assessing human risk. *Id*. at pp. 18, 75.

Regarding the marmoset studies, the CHAP paid particular attention to these studies and invited Richard Sharpe, the principal investigator of the Hallmark and McKinnell studies, to

[17] Doyle *et al.* (2013) and Ge *et al.* (2015).
[18] Barnes and Dourson (1988); CPSC (1992); EPA (1991).

present his findings at the CHAP meeting in November 2011. Dr. Sharpe agreed with the CHAP that both studies were limited by the small numbers of animals used and the brief duration of exposure. Dr. Sharpe added that his studies were very preliminary and that it would be premature to use his studies' results to support public health decisions. Even though limited, the published studies do show that the phthalate metabolite suppressed steroidogenesis in neonatal marmosets.

Regarding the xenograft studies, commenters cited two studies in which rat fetal testes or human fetal testicular tissue were transplanted (xenografted) into rats (Heger *et al.* (2012)) or mice (Mitchell *et al.* (2012)). As discussed by the CHAP, these studies are subject to a number of limitations. CHAP report at p. 17. Most of the human fetal tissue samples were obtained after the human window of maximum susceptibility to phthalates, meaning that the tissues were less susceptible to MRDE induced by phthalates. In contrast, constant exposure to phthalates in the womb would always expose the fetal tissue to phthalates at their time of maximum sensitivity. Staff provides more detailed responses concerning these studies on animals other than rats in comment/responses 1.1 through 1.5.

Comment: Implications of *in vitro* studies and studies involving chemicals other than phthalates. Some commenters discussed studies in which human testicular tissue or cells were cultured *in vitro* and then exposed to phthalates.[19] Commenters asserted that these studies raise questions about whether phthalate-induced testosterone reduction in rats is relevant to humans. Commenters also asserted that studies (which were not cited by the CHAP) of chemicals with the same mode of action as phthalates, DES and finasteride, show that humans are resistant to phthalates. (Comments 1.6 and 1.7).

[19] Desdoits-Lethimonier *et al. (*2012); Lambrot *et al.* (2009).

Response: *In vitro* studies use techniques that are performed in a controlled environment outside of a living cell or organism, while *in vivo* studies are performed inside living cells or organisms. CPSC staff reviewed the studies and concludes that the *in vitro* studies with human fetal testicular tissue are still preliminary and are generally not sufficient, by themselves, to support public health decisions. *In vivo* animal studies are generally given greater weight in risk assessment. As the CHAP noted, there is also a growing body of evidence in humans that shows associations between phthalate exposure and MRDE endpoints that are consistent with the rat data.

Regarding DES and finasteride, the CHAP assessed each phthalate based on the best available data for each individual chemical, and based its recommendations on those assessments. The CHAP did not base its conclusions on an assumption that all phthalates will behave the same way as DES or finasteride. The DES and finasteride publication cited by commenters implies that humans are less sensitive than rats to these two chemicals. However, this assertion does not mean that all phthalates will produce similar biological effects as DES or finasteride; phthalates do not have a similar chemical structure, are not metabolized or detoxified in the same way, and will not have similar dose-response curves to those of DES or finasteride.

b. *Uncertainty Factors*

Comment: Adjusting uncertainty factors. Some commenters asserted that, even if one accepts that studies on rats demonstrate that phthalates have some effect on humans, humans are less sensitive than rats, and one must adjust the interspecies uncertainty factor to avoid overestimating the risk to humans. Some commenters suggested that instead of an interspecies uncertainty factor of 10, which the CHAP used, the uncertainty factor should be 0.1 (*i.e.*, humans are 10x less sensitive than rodents) to 1 (humans are equally sensitive as rodents)." Other

commenters asserted that the CHAP should have used a different intraspecies uncertainty factor. They argued that the intraspecies uncertainty factor of 10 used by the CHAP is overly conservative because the PEAAs are already based on a sensitive population. Commenters on both types of uncertainty factors asserted that following their recommendations would have reduced the HI in the CHAP's cumulative risk analysis so that it would be less than one. (Comments 1.8 and 1.9).

Response: An uncertainty factor is used in risk assessments to account for differences among different species. An interspecies uncertainty factor of 10 is consistent with the general practice used by CPSC, EPA, and others in risk assessment, to account for interspecies differences.[20] Humans are frequently more sensitive to reproductive and developmental effects than animals,[21] and human males are considered more vulnerable than other mammals.[22] Commenters cited xenograft studies to support the assertion that humans are less sensitive than rats to phthalates effects. As discussed in the response above, these preliminary studies do not provide sufficient support for reducing the interspecies uncertainty factor.

An uncertainty factor is also used to account for differences in how members of the same species could react to a chemical (*i.e.*, human variability). In deriving PEAAs, the CHAP applied an intraspecies UF of 10 to account for differences in sensitivity among individuals. CHAP report at pp. 63-66. CPSC staff expects that the population of infants and fetuses will have a broad range of sensitivity, because age, sex, genetic composition, nutritional status, and preexisting diseases may all alter susceptibility to toxic chemicals.[23] Multiple federal agencies

[20] Barnes and Dourson (1988); CPSC (1992); Dankovic *et al.* (2015); EPA (1991); Pohl and Abadin (1995).
[21] EPA (1991).
[22] Klaassen (2001), p. 703.
[23] Pohl and Abadin (1995).

use an intraspecies uncertainty factor of 10.[24] The CHAP used only the interspecies uncertainty factor and intraspecies uncertainty factor in its analyses. The CHAP did not apply an additional UF to protect infants.

c. *Epidemiology Studies*

Comment: Role of epidemiology studies in CHAP's report and recommendations. Some commenters suggested that human epidemiological evidence for phthalate-induced effects was equivocal or inconsistent with results from animal studies, and did not support the CHAP's conclusions and recommendations. Some commenters asserted that these studies did not show consistent results and have not established a cause and effect relationship between phthalate exposure and MRDE effects in humans. (Comment 7.1).

Response: The CHAP's assessment and recommendations to the Commission are based primarily on animal studies. However, the CHAP reviewed epidemiology studies as well. CPSC staff agrees with the CHAP that these epidemiology studies indicate an association of exposure to phthalates with human health. Under CPSC's Chronic Hazard Guidelines and other agencies' guidance, epidemiological studies establishing a causal relationship between exposure and effect are not required to conclude that a substance or mixture is "probably toxic to humans." CPSC's Chronic Hazard Guidelines, 57 FR 46626, 46641 (Oct. 9, 1992). CPSC staff considers that there is sufficient evidence in animal studies to conclude that certain phthalates are probably toxic to humans. Epidemiological data provide supporting evidence for the animal data and also support the conclusion that the animal data are relevant to humans. In addition, staff states that the CHAP's conclusion is consistent with a recent NAS (2017) report that also concluded that there

[24] Barnes and Dourson (1988); CPSC (1992); Dankovic *et al*. (2015); EPA (1991).

is a "moderate level of evidence" from epidemiological studies that DEHP and DBP induce MRDE in humans (based on changes in AGD). The NAS report's conclusions provide additional confidence that phthalates cause MRDE in humans. Although there are a few inconsistencies in the findings from epidemiological studies, inconsistencies among epidemiological studies are common, due to differences in study methods, characteristics of the study population, study size, and the statistical power of the study to detect associations. Establishing cause and effect in epidemiological studies is not required by federal and international agencies to conclude that a substance is likely to cause similar effects in humans.

Comment: Studies on reduced anogenital distance (AGD). Several commenters raised questions about an association between phthalate exposure and reduced AGD in males. Commenters noted inconsistencies in results among published studies and noted that effects occurred sporadically and inconsistently, even when performed by the same laboratory. Some commenters pointed to inconsistencies between epidemiological and animal studies. Other commenters took a different view, noting that "these markers are linked with diminished reproductive health in males." (Comments 7.3 and 7.7).

Response: The CHAP considered and discussed the inconsistent epidemiological data, noting the need to evaluate carefully negative and positive findings. CHAP report at p. 21. The CHAP considered the available epidemiological evidence, along with the animal studies, and determined that human AGD is a relevant measure of the antiandrogenic mode of action of phthalates during fetal development. CPSC staff concludes that, with few exceptions, the epidemiology studies are generally consistent with one another and with the results of animal studies.

Reduced AGD is one of many effects associated with phthalate syndrome. Studies demonstrate that phthalates cause permanent effects on male reproductive development. [25] Jain and Singal (2013) reported that infants with undescended testis (cryptorchidism - an adverse clinical outcome) had a significantly shorter AGD and AGI when compared to infants with descended testis. Thankamony *et al.* (2014) reported the results of a comparative study involving AGD (and penile length) in infants that were normal and those with hypospadias or cryptorchidism. They determined that AGD was statistically reduced in boys with hypospadias or cryptorchidism when compared to boys without these pathologies. They concluded: "The findings support the use of AGD as a quantitative biomarker to examine the prenatal effects of exposure to endocrine disruptors on the development of the male reproductive tract."

Comment: DEHP exposure and medical procedures. One commenter stated that the lack of evidence showing effects occurring in adults and infants who are exposed to DEHP from intensive medical procedures makes it unlikely that less potent phthalates would induce adverse reproductive effects in humans. (Comment 7.4).

Response: Few studies have specifically investigated possible health outcomes from phthalate exposures from medical equipment. The commenter cited two studies, one that the CHAP also discussed. Although this study did not find phthalate-related health effects, the CHAP concluded that the very small sample size limits its usefulness. CPSC staff concludes that because of the uncertainties in the existing data, no conclusions can be drawn from high exposures to DEHP in medical procedures.

[25] *e.g.*, Boberg *et al*. (2011); Clewell *et al*. (2013b).

d. *Relevance of Endpoint to Rulemaking*

Comment: Disconnect between risk assessment's focus on fetus as target population and focus of rule. Commenters questioned how a rule restricting phthalates in children's toys and child care articles could reduce the risk of phthalate syndrome when the fetus, not infants and children who use toys and child care products, is the population primarily at risk for adverse effects on male reproductive development. Commenters noted that the CHAP's analysis shows that exposures of women to DINP from children's toys and childcare articles are negligible. (Comment 1.11).

Response: Although fetuses are considered to be the most sensitive population for MRDE, based on data from animal studies, the CHAP recognized that other populations such as infants, toddlers, and children also are susceptible to the effects of phthalates. CHAP report at p. 14. Testosterone production and other processes involved in reproduction remain critical throughout male development in animals and humans from the prenatal period through puberty. Testosterone production is required throughout a male's lifetime to maintain the ability to reproduce. [26] Moreover, CPSC, like other federal agencies, uses the most sensitive and appropriate human target population in risk assessments. The practice of selecting the most protective endpoints and potency estimates (*i.e.*, PODs) based on the best available studies is consistent with the statutory mandate to provide a reasonable certainty of no harm with an adequate margin of safety. Using the lowest POD also is consistent with CPSC Chronic Hazard Guidelines, 57 FR 46626 (Oct. 9, 1992), and other federal agency practices.[27]

3. National Academy of Sciences Report on Endocrine Disruptors

In July 2017, the National Academies of Sciences, Engineering, and Medicine

[26] Foster (2006).
[27] Barnes and Dourson (1988); EPA (1991).

(NAS) released a report entitled, *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals* (NAS 2017). [28] The study responds to EPA's request that the NAS develop a strategy to evaluate the evidence for potential human health effects from endocrine active chemicals at low doses. The NAS selected phthalates as one of two chemicals to demonstrate the systematic review methods and integration of results. In a chapter titled, "*Phthalates and Male Reproductive-Tract Development*, "the NAS study evaluated three health effects (fetal testosterone, anogenital distance (AGD), and hypospadias). CPSC staff reviewed the NAS study.

Unlike the CHAP report, the NAS study is not a risk assessment. Rather, the NAS study reviewed individual phthalates and three individual health effects, focusing on whether enough quality data existed to term the particular phthalates a reproductive hazard to humans. In contrast, the CHAP considered all phthalate syndrome effects. In spite of these differences, the NAS report's conclusions are consistent with the CHAP and staff's hazard conclusions. The phthalates section of the NAS report focused on DEHP, and provided a "final hazard conclusion" for each of the endpoints. Thus, for fetal testosterone and AGD, DEHP is presumed to be a reproductive hazard to humans; for hypospadias, DEHP is suspected to be a reproductive hazard to humans (NAS 2017, pp. 78–81). For the other assessed phthalates, including DINP, the NAS report did not conduct the final analysis step that results in a "final hazard conclusion." The report provides only the "initial hazard evaluations" for fetal testosterone, AGD, and hypospadias in humans. The report found for fetal testosterone, the phthalates BBP, DBP, DEP, DIBP, DINP, and DPP are presumed to be reproductive hazards to humans; DEP is not

[28] NAS (2017) Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. National Academies of Sciences, Engineering, and Medicine, National Research Council. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24758.

classifiable for this endpoint (NAS 2017, Table 3-30). AGD, BBP, DBP, and DEP are presumed to be reproductive hazards to humans, while DIBP, DIDP, and DINP are not classifiable (NAS 2017, Table 3-29). For hypospadias, BBP is suspected to be a reproductive hazard to humans and DBP is presumed to be a reproductive hazard to humans (NAS 2017, Table 3-31). The NAS committee did not evaluate DHEXP, DCHP, or DIOP.

With regard to DINP, the NAS study concluded:

- DINP effect on Fetal Testosterone: The NAS concluded: "there is a high level of evidence that fetal exposure to DINP is associated with a decrease in fetal testosterone in male rats," and that there was "inadequate evidence to determine whether fetal exposure to . . . DINP, . . . is associated with a reduction in fetal testosterone in male humans." Overall, the NAS' initial hazard evaluation of DINP and fetal testosterone in humans was that DINP was a "presumed human hazard."
- DINP effect on AGD: The NAS concluded: "there is an inadequate level of evidence to assess whether fetal exposure to DINP is associated with a decrease in AGD in male rats," and: "the available studies do not support DINP exposure being associated with decreased AGD." Overall, the NAS' initial hazard evaluation of DINP and AGD in humans was "not classifiable."

CPSC staff provides a more detailed discussion of the NAS report in the final rule briefing package at section III.B. of the briefing memorandum.

B. *Exposure to Phthalates*

As noted, the CHAP considered exposure in two ways: human biomonitoring studies that estimate total exposure to phthalates and the scenario-based assessment that estimates exposure to specific products and sources.

1. Human Biomonitoring

a. *Summary*

The CHAP used data from NHANES to estimate phthalate exposures to pregnant women. The CHAP also used human biomonitoring data from the SFF study to estimate exposures to infants and their mothers because NHANES does not collect data on children under 6 years old. The CHAP's analysis of NHANES data was based on the 2005/2006 data cycle. CPSC staff subsequently analyzed data from later NHANES data sets. Because the 2005/2006 data set was the last to sample a sufficient number of pregnant women to make reliable exposure estimates for pregnant women, CPSC staff's analyses are for women of reproductive age (WORA). Staff determined that WORA are a suitable surrogate for pregnant women. CPSC staff's June 2015 report; Tab A of staff's briefing package. CPSC staff then used the CHAP's methodology and later NHANES data sets (2007/2008, 2009/2010, 2011/2012) to estimate phthalate exposure, individual phthalate risk, and the cumulative risk (*i.e*, hazard index). *Id.* When CDC released another data set, 2013/2014, staff performed a similar analysis using that data. CPSC staff's February 2017 report; Tab A of staff's briefing package. No more recent SFF data are available.

In CPSC staff's analysis of NHANES data published following the CHAP's analysis, staff found that total phthalate exposures in WORA have changed. The median total exposure to the phthalates included in the CHAP's cumulative risk assessment (DEHP, DINP, BBP, DBP, DIBP) has increased by 20 percent in WORA. In particular, the estimated median DEHP

exposure in WORA has declined over time, while the estimated median DINP exposure in WORA has increased fivefold since 2005/2006.[29] Although DEHP was the major contributor to the cumulative risk in 2005/2006, DINP now contributes about as much as DEHP. *See* TAB A of staff's briefing package, Figures 6 and 7, and Table 8.

No new data on infants or pregnant women are available to quantify the effects of changing exposures. Given that the overall phthalate exposures to WORA have declined since 2005/2006, it is possible that exposures to infants and pregnant women have also declined. In general, studies indicate that infants' and children's exposures to chemicals tend to be greater than in adults.[30] With regard to phthalates, daily intakes of the phthalates the CHAP examined in its cumulative risk assessment were generally twofold to threefold greater in SFF infants than in their mothers. CHAP report at Table 2.7. In the CHAP's scenario-based exposure assessment, estimated daily intakes were twofold to fivefold greater in infants than in women. CHAP report, Appendix E1, Table E1-18. Additionally, a study of German nursery school children found they had roughly twice the DEHP exposure as their parents.[31] Because CPSC does not have exposure data for children more recent than the SFF data used by the CHAP, staff can only make a qualitative assessment that infants and children could have greater exposure to phthalates than what the NHANES data indicate for WORA. In section IV.C.1. of this preamble, we discuss the effect of the more recent NHANES data on risk.

[29] Zota *et al*. (2014).
[30] CHAP 2014; Sathyanarayana *et al*. (2008a); Swan (2008); Swan *et al*. (2005).
[31] Koch *et al*. (2004).

b. *Comments Concerning Biomonitoring Data*

i. Particular Data Sets

Comment: CHAP's use of 2005/2006 NHANES data. Several commenters criticized the CHAP's use of 2005/2006 NHANES data. Commenters noted that the CHAP report states: "the stopping point for CHAP analysis and interpretation was information available by the end of 2012." However, commenters stated, both 2007/2008 data and 2009/2010 data were available by then. A commenter noted that the 2009/2010 data set was available in September 2012, nearly 2 full years before the final CHAP report was issued and before the CHAP cutoff date for consideration of new information (end of 2012). The commenter noted that the 2011/2012 data set was available in November 2013, ahead of the meeting in January 2014 at which the CHAP discussed the peer review of its report. (Comment 3.1).

Response: The CHAP used 2005/2006 NHANES data on pregnant women to assess phthalate exposure as part of the cumulative risk assessment, to satisfy the CPSIA's charge to "examine the likely levels of children's, *pregnant women's*, and others' exposure to phthalates . . . ." 15 U.S.C. 2057c(b)(2)(B)(iii) (emphasis added). This data set was the most recent data on pregnant women available at the time the CHAP completed its analysis in July 2012. CHAP report at p. 31. The 2005/2006 NHANES study was the last data cycle to include a large sample of pregnant women. The CHAP included summary phthalate metabolite data from the 2007/2008 data cycle in its report, *id*. at Tables 2.5, 2.6., but did not calculate exposure and risk because this data set did not have sufficient numbers of pregnant women. Partial data for 2009/2010 were first released in September 2012, after the CHAP completed its analysis in July 2012. Although the 2011/2012 data on phthalate metabolites were initially released in November 2013, the data were revised in October 2014, and other files that were needed to

calculate exposure and risk were not published until January 2015, well after publication of the final CHAP report. Regarding the CHAP report's statement about a cutoff date, read in context, the cutoff date clearly refers to the final update of the CHAP's search of the biomedical literature for new peer-review publications in biomedical journals, specifically, National Library of Medicine databases. In any event, CPSC recognized that more recent NHANES data than the set on which the CHAP relied were available. Accordingly, CPSC staff analyzed the later NHANES data sets and used the most recent data in its analysis for the final rule.

Comment: Pregnant women and women of reproductive age. Some commenters stated that the 2005/2006 NHANES data on WORA were a reasonable surrogate for the data on pregnant women, and that the CHAP should have used WORA in its cumulative risk assessment because the WORA have an increased sample size in most NHANES datasets and phthalates exposures for both are statistically similar. Commenters asserted that the sample size for pregnant women in the CHAP's analysis was too small to yield reliable risk estimates. In contrast, another commenter supported the CHAP's decision to base its analysis on the 2005/2006 data that focused on pregnant women. (Comments 3.7 and 3.10).

Response: The CHAP stated that it chose to use biomonitoring data from the 2005/2006 NHANES and from the SFF "because of the CHAP's task to investigate the likely levels of children's, pregnant women's, and others' exposure to phthalates and to consider the cumulative effect of total exposure to phthalates both from children's products and other sources." CHAP report at p. 35. Although, as the CHAP stated, there are indications that exposures may be higher in pregnant women than in women in general, the CHAP stated: "the exposures were not found to be significantly different." *Id*. at p. 36. CPSC staff compared estimates from the 2005/2006 NHANES data set to determine whether WORA had similar daily intake (DI) and

Hazard Index as Pregnant Women. CPSC staff found that median and 95th percentile estimates of the DI for five phthalates were generally similar when comparing WORA to pregnant women. Regarding the sample size of pregnant women, CDC calculated the sample size necessary for statistical analysis of NHANES data. In the data sets after 2005/2006, NHANES no longer oversampled pregnant women. Therefore, the numbers of pregnant women in data sets after 2005/2006 were too small to generate statistical estimates for pregnant women. *See* Tab A of staff's briefing package.

ii. *Biomonitoring Methodology*

Commenters raised concerns about various technical aspects of the NHANES data (*e.g.*, effects of fasting, spot sampling rather than averaging urine samples over time, using hydrolic metabolites for DINP and DIDP, and appropriate metabolite markers) Key points are discussed below. More details are provided in Tab B of the staff's briefing package, particularly comments 1.13, 3.6, 3.11, and comments 3.14 through 3.17.

Comment: Urinary spot sampling. Several commenters raised concerns about urinary spot sampling. They noted that biomonitoring studies (and NHANES in particular) take one spot urine sample as opposed to averaging urine samples collected over a longer period of time. Commenters claimed that spot sampling does not accurately reflect the duration of exposure necessary to develop MRDE. They stated that the exposure information should match the exposure scenario of that hazard data to which it is compared (*e.g.*, chronic exposure to chronic hazard). They asserted that spot sampling would not capture the day-to-day variability in urinary concentration of most phthalates and would overestimate the risk. However, another commenter stated that spot samples are as predictive of urinary concentration as 24-hour urinary samples. (Comments 1.13 and 3.11).

Response: The CHAP and CPSC staff estimated daily intake of each phthalate by modeling creatinine-related metabolite measurements across participants in NHANES. NHANES measured metabolites from one spot urine sample per individual in the study. Spot urine samples were collected at different sites and at various times of the day and days of the week. Additionally, because participants for each NHANES study cycle were randomly selected from civilian, non-institutionalized individuals in the United States, according to a probability-based complex, multistage sample design, the estimated daily intakes are representative of the U.S. population. The estimated daily intakes and the resulting HQs and HIs represent estimated population per capita phthalate exposure across the 2-year NHANES cycle, not average daily estimates of an individual's exposure across time. Thus, an estimated proportion of the population with an HI less than one, using HBM from NHANES, represents the estimated proportion of the population within that cycle that would have an HI less than one at any one given time of that cycle. Estimates based on NHANES HBM do not imply that individuals with HI less than one at a given time will continue to have an HI less than one for all 2 years of a NHANES study cycle.

CPSC staff notes that longer-term exposures are not necessarily required to cause MRDE. Numerous studies in animals have demonstrated that MRDE and related effects can occur after one or a few doses.[32] Shorter-term elevated exposure could be related to adverse health outcomes in the fetus, if the exposure occurs during the window of susceptibility. Although human phthalate exposures may vary from day-to-day or during the course of a day, humans are exposed to phthalates every day.

[32] Carruthers and Foster (2005); Creasy *et al*. (1987); Ferrara *et al*. (2006); Gray *et al*. (1999); Hannas *et al*. (2011); Jobling *et al*. (2011); Jones *et al*. (1993); Li *et al*. (2000); Parks *et al*. (2000); Saillenfait *et al*. (1998); Saitoh *et al*. (1997); Spade *et al*. (2015); Thompson *et al*. (2004); Thompson *et al*. (2005).

Comment: Fasting time differences. Some commenters discussed whether fasting times affected the concentration of phthalate metabolites in the urine in NHANES results and whether there were differences in fasting times in the data sets of different years. (Comment 3.6).

Response: The CHAP paid special attention to the possible effects of fasting on NHANES data. Staff reviewed NHANES documentation[33,34] and spoke with CDC staff regarding fasting protocol changes between cycles. No fasting requirements changed. Therefore, fasting requirements were not a factor in the decision not to combine data from subsequent NHANES cycles with the 2005/2006 data. CPSC staff concludes that fasting may have an impact on food-borne phthalates; but if anything, this would result in underestimation of risk. CPSC staff concludes that the major conclusion or the recommendation of the CHAP report would not change whether the CHAP included the early NHANES data or not.

Comment: Urinary excretion rates and metabolites. Some commenters raised concerns about the urinary excretion rates and the metabolites used in the NHANES data. One commenter asserted that staff's analysis in its June 2015 report of the 2009/2010 and 2011/2012 NHANES data sets overestimated exposures because it did not consider urinary excretion rates. Another commenter stated that the metabolites used for DINP and DIDP could lead to underestimation of phthalate risk when compared to other phthalates, such as DEP, DBP, DIBP, and BBP. Five commenters asked CPSC to re-evaluate exposure using additional metabolite biomarkers for DINP, DNOP, and other phthalates and also re-evaluate using later NHANES data. One of the commenters asserted that the quantitative estimates of DINP risk from the 2017 analysis provided by CPSC staff were calculated incorrectly and were 17 percent too high. The

[33] National Health and Nutrition Examination Survey, 2005 - 2006 Data Documentation, Codebook, and Frequencies. Available at: https://wwwn.cdc.gov/Nchs/Nhanes/2005-2006/FASTQX_D.htm.
[34] National Health and Nutrition Examination Survey, 2003 - 2004 Data Documentation, Codebook, and Frequencies. Available at: http://wwwn.cdc.gov/nchs/nhanes/2003-2004/PH_C.htm.

commenter requested that staff use multiple metabolites (*e.g.*, MINP and MCOP) to estimate DINP exposure instead of just one (MCOP). The commenter noted that exposure estimated for DEHP used four metabolites. (Comments 3.14 through 3.17).

Response: Regarding staff's 2015 report and excretion rates, the additional information necessary to calculate directly urinary mass excretion rates was not collected during the 2005/2006 or 2007/2008 NHANES studies. Therefore, the extrapolation method was the only option available to the CHAP. Staff replicated the CHAP's reported exposure and risk estimates using the 2005/2006 NHANES data and applied the same methods to calculate estimates from the later NHANES studies. Regarding metabolite biomarkers, CPSC used MCOP to analyze phthalate exposure, as the CHAP did. This was appropriate because for exposed individuals, MCOP will be detected more frequently and at higher levels than other DINP metabolites. Regarding the use of both MINP and MCOP to estimate DINP exposures, staff does not agree that the estimated exposures for DINP in the 2015 and 2017 analyses were incorrect. CPSC staff used one metabolite, MCOP, to estimate DINP exposure in order to be consistent with the CHAP methodology and previous staff exposure and risk documents. The CHAP recognized that there are multiple ways to estimate phthalate exposure using individual and combined phthalate metabolites, and the CHAP provided a table of potential metabolites and associated fraction of the urinary metabolite excreted factors. CHAP report at Table D-1.

Comment: SFF data. A commenter noted that SFF data were collected before the CPSIA was implemented, and before an asserted sharp decline in DEHP exposure. Thus, according to the commenter, basing the NPR on the SFF data (which was the exposure data used to determine that 5 percent of infants have an HI greater than one) is not supportable. (Comment 3.5).

Response: Infants' and children's phthalate exposures tend to be greater than adults' exposure.[35] For the phthalates in the CHAP's cumulative risk assessment, daily intakes were generally twofold to threefold greater in SFF infants than in their mothers. CHAP report at Table 2.7. No more recent information on infant exposures is available than the 1999/2005 SFF data, which was used by the CHAP (and subsequently by CPSC in the NPR). Infant exposures may have changed since 2005, but staff has no infant data to quantify any change.

2. Scenario-Based Exposure Assessment

a. Summary

Because biomonitoring data do not provide any information about the sources of phthalate exposure, the CHAP also included a scenario-based exposure assessment in its report. CHAP report at pp. 49-60, Appendix E1. The exposure assessment evaluated exposure from individual sources, such as toys, personal care products, and household products. The assessment considered the exposure routes of inhalation, direct and indirect ingestion, and dermal contact. The CHAP stated that its goal was to determine the significance of exposure to phthalates in toys and to estimate exposure to toddlers and infants for all soft plastic articles, except pacifiers (because pacifiers do not contain phthalates). *Id*. at p. 49. For phthalates that are currently prohibited from being in children's toys and child care articles, the CHAP report provides estimated exposures that would hypothetically occur if phthalates were allowed in those products. *Id*. at pp. 49-50.

Scenario-based exposure estimates are developed using information about relevant sources of phthalate exposure (*e.g*., concentrations of phthalates in soil, dust, and in products); data on migration or leaching of phthalates from products; physiological information (*e.g*., body

[35] CHAP (2014); Sathyanarayana *et al.* (2008a); Swan (2008); Swan *et al*. (2005).

weight and skin surface area); and information about how the subpopulations use and interact with products, including frequency and duration of contact with products and environmental media.

The exposure assessment considered seven categories of exposure sources and activities involving those sources: diet, prescription drugs, personal care products, toys, child care articles, indoor environment, and outdoor environment. *Id.* at p. 50. For each subpopulation (pregnant women/WORA, infants, toddlers, and children), the assessment provides estimated daily aggregate exposures to each of the eight phthalates included in the cumulative risk assessment. *Id.* at pp. 50-51 and Table 2.11. The relative contribution (percent of total exposure) for each activity was determined. The analysis found that for women, diet contributes more than 50 percent of the exposure to DIBP, DNOP, DEHP, DINP and DIDP. *Id.* at Appendix E1-26. For infants and toddlers, more than 50 percent of DIBP, DINP, and DIDP exposure and more than 40 percent of DEHP exposure comes from diet.

Although certain phthalates had not been permitted in children's toys and child care articles since 2008, the exposure assessment considered what contribution these products could make to overall phthalate exposure if those phthalates were allowed in children's toys and child care articles. The exposure analysis showed that, on average, mouthing and dermal exposure to toys could contribute around 12.8 percent to the overall DINP exposure of infants, if DINP were used in these products. CHAP report at Appendix E1, Table E-21. The same analysis shows that dermal contact with child care articles could contribute up to an additional 16.5 percent of the overall exposure to infants. Therefore, if DINP were used in all of the products that were included in the scenario-based exposure assessment, children's toys and child care articles could account for around 29 percent of infants' total exposure from all evaluated sources. *Id.*

It is not possible to accurately quantify the number of toys that might have DINP in them if the interim prohibition were lifted or to quantify the effect that changes in DINP exposure would have on the percentage of the population (infants, pregnant women, or WORA) with HI less than or equal to one.

b. Comments Concerning Scenario-Based Exposure Assessment

Comment: Exposure through diet. Commenters noted that diet is the primary source of exposure to phthalates for infants and children and that children's toys and child care articles contribute very little to overall phthalate exposures, especially for women of reproductive age and fetuses. They reasoned that, therefore, a prohibition on phthalate-containing children's toys and child care articles would have little effect on overall risk. (Comment 5.3).

Response: CPSC disagrees that the contribution from sources other than diet are negligible, especially for DINP. The scenario-based exposure assessment in the CHAP report shows that mouthing and dermal exposure to toys could contribute an average of 12.8 percent, 5.4 percent, and 1 percent of the overall DINP exposure to infants, toddlers, and children, respectively, if DINP were used in these products. CHAP report at Appendix E1, Tables E1-21, E1-22 and E1-23. Mouthing and handling soft plastic teethers and toys could contribute 12.8 percent (mean exposure) or 16.6 percent (95^{th} percentile exposures) of total DINP exposure in infants. *Id*. at Appendix E1, Tables E1-21. Dermal contact with the evaluated toys and child care articles may contribute up to an additional 16.5 percent of exposures to infants. *Id.* Therefore, although infants' DINP exposure was primarily from diet, up to 29 percent may be due to the presence of DINP in the evaluated toys and child care articles (*Id.* Figure 2.1).

Comment: Exposure through house dust. One commenter noted that house dust contributed to background exposure, that DEHP was in 100 percent of dust samples, that

consumer products and building materials were the source of such dust, and that the EPA soil screening levels for DEHP were exceeded by the concentrations found. (Comment 5.4).

Response: The CHAP's and staff's analyses considered exposures to house dust. The CHAP's exposure scenarios estimated theoretical exposures from house dust. The CHAP found that for infants and toddlers, incidental ingestion of household dust contributed roughly 25 percent to the total BBP exposure and 15 percent to total DEHP exposure. For children, the CHAP found that household dust contributed about 18 percent to DEHP exposures. CHAP report at Appendix E1-35. Additionally, because NHANES includes exposures from all routes, the NHANES estimates would have included the survey individual's exposures to household dust.

C. Risk Assessment

As the CPSIA directed, the CHAP considered risks of phthalates in combination and in isolation. The CHAP conducted a cumulative risk assessment to evaluate the effects of multiple phthalates, specifically phthalates known to cause MRDE and other adverse effects on male fertility. As explained in section III.C.3, the CHAP used information from toxicity studies concerning MRDE and human biomonitoring studies to determine a hazard quotient (HQ) for each phthalate and the hazard index (HI) for each individual in the two populations of interest (pregnant women and children). To assess risks of phthalates in isolation, the CHAP used a margin of exposure (MOE) approach.

For reasons discussed in sections III.C.1 and IV.A.1. of this preamble, the CHAP and CPSC have focused on phthalates' association with MRDE. The CHAP's and CPSC's determination of risk associated with the use of phthalates in children's toys and child care articles is based on a cumulative risk assessment that considers the contribution that allowing

antiandrogenic phthalates to be used in children's toys and child care articles would have on the overall cumulative risk from phthalates. Relying on this cumulative risk assessment, the Commission determines that, to meet the CPSIA's criteria of reasonable certainty of no harm and protection of the health of children, it is necessary to prohibit children's toys and child care articles containing concentrations of more than 0.1 percent of the phthalates that can cause MRDE (DINP, DIBP, DPENP, DHEXP, and DCHP). In this section, we discuss the cumulative risk assessment and related comments. We discuss each phthalate in section IV.D of this preamble.

1. Cumulative Risk Assessment

a. Summary

i. CHAP's Analysis and NPR

A cumulative risk assessment estimates the potential risk following exposure to multiple "stressors," in this case, multiple phthalates. As discussed in section III.C of this preamble, the CHAP found, and CPSC agrees, that certain phthalates cause male reproductive developmental effects and may appropriately be considered in a cumulative risk assessment. CPSC concludes that a cumulative risk assessment is appropriate here because evidence indicates that phthalates are "dose additive." That is, for phthalates that cause MRDE, the chemicals will act together; the effects of one such phthalate will add to the effects of another such phthalate. As the CHAP report explained, experimental studies show the additive effects of phthalates on MRDE.[36] The CHAP also demonstrated that the phthalates included in the CHAP's cumulative risk assessment share a common mechanism of action (primarily antiandrogenicity) and affect the same target organ (primarily the testes).

[36] Hannas *et al.* (2012); (2011); Howdeshell *et al.* (2007); (2016);(2008).

This rule is based on a cumulative risk assessment that uses the methodology employed by the CHAP, along with exposure data from the most recent NHANES data sets. The cumulative risk assessment follows a hazard index (HI) approach that is commonly used for cumulative risk assessments. The CHAP's cumulative risk assessment was consistent with the recommendations of a National Academy of Sciences report on cumulative risk assessment of phthalates. Cumulative risk assessment of chemical mixtures has been an established practice since the 1980s. The CHAP introduced a minor modification to the standard methodology: the CHAP calculated hazard indices for each individual sampled in NHANES rather than the more common HI approach of using population percentiles from exposure studies on a per-chemical basis. This allowed the CHAP to calculate hazard quotients (HQs) for each phthalate and an HI for each individual in each study. This avoids overestimating the risk for individuals with higher than average exposures, such as those at the 90^{th} and 95^{th} percentiles.

The CHAP calculated an HQ for each phthalate using three sets of "potency estimates of antiandrogenicity" (PEAAs). The PEAA is an estimate of the exposure at which the risk of MRDE is negligible. The CHAP estimated a PEAA for each phthalate by dividing the MRDE "antiandrogenic" point of departure (POD; toxicity endpoint) by an uncertainty factor (UF). The POD is the lowest dose level at which an adverse effect was seen. A UF is a quantitative factor that is used to account for uncertainties associated with available data (*e.g.*, interspecies, intraspecies, database, and toxicity uncertainties). The CHAP stated that it used three sets of PEAAs to explore the effect of different methodology (*e.g.*, different uncertainty factors and PODs) on cumulative risk estimates to "determine the sensitivity of the results to the assumptions for PEAAs and the total impact on the HI approach." CHAP report at p. 4. Each case brings a different perspective to the risk assessment. The CHAP report discusses the three

cases at pages 63-64. Case 1 was based on published, peer-reviewed values using a study by Kortenkamp and Faust.[37] Case 2 was based on a relative potency method with DEHP as the index chemical, using multiple-dose studies of *in-vitro* fetal testosterone production by Hannas *et al*. (2011) .[38] For Case 3, the CHAP derived new PEAA values after considering all the available literature, including studies such as Boberg *et al.* (2011).[39] As explained in response to comments, CPSC staff concludes that each of the three cases has certain advantages, all three are appropriate, and the risks resulting from the three cases are quite similar.

The CHAP calculated HQs for each phthalate by dividing the exposure by the PEAA. The CHAP then calculated the HI by summing the HQs for each phthalate. If the HI is greater than one, there may be concern for antiandrogenic effects in the exposed population due to cumulative effects of phthalates. As explained previously, the CHAP used 2005/2006 NHANES data for exposure estimates for pregnant women and 1999-2005 SFF data for exposure estimates for mothers and infants. CPSC staff subsequently repeated the CHAP's analysis using more recent NHANES data. The CHAP found that pregnant women had median HIs of about 0.1 (0.09 to 0.14), while the 95th percentile HIs were about 5, depending on which set of PEAAs was used. Roughly 10 percent of pregnant women had HIs greater than one. CHAP report at Table 2.16. Infants had median HIs about 0.2, while the 95th percentiles were between 0.5 and 1.0. About 5 percent of infants had HIs greater than one. *Id.*

The CHAP characterized the distribution of the estimated HIs, by reporting the central tendency measure (statistical median[40]) and the upper percentiles (95th, and 99th). CHAP report at

[37] Kortenkamp and Faust (2010).
[38] Hannas *et al*. (2011).
[39] Boberg *et al*. (2011).
[40] The median is the midpoint of the distribution, where one-half of the values are smaller than *(i.e*., below) the median value, and one-half of the values are larger than the median. The 95th percentile of the distribution is the

Table 2.16. The CHAP's analysis showed that the median HIs for NHANES pregnant women were less than one (HIs of 0.09 to 0.14), but the 95th percentile HIs were greater than one (HIs of 3.6 to 6.1). Staff notes that the CHAP emphasized that an HI greater than one is the metric that defines excess exposure, relative to the acceptable exposure level; the CHAP did not indicate that the 95th percentile, or any other part of the cumulative risk distribution, should be used to establish unacceptable risk for risk management purposes. The CHAP, having determined that an HI greater than one was necessary to identify the population at risk, then used the distribution of HIs to identify the percentage of the population with an estimated HI greater than one. Staff notes that, while the CHAP presented the distribution statistics, described above, the CHAP focused on the proportion of the population with HIs exceeding one, not on any particular percentile of the distribution.

The CHAP's HI approach is consistent with the CPSC's chronic hazard guidelines (Chronic Guidelines). The Chronic Guidelines discuss a safety factor approach to determine acceptable risk for a reproductive or developmental toxicant. 57 Fed. Reg. 46626, 46656 (Oct. 9, 1992). Under the safety factor approach, one determines the acceptable daily intake (ADI) for a substance by adding a safety factor to the lowest no observed effect level (NOEL) seen among relevant studies. The Chronic Guidelines state that if the hazard is ascertained from human data, a factor of 10 is applied to the NOEL, and if the hazard is ascertained from animal data, a factor of 100 is applied. *Id*. Staff states that the safety factor approach is similar to the HI approach that the CHAP followed. The CHAP's PEAA values are equivalent to an ADI, and the HI is the ratio of the daily exposure to the ADI. The Chronic Guidelines do not define the percentage of

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value indicating 95 percent of values are smaller than this value, and 5 percent of values are larger. The median and 95th percentile values describe the data distribution, in this case the HI values estimated for the population of pregnant women or women of reproductive age who experience phthalate exposures. These values, by themselves, do not define acceptable risk levels. Rather, the acceptable risk level is a policy decision.

the population (*i.e.*, number of individuals versus the sample population or entire population) that must have an HI less than one to ensure a "reasonable certainty of no harm . . . with an adequate margin of safety."

As discussed in the NPR preamble, based on the CHAP report, the Commission proposed to prohibit children's toys and child care articles containing the antiandrogenic phthalates the CHAP had examined. The NPR stated that the Commission considers that an HI less than one is necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety and to protect the health of children. 79 FR at 78334. The NPR also stated that the Commission considers that an HI less than one is necessary to protect the health of children. *Id*. at 78335.

In the NPR, the Commission stated the CHAP's determination that approximately 10 percent of pregnant women and 5 percent of infants had an HI greater than one. The Commission did not establish directly, however, that there was a specific proportion of the population that must have an HI less than or equal to one to ensure a "reasonable certainty of no harm with an adequate margin of safety" or to "protect the health of children."

ii. Analysis Using Most Recent Data

After publication of the NPR, CPSC staff analyzed NHANES data for WORA (from 2007 through 2014). CPSC staff reports for 2015 and 2017; TAB A of CPSC staff's briefing package: Staff's analysis shows that the risk to WORA, as indicated by HI, has decreased. Median and 95th percentile HIs for WORA are both less than one. Staff estimates that between 98.8 and 99.6 percent of WORA have HIs less than or equal to one. Out of a sample of 538 WORA in the 2013/2014 cycle, 99.5 percent of WORA have an HI less than or equal to one when considering PEAA Case 1 and 99.6 percent when considering Case 3. For PEAA Case 2,

an estimated 98.85 percent of WORA have an HI less than or equal to one in the same cycle. *See* Tab A of staff's briefing package. This means that some individual WORA in the NHANES sample have an HI greater than one for each PEAA case. Out of a sample of 538 WORA, for PEAA Case 1, three WORA had an HI greater than one; for PEAA Case 2, nine WORA had an HI greater than one; and for PEAA Case 3, two WORA had an HI greater than one. However, the national population projection for HI greater than one is not estimable at the upper percentiles of the distribution due to sampling variability. Thus, staff is unable to estimate the percentage of WORA with an HI greater than one in the population of approximately 60 million WORA in the United States.

As noted in Tab A of the staff's briefing package, the decreases in HI are primarily due to decreases in DEHP exposures. The HQ for DINP is replacing the HQ for DEHP proportionally for contributions to the total HI. In each PEAA case, DINP has less potency than DEHP; thus, even though DINP's proportion of contribution to total HI is increasing, the values of HI have still decreased overall across cycles.

CPSC does not have exposure data for infants that is more recent than the SFF data on which the CHAP relied. Because the risk to WORA has declined since 2005/2006, it is possible that exposures and risks to infants have also declined. However, because the routes of exposure (*e.g.*, food, medicines, products) are different for each target population, it is not possible to quantify the changes in one population based on the other. As explained in section IV.B.1, infants' exposures generally are two- to threefold greater than adults. Thus, CPSC concludes that phthalate exposures and risks in WORA probably underestimate the risks to infants and children.

CPSC's assessment of the risk (and the need for this rule) is also informed by the fact that, although the overall risk as portrayed in the cumulative risk assessment has decreased, DINP's contribution to the cumulative risk has greatly increased. It is not possible to quantify accurately the number of toys expected to have DINP or the effect of changes in DINP exposure on the percentage of the population (infants, pregnant women, or WORA) with HI less than or equal to one. However, any increase in exposure due to resumed or increased use of DINP in products is likely to decrease the percentage of the population with HI less than or equal to one. Allowing DINP to be re-introduced into children's toys and child care articles would open a pathway of exposure to a phthalate that studies have clearly demonstrated causes adverse effects on male reproductive development. Although DIBP, DPENP, DHEXP, and DCHP are not currently found in children's toys and child care articles (or only rarely), these phthalates also cause MRDE and contribute to the cumulative risk.

b. *Comments on Cumulative Risk*

i. Appropriateness of Conducting a Cumulative Risk Assessment

Comment: General acceptance of cumulative risk assessment. Commenters asserted that cumulative risk assessment is not a generally accepted approach. They stated that cumulative risk assessment is not appropriate as a basis for regulatory action, but only as a screening analysis. However, another commenter noted that "when multiple phthalates act on a similar biologic target, it is critical to understand and regulate based on their combined effect on human health." (Comments 2.1 through 2.3).

Response: Cumulative risk assessment is a well-established approach to evaluate risks posed by mixtures of multiple chemicals. EPA first issued guidelines for the risk assessment of chemical mixtures in 1986. Subsequently, ATSDR and the World Health Organization (WHO)

issued guidance for cumulative risk assessment of chemical mixtures.[41] EPA routinely uses cumulative risk assessment to assess risks from pesticides, as required by the Food Quality Protection Act of 1996. Additionally, EPA and ATSDR use cumulative risk assessment to assess risks under Superfund. [42] EPA also has performed cumulative risk assessments, to assess phthalates.[43] The CHAP followed guidance issued by the National Academy of Science for conducting cumulative risk assessments with the one modification, explained above, that allowed the CHAP to calculate HQs for each phthalate and an HI for each individual in the NHANES and SFF studies.

Regarding the assertion that the CHAP's cumulative risk assessment was only a screening-level analysis, CPSC concludes that the CHAP's analysis is a refined assessment that could be considered tier 3, the highest tier, under the framework established by the WHO. The CHAP's CRA began with a comprehensive review of the toxicology and exposure literature. The primary exposure assessment for the CHAP report was based on measurements of phthalate metabolites in a statistically representative population (NHANES study) of actual people. As required for tier 3 assessments under the WHO framework, the CHAP's analysis included probabilistic measurements of exposure and risk.

Comment: Dose additivity. Several commenters asserted that there was not sufficient evidence of dose additivity, especially at low doses, to conduct a cumulative risk assessment for phthalates. Some commenters asserted that one needs a common mode or mechanism of action to support an assumption that phthalates are additive, and they stated that evidence of a common

[41] EPA (1986). EPA (2000b), ATSDR (2004), and WHO (Meek *et al*. 2011).
[42] ATSDR (2017; EPA (2017); Howdeshell *et al*. (2016).
[43] Christensen *et al*. (2014); Gallagher *et al*. (2015).

MOA was lacking. Commenters stated that the CHAP had not considered all the relevant papers on dose additivity. (Comments 2.4 through 2.8).

Response: The CHAP did not need to present evidence of a common MOA or mechanism of action to justify performing a cumulative risk assessment because data from laboratory studies by Hannas and Howdeshell show that phthalate mixtures, in fact, act in a cumulative, additive fashion.[44] Thus, the CHAP did not have to make any assumptions about additivity. In fact, one of the reasons that the CHAP chose MRDE as the health effect for its CRA is that MRDE is the only health endpoint that was extensively studied in phthalate mixtures. CHAP report at p. 2. Moreover, even without a common mechanism of action, chemicals can have cumulative effects in mixtures.[45] Substances can act on the same process, but in different ways, to produce additive effects. In any event, CPSC concludes that evidence demonstrates that the phthalates in the CRA do have a common mechanism of action. As discussed, the phthalates all act on the male reproductive system. More specifically, they act by inhibiting testosterone production in the testis during a critical period in development by decreasing expression of genes involved in steroid synthesis. [46] Additional factors, such as reduced expression of insulin-like hormone 3 gene (insl3), also are at work.[47]

Regarding low doses, studies of phthalate mixtures at low doses do not exist, and the commenters did not present any evidence of a threshold for phthalate-induced MRDE. Although mixture studies at low (environmental) doses have not been performed, there are published studies in which the doses of the individual phthalates produced little or no effect, but the

[44] Hannas et al. (2012); (2011); Howdeshell *et al.* (2007); (2016); (2008).
[45] Axelstad *et al*. (2014); Christiansen *et al*. (2009); Howdeshell *et al.* (2016); Levin *et al.* (1987); Rider *et al*. (2008; 2010; 2009).
[46] Foster *et al*. (2001); Gray *et al*. (2000); Mylchreest *et al*. (1998); Parks *et al*. (2000).
[47] Foster (2005); Howdeshell *et al.* (2016); NRC (2008); Wilson *et al*. (2004).

mixtures produced significant cumulative effects.[48] In a recent study, rats were exposed to phthalates and other antiandrogens at doses well below the NOAEL. Although the individual phthalates had no observable effect, the mixture induced MRDE-related effects. [49] Thus, additivity occurs even at doses where individual phthalates have no observable effect. As discussed in response to comments 2.6 and 2.7, CPSC concludes that the CHAP did consider all relevant papers and that dose addition is appropriate for assessing the cumulative effects of phthalates and other antiandrogens.

Comment: Mode or mechanism of action. Commenters asserted that the mechanism of action by which phthalates affect male reproductive development is not clear. They argued that, in the absence of clarity that phthalates share a common mechanism of action, the CHAP should not conduct a cumulative risk assessment. Some commenters focused particularly on DINP, asserting that DINP does not have the same mode or mechanism of action as other phthalates. (Comments 1.21 through 1.25).

Response: Knowledge of the mode or mechanism of action can help inform the risk assessment process. However, a detailed understanding of the mode/mechanism of action is never required to perform a risk assessment. Several studies have shown that the phthalates act by inhibiting testosterone production in the testis during any critical period in development,[50] by decreasing expression of genes involved in steroid synthesis. Reduced expression of insulin-like hormone 3 gene (insl3) is an additional pathway. [51] Furthermore, all of the phthalates in the cumulative risk assessment induce a similar spectrum of effects, known as the "phthalate

[48] Axelstad *et al*. (2014); Christiansen *et al*. (2010); Hotchkiss *et al.* (2004); Howdeshell *et al.* (2007); (2016); Rider *et al*. (2010).
[49] Conley *et al*. (2017).
[50] Foster *et al*. (2001); Gray *et al*. (2000); Mylchreest *et al*. (1998); Parks *et al*. (2000).
[51] Foster (2005), Howdeshell *et al*. (2016), NRC (2008), and Wilson *et al*. (2004).

syndrome," and which is also described as "antiandrogenic" effects. DINP has been clearly established by multiple studies as causing the same pattern of effects (phthalate syndrome) [52] and by other studies as acting by the same MOA as other phthalates in the cumulative risk assessment.[53] Other experts agree that the phthalates in the CHAP's cumulative risk assessment act by the same mechanism of action.[54] Staff also notes that mixtures studies including DINP show that the effects of DINP and other phthalates are additive. [55] Therefore, a common mechanism of action is not necessary to include DINP in the cumulative risk assessment.

Comment: Inclusion of permanently prohibited phthalates in CRA. Commenters asserted that it was not appropriate for the CHAP to include DEHP and other phthalates that are subject to CPSIA's permanent prohibition in the CHAP's cumulative risk assessment. Commenters asserted that nearly all of the risk in the CHAP's cumulative risk assessment is due to exposures to those phthalates, yet they can no longer contribute to the cumulative risk from exposure to children's products. At least one commenter stated that if the cumulative risk assessment excluded phthalates subject to the CPSIA's permanent prohibition, the HI would be less than one. The commenter reasoned that, therefore, there is a reasonable certainty of no harm from the use of any other phthalates in children's products. Thus, the statutory requirement to "ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety" is satisfied without continuing the interim prohibition. Another commenter stated that a cumulative risk assessment is useful when exposure to each single substance is below the level of concern, but exposures to multiple

[52] Adamsson *et al.* (2009); Boberg *et al*. (2011); Clewell *et al*. (2013b); Gray *et al*. (2000); Hannas *et al*. (2011); Masutomi *et al*. (2003).
[53] Gray *et al*. (2000); Hannas *et al*. (2011).
[54] Foster (2005); Howdeshell *et al.* (2016); NRC (2008).
[55] Hannas *et al*. (2012);(2011); Howdeshell *et al*. (2007); (2016); (2008).

chemicals with the same mechanism of action (or that affect the same endpoint) at the same time rise to levels of concern. However, the commenter asserted, with phthalates, only one chemical (DEHP) poses a risk in isolation. (Comments 2.9 and 5.2).

Response: In accordance with direction in the CPSIA, the CHAP examined phthalates in isolation and in combination with other phthalates. 15 U.S.C. 2057c(b)(2)(B)(ii). Moreover, to accurately assess cumulative risk, it was appropriate for the CHAP to include DEHP (and other phthalate subject to CPSIA's permanent prohibition). Although DEHP is not allowed in children's toys and child care articles, it is permitted in other products. DEHP is found in drinking water, surface water, storm water, soil, and wildlife.[56] It is found in indoor and outdoor air, household dust, and indoor surfaces. DEHP has been found in gloves, footwear, personal care products, medical devices, paints, adhesives, sealants, wallpaper, flooring and food. Thus, given the number and variety of sources of exposure, DEHP should be included in the cumulative risk assessment. The results of staff's cumulative risk assessment using more recent NHANES data, show that, even though exposure to DEHP is decreasing, phthalate exposures are still high enough that some women in the data sample have HIs exceeding one. The CHAP's and staff's analyses indicate that risk is not entirely driven by DEHP. Considering 2013/2014 NHANES data, DINP contributes approximately 6 to 51 percent (medians) or 18 to 76 percent (95th percentiles) of the overall risk. *See* TAB A of staff's briefing package.

ii. *NHANES Data in the Cumulative Risk Assessment*

Comment: Using the CRA to assess individual's risk. Some commenters asserted that calculating risk using NHANES data (that uses spot urine sampling rather than measurements over time) is not an accurate indication of a person's real exposure to phthalates and thus the

[56] Clark (2009); Versar (2010).

CHAP's HI calculations do not show true risk. They asserted it is inappropriate and not scientifically supportable to report results as a proportion of the population with an HI over one (because the individual spot urine samples are too variable and do not represent chronic exposures over time). For example, one commenter stated that an individual's HI from a spot urine sample "has essentially no bearing on risk to the individual" because it does not represent a repeat dose, longer term exposure is necessary to induce the adverse effects (phthalate syndrome) and that a few HIs (or HQs such as DINP) above one also are not representative of the population risk. Commenters thought that this approach was overly conservative and overestimated the risk. (Comments 3.11 through 3.13).

Response: Staff concurs that spot urine samples are variable and are not representative of long-term exposures, but also notes that numerous studies in animals have demonstrated that MRDE and related effects can occur after one or a few doses.[57] It is impossible to know whether a particular spot urine sample is overpredicting or underpredicting the actual exposure. HBM data are a direct measure of human exposure and, therefore, superior to alternatives such as modeled exposures. NHANES is a high quality study and provided exposure data that are representative of the U.S. population. Similar data with 24-hour or longer sampling times are not available.

Staff concludes that it is statistically appropriate to portray the individual NHANES data as a proportion of the NHANES sample population with an HI less than or equal to one. Staff notes that in the 2013/2014 NHANES sample of 538 WORA (of approximately 60 million WORA in the U.S. population), there were from two to nine individuals with a HI greater than

[57] Creasy *et al*. (1987); Jones *et al*. (1993); Saitoh *et al*. (1997); Saillenfait *et al*. (1998); Gray *et al*. (1999); Parks *et al*. (2000); Li *et al.* (2000); Thompson *et al*. (2004); Carruthers and Foster (2005); Thompson *et al.* (2005); Ferrara *et al*. (2006); Hannas *et al.* (2011); Jobling *et al.* (2011); Spade *et al*. (2015).

one (*i.e.*, at risk), depending on the PEAA case. As described in section 5.4 of TAB A of staff's briefing package, the 2013/2014 NHANES data set cannot be used to estimate how many WORA in the U.S. population have HIs greater than one.

Comment: Impact of more recent NHANES data on CRA. Several commenters stated that CPSC staff's analysis of more recent NHANES data shows that the risk from phthalates has declined. Commenters noted that that even at the 95th percentile, the HI is uniformly less than one and has decreased further from the HI values calculated for the 2011/2012 data cycle. They concluded that the CRA using current exposure data shows that there is a reasonable certainty of no harm. Thus, the statutory requirement is satisfied without Commission action. (Comment 3.2).

Response: The CHAP did not indicate that the 95th percentile, or any other part of the cumulative risk distribution, should be used to establish unacceptable risk. Therefore, discussions of acceptable risk should not be limited to the 95th or other percentile. Staff concurs with commenters that through the NHANES cycles, the population of WORA with an HI greater than one has decreased. In the 2013/14 NHANES sample of 538 WORA, there were from two to nine individuals with a HI greater than one (*i.e.*, at risk), depending on the PEAA case. The 2013/2014 NHANES data cannot be used to estimate how many WORA in the U.S. population have HIs greater than one.

Comment: Use of values above the 95th percentile. A commenter on the 2017 staff report asserted that it is "scientifically inappropriate to go above the 95th percentile in evaluating either individual or cumulative risks to the fetuses of women of reproductive age as indicated by the CRA." The commenter stated that going above the 95th percentile values are too unstable to provide a basis for regulatory decisions. The commenter noted that EPA's 2014 paper on five

phthalates reported the 95th percentile from the calculations of HIs for three of the five phthalates (and the CHAP and CPSC's previous analyses used the 95th percentile). (Comment 3.21).

***Response*:** The 95th percentile, as well as other measures such as the average, median, or 99th percentile, is a commonly used metric, included by the CHAP, to help characterize the distribution of exposure and risk in a population. The rule is not based on any particular percentile, but on the observation that people in the NHANES sample have HIs greater than one. CPSC disagrees with the blanket statement that it is scientifically inappropriate to go above the 95th percentile in interpreting a cumulative risk assessment. There is no scientific basis for an assertion that the 95th percentile of a distribution is the largest value that can be considered. The commenter specified that the values above the 95th percentile are unstable. In this case, staff agrees that the values associated with the upper tail of the distribution of HIs (*e.g.*, above the 95th percentile) have large variance estimates, due to sample size (*i.e.*, statistically unstable). The large variances mean that we are precluded from estimating the precise number of WORA with HIs greater than one in the larger population from which the sample was selected. However, individuals with HIs greater than one were observed in every NHANES data cycle analyzed. As the commenter mentioned, EPA's paper (Christensen *et al. (*2014)) states, "we present findings for the 95th percentile of estimated phthalate intake recognizing that there may be more variability in these values, because this information provides insight into the potential risk at the highest levels of exposure in a general population setting." Staff considers EPA's discussion to be consistent with the CHAP's and staff's presentation of results because the goal is to provide insight into the risks among the most highly exposed individuals. The CHAP's and staff's analyses are based on human biomonitoring, *i.e.*, actual observations of people. These observations should be considered in risk management and decision-making.

iii. *The Three Cases*

Comment: Criticism of the three cases (PEAAs) the CHAP used. Commenters raised concerns about all three of the CHAP's cases. Some commenters asserted that the cases inappropriately combined points of departure (PODs) for different types of endpoints (for example, reduced testosterone production, observation of MNGs, and retained nipples) for different effect measures. Commenters stated that the cases had treated transient, non-adverse biomarkers in the same way as adverse effects when selecting PODs. (Comments 4.1 through 4.3 and 4.6).

Response: We discuss the major criticisms of the specific cases in the following comment/responses. As discussed in the section on MRDE, a wide variety of effects of different types and severities are included under the umbrella of phthalate syndrome. Staff disagrees with commenters' assertions that these effects cannot be considered equal when selecting PODs. Any observed effect related to the male reproductive system is a marker of biological activity that could lead to a broad range of effects in the organism. Thus, such markers should be given equal weight in quantifying the biological activity.

Comment: Case 1. Commenters criticized the study that was the basis for Case 1 (Kortenkamp and Faust) , which calculated a potency estimate based on a lowest observed adverse effect level (LOAEL) rather than a no observed adverse effect level (NOAEL) which the commenters stated introduced greater uncertainties. Commenters also asserted that the publication of more robust studies since 2010 (*e.g.*, Boberg) indicating that the Case 1 PEAAs were overstated by a factor of 4 made Case 1 outdated. Commenters also criticized the use of larger uncertainty factors (UFs) for some phthalates. (Comments 4.7 and 4.8).

Response: CPSC agrees that more recent literature has been published regarding the selection of PODs and UFs for phthalates that cause phthalate syndrome. However, this does not mean that Case 1 should be excluded. Rather, alternate approaches (such as Case 1) to POD selection are useful to understand the potential effects of POD and UF selection on risk. Notably, the CHAP considered all relevant hazard studies (including those cited by the commenters) in its *de novo* review of the literature for Case 3.

Comment: Case 2. Commenters criticized various aspects of Case 2 and the study underlying it, (Hannas *et al*. (2011)). Several commenters asserted that CPSC should completely disregard Case 2. They asserted that Case 2 was based on a model that used a hypothetical NOEL for DINP and that the CHAP did not validate the assumptions in the model. The commenters stated that, because "real world data" exist that are more applicable and reliable, CPSC should not use Case 2. Commenters asserted that relative potency of DINP and DEHP was inappropriately estimated. For example, a commenter stated that an *in vivo* study (*i.e*., using live animals) by Gray *et al.* (2000) had previously estimated that DEHP is 10-20 times more active than DINP, so the CHAP should not have used Case 2's estimate that DEHP is 2.3 times more active than DINP. A commenter asserted that the study underlying Case 2 (Hannas *et al*. (2011)) has several flaws and limitations, such as the rats were obtained from different labs, dose-response curves for DINP and DEHP were different, and the study used a low number of animals per group. (Comments 4.9 through 4.13).

Response: The CHAP established alternate approaches (such as Case 2) to POD selection that are useful in understanding the potential effects of POD and UF selection on risk. By stating that Case 2 was based on a model, commenters imply that *Hannas et al.* (2011) was not an *in vivo* study. However, Hannas *et al*. did expose live animals to phthalates.

Measurements of the rate of testosterone synthesis were, by necessity, made in a biochemical assay (*in vitro* study) using tissue obtained from the animals. The CHAP's use of a study that included observation of effects from exposure both to DINP and DEHP allowed a direct comparison of the relative potencies of different phthalates because multiple phthalates were tested in the same laboratory using the same methods. This is the unique advantage of Case 2. Staff considers the estimation of relative potency in Hannas *et al*. (2011) to be valid and notes that substantially similar methods have been used in the estimation of relative potency.[58] Moreover, a 2009 review study estimated that DINP is 2.6 times less potent than DEHP. [59] This estimate is closer to the Hannas *et al* study underlying Case 2 than to the Gray study mentioned by commenters.

Regarding other alleged flaws in the Hannas *et al.* study, staff agrees that the rats used to study DEHP and DINP were obtained from different suppliers (as noted by Hannas *et al*.) and that control testosterone production was different for each group of rats (also identified in the publication). However, the study adequately controlled for these differences. Staff also concludes that the number of animals per dose group was appropriate.

Comment: Case 3. Commenters generally preferred Case 3. Some stated that the CHAP should have relied only on Case 3 in its cumulative risk assessment. However, some commenters had criticisms of Case 3. One commenter asserted that the POD for DINP was inadequately justified. A commenter characterized Case 3 as "muddled" and noted inconsistencies in how the CHAP discussed the NOEL for DINP. Comments questioned whether multi-nucleated gonocytes **(**MNGs), which are the basis of Case 3's point of departure for DINP, are relevant to antiandrogenicity and whether MNGs are an adverse effect. A

[58] Furr *et al*. (2014).
[59] Benson (2009);

comment questioned the choice of 50mg/kg/day as the POD for DINP, asserting that it is too conservative. (Comments 4.15 through 4.17).

Response: For Case 3, the CHAP derived PEAAs for each phthalate based on the CHAP's own literature review considering all published peer reviewed studies on each phthalate. The CHAP considered studies by Clewell *et al*. (2013a, 2013b), Hannas *et al*. (2011), and Boberg *et al*. (2011) as most relevant and highest quality for identifying a NOAEL for DINP. CHAP report at pp. 97–98. The CHAP found that the lowest no effect level seen in these studies was 50 mg/kg-day based on observance of MNGs in the Clewell study. As the CHAP noted, this was a conservative estimate. It is common practice in risk assessment to select the most conservative health endpoint (from quality data sets) when performing a hazard assessment.[60] Although MNG formation is not directly linked to changes in testosterone production, and not necessarily a direct antiandrogenic effect of phthalate exposure, MNGs are a characteristic effect routinely observed in phthalate syndrome.[61] Thus, the observation of MNGs formed after DINP exposure is consistent with the occurrence of MNGs associated with exposure to other active phthalates and is a marker of phthalates' effects in the developing male reproductive system. Although MNGs might not be an adverse effect, finding MNGs following DINP exposure supports that DINP has a biological effect similar to the other active phthalates. Staff concludes that the CHAP's assignment of the NOAEL for DINP at 50 mg/kg-day based on the observation of MNGs, is reasonable.

2. *Risk in Isolation*

In accordance with the CPSIA's direction, the CHAP also considered the risk of phthalates individually. 15 U.S.C. 2057c(b)(2)(B)(ii). As discussed in section III.C.3.b, to do

[60] Barnes and Dourson (1988); CPSC (1992); EPA (1991).
[61] NRC (2008), Howdeshell (2016), and Gaido (2007).

this, the CHAP used an MOE approach. The CHAP chose this approach, in part, due to the recommendation of a NRC report on risk assessment methodology.[62] Like the HI approach, the MOE is also widely accepted. *Id.* The MOE is the "no observed adverse effect level" (NOAEL) of the most sensitive endpoint in animal studies divided by the estimated exposure in humans. Higher MOEs indicate lower risks. Generally, MoEs greater than 100 to 1,000 are adequate to protect public health. CHAP report at pp. 20 and 69. The MOE approach is conceptually similar to the CPSC staff's default approach in CPSC's Chronic Hazard Guidelines for assessing non-cancer risks,[63] and would lead to similar conclusions about risk. We discuss the MOE for each phthalate the CHAP examined in section IV.D of this preamble, and we discuss comments concerning risks in isolation in that section as well.

D. Assessments/Determination for Each Phthalate

The CHAP assessed and made recommendations concerning each of the phthalates that it examined. CHAP report at pp. 82-121. Based on the CHAP report, CPSC staff's assessment, public comments on the NPR and staff's NHANES reports, the Commission issues this rule prohibiting children's toys and child care articles that contain concentrations of more than 0.1 percent of DINP, DIBP, DPENP, DHEXP, and DCHP. The Commission concludes that, based on the best available scientific data, all of these phthalates cause MRDE and all contribute to the cumulative risk. Previous sections of this preamble have discussed the health effect of MRDE, exposure to phthalates, and the risk assessment for these phthalates. This section presents the Commission's evaluation of each of the phthalates covered under this regulation.

[62] NRC (2009).
[63] 57 FR 46626 (Oct. 9, 1992).

1. Phthalates Subject to the Interim Prohibition

The CPSIA established an interim prohibition on children's toys that can be placed in a child's mouth and child care articles that contain concentrations of more than 0.1 percent of DINP, DIDP, and DNOP. 15 U.S.C. 2057c (b)(1). The CPSIA directs the Commission to determine, based on the CHAP report, whether to continue in effect the interim prohibitions on children's toys that can be placed in a child's mouth and child care articles containing DINP, DIDP, and DNOP "to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." Thus, for each of these phthalates, the Commission must decide whether it is appropriate to make the interim prohibitions permanent under the statutory criteria.

As explained in the preamble to the NPR and above, for phthalates causing MRDE, the Commission considered the cumulative risk, which was based on the CHAP's HI estimates. Consistent with the CHAP report, the Commission considers that the acceptable risk is exceeded when the HI is greater than one. This is also consistent with the CPSC's chronic hazard guidelines. 57 FR 46626 (Oct. 9, 1992). The CPSC's chronic hazard guidelines consider the "acceptable risk" for a reproductive or developmental toxicant to be equivalent to an exposure equal to or less than the "acceptable daily intake" (ADI), that is, an HI[64] of less than or equal to one for the population affected by the toxicant. Thus, the Commission considers that an HI less than or equal to one is necessary "to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." The chronic hazard guidelines do not define the percentage of the population (*i.e.*, number of

[64] HI is the ratio of the daily exposure to the ADI. The CHAP's PEAA values are equivalent to an ADI, EPA reference dose (RfD), ATSDR minimal risk level (MRL), or similar terms used by other agencies.

individuals versus the sample population or entire population) that must have an HI less than one in order to ensure a "reasonable certainty of no harm . . . with an adequate margin of safety."

In the NPR, the Commission proposed to prohibit children's toys and child care articles containing more than 0.1 percent of DINP, DCHP, DHEXP, and DPENP based on the CHAP's determination that approximately 10 percent of pregnant women and 5 percent of infants had an HI greater than one. 79 FR at 78334-35. Thus, in issuing the NPR, the Commission concluded that the proportion of populations not affected by cumulative exposure to phthalates (at least 90 percent of pregnant women and 95 percent of infants) did not meet the standard of "a reasonable certainty of no harm with an adequate margin of safety." The Commission did not establish directly, however, that there was a specific proportion of the population that must have an HI less than or equal to one to ensure a "reasonable certainty of no harm with an adequate margin of safety" or to "protect the health of children."

Staff's analysis of the most recent NHANES data showed that exposures to phthalates have changed. Using the CHAP's cumulative risk assessment methodology and the most recent NHANES data, staff has determined that between 98.8 and 99.6 percent of WORA (2013/2014 NHANES) had an HI less than or equal to one. As in previous NHANES data cycles, some individuals in the 2013/2014 NHANES data set still have an HI greater than 1. Depending on the PEAA case used for analysis, between two and nine of the approximately 538 WORA in the NHANES 2013/2014 data sample had an HI of greater than one.[65] Thus, a portion of WORA is exposed to phthalates at levels that can induce MRDE or other phthalate syndrome effects.

For non-antiandrogenic phthalates (*i.e.*, those that do not cause MRDE), the Commission considered the MOE, as estimated by the CHAP to assess risk. As mentioned previously, MOEs

[65] The NHANES data was analyzed using 3 methods (Cases 1-3) For Case 1, three WORA had HIs greater than 1. For Case 2, nine WORA had HIs greater than 1. For Case 3, two WORA had HIs greater than 1.

greater than 100-1,000 are generally considered adequate to protect human health. Thus, the Commission considers a MOE of 100 or greater to be necessary "to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety" or to "protect the health of children."

a. Diisononyl phthalate (DINP)

i. Summary

The CHAP recommended that "the interim prohibition on the use of DINP in children's toys and child care articles at levels greater than 0.1 percent be made permanent." CHAP report at p. 99. The CHAP stated that it made this recommendation "because DINP does induce antiandrogenic effects in animals, although at levels below that for other active phthalates, and therefore, can contribute to the cumulative risk from other antiandrogenic phthalates." *Id.* As discussed in section III.C.4.a. of this preamble, the CHAP cited multiple published studies that showed antiandrogenic effects after DINP exposure in rats. *Id.* at 96-97. DINP is less potent, by perhaps two- to 10-fold, than DEHP.[66] However, DINP contributes to the cumulative risk from all antiandrogenic phthalates. The CHAP found that 10 percent of pregnant women and up to 5 percent of infants have a HI greater than one based on data at that time.

CPSC staff examined more recent NHANES data than the dataset the CHAP considered. Using the CHAP's methodology and the 2013/2014 NHANES exposure data, CPSC staff determined that approximately 99 percent of WORA in the U.S. population now have an HI less than or equal to one (using the 2005/2006 NHANES data, 97 percent of WORA had an HI less than or equal to one). Additionally, CPSC staff's evaluation of recent NHANES data shows that

[66] Gray *et al.* (2000); Hannas *et al.* (2011b).

exposure to DINP has increased approximately five-fold since 2005/2006. DINP now contributes as much to the cumulative risk as DEHP.

As shown by the scenario-based exposure assessment included in Appendix E-1 of the CHAP report, lifting the interim prohibition on children's toys that can be placed in the mouth and child care articles containing more than 0.1 percent DINP could increase exposure to DINP from these products, compared to exposures if DINP is not allowed in these products. If DINP were used in all of the products that were included in the scenario-based exposure assessment, DINP exposure from children's toys and child care articles could account for up to about 29 percent of infants' total DINP exposure from all evaluated sources. Staff does not know the extent to which manufacturers would return to using DINP in children's toys and child care articles if the interim prohibition were lifted. Staff is also unable to quantify the impact of increased DINP exposure on the percent of WORA or infants that have an HI less than or equal to one. However, staff notes that increased exposure will increase the MRDE risk to the population.

The CHAP also assessed the risks of DINP in isolation and found that the MOEs ranged from 830 to 1,500. CHAP report at pp. 95-99. As discussed previously, MOEs of at least 100 are adequate to protect public health. CPSC agrees with the CHAP's analysis that the MOEs for DINP in isolation, did not present a risk. However, DINP exposure has been increasing since the CHAP completed its analysis. Current analysis suggests that DINP MOEs, in isolation, (*e.g.*, the MOE is now 220 to 14,000 at the 95th percentile) are below the upper limit, and are nearing the lower limit considered adequate for protecting public health. Based on the CHAP's analysis and staff's analysis of more recent NHANES data (and after consideration of the comments discussed below), the Commission determines that continuing the interim prohibition concerning

DINP is necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety.

The Commission proposed to expand the scope of the restriction on DINP's use so that the rule would prohibit all children's toys and child care articles containing DINP rather than only children's toys that can be placed in a child's mouth and child care articles. 79 FR at 78335. Likewise, the final rule prohibits all children's toys and child care articles containing concentrations of more than 0.1 percent of DINP. The Commission determines that this expansion of scope is necessary to protect the health of children. Covering all children's toys means that the rule will protect against exposure to DINP through dermal contact (through the skin from handling toys), indirect oral exposure from children handling a toy and then placing their hands in their mouths, and all mouthing behavior. The CHAP's estimates of oral exposure from mouthing toys included any behavior in which the toy contacts the mouth. CHAP report at Appendix E. However, the interim prohibition covers only toys that can be placed in a child's mouth. The CPSIA provides the following definition of "toy that can be placed in a child's mouth":

> For purposes of this section a toy can be placed in a child's mouth if any part of the toy can actually be brought to the mouth and kept in the mouth by a child so that it can be sucked and chewed. If the children's product can only be licked, it is not regarded as able to be placed in the mouth. If a toy or part of a toy in one dimension is smaller than 5 centimeters, it can be placed in the mouth.

15 U.S.C. 2057c(g)(2)(B). Thus, continuing the interim prohibition with regard to DINP without expanding the scope would exclude toys that are 5 centimeters or larger in one dimension (or have parts 5 centimeters or larger) even though children may be exposed to phthalates from licking or otherwise contacting the toy with the lips and tongue. Additionally, although staff does not have exposure estimates for indirect oral exposure from handling toys and normal hand-to-mouth behavior, staff concludes that exposures from handling toys will further contribute to the

cumulative risk. Based on the analysis provided in Appendix E of the CHAP report, the Commission believes that the rule should encompass any behavior in which the toy contacts the mouth because this behavior provides a pathway of exposure to antiandrogenic phthalates.

ii. *Comments Concerning DINP*

As noted in section IV.A, commenters presented numerous arguments questioning whether phthalates are antiandrogenic, *i.e.*, cause MRDE, and about the cumulative risk assessment. This section discusses the comments that focused on DINP.

(a) Health Effects of DINP Exposure

Comment: DINP and MRDE. Numerous commenters questioned whether DINP is antiandrogenic, that is, whether it causes MRDE. Commenters asserted that studies do not consistently show that DINP induces the effects associated with rat phthalate syndrome (*e.g.*, decreased fetal testosterone, changes in anogenital distance, nipple retention, reproductive tract malformation, decreased sperm production). They cited numerous studies to support their assertions that DINP is not antiandrogenic and they stated that, for these reasons, the CHAP should not have included DINP in the cumulative risk assessment. However another commenter supported the inclusion of DINP in the cumulative risk assessment because DINP is antiandrogenic. (Comment 1.14).

Response: The CHAP found, and CPSC agrees, that DINP-induced effects are consistent with phthalate syndrome in rats. Clewell *et al.* found changes in testosterone, nipple retention, and AGD, among other observations, by multiple laboratories, which indicate that DINP exposure is associated with outcomes similar to the effects of other phthalates such as DEHP and DBP that cause MRDE; these findings support the conclusion that DINP causes phthalate syndrome. CHAP report at pp. 97-98. CPSC's conclusions are based on the weight of the

evidence from review of multiple studies (discussed in comment responses 1.15 to 1.20). Phthalate syndrome is a spectrum of effects and thus one does not expect to observe all phthalate syndrome effects in all studies. The CHAP noted that effects of the phthalates it evaluated were dose-related. CHAP report at p. 2.

Although DINP is less potent than other antiandrogenic phthalates, DINP can contribute to the cumulative risk from other phthalates. DINP has similar effects as other antiandrogenic phthalates, and thus is considered antiandrogenic in the context of the cumulative risk assessment. CPSC concludes that because DINP causes phthalate syndrome, it was appropriate for the CHAP to include DINP in its cumulative risk assessment and for the Commission to prohibit children's toys and child care articles containing DINP.

Comment: DINP and effects on testosterone production. Some commenters stated that studies showed inconsistent results regarding the effect of DINP on the production of testosterone and that this indicates DINP does not induce rat phthalate syndrome. (Comment 1.15).

Response: As the commenters recognize, some studies *do* show reductions in testosterone following DINP exposure.[67] CPSC staff agrees that some studies (*e.g.*, Clewell *et al*. (2013a);(2013b)) involving repeated measurements over time have not shown permanent or persistent changes in testosterone. Sometimes this was due to differences in study design. However, permanent or persistent changes in testosterone are not required to have an adverse impact on male reproductive development; rather, transient reductions in the rate of testosterone synthesis at the critical period of development do have permanent effects (*e.g*., structural,

[67] Boberg *et al*. (2011); Borch *et al*. (2004); Clewell *et al*. (2013a); (2013b).

functional) on male reproductive organs.[68] Furthermore, staff agrees with the study by Hannas *et al.*, showing that the rate of testosterone synthesis, rather than plasma or testicular levels, is the most relevant measure of phthalate-induced effects on testosterone.[69] Additionally, testosterone measurements made after dosing lab animals with DINP has ended do not account for the possible effects of ongoing exposure, as could be expected for humans with exposures occurring after birth from food, water, or contact with consumer products. Staff notes that its conclusions are consistent with findings from a recent NAS systematic review of the DINP scientific literature.[70] In that review study, the authors asserted with high confidence that DINP could be considered a "presumed human hazard" because of its potential to reduce testosterone in male fetal rats

Comment: Effect of DINP on anogenital distance. Some commenters cited studies showing little or no effect on anogenital distance (AGD, *i.e.*, the distance from the anus to the genitalia) after dosing with DINP. They asserted that these studies show DINP does not induce phthalate syndrome. A commenter questioned the results of one study where a significant decrease in AGD was observed, because of the very small differences between the treated and control groups. (Comment 1.16).

Response: Reduced AGD is one of the abnormalities that characterizes rat phthalate syndrome. CHAP report at pp. 1-2. The commenter questioned the AGD reductions observed in the Boberg *et al.* (2011) and Clewell *et al*. (2013b) studies; however, these results were actually larger than the magnitude considered by the commenter as unlikely to be biologically significant. Overall, the weight of evidence in the studies cited by the commenter demonstrates that DINP

[68] Hannas *et al*. (2011).
[69] Hannas *et al*. (2011).
[70] NAS (2017).

causes permanent effects on male reproduction. Thus, the commenter's contention regarding a transient nature of DINP's effects on AGD conflicts with the body of evidence that DINP leads to phthalate syndrome. Furthermore, the animal studies, which involve short term exposures, do not reflect the continuous exposures that occur in humans.

Comment: Nipple retention. Commenters questioned whether nipple retention is a relative endpoint when considering phthalates' effects on humans and questioned the results of studies by Boberg *et al*. (2011) and Gray *et al*. (2000). Commenters also noted that Clewell *et al*. (2013b) reported no significant difference in nipples in male rats exposed to DINP. (Comment 1.17).

Response: The CHAP specifically discussed nipple retention as a relevant endpoint for antiandrogenic activity, and concluded that nipple retention in male animals is consistent with phthalate-induced reductions in testosterone levels. CHAP report at p. 16 and Appendix A-2. Staff notes that nipple retention is sensitive to exposure of the developing animal during key windows of susceptibility. Studies cited by the commenters that indicate the dosing ends during gestation or within the early part of the postnatal period do not consider possible effects of ongoing exposure, as could be expected for humans with exposures occurring after birth, but within early life periods of vulnerability from food, water, or contact with consumer products. As noted previously, phthalate syndrome is a spectrum of effects; all effects will not be present in every study.[71] Although nipple retention in animals may not correspond to a specific endpoint in humans, nipple retention is an antiandrogenic effect that could manifest in different ways in humans.

[71] Howdeshell *et al.* (2016).

Comment: Reproductive tract malformations. Commenters noted that a number of animal studies involving DINP have not reported male reproductive tract malformations, such as cryptorchidism or hypospadias. For example, commenters stated that in the study by Gray *et al.* (2000), the significance of the changes after DINP exposure were unclear and questionable. (Comment 1.18).

Response: Staff recognizes that the same specific male reproductive tract malformations have not been consistently observed following DINP exposure. As noted previously, phthalate syndrome is a spectrum of effects and not all effects will be observed in every study. As the CHAP recognized, the observation of effects depends on the dose level used in each study. CHAP report at p. 2. The three studies described by the commenter as "definitive" studies (Hellwig *et al.*, Hushka *et al.*, and Waterman *et al.*) were not designed or intended to detect phthalate syndrome effects. In fact, one of the "definitive" studies (Hushka *et al.*) was on DIDP, which does not cause phthalate syndrome. Staff acknowledges that the Clewell study demonstrates that DINP induces limited or no phthalate syndrome effects following dietary dosing to rats. In spite of this, the authors themselves conclude that DINP has less potency than DEHP or DBP, but more than DEP when considering effects on the male reproductive tract. They additionally state "DINP is simply less potent than DBP and DEHP, *i.e.*, it has lower potency in causing any adverse responses." Staff also notes that this study involved oral dosing via feed, which is different than oral dosing using a tube inserted into the stomach (gavage dosing), which is used in typical developmental toxicity studies for determining phthalate syndrome effects. Different dosing strategies may account for the lack of effects seen in the Clewell study. Staff responds to commenters' criticisms of other studies in comment/response 1.18 in Tab B of the staff's briefing package.

Comment: DINP's effects on sperm. Several commenters asserted that there is no strong evidence that DINP adversely affects sperm production or quality. They discussed a number of studies regarding DINP's effects on sperm parameters, male mating behavior, and fertility. (Comment 1.19).

Response: Three studies that commenters described as definitive were not actually designed or intended to detect phthalate syndrome effects. One of them was on DIDP, which does not cause phthalate syndrome. Inconsistencies could be due to study parameters or to the lower potency of DINP compared to other phthalates that have more consistent effects on sperm and fertility. Staff provides a more detailed response in comment/response 1.19 in Tab B of the staff's briefing package.

Comment: Multi-nucleated gonocytes (MNGs). Several commenters disagreed with the CHAP's use of MNG formation as a phthalate syndrome endpoint, and asserted that MNG formation is not a consequence of exposure to DINP. Some commenters asserted that MNG induction should not be considered an adverse effect because the MNGs are eliminated within a few weeks after birth. (Comment 1.20).

Response: Although MNG formation is not linked directly to changes in testosterone production, and not necessarily a direct antiandrogenic effect of phthalate exposure, MNGs are a characteristic effect routinely observed after dosing with phthalates.[72] Thus, the observation of MNGs formed after DINP exposure is consistent with results after exposure to other active phthalates, such as DBP, and is a marker of phthalates' effects in the developing male

[72] Spade *et al*. (2015).

reproductive system. Furthermore, one study suggests that the presence of MNGs may be linked to reduced fertility or testicular germ cell cancer in humans.[73]

Comment: Human epidemiology data and DINP antiandrogenicity. One commenter asserted that the available epidemiology data do not support the assertion that DINP is associated with reproductive effects in humans. The commenter presented a review of four studies that evaluated DINP's association with adverse human reproductive effects.[74] The review found lack of correlation or equivocal results in these studies. The commenter also found that a more recent study that reported slight reductions in AGD associated with DINP metabolites in mother's urine was equivocal.[75] Another commenter noted that statistical chance may have been responsible for some of the epidemiology studies' positive association. The commenter concluded that the weight of the current information did not support that humans developed reproductive or developmental issues following exposure to phthalates. (Comment 7.5).

Response: Of the four studies mentioned by the commenter, two were of adults and one was of boys aged 6–19 years. The CHAP concluded that studies in adult men were less relevant to the CHAP's work because exposures measured during adulthood cannot be used to infer childhood or early life exposure. Observational epidemiology studies control for the possibility of random chance, bias, or confounding in their study design and analysis. The primary studies that commenters mentioned discuss the studies' efforts to minimize these effects. Staff concludes that most of the studies cited by the commenters are not relevant to the current rulemaking on children's toys and child care articles because they involved adults or older children. Because humans are simultaneously exposed to multiple phthalates, it is difficult to

[73] Ferrara *et al*. (2006).
[74] The studies were (Joensen *et al*. (2012); Jurewicz *et al*. (2013); Main *et al*. (2006); Mieritz *et al*. (2012).
[75] Bornehag *et al*. (2015).

distinguish the effects of different phthalates in epidemiology studies. Staff concludes that the overall weight of the evidence demonstrates an association between prenatal phthalate exposure and MRDE effects in infants.

(b) DINP and Risk

Comment: DINP's contribution to risk. Several commenters asserted that DINP contributes little to the cumulative risk. They noted that the CHAP's cumulative risk assessment showed that the estimated risks associated with phthalate exposure were driven by DEHP and DBP, and that DINP contributed only a small portion of the combined risk (less than one percent). A comment on CPSC staff's 2017 report stated that as DINP continues to replace DEHP, the risk will continue to fall, thus increased replacement of phthalates by DINP will lower the cumulative risk further than it currently is. Along these lines, the commenter asserted that lifting the interim prohibition regarding DINP would have only an "inconsequential effect" on cumulative risk. Some commenters asserted that, because DINP is less potent than DEHP, even if DINP entirely replaced DEHP, the 95th percentile HI would be far below one. (Comments 3.3, 3.4, and 5.1).

Response: CPSC agrees that the median and 95th percentile HIs would be less than one if all CRA phthalate exposures were considered to be from DINP. However, a certain number of WORA in the 2013/2014 NHANES sample have HIs and DINP HQs greater than one. Any increase in DINP exposure could increase these individuals' risk. In addition, there are a number of individuals that have HIs and DINP HQs near one. Additional DINP exposure to these individuals could increase the risk to greater than an HI of one (see comment response 3.2 and TAB A). Based on the scenario-based exposure assessment, lifting the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing more than

0.1 percent of DINP could result in children's toys and child care articles accounting for up to about 29 percent of total DINP exposure to infants. However, if DINP is not allowed in children's toys and child care articles, such products would not contribute to total DINP exposure. Staff is unable to quantify the impact of changes in DINP exposure on the percent of WORA or infants that have an HI less than or equal to one, although staff notes that an increased exposure will increase the MRDE risk to the population. Staff does not consider that increasing MRDE risk to the population is "inconsequential," particularly to those affected.

As the commenter points out, in reality DINP would not replace all of the other phthalates because the differences in properties among the phthalates limit their use depending on the intended application. WORA with HQs greater than one were measured in each NHANES cycle despite the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing DINP. Any further increase in DINP exposure could increase the risk from DINP.

Comment: "Reasonable certainty of no harm" and DINP. Some commenters asserted that the standard "reasonable certainty of no harm" is met without continuing the interim prohibition regarding DINP. They reasoned that, because the CPSIA permanently prohibited children's toys and child care articles containing DEHP, DBP and BBP, those phthalates cannot contribute to any cumulative risk from these children's products in the future; and without those phthalates, the HI clearly is less than one, so there is a reasonable certainty of no harm from use of DINP in these children's products. In contrast, other commenters asserted that it "turns logic upside-down" to suggest that "as DEHP is replaced by less toxic phthalates, there is a reasonable certainty of no harm from increasing exposures to the remaining phthalates," because the level of future replacement is unknown, but it is known that the replacement phthalates present hazards.

Commenters on the staff's analysis of more recent NHANES data asserted that CPSC staff's analysis clearly demonstrates that the interim prohibition involving DINP can be lifted while meeting the "reasonable certainty of no harm" standard set forth in the CPSIA because the NHANES 2013/2014 data show that cumulative risk for WORA continues to decline with the HI consistently below one for the 50th and 95th percentiles. (Comment 3.20).

Response: As explained, studies show that DINP contributes to the cumulative risk. The CPSIA's permanent prohibition keeps DEHP, BBP, and DBP out of children's toys and child care articles; however these phthalates continue to be used in other products and thus they contribute to the cumulative risk. The CRA demonstrates that HIs greater than one were observed in WORA, in all NHANES data cycles, including the most recent (2013/2014). Thus, male children born to these women could be at risk for MRDE. Because a portion of the potentially sensitive population is still near the level of concern (HI greater than 1), permanently prohibiting children's toys and child care articles containing DINP is still necessary to "ensure a reasonable certainty of no harm" to children and pregnant women with an "adequate margin of safety."

Comment: Diet as source of exposure to DINP. Several commenters noted that diet is the primary source of exposure for DINP, as well as other phthalates, in infants and children. They asserted that DINP contributes so little to the combined risk from exposure to phthalates from all sources that a permanent prohibition on DINP's use in children's toys and child care articles would have little effect on the overall risk and, thus, the prohibition is not supported. (Comment 5.3).

Response: The CHAP report does show that food, rather than children's toys or child care articles, provides the primary source of phthalate exposure to women and children. CHAP

report at pp. 49-53. The other main contributors were soft plastic toys and teethers (via mouthing), and personal care products such as lotions, creams, oils, soaps, and shampoos via dermal contact. *Id*. Figure 2.1.

The scenario-based exposure assessment included in the CHAP report shows that mouthing and dermal exposure to toys could contribute an average of 12.8 percent, 5.4 percent, and 1 percent of the overall DINP exposure to infants, toddlers, and children, respectively, if DINP were used in these products. *Id.* at Appendix E1, Tables E1-21, E1-22, and E1-23. Mouthing and handling soft plastic toys and teethers could contribute 12.8 percent (mean exposure) or 16.6 percent (95th percentile exposures) of total DINP exposure in infants. *Id.* at Table E1-21. Dermal contact with the evaluated toys and child care articles may contribute up to an additional 16.5 percent of exposures to infants. *Id.* Therefore, although infants' DINP exposure was primarily from diet, up to 29 percent may be due to the presence of DINP in the evaluated toys and child care articles. *Id.*, Figure 2.1.

Comment: DINP in isolation. Commenters asserted that the CHAP found no significant health risk from exposure to DINP by itself (considered in isolation), given the very large MOE estimates for median exposures, as well as for the 95th percentile of exposure. Commenters concluded that because of the high MOEs for DINP from all sources, the margins of safety must be even larger for the children's products' contribution to DINP exposure, and thus, there is no basis for a permanent prohibition on children's toys and child care articles containing DINP. A commenter also stated that replacement of DEHP by DINP would not be expected to increase the risk because of DINP's lower potency. A commenter also asserted that even a doubling in DINP exposures would not increase the risk substantially, thus, restricting DINP's use is unwarranted. (Comment 5.5).

Response: As discussed previously, the CHAP's recommendations and the Commission's rule are based on the cumulative risk from DINP in combination with other phthalates. We note, however, that due to the increased exposure to DINP (as seen in the 2013/2014 NHANES data), DINP's risk in isolation has increased. Thus, DINP alone may dominate the cumulative risk in the future, and DINP exposure in isolation may approach the level of concern, especially considering Case 2. Using the most recent NHANES data, the MOEs for WORA exposed to DINP range from 2300 to 150,000 (median) and 220 to 14,000 (95^{th} percentile) for all three cases.

CPSC disagrees with the assertion that doubling the DINP exposure would not increase the risk substantially, and notes that currently, a certain proportion of WORA individuals have a DINP HQ greater than one and a certain proportion of WORA individuals have DINP HQs near one. Increasing exposure to DINP may increase the number of individuals with an HQ greater than one or may increase the HQs of individuals with an HQ greater than one. Furthermore, doubling DINP exposures would lower the MOE for DINP to 110 to 7000 (95^{th} percentile). The CHAP noted that MOEs exceeding 100 to 1000 are typically "considered adequate for protecting public health." CHAP report at p. 4. Current analysis suggests, therefore, that DINP MOEs, in isolation, (*e.g.*, the MOE is 220 for Case 2) are below the upper limit, and are nearing the lower limit considered adequate for protecting public health.

Comment: Safety of DINP compared to alternatives. Numerous commenters expressed concern about prohibiting the use of DINP in children's toys and child care articles when not much is known about the toxicity and safety of alternative chemicals. Some commenters stated that the safety of alternative plasticizers should be thoroughly tested before placing restrictions on DINP. Commenters stated that DINP is well studied, has been used for

over 50 years, and has been found safe for its intended uses. Commenters were concerned that prohibiting the use of DINP in children's toys and child care articles could potentially put people at greater risk as substitutes with uncertain safety are used instead. (Comment 10.5).

Response: CPSC shares the commenters' concerns about the shift of chemical use from phthalates with known toxicity to phthalate alternatives with less toxicity or exposure information. The CHAP identified several data gaps for phthalate alternatives. CPSC agrees with the CHAP's recommendation that appropriate federal agencies should perform additional research and risk assessment activities on phthalates and phthalate alternatives to fill in data gaps. However, CPSC does not believe that the lack of data on alternative plasticizers means we should not take action regarding DINP. DINP has in fact been covered by the interim prohibition since February 2009. As explained in the NPR and throughout this document and the staff's briefing package, based on the CHAP report and staff's analysis, we conclude that DINP causes adverse effects on male reproductive development and contributes to the cumulative risk of these effects from other antiandrogenic phthalates. Thus, the Commission determines that prohibiting children's toys and child care articles containing concentrations of more than 0.1 percent of DINP is necessary to ensure a reasonable certainty of no harm and to protect the health of children.

(c) Scope of Prohibition Regarding DINP

Comment: Support for expanding scope to all children's toys rather than those that can be placed in a child's mouth. Several commenters stated that the Commission lacked justification to expand the restriction on DINP from "children's toys that can be placed in a child's mouth" to all children's toys. One commenter noted that it is not clear the CHAP intended to recommend this expansion. Other commenters noted that because the MOEs for

DINP show that it does not present a risk in isolation, there is no basis for expanding the interim prohibition to cover all children's toys. Commenters asserted that the Commission had little justification for the change and that it would have little effect on the risk. They noted that any risk comes primarily from mouthing. However, other commenters, citing evidence that DINP is associated with MRDE and the CHAP's CRA analysis, stated that the CRA clearly supported the proposed prohibition involving DINP and the proposed expansion of scope from toys that can be placed in a child's mouth to all children's toys. (Comments 6.1 and 6.2).

Response: As discussed previously, this rule is based on the cumulative risk analysis demonstrating that DINP (and other antiandrogenic phthalates) causes MRDE and, and the most recent NHANES data that shows that there were from two to nine individuals with a HI greater than one in a sample of 538 WORA. Limiting the rule to children's toys that can be placed in a child's mouth would exclude toys that could also expose children to DINP through mouthing behaviors other than placing the toy in the mouth and through hand to mouth exposure (*e.g.*, licking) as well as direct exposure through dermal contact. The 2013/2014 NHANES data indicate that exposure to DINP is increasing, even with the CPSIA's interim prohibition in effect. Covering all children's toys (rather than only those that can be placed in a child's mouth) will decrease exposure to DINP and thus reduce the risk of MRDE.

Comment: Reliance on low cost and low dermal exposure as rationale in NPR. Commenters asserted that the NPR had provided faulty rationales for the expansion. A commenter asserted that the Commission had inappropriately based the expansion to all children's toys on consideration of testing costs rather than on risk. A commenter stated that the reasoning stated in the NPR in favor of expanding the rule to all children's toys was inconsistent with the reasons CPSC had stated for not expanding the prohibition to all children's products.

The commenter understood that CPSC did not propose to cover all children's products because of negligible exposure due to the infrequency of mouthing of children's products (that are not children's toys or child care articles). The commenter asserted that this same rationale indicates that the rule should not be expanded beyond children's toys that can be placed in a child's mouth. (Comment 6.3 and 6.6).

Response: The NPR mentioned that the proposed expansion would have little impact on testing costs. 79 FR 78335. However, the NPR merely noted this anticipated impact; the reason for the expansion is to reduce the risk of adverse health effects. Regarding any inconsistency between proposing to expand the interim prohibition to all children's toys and proposing not to cover additional children's products, we note that the proposal concerning all children's products was based primarily on a lack of information to assess the impact on children's health.

Comment: Reliance on European assessment as rationale in NPR. Commenters objected to the NPR's discussion of the Europe Union's regulations on phthalates. Commenters noted that the NPR stated that the European Commission's 2005 directive on phthalates had distinguished between all children's toys and toys that can be placed in the mouth due to uncertainties about DINP, DNOP and DIDP. The NPR suggested that, now that the CHAP had issued its report, these uncertainties no longer exist. Commenters objected to the NPR's reliance on this reasoning to support the expansion of the regulation of DINP. In addition, the EU submitted a related comment noting that the European Chemicals Agency (ECHA) conducted an extensive review in 2010 on DINP, DIDP and DNOP, and concluded that exposure other than mouthing did not present further risk. (Comments 6.4 and 6.5).

Response: Regarding the ECHA's re-evaluation, that report did not specifically address the distinction between children's toys and toys that can be placed in a child's mouth.

Additionally, the 2013 ECHA report used different health end points (liver toxicity) as the focus, rather than the MRDE focus used by the CHAP and CPSC. Moreover, the 2013 ECHA report did not consider cumulative health risks from multiple phthalates.

*b. D*i-*n*-octyl phthalate (*DNOP)*

The CHAP concluded that DNOP does not lead to male developmental reproductive toxicity in animals and, therefore, does not contribute to the cumulative risk. Although DNOP does cause other developmental (supernumerary ribs) and systemic effects (liver, thyroid, immune system, and kidney), the MOEs in humans are very high. Therefore, the CHAP recommended that the current prohibition involving DNOP be lifted. CHAP report at pp. 91-95. The NPR noted that DNOP levels in people are so low that they are not detectable in about 90 percent of humans, and that DNOP is not antiandrogenic, and, therefore, does not contribute to the cumulative risk. 79 FR 78334. Based on the CHAP report and staff's analysis, the Commission concludes that continuing the prohibition of children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DNOP is not necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety.

c. Diisodecyl phthalate (*DIDP)*

The CHAP concluded that DIDP does not lead to male developmental reproductive toxicity in animals and, therefore, does not contribute to the cumulative risk. The CHAP considered the risk of DIDP in isolation and found that DIDP does cause other developmental (supernumerary ribs) and systemic effects (liver, and kidney). However, because the MOEs in humans are sufficiently high (range from 2,500 to 10,000 for median DIDP exposures and 586 to 3,300 for upper-bound exposures), the CHAP recommended that the interim prohibition

involving DIDP be lifted. CHAP report at pp. 100-105. As noted in the NPR, DIDP exposure would need to increase by more than 250 times to exceed an acceptable level. 79 FR 78334. Based on the CHAP report and staff's analysis, the Commission concludes that continuing the prohibition of children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DIDP is not necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety.

d. Comments Concerning DNOP and DIDP

Comment: Prohibition concerning DNOP and DIDP should be made permanent. Some commenters asked the Commission to make the interim prohibition regarding DNOP and DIDP permanent. Commenters reiterated the CHAP's conclusions that DNOP is a potential developmental toxicant, causing supernumerary ribs, and a potential systemic toxicant, causing adverse effects on the liver, thyroid, immune system, and kidney. They noted that the CHAP stated that DIDP was a 'probable toxicant' based on reproductive and developmental effects, and adverse systemic effects on the liver and kidney. A commenter suggested that "there could be a cumulative impact from exposures to a mixture of DINP, DNOP and DIDP, which would enhance the concern about harm." Commenters asserted that without enough data to conduct a robust risk assessment, lifting the prohibition involving DNOP and DIDP will lead to elevated exposure to these two phthalates when others are covered by prohibitions. (Comments 5.8 and 5.9).

Response: The CHAP concluded that DIDP and DNOP do not appear to possess antiandrogenic potential and therefore the CHAP did not include them in the cumulative risk assessment. As discussed above, the CHAP's analysis of DIDP and DNOP in isolation showed

high MOEs (greater than 1000 for all populations) that are sufficient to protect human health. The CHAP found that DNOP exposure levels are so low that one of the metabolites, MNOP, was not detectable in about 90 percent of humans. CHAP report at Table 2.6. Exposures would have to increase by a large measure before the acceptable levels of exposure would be exceeded. Thus, the CHAP report and staff's analysis do not support a conclusion that prohibiting the use of DNOP or DIDP in children's toys that can be placed in a child's mouth and child care articles is necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety.

Comment: "Reasonable certainty of no harm" and DNOP and DIDP. Some commenters asserted that lifting the interim prohibition concerning DNOP and DIDP while banning other phthalates would raise questions about whether such action meets the "reasonable certainty of no harm" standard. They noted that the CHAP report found exposure to these chemicals from toys and child care articles and that the CHAP reported developmental and systemic toxic effects caused by these chemicals in animal studies. (Comment 5.9).

Response: The CHAP concluded that DIDP and DNOP do not appear to possess antiandrogenic potential and therefore the CHAP did not include these two phthalates in the cumulative risk assessment. Assessing these chemicals in isolation, the CHAP found that the margins of exposure were sufficiently high to protect human health. Therefore, staff concludes that there is no justification to continue the prohibition involving DNOP or DIDP.

2. Phthalates Subject to the Rule But Not Currently Prohibited Under the CPSIA In addition to determining what action to take regarding the interim prohibition, the CPSIA directed the Commission to "evaluate the findings and recommendations of the Chronic Hazard Advisory Panel and declare any children's product containing any phthalates to be a banned hazardous

product under section 8 of the Consumer Product Safety Act (15 U.S.C. 2057), as the Commission determines necessary to protect the health of children." 15 U.S.C. 2057c(b)(3)(B).

In the absence of a definition or other guidance on the meaning of the phrase "necessary to protect the health of children," CPSC interprets the phrase in the context of the CHAP report and CPSC's chronic hazard guidelines,[76] which consider that an HI less than or equal to one is necessary to protect the health of children. As explained in the CHAP report, the four additional phthalates all cause male reproductive developmental effects and would contribute to the cumulative risk.

The CHAP reviewed the potential health risks associated with eight phthalates that were not prohibited by the CPSIA, and it recommended that four additional phthalates (DIBP, DPENP, DHEXP, and DCHP) be prohibited from use in children's toys and child care articles. The CHAP found that these four phthalates are associated with adverse effects on male reproductive development and contribute to the cumulative risk from antiandrogenic phthalates. CPSC staff has reviewed the CHAP's assessment and agrees with the recommendation. Based on the CHAP's evaluation and the staff's assessment, the Commission proposed to prohibit children's toys and child care articles containing more than 0.1 percent of DIBP, DPENP, DHEXP, and/or DCHP. 79 FR 78335-78337. The Commission determines that prohibiting children's toys and child care articles that contain concentrations of more than 0.1 percent of DIBP, DPENP, DHEXP, and/or DCHP is necessary to protect the health of children and issues this final rule to establish this prohibition.

Although current exposures to these four phthalates are low, these phthalates could be used as substitutes for the phthalates subject to prohibition, thus increasing human exposures

[76] 57 Fed. Reg. 46626 (Oct. 9, 1992).

from MRDE phthalates. All of these four phthalates are capable of contributing to the cumulative risk. A 2014 study demonstrated that three of these four phthalates (DPENP, DHEXP, and DCHP) had much greater potency than DEHP which the CPSIA permanently prohibits from use in children's toys and child care articles. [77] The potency of the fourth (DIBP) was slightly less or similar to DEHP.[78] In addition, these four phthalates may have a greater potential for exposure than DINP, because lower molecular weight plasticizers generally have higher migration rates. [79]

a. Diisobutyl Phthalate (DIBP)

The CHAP recommended prohibiting the use of diisobutyl phthalate (DIBP) in children's toys and child care articles. CHAP report at pp. 110-113. DIBP is associated with adverse effects on male reproductive development and contributes to the cumulative risk from antiandrogenic phthalates. Furthermore, as noted in the NPR, DIBP has been found in some toys and child care articles during compliance testing by CPSC. The CHAP estimated that DIBP contributes up to 5 percent of the cumulative risk in infants from all products and sources. CHAP report at Table 2.16. More recent biomonitoring data show that DIBP exposures and risks have increased by about 50%. TAB A of staff briefing package.

DIBP is similar in toxicity to DBP, which is one of the phthalates subject to the CPSIA's permanent prohibition. DIBP was shown to be antiandrogenic in numerous studies and it acts in concert with other antiandrogenic phthalates. The CHAP found that current exposures to DIBP are low. When considered in isolation, DIBP has a MOE of 3,600 or more. CHAP report at pp. 24, 110-111. DIBP contributes roughly 1 to 2 percent of the cumulative risk from phthalate

[77] Furr *et al*. (2014).
[78] Furr *et al*. (2014); Hannas *et al*. (2011).
[79] Dreyfus and Babich (2011).

exposure to pregnant women and 1 percent to 5 percent in infants. However, the CHAP based its recommendation on cumulative risk.

Based on evaluation of the CHAP report and staff's review, the Commission concludes that there is sufficient evidence to conclude that DIBP is antiandrogenic and contributes to the cumulative risk. The Commission also concludes that, applying the CPSC chronic hazard guidelines, this phthalate is considered "probably toxic" to humans based on sufficient evidence in animal studies. As discussed previously, the Commission considers that a HI less than or equal to one is necessary "to protect the health of children." Using the most recent biomonitoring data, some WORA in the sample have an HI that exceeds one. For PEAA Case 1, three WORA had an HI greater than one; for PEAA Case 2, nine WORA had an HI greater than one; and for PEAA Case 3, two WORA had an HI greater than one. In addition, CPSC staff has identified DIBP in a small portion of toys and child care articles during routine compliance testing. Therefore, the rule prohibits children's toys and child care articles containing concentrations of more than 0.1 percent of DIBP. The Commission concludes that this action is necessary to protect the health of children because it would prevent current and future use of this antiandrogenic phthalate in children's toys and child care articles.

b. Di-n-pentyl Phthalate (DPENP)

The CHAP recommended prohibiting the use of DPENP in children's toys and child care articles. CHAP report at pp. 112-113. DPENP is associated with adverse effects on male reproductive development and contributes to the cumulative risk from antiandrogenic phthalates. Furthermore, DPENP is the most potent of the antiandrogenic phthalates. Prohibiting the use of DPENP would prevent its use as a substitute for other banned phthalates. The Commission agrees with the CHAP's recommendation for DPENP. Based on the CHAP report and previous

toxicity reviews by CPSC staff and a contractor,[80] the Commission concludes that there is sufficient evidence that DPENP is antiandrogenic and contributes to the cumulative risk. For example, the CHAP noted studies by Howdeshell *et al*. and Hannas *et al*., which found that exposure to DPENP reduced fetal testicular testosterone production. *Id*. at p. 112. The Commission also concludes that, applying the CPSC chronic hazard guidelines, this phthalate is considered "probably toxic" to humans, based on sufficient evidence in animal studies. Furthermore, DPENP is roughly two- to three-fold more potent than DEHP. [81] Although CPSC staff has not detected DPENP in children's toys or child care articles, metabolites of DPENP have been detected in humans,[82] indicating that some exposure to DPENP does occur. In the CHAP's analysis, up to five percent of infants and up to 10 percent of pregnant women exceed the negligible risk level (HI greater than one). Using the most recent biomonitoring data, some WORA in the sample have an HI greater than one. Allowing the use of DPENP in children's toys and child care articles would further increase the cumulative risk. As discussed previously, the Commission considers that a HI less than or equal to one is necessary "to protect the health of children." Therefore, the rule prohibits children's toys and child care articles containing concentrations of more than 0.1 percent of DPENP. The Commission concludes that this action is necessary to protect the health of children because it would prevent current and future use of this antiandrogenic phthalate in toys and child care articles.

c. Di-n-hexyl Phthalate (DHEXP)

The CHAP recommended prohibiting the use of DHEXP in children's toys and child care articles. CHAP report at pp. 114-116. DHEXP is associated with adverse effects on male

[80] (Patton, 2010).
[81] Hannas *et al*. (2011a).
[82] Silva *et al*. (2010).

reproductive development and may contribute to the cumulative risk from antiandrogenic phthalates. The Commission agrees with the CHAP's recommendation for DHEXP. Based on the CHAP report and previous review by CPSC staff and a contractor,[83] the Commission concludes that there is sufficient evidence that DHEXP is antiandrogenic and contributes to the cumulative risk. The CHAP report noted a 1980 study by Foster *et al.* that found severe testicular atrophy in rats, among other effects. *Id.* at p. 114. The Commission also concludes that, by applying the CPSC chronic hazard guidelines, this phthalate may be considered "probably toxic" to humans based on sufficient evidence in animal studies. The CHAP found that up to five percent of infants and up to 10 percent of pregnant women exceed the negligible risk level (HI greater than one). Using the most recent biomonitoring data, some WORA in the sample have an HI that exceeds one. Allowing the use of DHEXP in children's toys and child care articles would further increase the cumulative risk. As discussed previously, the Commission considers that a HI less than or equal to one is necessary "to protect the health of children." Although CPSC staff has not detected DHEXP in toys and child care articles during routine compliance testing thus far, prohibiting children's toys and child care articles containing DHEXP would prevent its use in these products as a substitute for other banned phthalates. Therefore, the rule prohibits children's toys and child care articles containing concentrations of more than 0.1 percent of DHEXP. The Commission concludes that this action is necessary to protect the health of children because it would prevent future use of this antiandrogenic phthalate in toys and child care articles.

[83] Patton (2010).

d. Dicyclohexyl Phthalate (DCHP)

The CHAP recommended prohibiting the use of DCHP in children's toys and child care articles. CHAP report at pp. 116-118. DCHP is associated with adverse effects on male development and contributes to the cumulative risk from antiandrogenic phthalates.

The Commission agrees with the CHAP's recommendation for DCHP. Based on the CHAP report and previous reviews by CPSC staff and a contractor,[84] the Commission concludes that there is sufficient evidence that DCHP is antiandrogenic and contributes to the cumulative risk. For example, the CHAP noted two studies that found such effects as reduced AGD and nipple retention in rats exposed to DCHP. *Id.* at p. 116. The Commission also concludes that, by applying the CPSC chronic hazard guidelines, this phthalate is considered "probably toxic" to humans based on sufficient evidence in animal studies. 57 FR 46626 (Oct. 9, 1992). The CHAP found that up to five percent of infants and up to 10 percent of pregnant women exceed the negligible risk level (HI greater than one). Using the most recent biomonitoring data, some WORA in the sample have an HI that exceeds one. Allowing the use of DCHP in children's toys and child care articles would further increase the cumulative risk. As discussed previously, the Commission considers that a HI less than or equal to one is necessary "to protect the health of children." Although the CPSC staff has not detected DCHP in toys and child care articles during routine compliance testing thus far, prohibiting the use of DCHP would prevent its use as a substitute for other banned phthalates. Therefore, the rule prohibits children's toys and child care articles containing concentrations of more than 0.1 percent of DCHP. The Commission concludes that this action is necessary to protect the health of children because it would prevent future use of this antiandrogenic phthalate in toys and child care articles.

[84] Versar/SRC (2010b).

e. Comments Concerning Phthalates Subject to the Rule But Not Currently Prohibited Under the CPSIA

Comment: Regulating DIBP, DPENP, DHEXP, DCHP. One commenter stated that DIBP, DPENP, DHEXP and DCHP are not widely used in children's toys and child care articles and are not prohibited in the European Union. The commenter stated that the proposed rule "inevitably will extend inspection range, add cost to manufacturers and exporters and result in an unnecessary trade barrier." (Comment 5.7).

Response: CPSC agrees that DIBP, DPENP, DHEXP and DCHP are not widely used in children's toys and child care articles. However, as explained above, studies demonstrate that these four phthalates all cause MRDE and they are as, or more, potent than DEHP. Regarding the commenter's assertion that the prohibition of children's toys and child care articles containing these four phthalates would add costs and result in a trade barrier, because these phthalates are not widely used in children's toys and child care articles, the cost to manufacturers to reformulate the few products that might contain these phthalates should be small. Moreover, third party testing is already required for children's toys and child care articles containing prohibited phthalates and the incremental cost of adding the additional phthalates to the analysis is expected to be very small. Staff estimates that the additional materials needed would cost $0.35 per test or about 0.1 percent of a typical $300 phthalates test for a component part or material. The data analysis procedure would need to be modified to include the new phthalates, but staff does not expect this would additional burdens to qualified laboratories.

f. Children's Products

The scope of this rule covers children's toys and child care articles. The CPSIA authorizes the Commission to "declare any children's product containing any phthalates to be a banned hazardous product" if such action is necessary to protect the health of children. 15

U.S.C. 2057c(b)(3)(B). As explained in the NPR, the Commission is not expanding the rule to cover other children's products. 79 FR 78337-78338. Only limited data on exposure to phthalates from other children's products exist. The general information available does not support a determination that prohibiting any products other than children's toys and child care articles is necessary. Toys are more likely than many other children's products to be made of materials that could be plasticized with phthalates. Toys and child care articles are more likely than other children's products to provide a pathway of exposure to phthalates both through oral exposure (from direct contact with the mouth and indirect contact when children place their hands in their mouths) and dermal exposure. We received few comments in response to the NPR that addressed expansion of the scope of the regulation to all children's products.

Comment: Expanding the scope to all children's products. One commenter expressed disappointment that CPSC is not expanding the scope of the provisions involving phthalates to include other children's items such as raincoats, footwear, backpacks, school supplies, and clothes. The commenter asserted that a lack of data does not mean CPSC should assume there is no problem. (Comment 6.6).

Response: Staff has not found new information that would change the basis underlying the Commission's decision not to propose expanding the scope of the rule to all children's products. There is not enough information to adequately assess the health impact of children's products other than children's toys and child care articles. In contrast to children's products in general, a wealth of information regarding use exists for children's toys and child care articles from other agencies, such as EPA, and in scientific publications. The general information available indicates that exposure from children's products is comparatively less than that from children's toys and childcare articles.

g. Other Phthalates Not Included in the Rule

The CHAP examined 14 phthalates: the three subject to the CPSIA's permanent prohibition, the three subject to the CPSIA's interim prohibition, and eight additional phthalates. Of the eight additional phthalates, the CHAP recommended that four be prohibited from use in children's toys and child care articles, that three (Dimethyl Phthalate (DMP), Diethyl Phthalate (DEP), Di(2-propylheptyl) Phthalate DPHP) be free of any restriction, and the one (Diisooctyl Phthalate (DIOP)) be subject to an interim prohibition. CHAP report at pp. 1118-119. As discussed in the NPR, DIOP has a chemical structure consistent with other antiandrogenic phthalates. However, the CHAP concluded that there is not sufficient evidence to support a permanent prohibition. 79 FR 78337. The CPSIA did not provide for an interim prohibition as an option for the Commission's rule under section 108, and as the CHAP explained, insufficient data exists to determine that a permanent prohibition of DIOP is necessary to protect the health of children.

We received a few comments concerning phthalates that the CHAP assessed but are not covered by CPSC's rule.

Comment: DIOP. Some commenters suggested that the CPSC permanently prohibit children's toys and child care articles containing DIOP. They stated that the CHAP had noted DIOP's structural similarity to antiandrogenic phthalates and they concluded that CPSC should not assume that it would meet the CPSIA criteria when hazard and exposure data are lacking. (Comment 5.10).

Response: Although the CHAP recognized that the structure of DIOP suggests that it may be associated with antiandrogenic effects, no experimental data exist that would support a

conclusion that DIOP causes MRDE. Additionally, potency and exposure data are lacking. Thus, there is no basis for regulatory action on DIOP at this time.

Comment: Prohibitions involving other phthalates. Some commenters asserted that "The CHAP's lack of recommendations for additional regulatory action on phthalates like DIOP, DMP, DEP, DPHP or many of the alternatives evaluated is not an endorsement of their safety" because of the lack of sufficient hazard and exposure data on these chemicals. The commenters suggested that CPSC continue to review and monitor these phthalates and to recommend that other federal agencies take appropriate actions. (Comment 10.4).

Response: CPSC staff participates in several interagency collaborations to discuss issues of mutual interest, including phthalates. CPSC will continue these cooperative activities.

E. The Concentration Limit

For both the permanent and interim prohibitions, the CPSIA established a concentration limit of 0.1 percent. The CHAP stated:

When used as plasticizers for polyvinyl chloride (PVC), phthalates are typically used at levels greater than 10%. Thus, the 0.1% limit prohibits the intentional use of phthalates as plasticizers in children's toys and child care articles but allows trace amounts of phthalates that might be present unintentionally. There is no compelling reason to apply a different limit to other phthalates that might be added to the current list of phthalates permanently prohibited from use in children's toys and child care articles.

CHAP report at p. 79. As discussed in the NPR, this concentration limit is not based on risk, and the Commission found no risk-based justification to change the limit from the 0.1 percent specified in the CPSIA. Thus, the Commission proposed to maintain this concentration limit. 79 FR 78338. We did not receive any comments concerning the concentration limit. The final rule retains the 0.1 percent concentration limit.

F. International and Other Countries' Requirements for Children's Toys and Child Care Articles Containing Phthalates

1. Summary of Requirements

Other countries have restrictions concerning the use of various phthalates in children's toys and child care articles. The requirements vary, but the following countries have some regulatory restrictions on phthalates that can be used in children's toys and child care articles: the European Union (EU), Denmark, Canada, Japan, Australia, Brazil, Argentina, Taiwan, and Hong Kong. The requirements differ on the phthalates restricted and products covered. Unlike CPSC's rule, these restrictions are based on evaluations of phthalate exposures in isolation, not in combination with other phthalates. There is no international standard that establishes substantive requirements for phthalates in children's toys and child care articles. International Organization for Standardization (ISO) 8124-6:2014 specifies a method for testing toys and children's products to determine if they contain phthalates; it does not establish any content limits. We provide a summary of other countries' requirements concerning phthalates in children's toys and child care articles:

DINP:

- Denmark: prohibits all phthalates at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old.
- EU: limits the use of DINP (as well as DIDP and DNOP) individually or as mixtures in toys and child care articles which can be placed in the mouth by children to no greater than 0.1 percent by weight of the plasticized material.
- Canada: limits use in the vinyl in any part of a toy or child care article that can be placed in the mouth of a child under four years of age to no greater than 0.1 percent of DINP, DIDP or DNOP.

- Japan: for toys that are intended to come in contact with the mouth (excluding pacifiers and teething rings), parts made from plasticized materials that are intended to come in contact with the mouth must not contain more than 0.1 percent DINP (or DIDP or DNOP); PVC parts not intended to come in contact with mouth must not use DINP as a raw material.
- Brazil: limits use of DINP in plastic materials in all kinds of toys for children under three to no greater than 0.1 percent.
- Argentina: limits use of DINP in toys and child care articles made of plastic material that can be placed in the mouth to no greater than 0.1 percent.
- Taiwan: limits DINP use in toys and child care articles to no greater than 0.1 percent individually or in combination with DEHP, DBP, BBP, DIDP, or DNOP.
- Hong Kong: limits the combination of DINP, DIDP and DNOP to no greater than 0.1 percent of the total weight of the plasticized materials in toys or children's products any part of which can be placed in the mouth of a child under four years of age.
- Australia: considered but rejected limiting DINP in children's toys and child care articles.

<u>Other Phthalates covered by CPSC's rule (DIBP, DPENP, DHEXP, DCHP)</u>

- Denmark: in 2009 instituted a national prohibition on all phthalates at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old. This covers all four phthalates: DIBP, DPENP, DHEXP, DCHP.

- No restrictions concerning DIBP, DPENP, DHEXP, DCHP in children's toys and child care articles in other countries.

As this summary demonstrates, requirements concerning DINP in children's toys and child care articles vary across different countries. However, even if the precise requirements differ, numerous countries have some limitation on the use of DINP in children's toys and child care articles, and one other country restricts the use of DIBP, DPENP, DHEXP, and DCHP in children's toys and child care articles.

2. Comments Concerning Other Countries' and International Requirements

Comment: Differences between CPSC's proposed rule and other countries' requirements. Some commenters observed that CPSC's NPR differed from restrictions in other countries. These comments focused on CPSC's expansion of the interim prohibition regarding DINP to cover all children's toys. Commenters noted the inconsistency between the EU's requirements concerning DINP and the CPSC's proposed rule. Two commenters stated that the CPSC's rule is consistent with the EU. A commenter expressed concerns that the rule might be a barrier to international trade under the World Trade Organization (WTO) Agreement on Technical Barriers to Trade (TBT) due to the differences between CPSC's rule and other countries' approaches. (Comment 5.6).

Response: As discussed above, CPSC's rule concerning DINP differs from other countries' restrictions. However, there is variation among these countries; no uniform consensus on regulation of DINP in children's toys and child care articles exists. Regarding the TBT, we note that there is no international standard establishing restrictions on phthalates in toys. ISO 8124-6:2014 only specifies a test method to determine if toys and children's products contain phthalates. Rather, countries have established their own technical regulations. The TBT states

that technical regulations shall not be more trade-restrictive than necessary to fulfill a legitimate objective. CPSC's rule would not be a barrier to trade because it will apply equally to both domestic manufacturers and importers. We also note that the TBT recognizes that protection of human health or safety is a legitimate objective.

G. Description of the Final Rule

The text of the final rule is the same as the proposed rule with one exception. For clarity, we have added language from section 108(c) of the CPSIA (as amended by Public Law 112-28) regarding the application of the rule. This addition does not change the substance of the rule because the statutory provision applies regardless of whether it is stated in the rule. Section 108(c) of the CPSIA states that the permanent and interim phthalate prohibitions, and any phthalates rule the Commission issues under section 108(b)(3) of the CPSIA, "shall apply to any plasticized component part of a children's toy or child care article or any other component part of a children's toy or child care article that is made of other materials that may contain phthalates." 15 U.S.C. 2057c(c).

The Commission received comments on various aspects of the substance of the proposed rule. These comments and responses to them are summarized throughout this document. More detailed comment summaries and responses are at Tab B of staff's briefing package.

Section 1307.1 – Scope and Application

Section 1307.1 describes the actions that the rule prohibits. This provision tracks the language in section 108(a) of the CPSIA regarding the permanent prohibition and prohibits the same activities: manufacture for sale, offer for sale, distribution in commerce, or importation into the United States of a children's toy or child care article that contains any of the prohibited phthalates.

Section 1307.2 - Definitions

Section 1307.2 provides the same definitions of "children's toy" and "child care article" found in section 108(g) of the CPSIA. "Children's toy" means a consumer product designed or intended by the manufacturer for a child 12 years of age or younger for use by the child when the child plays. "Child care article" means a consumer product designed or intended by the manufacturer to facilitate sleep or the feeding of children age 3 and younger, or to help such children with sucking or teething. Although these definitions are stated in the CPSIA, the rule text restates them for convenience. We did not receive comments on these definitions, which re-state statutory definitions.

Section 1307.3 - Prohibition on Children's Toys and Child Care Articles Containing Specified Phthalates

Section 1307.3(a) states the products the rule prohibits. For convenience, this section provides both the items that are subject to the CPSIA's existing permanent prohibition and the items that are subject to prohibition under the rule. Stating all prohibitions in this section will allow a reader of the CFR to be aware of all the CPSC's restrictions concerning phthalates, both statutory and regulatory.

Paragraph (a) sets out the CPSIA's existing permanent prohibition which makes it unlawful to manufacture for sale, offer for sale, distribute in commerce, or import into the United States any children's toy or child care article that contains concentrations of more than 0.1 percent of DEHP, DBP, or BBP. The restriction on these products was established by section 108(a) of the CPSIA. This statutory prohibition is not affected by the rule, but is merely restated in the regulatory text.

Paragraph (b) prohibits the manufacture for sale, offer for sale, distribution in commerce, or importation into the United States of any children's toy or child care article that contains concentrations of more than 0.1 percent of DINP, DIBP, DPENP, DHEXP, and DCHP. As explained above, in accordance with section 108(b)(2) of the CPSIA, the Commission appointed a CHAP that considered the effects on children's health of phthalates and phthalate alternatives as used in children's toys and child care articles and presented the Commission with a report of its findings and recommendations. After reviewing the CHAP's report, the most recent exposure data, and public comments, the Commission is finalizing this rule in accordance with section 108(b)(3) of the CPSIA.

For the reasons explained in this preamble, the Commission concludes that prohibiting children's toys and child care articles that contain concentrations of more than 0.1 percent of DINP would ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety. DINP is currently subject to the CPSIA's interim prohibition. 15 U.S.C. 2057c(b)(1). Section 1307.3(b) changes the scope of regulation of DINP from the current interim scope of "any children's toy that can be placed in a child's mouth"[85] (and child care articles) to include all children's toys. Based on the recommendations in the CHAP report, the Commission is not continuing the interim prohibitions on DIDP and DNOP.

Additionally, § 1307.3(b) prohibits children's toys and child care articles containing four phthalates that are not currently subject to restrictions under the CPSIA: DIBP, DPENP, DEXP, and DCHP. For the reasons explained previously, the Commission concludes that prohibiting

[85] Section 108(g)(2)(B) of the CPSIA states that "a toy can be placed in a child's mouth if any part of the toy can actually be brought to the mouth and kept in the mouth by a child so that it can be sucked and chewed. If the children's product can only be licked, it is not regarded as able to be placed in the mouth. If a toy or part of a toy in one dimension is smaller than 5 centimeters, it can be placed in the mouth."

children's toys and child care articles containing concentrations of more than 0.1 percent of DIBP, DPENP, DEXP, or DCHP is necessary to protect the health of children.

The final rule adds paragraph (c) to § 1307.3 to clarify the application of the rule. Section 108(c), as amended by Public Law 112-28 (August 12, 2011), addresses the application of the Commission's phthalates rule. For convenience and clarity, we are restating that statutory provision in § 1307.3 (c).

H. Effective Date

The APA generally requires that the effective date of a rule be at least 30 days after publication of the final rule. 5 U.S.C. 553(d). The Commission proposed an effective date of 180 days after publication of the final rule in the *Federal Register*. The final rule provides a 180-day effective date. As discussed in the NPR and in section V. of this preamble, the Commission expects that this rule will have a minimal impact on manufacturers, and that changes to testing procedures to include children's toys and child care articles containing the four additional prohibited phthalates would require minimal effort by testing laboratories. 79 FR 78339. In accordance with the CPSIA, restrictions on the use of certain phthalates in children's toys and child care articles are currently in effect. This rule does not affect the permanent prohibition on children's toys and child care articles containing more than 0.1 percent of DEHP, BBP, and DBP. The CPSIA's interim prohibition currently applies to children's toys that can be placed in a child's mouth and child care articles containing DINP. Thus, with regard to DINP, the impact from the rule would be only on children's toys that cannot be placed in a child's mouth. CPSC expects that a relatively small percentage of children's toys that cannot be placed in a child's mouth would need to be reformulated to remove DINP. Because the four additional phthalates (DIBP, DPENP, DHEXP, and DCHP) are not widely used in children's toys and child

care articles, few manufacturers will need to reformulate products to comply with this aspect of the rule. Regarding third party testing, testing laboratories are already testing children's toys and child care articles for the permanently prohibited phthalates and are testing children's toys that can be placed in a child's mouth and child care articles for DINP. Testing laboratories can expand their procedures to include the four additional phthalates with minimal effort. CPSC received a few comments, summarized below, concerning the effective date.

Comment: Effective date. Two commenters stated that the Commission should set an effective date of at least 1 year from finalizing the rule. They asserted that DIDP and DINP are difficult to differentiate through testing, and that if the interim prohibition concerning DIDP was lifted while DINP continues to be restricted, laboratories would need additional time to address the technical testing difficulties. Another commenter urged the Commission to shorten the proposed 180-day effective date based on the minimal impact CPSC anticipates to "ensure that there is no gap in the protections from DINP." Another commenter asked for clarification that the rule would not be retroactive (back to 2011). (Comment 5.11).

Response: CPSC acknowledges that differentiating DINP and DIDP may be difficult. However, laboratories can differentiate DINP and DIDP using currently available equipment and methods. Manufacturers can maintain current formulations while they address any perceived challenges differentiating DINP and DIDP. As explained above, CPSC expects that the rule will require minimal changes for manufacturers and testing laboratories. Therefore 180 days from publication in the *Federal Register* should be sufficient time for the rule to take effect. We see no need to shorten the effective date. The interim prohibition established by section 108(b)(1) remains in effect until this rule becomes effective. We confirm that the rule is prospective and

will apply to products manufactured and imported on or after the effective date. As mentioned, however, the interim prohibition remains in place until the final rule takes effect.

V. Regulatory Flexibility Act

A. Certification

The Regulatory Flexibility Act (RFA) requires an agency to prepare a regulatory flexibility analysis for any rule subject to notice and comment rulemaking requirements under the Administrative Procedure Act or any other statute unless the agency certifies that the rulemaking will not have a significant economic impact on a substantial number of small entities. U.S.C. 603 and 605. Small entities include small businesses, small organizations, and small governmental jurisdictions. The Commission certified in the NPR that this rule will not have a significant impact on a substantial number of small entities pursuant to section 605(b) of the RFA, 5 U.S.C. 605(b) in the NPR. 79 FR 78324, 78339-41. Some comments expressed general concerns about the economic impact of the proposed rule, but none provided information or evidence that the rule would have a significant impact on a substantial number of small entities. Summaries of these comments and CPSC's responses are provided below. More detailed summaries and responses are in Tab B of the staff's briefing package. None of the comments received by the Commission changes the basis for the certification, nor has Commission staff received any other information that would require a change or revision the Commission's previous analysis of the impact of the rule on small entities. Therefore, the certification of no significant impact on a substantial number of small entities is still appropriate.

As explained in greater detail in the NPR, the certification is based on CPSC's determination that:

(1) Few, if any, manufacturers would need to alter their formulations to comply with the rule because:

- Children's toys that can be placed in a child's mouth and child care articles containing DINP have been prohibited since 2009. Thus, no manufacturer would have to reformulate any products in these categories.
- Only children's toys that cannot be placed in a child's mouth (no dimension of the toy is less than 5 cm.) containing DINP would have to be reformulated. Thus, only a small subset of children's toys that cannot be placed in a child's mouth would be affected by the rule.
- DIBP, DPENP, DHEXP, and DCHP are not widely used in children's toys and child care articles. Therefore, relatively few manufacturers would have to reformulate products to eliminate these phthalates due to the rule.

(2) The rule would have a small marginal impact on the cost of third party testing because:

- All children's toys and child care articles are already subject to third party testing for DEHP, DBP, and BBP.
- Currently, children's toys that can be placed in a child's mouth and child care articles must also be tested for the presence of DINP.
- Laboratory equipment and methods are already in place for testing the prohibited phthalates, therefore the additional cost of testing for DIBP, DPENP, DHEXP, and DCHP would be very low.
- Identification and quantification protocols for prohibited phthalates would need minimal modification to include DIBP, DPENP, DHEXP, and DCHP because

each of these phthalates can be isolated at unique elution times by gas chromatography. Thus, the additional cost of analysis would be very low.

- The additional cost of laboratory materials would be very low. Chemical standards for testing would be required for the four additional phthalates, but the standards for DNOP and DIDP would no longer be required. Therefore, the number of chemical standards needed would increase by two which CPSC expects would increase the cost of third party testing for phthalates by less than 35 cents per test, which is relatively small compared to current cost of phthalate testing (approximately $300 per product or component part).

B. Comments Concerning Impact on Small Business

Comment: Testing costs: Two commenters agreed with CPSC that the rule will have a small impact on testing costs. One commenter asked for CPSC to clarify how testing of technical mixtures of DINP and DIDP would be performed, noting that when DINP is detected in a sample, additional analytical steps are needed (at additional cost) to determine if the DINP is present as a 'pure' chemical or if the DINP is part of a technical mixture. Some commenters asked the Commission to take action to reduce testing costs. (Comment 9.1).

Response: For the reasons explained above, CPSC expects that the additional burden associated with the rule is small, with no significant impact on a substantial number of small entities. Regarding testing of mixtures of DINP and DIDP, the restriction on DINP applies whether DINP is in the product intentionally or unintentionally. Thus, laboratories will not need to undertake any additional effort to determine the source of DINP found in a children's toy or child care article. Regarding steps to reduce testing burdens, the Commission has recently issued determinations that will lower testing costs for some children's toys and child care article

manufacturers. 82 FR 41163 (August 30, 2017). The determination rule takes effect September 29, 2017.

Comment: Costs and benefits of NPR. Regarding the NPR's determination that the proposed rule's economic impact would be minimal, one commenter stated CPSC had not considered the effect on consumers or the possibility that smaller manufacturers would be burdened by the rule in the future, "which offers no demonstrated public health benefits in exchange for even 'minimal' costs." The commenter asserted that the rule would take a "safe and useful chemical" away from consumers. (Comment 9.4).

Response: Because CPSC followed the rulemaking requirements stated in section 108 of the CPSIA, which differ from rulemaking requirements under the CPSA and the FHSA, CPSC did not prepare a regulatory analysis of the costs and benefits of the rule. However, as discussed above, CPSC did conduct an analysis of the impact of the proposed rule on small entities. The commenter did not explain how future small manufacturers would be burdened. For the reasons explained above and in the NPR, CPSC expects the costs for small businesses subject to this rule would be small.

VI. Notice of Requirements

The CPSA establishes certain requirements for product certification and testing. Children's products subject to a children's product safety rule under the CPSA must be certified as complying with all applicable CPSC-enforced requirements. 15 U.S.C. 2063(a). Certification of children's products subject to a children's product safety rule must be based on testing conducted by a CPSC-accepted third party conformity assessment body. *Id*. 2063(a)(2). The Commission must publish a notice of requirements (NOR) for the accreditation of third party conformity assessment bodies (or laboratories) to assess conformity with a children's product

safety rule to which a children's product is subject. *Id.* 2063(a)(3). The final rule for 16 CFR part 1307, "*Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates*," is a children's product safety rule that requires the issuance of an NOR. The Commission previously published in the *Federal Register* an NOR for the phthalate-containing products prohibited by the permanent and interim prohibitions state in section 108 on August 10, 2011. (76 FR 49286). The codified listing for the NOR can be found at 16 CFR 1112.15(b)(31). In this same issue of the *Federal Register* the Commission is publishing a notice of proposed rulemaking that would update the existing NOR for the phthalate-containing products prohibited by this final rule.

VII. Paperwork Reduction Act

The final rule does not include any information collection requirements. Accordingly, this rule is not subject to the Paperwork Reduction Act, 44 U.S.C. 3501–3520.

VIII. Preemption

Section 26(a) of the CPSA, 15 U.S.C. 2075(a), provides that where a "consumer product safety standard under [the Consumer Product Safety Act (CPSA)]" is in effect and applies to a product, no state or political subdivision of a state may either establish or continue in effect a requirement dealing with the same risk of injury unless the state requirement is identical to the federal standard. (Section 26(c) of the CPSA also provides that states or political subdivisions of states may apply to the Commission for an exemption from this preemption under certain circumstances.) Section 108(f) of the CPSIA is entitled "Treatment as Consumer Product Safety Standards; Effect on State Laws." That provision states that the permanent and interim prohibitions and any rule promulgated under section 108(b)(3) "shall be considered consumer product safety standards under the Consumer Product Safety Act." That section further states:

"Nothing in this section of the Consumer Product Safety Act (15 U.S.C. 2051 et seq.) shall be construed to preempt or otherwise affect any State requirement with respect to any phthalate alternative not specifically regulated in a consumer product safety standard under the Consumer Product Safety Act." 15 U.S.C. 2057c(f). This provision indicates that the preemptive effect of section 26(a) of the CPSA will apply to the final rule.

IX. Environmental Considerations

The Commission's regulations provide a categorical exclusion for the Commission's rules from any requirement to prepare an environmental assessment or an environmental impact statement because they "have little or no potential for affecting the human environment." 16 CFR 1021.5(c)(2). Because this rule falls within the categorical exclusion, no environmental assessment or environmental impact statement is required.

X. List of References

This section provides a list of the documents referenced in this preamble and in the staff's briefing package.

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List of Subjects in 16 CFR Part 1307

Consumer protection, Imports, Infants and children, Law enforcement, and Toys.

For the reasons discussed in the preamble, the Commission amends title 16 of the Code of Federal Regulations by adding part 1307 to read as follows:

PART 1307 – PROHIBITION OF CHILDREN'S TOYS AND CHILD CARE ARTICLES CONTAINING SPECIFIED PHTHALATES

Sec.

AUTHORITY: The Consumer Product Safety Improvement Act of 2008, Pub. L. 110-314, Sec. 108, 122 Stat. 3016 (August 14, 2008); Pub. L. 112-28, 125 Stat. 273 (August 12, 2011).

§ 1307.1 Scope and application.

This part prohibits the manufacture for sale, offer for sale, distribution in commerce or importation into the United States of any children's toy or child care article containing any of the phthalates specified in § 1307.3.

§ 1307.2 Definitions.

The definitions of the Consumer Product Safety Act (CPSA) (15 U.S.C. 2052)(a)) and the Consumer Product Safety Improvement Act of 2008 (CPSIA) (Pub. L. 110-314, 108)(g)) apply to this part. Specifically, as defined in the CPSIA:

(a) *Children's toy* means a consumer product designed or intended by the manufacturer for a child 12 years of age or younger for use by the child when the child plays.

(b) *Child care article* means a consumer product designed or intended by the manufacturer to facilitate sleep or the feeding of children age 3 and younger, or to help such children with sucking or teething.

§ 1307.3 Prohibition of children's toys and child care articles containing specified phthalates.

(a) As provided in section 108(a) of the CPSIA, the manufacture for sale, offer for sale, distribution in commerce, or importation into the United States of any children's toy or child care

article that contains concentrations of more than 0.1 percent of di-(2-ethyhexyl) phthalate (DEHP), dibutyl phthalate (DBP), or benzyl butyl phthalate (BBP) is prohibited.

(b) In accordance with section 108(b)(3) of the CPSIA, the manufacture for sale, offer for sale, distribution in commerce, or importation into the United States of any children's toy or child care article that contains concentrations of more than 0.1 percent of diisononyl phthalate (DINP), diisobutyl phthalate (DIBP), di-*n*-pentyl phthalate (DPENP), di-*n*-hexyl phthalate (DHEXP), and dicyclohexly phthalate (DCHP) is prohibited.

(c) In accordance with section 108(c) of the CPSIA, the restrictions stated in paragraphs (a) and (b) of this section apply to any plasticized component part of a children's toy or child care article or any other component part of a children's toy or child care article that is made of other materials that may contain phthalates.

Dated: _____

_____
Alberta E. Mills, Acting Secretary
U.S. Consumer Product Safety Commission

Staff Briefing Package

Draft Final Rule: Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates

September 13, 2017

The views expressed in this report are those of the CPSC staff, and they have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

Table of Contents

Abbreviations

ADI	acceptable daily intake
APA	Administrative Procedure Act
ASTM	ASTM International
ATBC	acetyl tributyl citrate
BBP	butyl benzyl phthalate
CDC	Centers for Disease Control and Prevention (U.S.)
CHAP	Chronic Hazard Advisory Panel
CPSC	U.S. Consumer Product Safety Commission
CPSIA	Consumer Product Safety Improvement Act of 2008
CRA	cumulative risk assessment
CSA	Canadian Standards Association
DBP	dibutyl phthalate
DCHP	dicyclohexyl phthalate
DEHA	di(2-ethylhexyl adipate
DEHP	di(2-ethylhexyl) phthalate
DEHT	di(2-ethylhexyl) terephthalate
DHEXP	di-*n*-hexyl phthalate
DIBP	diisobutyl phthalate
DIDP	diisodecyl phthalate
DINP	diisononyl phthalate
DINX	diisononyl 1,2-dicyclohexanedicarboxylate
DIOP	diisooctyl phthalate
DNOP	di-*n*-octyl phthalate
DPENP	di *n*-pentyl phthalate
EC	European Commission
ECHA	European Chemicals Agency
EPA	U.S. Environmental Protection Agency
EU	European Union
FHSA	Federal Hazardous Substances Act
FDA	Food and Drug Administration
FQPA	Food Quality and Protection Act
HBM	human biomonitoring
HI	hazard index
HQ	hazard quotient
IQA	Information Quality Act
ISO	International Organization for Standardization
MNG	multinucleated gonocytes
MOA	mode or mechanism of action
MOE	margin of exposure
MRDE	male reproductive developmental effects
NGO	non-governmental organization
NHANES	National Health and Nutrition Examination Survey
NPR	notice of proposed rulemaking

OMB	Office of Management and Budget
PEAA	potency estimate for antiandrogenicity
RFA	Regulatory Flexibility Act
SFF	Study for Future Families
TBT	Technical Barriers to Trade
TERA	Toxicology Excellence for Risk Assessment
TPIB	2,2,4-trimethyl-1,3 pentanediol diisobutyrate
TOTM	tris(2-ethylhexyl) trimellitate
WOE	weight of evidence
WORA	women of reproductive age (non-pregnant women ages 15 through 45)
WTO	World Trade Organization

BRIEFING MEMORANDUM

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MD 20814

Memorandum

This document has been electronically approved and signed.

September 13, 2017

TO : The Commission
Alberta E. Mills, Acting Secretary

THROUGH: Mary T. Boyle, General Counsel
Patricia H. Adkins, Executive Director
J. DeWane Ray, Deputy Executive Director for Safety Operations

FROM : George A. Borlase, Ph.D., P.E., Assistant Executive Director
Office of Hazard Identification and Reduction
Kent R. Carlson, Ph.D., Toxicologist, Division of Toxicology & Risk Assessment, Directorate for Health Sciences

SUBJECT : Draft Final Rule: Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates

I. Introduction

Section 108 of the Consumer Product Safety Improvement Act of 2008 (CPSIA)[1] established requirements concerning phthalates in children's toys and child care articles. As required by the CPSIA, the Consumer Product Safety Commission (CPSC) convened a Chronic Hazard Advisory Panel (CHAP) to assess the potential health risks of phthalates and phthalate alternatives. The CHAP issued its final report in July 2014. Based on the CHAP report, the Commission published a notice of proposed rulemaking (NPR) in the *Federal Register* in December 2014. The NPR proposed making permanent the interim prohibition of children's toys that can be placed in a child's mouth, and child care articles containing diisononyl phthalate (DINP); expanding the scope of the DINP prohibition from "toys that can be placed in a child's mouth" to all children's toys; permanently prohibiting children's toys and child care articles containing four additional phthalates; and lifting the interim prohibitions on children's toys that can be placed in a child's mouth and child care articles containing DNOP and/or DIDP. Since the publication of the NPR, CPSC staff has reviewed and analyzed the NHANES data cycles released by the Centers for Disease Control (CDC) after the 2005/2006 data cycle (2007/2008, 2009/2010, 2011/2012, and 2013/2014). Staff released the analysis in June 2015 (CPSC 2015a), and the Commission requested public comment. Additional NHANES (2013/2014) data was publicly released in late December 2017, at the same time that the staff was addressing public

[1] A list of abbreviations appears on page v.

comments on the NPR and the staff biomonitoring report released in 2015. The staff analyzed this new NHANES data and subsequently released a second biomonitoring report in February 2017 (CPSC 2017a). The Commission again sought public comment.

This memorandum includes:

- Summaries of the CPSIA, CHAP, rulemaking, biomonitoring and risk analysis, public comments/responses, and phthalate regulation in other countries (Sections II-V);
- Discussion regarding the proposed rulemaking (Section VI);
- Discussion regarding "reasonable certainty of no harm" and "adequate margin of safety" (Section VII); and
- Staff rationales and recommendations (Section VII and VIII);
- Detailed staff analyses of more recent phthalate biomonitoring data and risk (TAB A);
- Detailed responses to public comments on the NPR and NHANES analyses (TAB B); and
- Discussion of the impact on small businesses (TAB C).

II. Consumer Product Safety Improvement Act (CPSIA)

A. Statutory Prohibitions

Section 108(a) of the CPSIA permanently prohibits the manufacture for sale, offer for sale, distribution in commerce, or importation into the United States of any "children's toy or child care article" that contains concentrations of more than 0.1 percent of di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), or butyl benzyl phthalate (BBP). Section 108(b)(1) of the CPSIA prohibits on an interim basis (i.e., until the Commission promulgates a final rule), the manufacture for sale, offer for sale, distribution in commerce, or importation into the United States of "any children's toy that can be placed in a child's mouth" or "child care article" containing concentrations of more than 0.1 percent of di-*n*-octyl phthalate (DNOP), diisononyl phthalate (DINP), and diisodecyl phthalate (DIDP).

The CPSIA defines a "children's toy" as "a consumer product designed or intended by the manufacturer for a child 12 years of age or younger for use by the child when the child plays." *Id.* Section 108(g)(1)(B). A "child care article" is defined as "a consumer product designed or intended by the manufacturer to facilitate sleep or the feeding of children age 3 and younger, or to help such children with sucking or teething." *Id.* Section 108(g)(1)(C).

A "toy can be placed in a child's mouth if any part of the toy can actually be brought to the mouth and kept in the mouth by a child so that it can be sucked and chewed. If the children's product can only be licked, it is not regarded as able to be placed in the mouth. If a toy or part of a toy in one dimension is smaller than 5 centimeters, it can be placed in the mouth." *Id.* Section 108(g)(2)(B).

These statutory prohibitions became effective in February 2009. The interim prohibitions remain in effect until the Commission issues a final rule determining whether to make the interim prohibitions permanent. *Id.* Section 108(b)(1).

B. Chronic Hazard Advisory Panel (CHAP)

Section 108(b)(2) of the CPSIA directed the Commission to convene a Chronic Hazard Advisory Panel (CHAP) of independent scientists "to study the effects on children's health of all phthalates and phthalate alternatives as used in children's toys and child care articles." Section 108(g) of the CPSIA defined a "phthalate alternative" as "any common substitute to a phthalate, alternative material to a phthalate, or alternative plasticizer."

Specifically, CPSIA § 108(b)(2)(B) directed the CHAP to:

> 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, 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.

The panel's examinations under this paragraph shall be conducted *de novo*. The findings and conclusions of any previous CHAP on this issue and other studies conducted by the Commission shall be reviewed by the panel but shall not be considered determinative.

In the final report, the CHAP must recommend to the Commission whether any "*phthalates (or combinations of phthalates)*" in addition to those permanently prohibited, including the

phthalates covered by the interim prohibition, or phthalate alternatives should be declared banned hazardous substances. CPSIA § 108(b)(2)(C). The CHAP held its first meeting in April 2010, and presented its final report to the Commission in July 2014.

C. Rulemaking

The CPSIA requires the Commission to promulgate a final rule, pursuant to section 553 of the Administrative Procedure Act (APA), not later than 180 days after the Commission receives the CHAP's final report. CPSIA § 108(b)(3). Specifically, the Commission must:

> A. . . . determine, based on such report, whether to continue in effect the prohibition under paragraph (1), in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety . . ." CPSIA 108 (b)(3)(A).
>
> B. . . . evaluate the findings and recommendations of the Chronic Hazard Advisory Panel and declare any children's product containing any phthalates to be a banned hazardous product under section 8 of the Consumer Product Safety Act (15 U.S.C. 2057), as the Commission determines necessary to protect the health of children. CPSIA § 108(b)(3)(B).

On December 17, 2014, the Commission voted to publish the NPR, "Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates," in the *Federal Register*. The NPR proposed:

1) To make permanent the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DINP.
2) To expand the scope of products that may not contain more than 0.1 percent of DINP from "children's toys that can be placed in a child's mouth and child care articles" to "all children's toys and child care articles".
3) To prohibit children's toys and child care articles containing more than 0.1 percent of diisobutyl phthalate (DIBP), di-*n*-pentyl phthalate (DPENP), di-*n*-hexyl phthalate (DHEXP), or dicyclohexyl phthalate (DCHP).
4) To make the effective date for new phthalate requirements 180 days following publication of the final rule.

The NPR also proposed removing the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing DNOP and/or DIDP, and proposed no regulatory action for:

- diisooctyl phthalate (DIOP);
- acetyl tributyl citrate (ATBC);
- di(2-ethylhexyl) terephthalate (DEHT);
- diisononyl 1,2-dicyclohexanedicarboxylate (DINX);
- 2,2,4-trimethyl-1,3 pentanediol diisobutyrate (TPIB);
- di(2-ethylhexyl adipate (DEHA); and

- tris(2-ethylhexyl) trimellitate (TOTM).

The NPR did not propose to change the scope of product regulation for all phthalates from "children's toys and child care articles" to "children's products," and did not propose to modify the concentration limit of 0.1 percent for all prohibitions involving phthalates.

In addition, the Commission certified, under the Regulatory Flexibility Act (RFA), that the proposed prohibitions will not have a significant impact on a substantial number of small businesses.

III. Staff Analysis of Additional Data

A. Staff Analysis of Additional NHANES Data

Staff analyzed more recent NHANES biomonitoring data sets. This analysis addressed two issues in the CHAP report identified by the Commission and public commenters: (1) the most recent NHANES data sets were not available when the CHAP performed its analysis; and (2) analysis of the more recent data sets to determine the potential risk for women of reproductive age (WORA)[2] had not been done.

Staff analyzed NHANES data from the 2005/2006, 2007/2008, 2009/2010, and 2011/2012 data sets. Staff completed its report in June 2015 (CPSC 2015a) and the Commission subsequently published a notice of availability requesting public comment on the report (CPSC 2015b).

Following release of the June 2015 staff report, a more current NHANES data cycle (2013/2014) became available (late December 2016). Staff completed a report in February 2017 analyzing these data (CPSC 2017a) using the same methodology outlined in the previous report, and the Commission sought additional public comments (CPSC 2017b). A compilation of both reports (CPSC 2015a; 2017a) may be found in TAB A.

The data from both staff analyses show that total phthalate exposures in WORA have changed since 2005/2006 (TAB A). Although DEHP exposure has decreased by about 66 percent from 2005/2006 to 2013/2014, DINP has increased roughly fivefold (TAB A, Table 6), and total phthalate exposure (DEHP, DINP, BBP, DBP, DIBP) increased approximately 20 percent. As a result of changing phthalate exposures, the risk to WORA, as indicated by the hazard index (HI),[3] has declined. Median and 95th percentile HIs estimated for WORA are now both less than one (TAB A, Table 7). In addition, the percentage of WORA with an HI less than or equal to one has increased (TAB A). In 2005/2006, between 95.8 and 97.1 percent of WORA had an HI less than or equal to one, depending on the PEAA case (TAB A, Table 9).

In 2013/2014, between 98.8 and 99.6 percent of WORA had an HI less than or equal to one. In the 2013/2014 NHANES sample of 538 WORA (of approximately 60 million WORA in the U.S. population), there were from two to nine individuals with a HI greater than one (i.e., at risk),

[2] Staff analyses used women of reproductive age (WORA; 15-45 year of age) as the population of interest, because NHANES data cycles published after 2005/2006 did not have sufficient numbers of pregnant women to be statistically relevant. NHANES does not collect data on children under 6 years old.
[3] HI less than or equal to one equates to an acceptable risk of adverse effects from phthalate exposure (CPSC 1992).

depending on the PEAA case. As described in section 5.4 of TAB A, the 2013/2014 NHANES data set cannot be used to estimate how many WORA in the U.S. population have HIs greater than one.

Although DEHP was the major contributor to the cumulative risk in 2005/2006, the relative contribution of DEHP has decreased from 2005/2006 to 2013/2014 and DINP has increased (TAB A, Table 8, Figures 6, 7). In 2005/2006, DINP contributed between 0.5 and 8.1 percent of the total risk from phthalates (based on median HIs and HQs). In 2013/2014, DINP contributed between 6.5 and 51 percent of the risk and DEHP contributed between 30 and 83 percent of the risk (based on the median HIs and HQs). At the 95th percentile, the relative contribution of DINP was even greater, and ranged from 18 to 76 percent, while DEHP's relative contribution ranged from 14 to 72 percent. Thus, in 2013/2014, DINP contributed more to the total risk than DEHP.

The impact of the new NHANES data on staff's recommendations is discussed further in Sections VI (Discussion) and VII (Staff Rationale and Recommendations).

B. NAS Report on Endocrine Disruptors

1. NAS Process and Conclusions

In July 2017, the National Academies of Sciences, Engineering, and Medicine (NAS) released a new report entitled, *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals* (NAS 2017). The U.S. Environmental Protection Agency (EPA) sponsored the NAS report and associated work in order to determine if EPA's current regulatory toxicity-testing strategy was adequately considering "evidence of low-dose adverse human effects that act through an endocrine-mediated pathway."

EPA requested that the NAS develop a strategy to evaluate the evidence for potential human health effects from endocrine active chemicals at low doses. The NAS convened an ad hoc committee of experts to address this task. The task also specified that the committee perform systematic reviews of animal and human studies on at least two chemicals and demonstrate how the results can be integrated and considered with other relevant data to draw conclusions about causal associations.

After going through a process that included convening a public workshop, surveying the scientific literature, and collecting information about human exposure, the committee selected phthalates and polybrominated diphenyl ethers as the two chemicals to demonstrate the systematic review methods and integration of results. Thus, the report included a chapter entitled *Phthalates and Male Reproductive-Tract Development*, evaluating three health effects (fetal testosterone, anogenital distance (AGD), and hypospadias). Staff reviewed the NAS report, and the phthalates chapter and associated appendices in particular, given their potential relevance to the phthalates rulemaking. Staff found nothing in the NAS report that indicates that the reviews of the phthalates (or polybrominated diphenyl ethers) were intended to be comprehensive toxicity assessments that considered all relevant health effects. The report's discussion of the committee's process and the example analyses focus on the overall project goal to develop a strategy for evaluating evidence. Specifically, the report states that the "committee undertook these example reviews to demonstrate how these approaches could be used in a strategy to

evaluate low-dose toxicity of [endocrine active chemicals] and to identify lessons learned that could help EPA employ these approaches successfully." (NAS 2017, p. 5). The report indicates that the overall purpose of the project was part of the rationale for choosing the specific health endpoints examined (see, for example, the discussion of cryptorchidism as a possible endpoint to include in the analysis, NAS 2017, p. 43).

The NAS report presented separate evaluations for each of the assessed phthalates and individual health effects. The phthalates section of the report focused on DEHP, and provided a "final hazard conclusion" for each of the endpoints. Thus, for fetal testosterone and AGD, DEHP is presumed to be a reproductive hazard to humans; for hypospadias, DEHP is suspected to be a reproductive hazard to humans (NAS 2017, pp. 78–81).

For the other assessed phthalates, including DINP, the NAS report did not conduct the final analysis step that results in a "final hazard conclusion." The report provides only the "initial hazard evaluations" for fetal testosterone, AGD, and hypospadias in humans. The report found for fetal testosterone, the phthalates BBP, DBP, DEP, DIBP, DINP, and DPP are presumed to be reproductive hazards to humans; DEP is not classifiable for this endpoint (NAS 2017, Table 3-30). For AGD, BBP, DBP, and DEP are presumed to be reproductive hazards to humans, while DIBP, DIDP, and DINP are not classifiable (NAS 2017, Table 3-29). For hypospadias, BBP is suspected to be a reproductive hazard to humans and DBP is presumed to be a reproductive hazard to humans (NAS 2017, Table 3-31). The NAS committee did not evaluate DHEXP, DCHP, or DIOP.

2. Comparison of NAS and CHAP Assessment

The CHAP and NAS hazard reviews were different in many ways. The NAS committee considered only three adverse effects associated with MRDE (decrements in fetal testosterone, increases in the incidence of decreased AGD, and increases in the incidence of hypospadias). The NAS review was thus for individual phthalates and individual health effects, focusing on whether enough quality data existed to term it a reproductive hazard to humans. In contrast, the CHAP considered all phthalate syndrome effects (as discussed above) when concluding if a phthalate was antiandrogenic (a reproductive hazard to humans). Staff notes that phthalate syndrome includes effects on fertility and male reproductive developmental effects (MRDE). MRDE itself is a collection of multiple adverse effects, the presence of any one of which is indicative of phthalate syndrome (i.e., multiple end points do not have to be identified in any particular study for the identification of phthalate syndrome – see comment response 1.14).

Health effects associated with MRDE (Foster 2006; Foster et al., 2001; Howdeshell et al., 2016; Howdeshell et al., 2008) specifically include:

- reduced testosterone synthesis (an endpoint considered by NAS);
- reduced AGD (an endpoint considered by NAS);
- genital malformations (hypospadias) (an endpoint considered by NAS);
- nipple retention (which normally does not occur in male rats);
- undescended testes (cryptorchidism);

- testicular atrophy;
- testicular histopathology;
- multi-nuclear gonocytes (MNGs);
- reduced production of insulin-like hormone 3 (insl3); or
- underdeveloped gubernacular cords.

In addition, the NAS committee's evaluation of phthalates and polybrominated diphenyl ethers was not an assessment of risk. The NAS committee considered whether phthalates are capable of causing certain health effects related to MRDE. The committee did not estimate health risks to people who might be exposed to certain phthalates. In contrast, the CHAP was charged with completing a risk assessment including several phthalates. This risk evaluation included the consideration of both phthalate hazard and exposure. Another important difference between the NAS and CHAP reports was that the CHAP's hazard evaluation included a larger body of published studies. The CHAP did not follow a specific review format for evaluating the available studies, but it did consider the strengths and weaknesses of the available body of evidence, as discussed in the "weight of evidence" sections of the CHAP report for each evaluated phthalate (see, for example, CHAP 2014, p. 83).

In spite of these differences, the NAS report conclusions are consistent with the CHAP and staff's hazard conclusions that DEHP, DBP, BBP, DINP, DPP, and DIBP are antiandrogenic, because the NAS committee found that each of these phthalates is presumed to be a reproductive hazard to humans based on one or more of the three MRDE endpoints considered.

Staff discusses the NAS committee's evaluation of DINP for each of the assessed health effects below.

a. DINP and Fetal Testosterone

The NAS committee concluded that DINP is a presumed human hazard based on effects on fetal testosterone (NAS 2017, Table 3-30). The NAS committee concluded that there is high confidence in the body of evidence for DINP and fetal testosterone in animal studies, based on four studies. The committee indicated that confidence in the evidence was not downgraded because of any risk of bias[4] concerns. Confidence in the evidence was downgraded because of imprecision in the study results, and, in contrast, upgraded because the studies showed large magnitude of effect and similar magnitude of response with the same dose range (NAS 2017, p. 93). The committee concluded that there is a high level of evidence that fetal exposure to DINP is associated with decreased fetal testosterone in male rats. The committee reported an inadequate level of evidence to assess whether exposure to DINP is associated with decreased fetal testosterone in humans.

[4] The NAS report states that "[r]isk of bias is related to the internal validity of a study and reflects study design characteristics that can introduce a systematic error (or deviation from the true effect) that might affect the magnitude and even the direction of the apparent effect." (NAS 2017, p. 45). The committee assessed internal validity/risk of bias for individual studies using a tool developed for the National Toxicology Program's Office of Health Assessment and Translation systematic review method (NTP 2015). Staff notes that the committee did not evaluate bias in individual studies; rather, the committee considered risk of bias.

Staff considers the NAS committee's conclusion that DINP is a presumed human hazard based on effects on fetal testosterone to be consistent with a conclusion that DINP is antiandrogenic. The fact that DINP is associated with reduced testosterone means, by definition, that DINP is antiandrogenic. Antiandrogenicity, manifested as reduced fetal testosterone and other MRDE endpoints as discussed above, was the primary criterion used by the CHAP to include DINP (and DEHP, BBP, DBP, and DIBP) in the CRA. Thus, the CHAP concluded that DINP is associated with a number of effects related to phthalate syndrome in male rat pups following prenatal exposure, including reduced fetal testosterone. As noted previously, the CHAP did not evaluate the body of evidence for fetal testosterone or other specific effects individually, but considered the overall body of evidence for MRDE and phthalate syndrome-related effects.

The NAS committee's conclusion regarding DINP-induced decrements in fetal testosterone is consistent with the CHAP and staff's hazard determination for DINP, and therefore consistent with the CHAP's inclusion of DINP in the CRA that informed the Commission's proposal to make permanent the interim prohibition of children's toys and child care articles containing more than 0.1 percent of DINP.

b. DINP and Anogenital Distance

The NAS committee concluded that DINP is not classifiable as to whether it is a reproductive hazard to humans based on AGD (NAS 2017, Table 3-29).The NAS committee concluded that there is very low confidence in the body of evidence for DINP and AGD in animal studies, based on unexplained inconsistency and imprecision in the results of the four studies evaluated, and for a probably high risk of bias rating in key areas involving two of the four studies (NAS 2017, pp. 88–89). The committee considered that only one of the four studies found evidence of decreased AGD (Boberg et al., 2011), and based on its evaluation, the committee concluded that there is an inadequate level of evidence to assess whether fetal exposure to DINP is associated with a decrease in AGD in male rats. The committee reported moderate confidence in the evidence for DINP and AGD in human studies, but determined that there was an inadequate level of evidence to assess whether fetal exposure to these phthalates is associated with a decrease in AGD in male infants.

At the time of its analysis, the CHAP did not locate human studies for DINP in relation to male reproductive health outcomes. The three epidemiology studies reviewed by NAS were published after the CHAP report was completed (Bornehag et al., 2015; Swan et al., 2015, Jensen et al., 2016). The CHAP concluded that DINP is associated with a number of effects related to phthalate syndrome in male rat pups following prenatal exposure, including reduced AGD.

Staff acknowledges that the animal studies on AGD gave mixed results. Staff notes that the CHAP and the NAS committee interpreted at least one of the relevant studies differently. Specifically, Clewell et al., (2013) measured AGD at 2, 14, and 49 days after birth. AGD was significantly reduced on day 14, but not on days 2 or 49. The CHAP considered this result as evidence that DINP affects AGD (CHAP 2014, pp, 95-99). In contrast, the NAS committee concluded that this study did not find decreased AGD, because the NAS method only considered AGD measurements made at the earliest time point in studies that reported AGD at multiple time points in the same animals (i.e., day 2 in Clewell et al. 2013).

Staff notes that AGD effects alone were not the basis of the CHAP's conclusions about DINP, and the studies of this endpoint were not used in the CHAP's quantitative analyses. Specifically,

as noted previously, the CHAP did not evaluate the body of evidence for AGD or other specific effects individually, but considered the overall body of evidence for MRDE and phthalate syndrome-related effects. Therefore, the NAS evaluation of AGD does not directly affect the hazard identification conclusions of the CHAP or CPSC staff, or the Commission's proposal to prohibit children's toys and child care articles containing more than 0.1 percent of DINP, as the health effect is already supported by the NAS conclusion on fetal testosterone.

c. DINP and Hypospadias

Compared to other possible male reproductive health endpoints associated with phthalate exposure, relatively few studies considered hypospadias. The NAS report identified nine studies in which hypospadias were assessed following DEHP exposure, eight studies for DBP exposure, and two studies for BBP exposure. The committee did not evaluate any other phthalates, including DINP, for hypospadias.

The NAS committee concluded that DEHP is suspected to be a reproductive hazard to humans based on hypospadias (NAS 2017, p. 81). The NAS committee concluded that there is moderate confidence in the body evidence, based on a risk of bias rating in key areas among nine studies, and the committee concluded that there is a moderate level of evidence for DEHP and hypospadias in animal studies (NAS 2017, p. 62). The committee concluded that there is inadequate evidence to assess this endpoint in humans (NAS 2017, p. 73).

The NAS committee concluded that DBP is a presumed human hazard based on hypospadias (NAS 2017, Table 3-31).The NAS committee concluded that there is high confidence in the body evidence, and a high level of evidence for DBP and hypospadias in animal studies. The committee concluded that there is inadequate evidence to assess this endpoint in humans.

The NAS committee concluded that BBP is a suspected human hazard based on hypospadias (NAS 2017, Table 3-31). The NAS committee concluded that there is moderate confidence in the body of evidence, based on a risk of bias rating in key areas among the two studies, and a moderate level of evidence for BBP and hypospadias in animal studies. The committee concluded that there is inadequate evidence to assess this endpoint in humans.

The CHAP noted that studies evaluated hypospadias for several phthalates, and this endpoint was considered as part of the range of health effects associated with MRDE or the phthalate syndrome. Hypospadias alone did not form the basis of the CHAP's conclusions about any of the evaluated phthalates, and the studies of this endpoint were not used in the CHAP's quantitative analyses. The conclusions of the NAS committee are consistent with the CHAP and staff's conclusions that DEHP, BBP, and DBP are antiandrogenic. Because the NAS committee did not evaluate other phthalates, including DINP, for this endpoint, the NAS evaluation of hypospadias does not directly affect the conclusions of the CHAP or CPSC staff regarding other phthalates, including DINP, or the Commission's proposal to prohibit children's toys and child care articles containing the specified phthalates.

d. Boberg et al., 2011

The CHAP and NAS evaluations of DINP included a study by Boberg et al., (2011). The CHAP reviewed and considered Boberg et al., during the Case 3 *de novo* hazard assessment for DINP.

The CHAP ultimately decided, however, that a different point of departure (increased MNGs; Clewell et al., 2013) was more appropriate to use in the quantitative CRA. The NAS evaluated Boberg et al., (2011) during the systematic review of DINP for effects on fetal testosterone and of DINP effects on AGD. The committee noted that "[o]nly one study found decreased AGD after development exposure to DINP (Boberg et al., 2011)." (NAS 2017, p. 88).

The Commission received critical public comments from stakeholders regarding the Boberg et al. study following publication of the NPR (see comment responses 1.15 - 1.19, 4.6, and 4.16). Staff responded to public comments, but did not perform a review of the risk of bias associated with the Boberg study. The NAS report, however, provided that review of the risk of bias associated with the Boberg et al. study.

The NAS committee used ten criteria for animal studies to evaluate all literature reviewed for risk of bias. For the effects of DINP on AGD, the NAS found that for eight of these criteria, Boberg et al. had a "probably low risk of bias" or "definitely low risk of bias," and that data for the remaining two were "not reported."[5] The assessment of Boberg et al. was similar to the other literature reviewed, as shown in Table 1 below. Overall, the NAS downgraded the confidence in DINP effects on AGD given specific concerns with the Li and Masutomi studies (NAS 2017, p. 230).

Table 1. Count of NAS Risk of Bias Determinations for Studies of DINP and AGD in Rats (NAS 2017, Figure 3-20)

	Boberg et al., 2011	Clewell et al. 2013	Li et al., 2015	Masutomi et al., 2003
Definitely high risk of bias	0	0	0	0
Probably high risk of bias	0	0	1	0
Not reported (ultimately assessed as "Probably high risk of bias)	2	2	3	4
Probably low risk of bias	4	2	5	3
Definitely low risk of bias	4	6	1	3

Similarly, for the effects of DINP on fetal testosterone, the committee's evaluation for Boberg et al. included "probably low risk of bias" or "definitely low risk of bias" for eight of the ten criteria, and noted that data for the remaining two were "not reported" (i.e., no data on which to draw a conclusion). These conclusions are similar to the other literature reviewed, as shown in Table 2. The NAS committee did not downgrade confidence in DINP effects on fetal testosterone, and concluded that there is a "high level of evidence that fetal exposure to DINP is associated with a decrease in fetal testosterone in male rats."

[5] The NAS report noted that "[i]nformation or study procedures that were not reported are assumed not to have been conducted, resulting in an assessment of 'probably high' risk of bias."

Table 2. Count of NAS Risk of Bias Determinations for Studies of DINP and Fetal Testosterone in Rats (NAS 2017, Figure 3-24)

	Adamsson et al., 2009	Boberg et al., 2011	Hannas et al., 2011	Li et al., 2015
Definitely high risk of bias	0	0	0	0
Probably high risk of bias	0	0	0	1
Not reported (ultimately assessed as "Probably high risk of bias)	4	2	3	3
Probably low risk of bias	4	4	2	5
Definitely low risk of bias	2	4	5	1

Overall, the NAS report demonstrated that the Boberg et al. study had risk of bias factors that were similar to other studies. Staff finds nothing in the NAS report suggesting that the Boberg et al. study should be excluded from the body of literature used by the CHAP and staff to evaluate hazard endpoints for DINP.

3. NAS Evaluation of DIBP, DPENP, DEHP, DBP, and BBP

The NAS report concluded that DIBP and DPENP are "presumed human hazards." The NAS report did not evaluate DCHP or DHEXP. The NAS report confirmed that DEHP, DBP, and BBP, the three permanently prohibited phthalates in children's toys and child care articles, are "presumed human hazards." Furthermore, the NAS report concluded that there is a moderate level of the epidemiological evidence that DEHP and DBP are associated with reduced AGD, and are "presumed human hazards" (NAS 2017, p. 71, p. 78, and Table 3-29). These conclusions provide additional confidence that MRDE occurs in humans.

4. Conclusions

In summary, the NAS report concluded the following regarding DINP effects:

- DINP effect on Fetal Testosterone: The NAS concluded that "there is a high level of evidence that fetal exposure to DINP is associated with a decrease in fetal testosterone in male rats," and that there was "inadequate evidence to determine whether fetal exposure to…DINP,… is associated with a reduction in fetal testosterone in male humans." Overall, the NAS' initial hazard evaluation of DINP and fetal testosterone in humans was that DINP was a "presumed human hazard."

- DINP effect on AGD: The NAS concluded that "there is an inadequate level of evidence to assess whether fetal exposure to DINP is associated with a decrease in AGD in male rats," and that "the available studies do not support DINP exposure being associated with decreased AGD." Overall, the NAS' initial hazard evaluation of DINP and AGD in humans was "not classifiable."

Although the NAS study is not, as discussed previously, a risk assessment, the NAS hazard evaluation findings support the CHAP's and staff's conclusions that DINP is antiandrogenic, does induce effects that are consistent with phthalate syndrome, and that it was appropriate to include DINP in the CRA.

The NAS report further concluded that both DIBP and DPENP are "presumed human hazards" for effects on fetal testosterone in male rats. As with DINP, this conclusion supports the CHAP's and staff's conclusions that DIBP and DPENP are antiandrogenic, do induce effects that are consistent with phthalate syndrome, and that it was appropriate to include DIBP in the CRA. The NAS report did not evaluate DCHP or DHEXP.

IV. Responses to Public Comments

The Commission received a total of 109 public comments,[6] including 91 comments on the NPR and 18 comments on the CPSC staff's biomonitoring reports (CPSC 2015a; CPSC 2017a) (integrated in TAB A). Commenters included the general public, manufacturers of phthalates or products containing phthalates, non-governmental organizations (NGOs), and members of Congress.

The following section briefly summarizes the most significant public comments and staff's responses on broad issues such as:

1. Selection of Health Endpoints and Interspecies Differences;
2. Cumulative Risk Assessment;
3. Human Biomonitoring (HBM) Data;
4. CHAP's Three Cases (Potency Estimates for Antiandrogenicity);
5. Relative Contributions of Phthalates and Sources of Exposure to Cumulative Risk;
6. Scope of Prohibitions;
7. Epidemiology;
8. Legal Issues and Peer Review;
9. Economic and Compliance Issues; and
10. Other Comments.

Staff's detailed responses to public comments may be found in TAB B.

A. Selection of Health Endpoint and Interspecies Differences

After reviewing all of the available data on the health effects of phthalates, the CHAP selected male reproductive developmental effects (MRDE) and other adverse effects on male fertility, both part of a spectrum of effects termed "phthalate syndrome," as the critical group of related health effects for the purpose of performing a cumulative risk assessment (CRA) (CHAP 2014;

[6] Public comments are available at https://www.regulations.gov/docket?D=CPSC-2014-0033.

pp. 13-15). Many but not all phthalates cause MRDE (CHAP 2014, p. 16). Although the male fetus is considered the most sensitive life stage to MRDE, phthalates also cause effects at all life stages, including adulthood.

Some industry comments discussed whether MRDE was appropriate for a CRA involving phthalates. Commenters made several assertions, including that: (a) humans are resistant to the adverse effects induced by phthalates when compared to rodents, or at least, humans are less sensitive than rodents; (b) the proposed regulations are intended to protect infants, but only the fetus is sensitive to the effects of phthalates; (c) DINP is not antiandrogenic (i.e., does not cause MRDE or fertility effects); and (d) the mode or mechanism of action of many phthalates is not well understood. (TAB B, Section 1).

CPSC staff concludes that MRDE and effects on male fertility are the most appropriate endpoints for a CRA involving phthalates. Abundant evidence demonstrates that DEHP, BBP, DBP, DIBP, and DINP induce MRDE or related effects in animals. Ample experimental evidence shows that the effects of these phthalates on MRDE are additive (cumulative). The National Academy of Sciences recommended MRDE and effects on male fertility (common adverse outcomes) for conducting a CRA for phthalates (NRC 2008).

Regarding (a), staff concludes that while a few studies suggest that humans may be less sensitive than rodents to phthalate effects, the majority of empirical evidence supports the use of the rat as an appropriate model for estimating phthalate risks in humans (comment response 1.3-1.6). In addition, a growing number of epidemiological studies have reported associations between phthalate exposure and MRDE effects in male infants and adults, supporting the relevance of rodent data to humans.

Regarding (b), the proposed regulations on children's toys and child care articles are primarily intended to protect infants and children (comment response 1.11). The potency estimates derived by the CHAP (potency estimates for antiandrogenicity, PEAAs) are intended to protect the male fetus, infants, children, and adult populations. Although the male fetus is considered to be the most sensitive to MRDE, MRDE and impaired fertility affects males of all ages, including adults.

Regarding (c), staff concludes that the overwhelming weight of the evidence demonstrates that DINP can induce MRDE (phthalate syndrome) in animals, and that it is less potent than DEHP (comment response 1.14).

Finally, regarding (d), staff concludes that the phthalates that cause MRDE and male infertility share a common mode of action and induce cumulative effects (i.e., dose additivity) (Conley et al. 2017; Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008). However, staff notes that a common mode of action is not necessary for cumulative effects to occur (ATSDR 2004; Howdeshell et al. 2016) (comment response 1.21).

B. Cumulative Risk Assessment

A cumulative risk assessment (CRA) estimates the potential risk following exposure to multiple "stressors," in this case, multiple phthalates. The CPSIA required the CHAP to assess the risk from phthalates "both in isolation and in combination with other phthalates." CPSIA § 108(b)(2). The CHAP assessed phthalate risks in combination with other phthalates by performing a CRA. The CHAP limited their CRA to phthalates that were: (1) known to cause male reproductive

developmental effects (MRDE) in laboratory animals, also known as the "phthalate syndrome," and (2) measured in human biomonitoring data (HBM) studies (DEHP, BBP, DBP, DIBP, DINP).

To perform the CRA, the CHAP used animal data to assess the hazard/dose response (potency) of phthalates and HBM from the National Health and Nutrition Examination Survey (NHANES) and Studies for Future Families (SFF) to estimate exposure. The CHAP combined hazard/dose response information and exposure estimates in a hazard index (HI) approach for determining the risk to sensitive populations.

Public comments addressed several topics. (a) Several commenters claimed that CRA is not widely used and is not generally accepted for use in human health risk assessment. They added that federal agencies, including CPSC, have little experience with CRA and have not used CRA to support regulations. (b) Some commenters criticized the CHAP's use of a "novel" method in the CRA. (c) Some commenters also asserted that it is not appropriate to perform a CRA for phthalates because phthalates do not share a common mechanism of action.

Regarding (a), the CPSC staff concludes that the hazard index approach to a CRA used by the CHAP is appropriate to use for determining the risk of phthalates. CPSC staff notes that CRA of chemical mixtures has been an established practice since the 1980s (EPA 1986) and has been used to support multiple federal regulations (ATSDR 2017; 2002a; EPA 2002b; 2006; 2015b; 2015c). The CHAP's CRA was consistent with the recommendations of a National Academy of Sciences report on cumulative risk assessment of phthalates (NRC 2008) (comment response 2.1).

Regarding (b), to avoid overestimating risk using NHANES exposure data, the CHAP introduced a minor improvement to the standard CRA methodology. This improvement was accepted by the CHAP peer review panel and has been adopted for use by Christensen et al. (2014) (comment response 2.2).

Regarding (c), staff concludes that there is adequate experimental support for the cumulative (i.e., dose additive) effects of phthalates (Conley et al. 2017; Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008), even at low doses. Furthermore, although a common mechanism of action is not necessary for additivity to occur (ATSDR 2004; Howdeshell et al. 2016), staff concludes that the phthalates in the CRA act through a common mechanism of action (comment response 2.4-2.8).

Staff concludes that CRA of chemical mixtures has been in use for many years; it is used by federal agencies to regulate chemicals; an acceptable improvement was made by the CHAP to the CRA methodology; and the CHAP followed the recommendations of the National Academy of Sciences.

C. Human Biomonitoring Data

Human biomonitoring (HBM) is the measurement of a chemical or its metabolites in human biological samples, such as blood or urine. The concentration of urinary phthalate metabolites in HBM samples can be used to estimate exposure to the parent phthalate.

To understand exposures to phthalates, the CHAP analyzed urinary biomonitoring data on pregnant women included in NHANES (2005/2006 data cycle), a national, statistically representative survey of the U.S. population. The CHAP also analyzed urinary metabolite data

from another biomonitoring survey, the Study for Future Families (SFF; 1999-2005), to estimate phthalate exposure to children from ages 2 to 36 months old and their mothers.

The public comments covered several topics. (a) The primary criticism commenters raised was that the CHAP's analysis was based on 2005/2006 data, and that more recent NHANES data have become available and should be analyzed. (b) Commenters also noted that the more recent NHANES data show that phthalate risks in adults have decreased, and thus, fetuses and infants are no longer at risk for phthalate-induced MRDE. (c) Other comments criticized the NHANES survey method of using "spot urine samples," claiming that spot sampling does not accurately reflect the duration of exposure necessary to develop MRDE (TAB B, Section 3).

Regarding (a), subsequent to the NPR, staff analyzed NHANES data for women of reproductive age (WORA) (from 2005 through 2014) (TAB A). Staff notes that the 2005/2006 data cycle was the last to sample with a sufficient number of pregnant women to make statistically reliable exposure estimates for that subpopulation. Thus, all subsequent analyses are for WORA (comment response 3.1).

Regarding (b), staff analysis (TAB A, Table 6) found that total phthalate exposures in WORA have increased over time (see above, Section III). Although DEHP exposure has declined, DINP exposure has increased roughly fivefold since 2005/2006 (Figure 1). Although DEHP was the major contributor to the cumulative risk in 2005/2006, DINP now contributes about as much to the cumulative risk as DEHP, despite its lower potency. Although the net exposures have increased, the risk to WORA, as indicated by HI, has decreased. Median and 95th percentile HIs for WORA are all less than one. Staff estimates that between 98.8 and 99.6 percent of WORA have HIs less than or equal to one, compared to the 95.8 to 97.1 percent range found in the 2005/2006 cycle. As described in section 5.4 of TAB A, the 2013/2014 NHANES data cannot be used to estimate how many WORA in the U.S. population have HIs greater than one. However, individuals in the sample were observed to have HIs greater than one. Specifically, out of a sample of 538 WORA in the 2013/2014 NHANES data cycle, between two and nine WORA, depending on the PEAA Case, were observed with HIs greater than one. Male children for these women were at increased risk for MRDE. There are also WORA individuals in each recent data set with a DINP hazard quotient (HQ) (and thus HI) greater than one (comment response 3.1, 3.2).

If the overall phthalate risk to WORA has declined since 2005/2006, it is possible that exposure, and thus risk[7] to infants also has declined. However, no new urinary phthalate data on infants are available to quantify these changing exposures, and staff cannot calculate new percentages of the infant population with an HI less than one. Staff notes that infants' and children's exposures tend to be greater than in adults, on average by two- to threefold (CHAP 2014; Koch et al. 2004; Sathyanarayana et al. 2008a; Swan 2008; Swan et al. 2005) (comment response 3.5). Therefore, staff can only make a qualitative assessment that the risk to infants has possibly reduced over the past decade, and that the risk to infants is probably greater on average than the risk to WORA.

Regarding (c), spot urine samples, staff concludes that commenter concerns regarding the use of older NHANES data have been addressed by CPSC staff's analysis of the newest publicly

[7] Risk can be considered as a function of toxicity and exposure. The toxicity of DINP is a constant value. Thus, if exposure decreases, the associated risk should decline by a proportional amount.

available NHANES data sets. In addition, staff considers spot urine samples adequate for assessing exposures from MRDE-inducing phthalates because short-term phthalate exposures (which are reflected in a spot urine sample) have been demonstrated to induce MRDE effects in laboratory animals (comment response 3.11).

D. The CHAP's Three Cases (Potency Estimates for Antiandrogenicity)

The CHAP selected phthalate potency estimates for each MRDE-inducing phthalate using three independent methods, and referred to these as potency estimates for antiandrogenicity (PEAAs). The CHAP used three sets of PEAAs (Cases) to explore the effect of different methodology (e.g., different uncertainty factors and PODs) on cumulative risk estimates to "determine the sensitivity of the results to the assumptions for PEAAs and the total impact on the HI approach" (CHAP 2014, pp. 63-66). Each independent PEAA was used to assess the cumulative risk of phthalates (CHAP 2014, pp. 62-66). Case 1 PEAAs were based on published, peer-reviewed values (Kortenkamp and Faust 2010). Case 2 PEAAs were based on the use of relative potency factors and comparison to an index phthalate (DEHP; (Hannas et al. 2011)). Case 3 PEAAs were selected from a *de novo* review of the available literature.

The public comments covered several topics for the PEAA cases. (a) Some commenters noted that Case 1, which was based on PEAA values published in 2010, was out of date. (b) Some commenters claimed that Case 2 was based on an *in vitro* study and that the relative potency estimates in Case 2 (e.g., for DINP) were not needed because *in vivo* data already existed. (c) Comments on Case 3 questioned the use of particular hazard endpoints, such as multinucleate gonocytes (MNGs) for DINP.

Overall, staff concurs with the CHAP's use of three Cases because each represents a different, but scientifically valid and informative method for estimating the hazard and potency of a phthalate. Staff concludes that each of the three cases has certain advantages, as noted above, and that all three are appropriate for estimating human risk.

Regarding (a), the source of the published PEAA values (Kortenkamp and Faust 2010) was new when the CHAP began its deliberations in April 2010. In addition, the Kortenkamp and Faust publication outlined a CRA method and selection of hazard and exposure factors that was scientifically credible. Therefore, Case 1 was valid to use as an independent method for estimating phthalate risk (comment response 4.7).

Regarding (b), Case 2 elicited numerous comments and is based on a comparison of the relative potencies of the different phthalates. Case 2 has the advantage that most of the phthalates were assayed in the same laboratory using the same methodology. Thus, Case 2 is ideal for comparing the potencies of individual phthalates. Staff notes that Case 2 was based on a study (Hannas et al. 2011) in which animals were exposed to phthalates *in vivo*, although the rate of testosterone synthesis, by necessity, was measured *in vitro*. As noted above and in comment responses (4.9-4.14), staff concludes that the CHAP's approach of using three Cases is not only appropriate, but also provides added reliability to their CRA. Therefore, using relative potency estimates in Case 2 was acceptable, irrespective of whether other *in vivo* potency estimates existed.

Regarding (c), staff notes that the induction of MNGs is one of a spectrum of effects that is commonly included in "phthalate syndrome" and may be linked to reduced fertility and testicular

germ cell cancer. Therefore, the use of MNG induction as a DINP hazard endpoint for the CRA is appropriate (comment response 1.20, 4.17).

E. Relative Contributions of Phthalates and Sources of Exposure to Cumulative Risk

The CHAP and staff included the relative contribution of each phthalate risk (HQs) to the total phthalate risk (HI) when reporting results using NHANES biomonitoring analyses (CHAP, Appendix D; CPSC, 2015; CPSC, 2017). The CHAP report also included an analysis of the relative sources of exposure (e.g., diet, medications, toys) and their contribution to total exposure when reporting on modeled exposure activity scenarios (CHAP 2014, Appendix E1). Public commenters raised a number of issues. (a) Several commenters claimed that DINP contributes little to cumulative risk and that the primary risk driver has always been DEHP, which is permanently prohibited in children's toys and child care articles. (b) Some commenters also argued that the permanently prohibited phthalates (DBP, BBP, and DEHP) should not have been included in the CHAP's CRA. (c) Commenters also claimed that children's toys and child care articles contributed little to the overall risk.

Staff generally disagrees with the commenters' conclusions. Regarding (a), overall, CPSC staff concludes that the contribution of DINP to the cumulative risk is substantial and has increased since the CHAP completed its analysis. Analysis of recent NHANES data indicates that DINP exposure has increased fivefold between 2005/2006 and 2013/2014 (CPSC 2017a). DINP now contributes roughly as much as DEHP to the cumulative risk (TAB A, Table 8) (comment response 5.1).

Regarding (b), staff agrees with the CHAP's inclusion of the permanently prohibited phthalates (DBP, BBP, and DEHP) in the CRA, because exposures to DBP, BBP, and DEHP continue to occur from multiple sources (not just toys and child care articles), and therefore, contributes to the cumulative risk (comment response 5.2).

Regarding (c), staff notes that mouthing and dermal exposure[8] to children's toys and child care articles could contribute up to about 29 percent of the total DINP exposure to infants if phthalates were allowed in these products, as shown in the results of the exposure scenarios developed by staff at the request of the CHAP (CHAP 2014, Appendix E1, Table E1-21) (comment response 5.3). We note that the 29 percent increase in exposure is what would happen if all manufacturers return to using DINP in these products Staff cannot determine how much a 29 percent increase in average exposure would translate to the percentage of those with a HI greater than one.

[8] Staff interprets "mouthing" to include any contact of the toys or child care article with the mouth, lips, or tongue (Greene 2002; Kiss 2002). Dermal exposure occurs from contact with the skin, including handling toys (holding in the hand) or contact of child care articles with any skin surface (CHAP 2014, Appendix E-1).

F. Scope of Prohibitions

1. All Children's Toys

The CHAP recommended "that the interim ban on the use of DINP in children's toys and child care articles at levels greater than 0.1 percent be made permanent" (CHAP 2014, p. 99). Public comments on this recommendation and the proposed rule made two main points: (a) Several commenters objected to the proposal to expand the scope of the prohibition from "toys that can be placed in a child's mouth," to "children's toys" for DINP, arguing that mouthing toys is the primary source of risk from toys, and therefore, no oral exposure can occur from toys too large (greater than 5 cm in all dimensions). (b) Some commenters cited a report by the European Chemicals Agency (ECHA) to support not expanding the prohibition to all children's toys for DINP. The ECHA report recommended retaining the prohibition involving DINP, which in Europe, applies to toys and child care articles that can be placed in a child's mouth (ECHA 2013). In contrast, other commenters supported the expanded scope.

Regarding (a), staff notes that researchers studying children's mouthing activity consider "mouthing" (a form of oral exposure) to include any contact of the toys or child care article with the mouth, lips, or tongue (EPA 2011; Greene 2002; Groot et al. 1998; Juberg et al. 2001; Kiss 2002). In addition, handling toys and then putting fingers and hands in the mouth is considered an additional form of oral exposure. The CHAP used mouthing data from Greene (2002); therefore, their estimates of oral exposure from mouthing toys (CHAP 2014, Appendix E-1) include any behavior in which the toy contacts the mouth. The ECHA report cited by commenters (ECHA 2013) also used mouthing data from Greene (2002). Thus, both the CHAP's and ECHA's assessments of DINP exposure include all children's toys (comment response 6.1, 6.2).

Regarding (b), the ECHA report concluded that the prohibition on toys and child care articles containing DINP that can be placed in a child's mouth should not be lifted, but the report did not state any conclusions about whether to expand the prohibition's scope to all children's toys. There was no indication that the issue of expanding the scope to all toys was even considered by ECHA (comment response 6.4).

Staff concludes that expanding the scope of the proposed permanent prohibition to include all children's toys containing more than 0.1 percent of DINP would prevent additional mouthing and dermal exposures from handling toys not included in the interim prohibition.

2. All Children's Products

The CHAP was unable to assess exposure and risk from the broader range of children's products, largely due to the lack of information (CHAP 2014, Appendix E-1, p. E1-47).

A few commenters expressed disappointment that the Commission did not expand the scope of the phthalate regulations to encompass all children's products. The sources of information identified by commenters were not of sufficient relevance, quality, or quantity, to support expanding the scope of prohibitions involving phthalates to all children's products. Commenters' assumption that the theoretical exposure from children's products would justify expanding the

scope to all children's products is contradicted by the science estimating less exposure from children's products than from children's toys and childcare articles. (comment response 6.6).

G. Epidemiology

The CHAP discussed phthalate-associated epidemiology in detail (CHAP 2014, pp. 27-29) and used epidemiological summaries to support their weight-of-evidence recommendations for each phthalate (CHAP 2014, pp. 79-142). Several public comments addressed this topic. (a) Some commenters claimed that the epidemiological literature on phthalates does not support the CHAP's recommendations due to study-to-study uncertainties and inconsistencies. (b) Some commenters asserted that the epidemiology studies have not established a cause-and-effect relationship between phthalate exposure and MRDE effects in humans, and thus, there is no human evidence to support the CHAP's recommendations and the Commission's proposed regulations.

Regarding (a), staff disagrees with commenters. Staff has considered available information, and concluded as did the CHAP (CHAP 2014, p. 27), that there is a growing body of studies showing an association of phthalate exposure with MRDE effects in infant and adult males (comment response 7.1).

Regarding (b), staff agrees that existing phthalate epidemiological studies have not established a cause-and-effect relationship. However, the CHAP's recommendations are primarily based on animal data. Therefore, epidemiological studies establishing a definitive causal relationship between exposure and effect are not required to conclude that a substance or mixture is "probably toxic to humans" (CPSC 1992; EPA 1991; IARC 2002; NTP 2016) or to support a regulation (CPSC 1992). 16 C.F.R. § 1500.3 (c)(2)(ii). Epidemiological data are rarely able to establish cause and effect for any exposure. Based on the CPSC's chronic hazard guidelines (CPSC 1992), staff considers that there is sufficient evidence in animal studies to conclude that certain phthalates are probably toxic to humans. Epidemiological data provide supporting evidence for the animal data and also support the conclusion that the results of animal studies are relevant to humans (comment response 7.1).

H. Legal Issues

Section 108 of the CPSIA establishes the legal framework for the CHAP's work and the CPSC's rulemaking. The CHAP and CPSC followed all applicable legal requirements. Several comments raised legal issues, focusing primarily on the Information Quality Act (IQA), peer review, and statutory requirements of the CPSIA and APA.

IQA/peer review. Some commenters asserted that the CHAP report and CPSC's rulemaking did not comply with the IQA and the information quality guidelines issued by the Office of Management and Budget (OMB) and CPSC, as well as OMB's peer review bulletin issued under the IQA.

Even if considered a highly influential scientific document disseminated by CPSC, the CHAP report met all aspects of the OMB's and CPSC's information quality guidelines and OMB's peer-review bulletin. We note that these are all guidance documents that provide agencies with flexibility in determining how to meet their guidelines. The CHAP's process was transparent and

objective–the CHAP held seven public meetings and eight public teleconferences, heard testimony from stakeholders, and sought input from scientific experts. The CHAP report clearly explained the CHAP's methods and how the CHAP reached its conclusions. In addition, the report was subjected to an independent peer review. Both the CHAP members and peer reviewers were nominated by the National Academy of Sciences and were subject to specific conflict of interest requirements (comment responses 8.1-8.8).

CPSIA and APA requirements. Some commenters asserted that the CHAP and CPSC failed to comply with the CPSIA's requirements for the CHAP and for the phthalates rulemaking. For example, some commenters asserted that the CHAP had not reviewed all relevant data and that the CPSIA did not require a cumulative risk assessment. Commenters opined on the role of the CHAP report in the rulemaking. Commenters also expressed opinions about the meaning of the term "reasonable certainty of no harm" and the relevance of the CPSA and the FHSA.

The CHAP and CPSC followed all requirements stated in the CPSIA (comment responses 8.17-8.26). The CHAP considered all relevant data available at the time of their analysis, and CPSC staff subsequently reviewed (and requested comment on) more recent relevant data. Although the CPSIA did not require the CHAP to conduct a cumulative risk assessment, it did require the CHAP to "consider the cumulative effect of total exposure to phthalates" and to consider health effects of phthalates "in isolation and in combination with other phthalates." The CHAP reasonably determined that a cumulative risk assessment was the most appropriate method to fulfill this direction. We believe that the CPSIA does not require the Commission to adhere rigidly to the CHAP's recommendations. Rather, the CHAP report is advisory, and the Commission must consider the criteria in section 108(b)(3)(A) and (B) of the CPSIA, and public comments to determine appropriate regulatory action. This rulemaking follows that approach. Regarding the meaning of "reasonable certainty of no harm," section 108 of the CPSIA established this as the standard the Commission should use for the phthalates rulemaking; other statutory metrics (e.g., unreasonable risk under the CPSA or banned hazardous substance under the FHSA) do not apply. We believe that "reasonable certainty of no harm" requires a highly protective standard, but does not require 100 percent certainty of no harm. Following direction in section 553 of the APA, the Commission issued a proposed rule requesting public comments, and staff has considered issues raised by those comments (comment response 8.9-8.16).

I. Economic and Compliance Issues

The CHAP did not discuss the economic impacts of phthalate regulation or particular compliance issues. However, the NPR did discuss the impact the proposed rule would have on small businesses. Two commenters agreed with staff's conclusion that the proposed regulations would have a small impact on testing costs. Other comments raised issues regarding costs and compliance. (a) Some commenters, without providing any specifics, claimed that the proposed regulations could be detrimental to small manufacturers. (b) One commenter asked whether the

CPSC guidance on component part testing (16 C.F.R. part 1199)[9] would apply to DIBP, DPENP, DHEXP, and DCHP.

Regarding (a), staff maintains that any increase in testing costs would be small, and that there will be no significant impact on small entities (comment response 9.1).

Regarding (b), staff notes that the principles in the guidance on component part testing should apply to all children's toys and child care articles containing prohibited phthalates (comment response 9.2).

J. Other Comments

Commenters submitted statements on non-technical issues, such as systematic review, weight of the evidence, transparency, and phthalate alternatives for staff and the Commission to consider. These broader topics are discussed below.

1. Systematic Review

"Systematic review" refers to a specific approach to increase objectivity and transparency when collecting and analyzing scientific data (Rooney et al. 2014). The use of systematic review is well established for analyzing clinical studies and making health care recommendations, where such analyses generally involve limited numbers and types of studies. However, systematic review only recently has been adopted for use in assessing environmental health questions (EPA 2015a; NTP 2015). As discussed by the CHAP, environmental health includes many different scientific fields and types of data, such as animal toxicology, human epidemiology, and exposure and risk estimation. Because the included fields are disparate and broad, applying systematic review procedures to environmental health poses special challenges.

Some industry commenters stated that the CHAP report was not a "systematic review." In response, staff notes that the CHAP explained: "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" (CHAP 2014, p. 12). Nonetheless, staff notes that the CHAP included elements of systematic review in its work, such as a defined literature search strategy, describing criteria for evaluating studies, and describing criteria for formulating its recommendations. Staff further notes that, when the CHAP convened in 2010, federal agencies, such as the EPA and National Toxicology Program (NTP), had not yet adopted systematic review methods, and tools such as specialized software for characterizing publications were also not available. Systematic review is only recently being adopted by federal agencies for use in assessing environmental health (EPA 2015a; NTP 2015) (comment response 10.1).

2. Weight of Evidence

A weight-of-evidence (WOE) approach considers multiple types of positive and negative evidence to reach conclusions. The evidence considered is usually interpreted and weighted (relative values or weights) by criteria relevant to the issue being investigated.

[9] Available at: http://www.ecfr.gov/cgi-bin/text-idx?SID=a0c4999f6a33294f4921e81a0f48180c&node=pt16.2.1199&rgn=div5.

Industry commenters also claimed that the CHAP did not consider the WOE in its report. Staff notes that the CHAP specifically included WOE in the criteria for making recommendations (CHAP 2014, p. 79). The CHAP also included a section on WOE in its recommendations for each phthalate and phthalate alternative (CHAP 2014, pp. 82-142) (comment response 10.1).

3. Transparency

Several commenters raised concerns about the transparency of the CHAP process. Some commenters claimed that the CHAP process was secret and performed behind closed doors, while others commended the transparency of the process. Other commenters stated that the technical studies and data that CPSC used to make decisions should be made public.

CPSC staff disagrees with claims that the CHAP process was secret or lacking transparency. The CHAP held seven public meetings and six public teleconferences. The CHAP heard testimony from stakeholders in public, and received written comments throughout the CHAP process. All written submissions, oral presentations, and data submitted to the CHAP are available on the CPSC website (www.cpsc.gov/chap). The CHAP did not use information that was not available to the public (comment response 10.3).

4. Phthalate Alternatives

Some commenters stated that if children's toys and child care articles are prohibited if they contain certain phthalates, then manufacturers will be forced to use alternative plasticizer chemicals whose safety or toxicity are not known, thus, potentially putting people at greater risk. Staff agrees that for some phthalate alternatives, the available data on either toxicity or exposure were limited (CHAP 2014, pp. 121-142). For one alternative (DINX), toxicity data exist, but the data were not available to the CHAP.[10] Staff notes that CPSC lacks the authority to require manufacturers to perform toxicity or exposure tests, or to provide existing data. Staff plans to work with other federal agencies, including the National Toxicology Program (NTP) and EPA to obtain additional data on phthalate alternatives (comment response 10.5).

V. Regulation of Products with Phthalates and Phthalate Alternatives in Other Countries

As a party to the World Trade Organization (WTO) Agreement on Technical Barriers to Trade (TBT), the United States must consider international standards and use them as the basis for U.S. regulations, except if the international standards would be an ineffective and inappropriate means to fulfill a legitimate objective (e.g., protecting human health and safety). The only international standard on phthalates is International Organization for Standardization (ISO) 8124-6:2014. This ISO standard specifies a method for testing toys and children's products to determine if they contain phthalates; it does not establish any content limit. Staff also considers it good practice to review how (or if) foreign jurisdictions have addressed product hazards that the CPSC has identified, in case those approaches may provide useful solutions.

[10] Presentation of Dr. Rainer Otter, BASF, to the CHAP. July 2010.

In reviewing foreign requirements for regulatory limits for phthalates, staff searched for and considered mandatory regulations of individual countries that addressed phthalates (DBP, BBP, DEHP, DNOP, DINP, DIDP, DMP, DEP, DIBP, DPENP, DHEXP, DCHP, DIOP, and DPHP) and phthalate alternatives (TPIB, DEHA, DEHT, ATBC, DINX, TOTM) in children's toys and child care articles, including the European Union (EU), Denmark, Canada, Japan, Australia, Brazil, Argentina, Taiwan, and Hong Kong (Table 3).

Consistent with the published NPR, the CPSC staff draft final rule prohibits permanently children's toys and childcare articles containing DINP, DIBP, DCHP, DHEXP, and DPENP at levels greater than 0.1 percent. The draft final rule expands the scope of the prohibition from children's toys that can be placed in the mouth to all children's toys for DINP to address other oral and dermal exposures necessary to ensure a reasonable certainty of no harm to susceptible populations with an adequate margin of safety.

Most phthalate regulations of other countries for DINP use the same concentration limit (usually 0.1 percent), but differ about whether the regulated phthalate concentrations for comparison with the threshold level are for DINP only, or DINP included with other regulated phthalates; the type of products or toys tested; whether these are placed in a child's mouth; and the product's age range for use by children. Denmark has a more stringent threshold (0.05 percent), but this is applicable only to toys and child care articles intended for children under 3.

The draft final rule prohibits children's toys and child care articles containing any of these four additional phthalates (DIBP, DCHP, DHEXP, and DPENP). DIBP (an ester of *o*-phthalic acid) is nationally prohibited in Denmark at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old,[11] and at concentrations above 0.1 percent in products for indoor use and products that can come into direct contact with the skin or mucous membranes[12]. DCHP, DHEXP, and DPENP (esters of *o*-phthalic acid) are also nationally prohibited in Denmark at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old. Currently, DIBP, DCHP, DHEXP, and DPENP are not regulated in other countries.

Diisononyl phthalate (DINP) – Esters of *o*-phthalic acid - Denmark instituted a national prohibition on all phthalates in 2009 at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old.

Europe limits the use of DINP, DIDP, and DNOP individually or as mixtures in children's toys that can be placed in the mouth and child care articles to no greater than 0.1 percent by weight of the plasticized material. Canada limits use in the vinyl in any part of a toy or child care article that can be placed in the mouth of a child under 4 years of age to no greater than 0.1 percent of diisononyl phthalate (DINP), diisodecyl phthalate (DIDP) or di-*n*-octyl phthalate (DNOP). Japan prohibits parts of toys made from PVC that are not intended to contact the mouth when containing DINP and limits use of DINP, DIDP, or DNOP in the parts of designated toys made from plasticized material intended to contact the mouth to no greater than 0.1 percent. Brazil limits use of DINP in plastic materials in all kinds of toys for

[11] Denmark Statutory Order no. 855 of 5 September 2009.
[12] Denmark Statutory Order no. 1113 of 26 November 2012.

children under three to no greater than 0.1 percent. Argentina limits use of DINP in toys and child care articles made of plastic material that can be placed in the mouth to no greater than 0.1 percent. Taiwan limits DINP use in toys and child care articles to no greater than 0.1 percent individually or in combination with DEHP, DBP, BBP, DIDP, or DNOP. Hong Kong limits the combination of DINP, DIDP, and DNOP to no greater than 0.1 percent of the total weight of the plasticized materials in toys or children's products any part of which can be placed in the mouth of a child under four years of age. There are no regulations for DINP in Australia.

Diisobutyl phthalate (DIBP) – Esters of *o*-phthalic acid - Denmark instituted a national prohibition on all phthalates in 2009 at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old.

Furthermore, Denmark instituted a national prohibition on DIBP in 2012 at concentrations "above 0.1% in products for indoor use and products that can come into direct contact with the skin or mucous membranes."

There are no other regulations that addressed DIBP in Europe, Canada, Japan, Brazil, Argentina, Taiwan, or Hong Kong.

Dicyclohexyl phthalate (DCHP) - Esters of *o*-phthalic acid - Denmark instituted a national prohibition on all phthalates in 2009 at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old. There are no other regulations that addressed DCHP in Europe, Canada, Japan, Brazil, Argentina, Taiwan, or Hong Kong.

Di-*n*-hexyl phthalate (DHEXP) - Esters of *o*-phthalic acid - Denmark instituted a national prohibition on all phthalates in 2009 at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old. There are no other regulations that addressed DHEXP in Europe, Canada, Japan, Brazil, Argentina, Taiwan, or Hong Kong.

Di-*n*-pentyl phthalate (DPENP) - Esters of *o*-phthalic acid - Denmark instituted a national prohibition on all phthalates in 2009 at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old. There are no other regulations that addressed DPENP in Europe, Canada, Japan, Brazil, Argentina, Taiwan, or Hong Kong.

Esters of *o*-phthalic acid - Denmark instituted a national prohibition on all phthalates in 2009 at concentrations above 0.05 percent in toys and child care articles intended for children under 3 years old.

In addition, staff found no regulations for the phthalate alternatives (TPIB, DEHA, DEHT, ATBC, DINCH, and TOTM).

In summary, regulations concerning children's toys and child care articles containing phthalates are heterogeneous among countries and do not inform current or proposed prohibitions in the United States. Additionally, in contrast to the approach required by Congress, European and Australian evaluations considered phthalate exposures in isolation, not in combination with other phthalates. International regulations also differ in the scope of products, and age ranges covered.

Table 3. Phthalate Regulations for children's toys and child care articles in USA, Europe, Denmark, Canada, Japan, Australia, Brazil, Argentina, Taiwan, and Hong Kong

	U.S. Reg/Leg (CPSIA sec 108, 2008; NPR, 2014)	Europe (EU) Reg/Leg (Directive 76/769/EEC, 2005/84/EC, Annex I [XXa]); Commission Regulation (EC) No 552/2009; REACH Annex XVII ent. 51/52, 2015)	Denmark BEK nr 855 af 05/09/2009 Danish Environmental Protection Agency no. MST-620-00064 Law # 1755 (Dec 22, 2006) as amended by Law # 97 (Feb 10, 2009), also BEK nr1113 af 26/11/12	Canada Reg/Leg (SOR/2016-188)	Japan Reg/Leg (10th edition, Toy Safety Standard, ST-2002, revised August 23, 2011)	Australia Reg/Leg (Competition and Consumer Act 2010, Consumer Protection Notice No. 11 of 2011)	Brazil Reg/Leg (Ministerial Act: Compulsory Testing and Licensing Requirements for Imports of Toys, Circular No. 520/2007)	Argentina Reg/Leg (resolution 583/2008 , file 2002-2041/08-3, 2008)	Taiwan Reg/Leg (CNS 4797, General Requirements of Safety of Toys, July 1, 2008)	Hong Kong (China) Reg/Leg (L.N. 17 of 2014 B117, Toys and Children's Products Safety Regulation)
DEHP	Prohibit children's toys[1] and child care articles[2] containing concentrations >0.1 percent	CAS 117-81-7 DEHP, DBP, and BBP not used in concentrations greater than 0.1 percent by weight of the plasticized material, in toys and childcare articles[3].	See EU Regulation and DIBP	The vinyl in a toy[4] or child care article[5] has no more than 1000 mg/kg of DEHP, DBP, or BBP.	Plasticized material used in designated toy does not contain over 0.1 percent DEHP, DBP, or BBP. Synthetic resin mainly composed of PVC used in non-designated toys intended for children under six years shall follow DEHP and DINP requirement only. No synthetic resin containing PVC is used in Pacifiers and teething rings.	Plastic children's sucking and/or chewing products for children up to 36 months of age do not contain more than 1 percent DEHP in.	Limit: 0.1 percent in plastic material in all kinds of toys made from vinyl plastics	Max. Limit: 0.1 percent in toys and childcare articles made of plastic materials.	DEHP, DBP, BBP, DINP, DIDP, or DNOP in toys[6] or child care articles should be individually, or in combination less than 0.1 percent.	≤ 0.1 percent sum of DEHP, DBP and BBP of the total weight of all the plasticized materials in toy or children's product

Table 3. (cont.) Phthalate Regulations for children's toys and child care articles in USA, Europe, Denmark, Canada, Japan, Australia, Brazil, Argentina, Taiwan, and Hong Kong

	U.S.	Europe (EU)	Denmark	Canada	Japan	Australia	Brazil	Argentina	Taiwan	Hong Kong
DBP	See DEHP	See DEHP	See EU Regulation and DIBP	See DEHP	Plasticized material used in designated toy shall not contain over 0.1 percent DEHP, DBP, or BBP. Pacifiers and teething rings shall not use synthetic resin containing PVC as raw material.	No Regulation	See DEHP	See DEHP	See DEHP	See DEHP
BBP	See DEHP	See DEHP	See EU Regulation and DIBP	See DEHP	See DBP	No Regulation	See DEHP	See DEHP	See DEHP	See DEHP
DINP	Proposal to Prohibit children's toys[1] and child care articles[2] containing concentrations >0.1 percent	CAS 28553-12-0 and CAS 68515-48-0 DNOP, DINP, and DIDP individually or in mixtures, no greater than 0.1 percent by weight of the plasticized material in toys and childcare articles[3] which can be placed in the mouth by children.	See EU Regulation and DIBP	The vinyl in a toy[4] or child care article[5] that can be placed in the mouth of a child under four years of age has no more than 1000 mg/kg of DINP, DIDP or DNOP.	Plastic parts of mouthable designated toys (excluding pacifiers and teething rings): - contain no more than 0.1 percent DINP, DIDP, or DNOP; PVC in non-designated toys for children under six years shall meet DEHP, DINP limits; no PVC resins in Pacifiers and teething rings	No Regulation	Limit: 0.1 percent in plastic material in all kinds of toys made from vinyl plastics for children under three years of age	Limit: 0.1 percent in toys and childcare articles made of plastic materials that can be placed in a child's mouth	DEHP, DBP, BBP, DINP, DIDP, or DNOP in toys[6] or child care articles should be individually, or in combination less than 0.1 percent	≤ 0.1 percent sum of DINP, DIDP and DNOP of the total weight of all the plasticized materials in toy or children's product that can be placed in the mouth of child under 4 years of age

Table 3. (cont.) Phthalate Regulations for children's toys and child care articles in USA, Europe, Denmark, Canada, Japan, Australia, Brazil, Argentina, Taiwan, and Hong Kong

	U.S.	Europe (EU)	Denmark	Canada	Japan	Australia	Brazil	Argentina	Taiwan	Hong Kong
DINP	Proposal to Prohibit children's toys[1] and child care articles[2] containing concentrations >0.1 percent	CAS 28553-12-0 and CAS 68515-48-0 DNOP, DINP, and DIDP as substances or in mixtures, no greater than 0.1 percent by weight of the plasticized material, in toys and childcare articles[3] which can be placed in a child's mouth.	See EU Regulation and DIBP	The vinyl in a toy[4] or child care article[5] that can be placed in the mouth of a child under four years of age has no more than 1000 mg/kg of DINP, DIDP or DNOP	Plastic parts of mouthable designated toys (excluding pacifiers and teething rings): - contain no more than 0.1 percent DINP, DIDP, or DNOP; PVC in non-designated toys for children under six years shall meet DEHP, DINP limits; no PVC resins in Pacifiers and teething rings	No Regulation	Limit: 0.1 percent in plastic material in all kinds of toys made from vinyl plastics for children under three years of age	Limit: 0.1 percent in toys and childcare articles made of plastic materials that can be placed in the month by children	DEHP, DBP, BBP, DINP, DIDP, or DNOP in toys[6] or child care articles should be individually, or in combination less than 0.1 percent.	≤ 0.1 percent sum of DINP, DIDP and DNOP of the total weight of all the plasticized materials in toy or children's product capable of being entirely or partly (one part or more than one part) placed into the mouth of child under 4 years of age.
DNOP	Proposal to discontinue interim prohibition	CAS 117-84-0 See DINP	See EU Regulation and DIBP	See DINP	Plastic parts of mouthable designated toys (excluding pacifiers and teething rings): - contain no more than 0.1 percent DINP, DIDP, or DNOP; PVC in non-designated toys for children under six years shall meet DEHP, DINP limits; no PVC resins in Pacifiers and teething rings	No Regulation	See DINP	See DINP	See DINP	See DINP
DIDP	See DNOP	CAS 26761-40-0 and CAS 68515-49-1 See DINP	See EU Regulation and DIBP	See DINP	See DNOP	No Regulation	See DINP	See DINP	See DINP	See DINP

Table 3. (cont.) Phthalate Regulations for children's toys and child care articles in USA, Europe, Denmark Canada, Japan, Australia, Brazil, Argentina, Taiwan, and Hong Kong

	U.S.	Europe (EU)	Denmark	Canada	Japan	Australia	Brazil	Argentina	Taiwan	Hong Kong
DIBP	Proposal to Prohibit children's toys[1] and child care articles[2] containing concentrations >0.1 percent	No Regulation	Prohibits phthalates use in the manufacture or import of toys[7] and child care articles[8] or parts thereof in conc. exceeding 0.05 percent expressed in mass. Prohibition does not include childcare articles that are intended to come in contact with food.	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation
DPENP	See DIBP	No Regulation	See DIBP	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation
DHEXP	See DIBP	No Regulation	See DIBP	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation
DCHP	See DIBP	No Regulation	See DIBP	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation	No Regulation

[1] a consumer product designed or intended by the manufacturer for a child 12 years of age or younger for use by the child when the child plays.

[2] a consumer product designed or intended by the manufacturer to facilitate sleep or the feeding of children age 3 and younger, or to help such children with sucking or teething.

[3] any product intended to facilitate sleep, relaxation, hygiene, the feeding of children or sucking on the part of children 0-14 years.

[4] a product that is intended for use by a child under 14 years of age in learning or play.

[5] a product that is intended to facilitate the relaxation, sleep, hygiene, feeding, sucking or teething of a child under four years of age.

[6] Toys are defined as any product designed for, made for, marketed for, or displayed for children under 14 years of age.

[7] Toys are defined as any product or article that is clearly designed or intended for play purposes for children aged 0-3 years.

[8] Child care articles are defined as any product or article that is intended to be or would normally be expected to be placed in the mouths of children aged 0-3 years.

Note: Fourteen other countries including Mexico and Israel have also prohibited phthalates in children's toys following the initial European Union phthalate prohibitions. Detailed information for some of these prohibitions were not available to staff.

VI. Discussion

A. Regulatory Framework

Congress, in the CPSIA, required the Commission to determine, based on the CHAP report, whether to continue in effect the interim prohibitions on children's toys that can be placed in a child's mouth and child care articles containing DNOP, DIDP, and DINP "*to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety*." CPSIA 108 (b)(3)(A) [emphasis added].

The CPSIA also required the Commission to "evaluate the findings and recommendations" of the CHAP and consider whether to prohibit "any children's product containing any phthalates" if the Commission determines that this is "necessary to protect the health of children." CPSIA § 108 (b)(3)(B).

The CPSIA does not define the phrases "reasonable certainty of no harm," "adequate margin of safety," or "necessary to protect the health of children," nor does it provide any guidance on the meaning of those terms. Likewise, the statute does not provide guidance on the qualitative or quantitative framework to be used by the Commission to determine if the standard of "reasonable certainty of no harm . . . with an adequate margin of safety" or "necessary to protect the health of children" is met (Section VII).

1. Reasonable Certainty of No Harm with an Adequate Margin of Safety

The standard of "reasonable certainty of no harm with an adequate margin of safety" applies to the Commission's proposal to make permanent the interim prohibition of any children's toy that can be placed in a child's mouth and child care articles containing more than 0.1 percent DINP (see below, Sections VI.C and VII.E.1). As noted above, the CPSIA does not define the terms "reasonable certainty of no harm" or "adequate margin of safety." Similar terms are used in other federal statutes, where they are also undefined. The CPSC's chronic hazard guidelines (CHG) consider the "acceptable risk" for a reproductive or developmental toxicant to be equivalent to an exposure equal to or less than the "acceptable daily intake" (ADI), that is, an HI[13] of less than or equal to one for the population affected by the toxicant (CPSC 1992, VI.F.4.ii). 16 C.F.R. 1500.135 (d)(4)(ii). The CHAP (2014, pp. 61-62), EPA (1991), and others (e.g., Barnes and Dourson 1988; Teuschler and Hertzberg 1995) also generally consider an HI less than or equal to one for an individual or the population as equivalent to acceptable risk. The CHG does not define the percentage of the population (i.e., number of individuals versus the sample population or entire population) that must have an HI less than one in order to ensure a "reasonable certainty of no harm . . . with an adequate margin of safety."

[13] HI is the ratio of the daily exposure to the ADI. The CHAP's PEAA values are equivalent to an ADI, EPA reference dose (RfD), ATSDR minimal risk level (MRL), or similar terms used by other agencies.

a. CHAP CRA

Based on its cumulative risk assessment, the CHAP determined that approximately 10 percent of pregnant women and 5 percent of infants had an HI greater than one (CHAP 2014, Table 2.16), and determined correspondingly, that 90 percent of pregnant women and 95 percent of infants had an HI of less than or equal to one. Based on these results, the CHAP recommended that the Commission make permanent the interim prohibition of children's toys and child care articles containing more than 0.1 percent of DINP (CHAP 2014, p. 99).

b. NPR

In the NPR, the Commission proposed prohibitions for children's toys and child care articles containing more than 0.1 percent of DINP, having considered the results of the CHAP's cumulative risk assessment. Thus, in issuing the NPR, the Commission concluded that the proportion of populations not affected by cumulative exposure to phthalates (at least 90 percent of pregnant women and 95 percent of infants) did not meet the standard of "a reasonable certainty of no harm with an adequate margin of safety." The Commission did not establish directly, however, that there was a specific proportion of the population that must have an HI less than or equal to one to ensure a "reasonable certainty of no harm with an adequate margin of safety."

c. Conclusion

Staff concludes that a portion of WORA is exposed to phthalates at levels that can induce MRDE or other phthalate syndrome effects. Staff also concludes that the proportion of the WORA population not at risk is approximately 99 percent.

In the 2013/2014 NHANES sample of 538 WORA, there were from two to nine individuals with a HI greater than one (i.e., at risk), depending on the PEAA case. As described in section 5.4 of TAB A, the 2013/2014 NHANES data cannot be used to estimate how many WORA in the U.S. population have HIs greater than one.

Up-to-date estimates of risk are not available for pregnant women. The most recent data, as cited in the CHAP report (CHAP 2014, Table 2.16), showed that about 90 percent of pregnant women had an HI of less than or equal to one. Thus, 10 percent of pregnant women were at risk. However, it appears that exposures and risks to WORA reasonably approximate the exposures and risks to pregnant women.

Up-to-date estimates of risk are not available for infants. The most recent data, as cited in the CHAP report, showed that about 95 percent of infants had an HI of less than or equal to one. Thus, 5 percent of infants were at risk. It is possible that the percentage of infants at risk has declined since the CHAP report, as is the case for WORA. However, staff notes that infants' and children's exposures are generally greater than their parents' exposures (CHAP 2014, Appendix E1, Table E1-18; Koch et al. 2004; Sathyanarayana et al. 2008a; Swan 2008; Swan et al. 2005). Therefore, staff concludes that phthalate exposures and risks in WORA probably underestimate the risks to infants and children. Because staff cannot conclude that a "reasonable certainty of no harm with an adequate margin of safety" has been met for WORA, we also cannot conclude that a "reasonable certainty of no harm with an adequate margin of safety" has been satisfied for infants. Therefore, staff concludes that a "reasonable certainty of no harm with an adequate margin of safety" has not been satisfied for infants.

2. Necessary to Protect the Health of Children

The CPSIA requires the Commission to "evaluate the findings and recommendations" of the CHAP and consider whether to prohibit "any children's product containing any phthalates" if the Commission determines that this is "necessary to protect the health of children." CPSIA §108 (b)(3)(B). The phrase "necessary to protect the health of children" is not defined, however, in the CPSIA or its legislative history.

The standard of "necessary to protect the health of children" applies to the Commission's proposal to prohibit children's toys and child care articles containing more than 0.1 percent of any of four additional phthalates (DIBP, DPENP, DHEXP, and DCHP) (Sections VI.E and VII.E.3) and to the proposal to expand the scope of the prohibition from "toys that can be placed in a child's mouth" to "all children's toys" containing more than 0.1 percent of DINP (Sections VI.D and VII.E.2). In the absence of a definition or other guidance, staff interprets "necessary to protect the health of children" in the context of the CHAP report (CHAP 2014, pp. 61-62) and CPSC chronic hazard guidelines (CPSC 1992),[14] which consider that an HI less than or equal to one is necessary to protect the health of children. As explained in the CHAP report, the four additional phthalates all cause male reproductive developmental effects and would contribute to the cumulative risk.

B. Human Biomonitoring Data

The CHAP and staff's CRAs are based on HBM data. Specifically, the CHAP used NHANES data (2005/2006 data cycle) to estimate total exposure to pregnant women and SFF data (1999 through 2005) to estimate exposure to infants. Staff used more recent NHANES data (up through the 2013/2014 data cycle) to estimate exposure to women of reproductive age (WORA) because pregnant women were insufficiently represented in NHANES sample years following the 2005/2006 data cycle.[15] Exposures (daily intakes; DI) from all analyses were combined with toxicological hazards to determine each individual's phthalate hazard quotient (HQ), and cumulative, total-phthalate hazard index (HI) risks.

1. Infants and Pregnant Women

As mentioned above, the CHAP determined that 10 percent of pregnant women (NHANES) and 5 percent of infants (SFF) had an HI greater than one (CHAP 2014, Table 2.16). In other words, about 90 percent of pregnant women and 95 percent of infants had an HI less than or equal to one. Staff notes that no new data on infants or statistically relevant data on pregnant women are available in current NHANES or nationally representative data sets.

The overall phthalate risk to WORA has declined since 2005/2006. It is, therefore, likely that exposures and risks to infants and pregnant women have also declined (Sathyanarayana et al. 2015). Because the routes of exposure (e.g., food, medicines, products) are different for each

[14] 16 C.F.R. § 1500.135 (d)(4)(ii).
[15] The 2005/2006 data cycle was the last time NHANES by design intentionally oversampled for pregnant women.

target population, however, it is not possible to quantify the changes in one population based on the other. Therefore, it is not possible to determine how much the risk to the current population of pregnant women or infants has changed regarding risk.

Staff notes that infants' and children's exposures are generally two- to threefold greater than their parents (CHAP 2014, Appendix E1, Table E1-18; Koch et al. 2004; Sathyanarayana et al. 2008a; Swan 2008; Swan et al. 2005). Therefore, staff concludes that phthalate exposures and risks in WORA probably underestimate the risks to infants and children.

2. Women of Reproductive Age

CPSC staff analyzed NHANES data from 2005/2006 through 2013/2014 (TAB A). WORA were used as a surrogate for pregnant women because NHANES stopped sampling for pregnant women after 2005/2006. Staff determined that between 98.8 and 99.6 percent of WORA (2013/2014 NHANES) had an HI less than or equal to one. Some WORA from each NHANES cycle had HIs greater than one for each PEAA Case. However, the national population projection for HI greater than one is not estimable at the upper percentiles of the distribution due to sampling variability.

a. Cumulative Risk

More recent NHANES data cycles (2009/2010 through 2013/2014) showed that phthalate exposures in the general population have changed. The median total exposure to the phthalates included in the CHAP's CRA has increased by 20 percent in WORA. In particular, the estimated median DEHP exposure in WORA has declined over time, while the estimated median DINP exposure in WORA has increased fivefold (Zota et al. 2014) (TAB A, Table 6). A similar trend was observed in Europe between 1988 and 2008 (Goen et al. 2011).

Overall, the cumulative risk (HI) declined between 2005/2006 and 2013/2014. In 2005/2006, 95.8 to 97.1 percent of WORA had an HI less than or equal to one (TAB A, Table 9). In 2013/2014, 98.8 to 99.6 percent of WORA had an HI less than or equal to one.

The changes in HI across NHANES cycles can be attributed primarily to changes in DEHP and DINP exposures. Decreases in overall HI with in each NHANES cycle are primarily due to decreases in DEHP exposure. DINP exposures are replacing DEHP exposures within each NHANES data cycle. DINP is less toxic than DEHP. Therefore, however, even though DINP's exposure is replacing that of DEHP, the overall HIs have still decreased.

b. DINP in Isolation

Because DINP exposures have increased, the relative contribution of DINP to the cumulative risk has also increased. DINP contributes more to the cumulative risk than DEHP when considering PEAA Case 2 (TAB A, Table 8). DINP contributes 27 percent of the cumulative risk when considering PEAA Case 3. The CHAP's analysis of HBM data suggested that DINP in isolation of other phthalates did not present a hazard to pregnant women or infants (CHAP 2014, Table 2.16). However, because DINP exposure has increased fivefold over the past 10 years, it is worthwhile reconsidering the potential risks from DINP in isolation. In 2013/2014 WORA, the median DINP daily intake was 5.0 µg/kg-d, with a 95th percentile of 53.2 µg/kg-d (TAB A, Table 6).

Using the Case 2 point of departure of 11.5 mg/kg-d for MRDE (CHAP 2014, Table 2.15), the margins of exposure (MOEs) are 2,300 (median) and 220 (95th percentile). Current analysis suggests that the DINP margin of exposure (MOE), in isolation, (e.g., the MOE is 220 for Case 2) is below the upper limit (1000) and nearing the lower limit (100) considered adequate for protecting public health (comment response 5.5).

Based on the 2013/2014 NHANES data, WORA with HQs (for DEHP and DINP) and HIs greater than one were measured in each NHANES cycle despite the interim prohibition in children's toys and child care articles (comment response 3.2; TAB A).

C. Effect of Lifting the Prohibition on Children's Toys that Can Be Placed in a Child's Mouth and Child Care Articles Containing DINP

The CHAP estimated human exposure to phthalates using two independent and complementary methods: (1) Total phthalate exposure to actual individuals was calculated from HBM data (NHANES and SFF) (CHAP 2014, pp. 34-48). Although HBM provides good estimates of total exposure, it does not provide information on the sources of exposure. (2) Therefore, the CHAP also estimated human exposure for individual exposure scenarios, such as using specific products or contact with environmental media (CHAP 2014, pp. 49-60 and Appendix E1). The scenario-based exposure estimates can be developed using information about relevant sources of phthalate exposure (e.g., concentrations of phthalates in soil, dust, and in products); data on migration or leaching of phthalates from products; physiological information (e.g., body weight and skin surface area); and information about how the subpopulations use and interact with products, including frequency and duration of contact with products and environmental media.

The CHAP presented scenario-based exposure estimates[16] (method 2, described above) for infants, toddlers, children, and women of reproductive age/pregnant women. Scenarios included common activities such as (CHAP 2014, Table 2.10):

- playing with toys;
- interacting with child care articles;
- using household products such as paints, air fresheners or adhesives;

[16] Appendix E of the CHAP Report describes scenario-based estimates of phthalate exposure, which were performed by CPSC staff under the direction of the CHAP.

- sitting on furniture;
- using vinyl gloves;
- using personal care products (soaps, shampoos, lotions, deodorants, perfumes, hair spray, and nail polish);
- interacting with the environment (indoor and outdoor air, dust, and soil);
- eating;
- drinking; and
- taking medications.

The scenario-based approach was used to estimate the relative contribution (percent of total exposure) for each activity (CHAP 2014, pp. 49-50; CHAP 2014, Appendix E1). Although children's toys and child care articles containing certain phthalates are currently prohibited, the CHAP estimated exposures that would hypothetically occur if phthalates were allowed in these products (CHAP 2014, pp. 49-50). This approach was able to provide exposure estimates for each of these activities as well as for the total exposure. The scenario-based exposure analysis shows that, on average, mouthing and dermal exposure to toys could contribute around 12.8 percent to the overall DINP exposure of infants, if DINP were used in these products (CHAP 2014, Appendix E1, Table E-21). The same analysis shows that dermal contact with child care articles could contribute up to an additional 16.5 percent of the overall exposure to infants. Therefore, if DINP were used in all of the products that were included in the scenario-based exposure assessment, children's toys and child care articles could account for around 29 percent of infants' total exposure from all evaluated sources (CHAP 2014; Appendix E1, Table E1-21).

If DINP were used in the assessed toys and child care articles, these products could contribute about 6.0 µg/kg-d to the average daily phthalate intake for infants (CHAP 2014, Appendix E1, Table E1-S2).

It is not possible to quantify accurately the number of toys expected to have DINP or the effect of changes in DINP exposure on the percentage of the population (infants, pregnant women, or WORA) with HI less than or equal to one. However, any increase in exposure due to resumed or increased use of DINP in products is likely to decrease the percentage of the population with HI less than or equal to one.

D. Effect of Expanding the Scope of the Prohibition to All Children's Toys Containing DINP

In the NPR, in addition to making permanent the prohibition of children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DINP, the Commission proposed expanding the scope of the prohibition from child care articles and "toys that can be placed in a child's mouth" to "all children's toys." The expanded scope would be consistent with the other permanent prohibitions involving phthalates.

The CHAP report's estimate of DINP exposure included mouthing of all toys, not only toys that can be placed in a child's mouth, and thus, did not assess the difference in exposure and risk of "toys than can be placed in a child's mouth" and "all children's toys." For this reason, it is not possible to quantify the impact of expanding the scope on children's exposure and risk (CHAP

2014, Appendix E-1; ECHA 2013, Table 4.90). Staff notes, however, that children's mouthing, which is the most important route of exposure, consists of any contact of the toy with mouth, lips, or tongue. Therefore, expanding the scope would cover all these routes, instead of focusing on a subset of oral exposure routes (children's toys that can be mouthed).

E. Permanent Prohibition of DIBP, DCHP, DHEXP, and DPENP

The CPSIA required the Commission to . . . "evaluate the findings and recommendations of the Chronic Hazard Advisory Panel and declare any children's product containing any phthalates to be a banned hazardous product under section 8 of the Consumer Product Safety Act (15 U.S.C. 2057), as the Commission determines necessary to protect the health of children." CPSIA § 108(b)(3)(B). Thus, the Commission proposed permanent prohibitions of children's toys and child care articles containing more than 0.1 percent of DIBP, DPENP, DHEXP, and/or DCHP, as the CHAP recommended.

1. DIBP

As noted above, based on its cumulative risk assessment, the CHAP determined that approximately 10 percent of pregnant women and 5 percent of infants had an HI greater than one (CHAP 2014, Table 2.16) and correspondingly, that 90 percent of pregnant women and 95 percent of infants had an HI of less than or equal to one. Based on these results, the CHAP recommended that the Commission permanently prohibit children's toys and child care articles containing more than 0.1 percent of DIBP (CHAP 2014, p. 110).

In the NPR, the Commission proposed permanently prohibiting children's toys and child care articles containing more than 0.1 percent of DIBP, having considered the results of the CHAP's cumulative risk assessment. Thus, in issuing the NPR, the Commission concluded that the proportion of populations not affected by cumulative exposure to phthalates (at least 90 percent of pregnant women and 95 percent of infants) was not consistent with an acceptable risk. Thus, the Commission concluded that permanently prohibiting children's toys and child care articles containing more than 0.1 percent of DIBP was "necessary to protect the health of children."

2. DCHP, DHEXP, and DPENP

The CHAP also determined that other phthalates (DCHP, DHEXP, and DPENP) not measured by NHANES could induce MRDE or other phthalate syndrome effects that would contribute to the cumulative risk. Therefore, the CHAP recommended that the Commission permanently prohibit children's toys and child care articles containing more than 0.1 percent of these phthalates.

In issuing the NPR, the Commission concluded that prohibiting children's toys and child care articles containing more than 0.1 percent of these phthalates was necessary to "protect the health of children," noting that there are already individuals in the sampled NHANES population with an HI greater than one, and that preventing the use of these MRDE phthalates would eliminate any future contributions of these phthalates from children's toys and child care articles to the cumulative risk.

3. Conclusion

Staff concludes that a portion of infants is exposed to phthalates at levels that can induce MRDE or other phthalate syndrome effects. Not prohibiting these phthalates would allow their use in toys and child care articles. We currently see DIBP in some toys and child care articles. These are potent phthalates. Allowing their use would NOT protect the health of children. Not prohibiting children's toys and child care articles containing DIBP, DCHP, DHEXP, or DPENP could result in a decrease in the proportion of the population not at risk, and therefore, would not "protect the health of children." Therefore, staff recommends permanently prohibiting children's toys and child care articles containing more than 0.1 percent of DINP, DIBP, DCHP, DHEXP, or DPENP (Section VII.E.3).

VII. Staff Rationale and Recommendations

A. Basis of the NPR

The CHAP's charge in section 108 of the CPSIA includes completing "an examination of the full range of phthalates that are used in products for children." As part of this charge, the CPSIA directed the CHAP to assess the potential risks from the full range of phthalates, and the cumulative effect of total exposure to phthalates. To satisfy the charge, the CHAP conducted a cumulative risk assessment for phthalates associated with male reproductive developmental effects (DEHP, DBP, BBP, DIBP, and DINP).

The CHAP estimated exposure to each phthalate using creatinine-related phthalate metabolite measurements for each participant using biomonitoring data in the CDC's National Health and Nutrition Examination (NHANES) Survey, and the Study for Future Families (SFF). Cumulative risk for each individual was then estimated using the biomonitoring data-derived exposures to the phthalates and the acceptable exposure level for each phthalate, expressed as potency estimates for antiandrogenicity (PEAAs) to derive the hazard quotients, and the cumulative hazard index (HI). The hazard indices for all individuals in the sample formed a distribution of hazard indices. An HI greater than one means that the estimated exposure exceeds the acceptable exposure for the mixture of phthalates. The CHAP indicated that when an HI exceeds one, there is a risk for adverse health effects in the exposed population. The CHAP stated that its recommendations to CPSC for regulatory actions were derived from the combination of toxicity findings in animals and humans, together with the HI calculations regarding the risk of male reproductive developmental effects from phthalate exposure in the vulnerable subpopulations — children, pregnant women, and other susceptible individuals.

The CHAP characterized the distribution of the estimated HIs, by reporting the central tendency measure (statistical median[17]) and the upper percentiles (95th, and 99th) (CHAP 2014, Table 2.16). The CHAP's analysis showed that the median HIs for NHANES pregnant women were

[17] The median is the midpoint of the distribution, where one half of the values are smaller than (i.e., below) the median value, and one half of the values are larger than the median. The 95th percentile of the distribution is the value indicating 95 percent of values are smaller than this value, and 5 percent of values are larger. The median and 95th percentile values describe the data distribution, in this case the HI values estimated for the population of pregnant women or women of reproductive age who experience phthalate exposures. These values, by themselves, do not define acceptable risk levels. Rather, the acceptable risk level is a policy decision.

less than one (HIs of 0.09 to 0.14) but the 95th percentile HIs were greater than one (HIs of 3.6 to 6.1). Staff notes that the CHAP emphasized that an HI greater than one is the metric that defines excess exposure, relative to the acceptable exposure level; the CHAP did not indicate that the 95th percentile, or any other part of the cumulative risk distribution, should be used to establish unacceptable risk for risk management purposes. The CHAP, having determined that an HI greater than one was necessary to identify the population at risk, then used the distribution of HIs to identify the percentage of the population with an estimated HI greater than one. The CHAP's analysis showed that about 10 percent of pregnant women (NHANES 2005/2006 data set), and about 5 percent of infants (SFF dataset), have phthalate exposures that result in HIs greater than one.[18] Staff notes that while the CHAP presented the distribution statistics, described above, the CHAP focused on the proportion of the population with HIs exceeding one, not on any particular percentile of the distribution.

The CHAP also presented estimates for the contribution to DINP exposure if DINP were used in children's toys and child care articles. The CHAP estimated that if DINP were used in these products, infants' and toddlers' exposure to DINP from toys and child care articles would account for up to 29 percent of infant exposure and up to 19 percent of toddler exposure from all sources (CHAP 2014, Appendix E1, Table E1-21 and Table E1-22). Therefore, staff concludes that lifting the interim prohibition involving DINP could lead to increased DINP exposure and risk to infants and toddlers.

The CHAP's and staff's recommendations to the Commission were based on:

- the cumulative risk assessment for phthalates, including DINP, associated with MRDE;
- the conclusion that reasonable certainty of no harm with an adequate margin of safety was not met because susceptible individuals had HIs greater than one;
- the conclusion that the proportion of the population with HIs exceeding one (10 percent of pregnant females in the 2005/2006 NHANES data cycle and 5 percent of infants in the SFF data) did not provide a reasonable certainty of no harm with an adequate margin of safety; and
- the contribution of DINP to the CRA, including the estimate of infants' and toddlers' increased exposure to DINP, if DINP were used in children's toys and child care articles.

The Commission voted to publish the NPR in the *Federal Register* based on the CHAP's and staff's analysis and recommendations. The Commission, in publishing its proposed rule, accepted the CHAP's and staff's analyses and recommendations, and therefore, concluded:

- an HI less than one for children, pregnant women, or other susceptible individuals is necessary to ensure a reasonable certainty of no harm with an adequate margin of safety;
- that exposures resulting in 90 percent of pregnant women and 95 percent of infants with an HI less than or equal to one do not meet the statutory mandate of "reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety"; and

[18] These results are equivalently expressed as about 90 percent of pregnant women (NHANES 2005/2006 data set), and about 95 percent of infants (SFF dataset) with phthalate exposures that result in HIs less than or equal to one. In addition to the CHAP's results for pregnant women in the NHANES 2005/2006 data set, staff estimated that about 97 percent of women of reproductive age (WORA) had an HI less than or equal to one.

- that the rule is necessary to fulfill the statutory requirement "to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety."

Staff notes that the NPR did not specify a percentage of the population of susceptible individuals with an HI greater than one that would meet the statutory standard of reasonable certainty of no harm with an adequate margin of safety.

B. Consideration of Newer Biomonitoring Data

Staff analyzed the 2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 NHANES biomonitoring data to estimate phthalate exposure for women of reproductive age (WORA). WORA were used as a proxy for pregnant women, which were not oversampled in data cycles after 2005/2006. Staff's analysis of these data demonstrated that phthalate exposures have changed over time. Specifically, exposure to DEHP has decreased while exposure to DINP has increased.

Staff analysis also demonstrated that the overall median and 95th percentile HIs decreased for WORA in the newer data set, compared to previous data sets and that both the median and 95th percentile HIs are currently less than one for all three Cases in the 2013/2014 data set. Staff notes that the median and 95th percentile HIs reported by the CHAP and staff are commonly used statistical constructs for comparing risks among all the NHANES data sets but are not used by CPSC as risk management thresholds.

The proportion of WORA in the U.S. population with an HI less than or equal to one also changed. Analysis of the newer data set showed that approximately 99 percent of WORA in the U.S. population now have an HI less than or equal to one. This estimate increased from about 97 percent as estimated from the 2005/2006 data.

As in previous NHANES data cycles, some individuals in the 2013/2014 NHANES data set still have an HI greater than one. Depending on the PEAA case used for analysis, between two and nine of the 538 WORA in the NHANES 2013/2014 data sample had an HI of greater than one.[19] Male children for these women were at increased risk for MRDE. As described in section 5.4 of TAB A, the 2013/2014 NHANES data cannot be used to estimate how many WORA in the U.S. population have HIs greater than one.

C. Consideration of Comments

In making its recommendation to the Commission, staff has considered the public comments submitted in response to the NPR and the staff's subsequent analyses of NHANES data. Staff provides a summary of the key comment issues and responses in section IV of this briefing package and also provides a detailed assessment of those comments in TAB B.

[19] The NHANES data was analyzed using 3 methods (Cases 1-3) For Case 1, 3 WORA had HIs greater than 1. For Case 2, 9 WORA had HIs greater than 1. For Case 3, 2 WORA had HIs greater than 1.

D. Staff's Conclusions about Phthalate Risks

Staff followed the analysis of the CHAP and considered a number of factors when assessing the potential risks associated with phthalate exposures. Staff primarily considered:

- what is the health effect of concern;
- what does reliable data indicate about toxicity of the phthalates examined;
- what is the human population affected;
- which phthalates contribute to the cumulative risk;
- how has exposure to specific phthalates changed;
- are there WORA who have HIs greater than one; and
- what portion of the population would remain at risk without Commission action.

Based on these considerations, and as explained in this briefing package, staff concludes that:

- certain phthalates, including DEHP, BBP, DBP, DINP, DIBP, DPENP, DCHP, and DHEXP, cause male reproductive developmental effects or other phthalate syndrome related effects;
- fetuses, infants, toddlers, and children are the most sensitive populations affected, and that exposure to the fetus can be assessed through surrogate populations including pregnant women and WORA;
- the CHAP's CRA using NHANES data on pregnant women and the staff's analyses of more recent NHANES data for WORA demonstrate that between two and nine individuals in the NHANES sample of WORA have HIs greater than one;
- the CHAP's CRA using SFF data on infants shows that a proportion of infants in the population have HIs exceeding one. Staff notes that these data have limitations, such as not being nationally representative and collected before CPSIA. However, SFF is the only available biomonitoring data for assessing risk to infants;
- DINP exposure and risk have increased over time, as observed in HQs estimated from NHANES data;
- Between two and nine (depending on the PEAA case) WORA in 2013/2014 NHANES sample populations have overall HIs greater than one, and HQs for DEHP and DINP greater than one;
- DINP exposures from children's toys and child care articles could increase if the interim prohibition involving DINP in these products is lifted; and [20]

[20] As discussed above, the CHAP report included an assessment of exposure in the absence of the phthalates prohibitions. The assessment estimated that if DINP were used in these products, infants' and toddlers' exposure to DINP from toys and child care articles would account for up to 29 percent of infant exposure and up to 19 percent of toddler exposure from all sources CHAP (2014) Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives. U.S. Consumer Product Safety Commission, Bethesda, MD. July 2014. http://www.cpsc.gov/chap.CHAP (2014) Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives. U.S. Consumer Product Safety Commission, Bethesda, MD. July 2014. http://www.cpsc.gov/chap.CHAP (2014) Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives. U.S. Consumer Product Safety Commission, Bethesda, MD. July 2014.

- DIBP, DPENP, DHEXP, and DCHP use in children's toys and child care articles would contribute to the cumulative risk unless the use of these phthalates is prohibited to protect the health of children.

Staff concludes that the presence of individual WORA with an HI greater than one in each NHANES sample suggests that the requirement of the CPSIA regarding *a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety* for the U.S. population is not met without Commission action. Staff thus recommends that the Commission finalize the proposed permanent prohibition of children's toys and child care articles containing more than 0.1 percent of DINP. Staff also concludes that prohibiting children's toys and child care articles containing more than 0.1 percent DIBP, DPENP, DHEXP, and DCHP is necessary to protect the health of children.

E. Specific Recommendations

1. To Make Permanent the Interim Prohibition Involving DINP

Multiple animal studies indicate that DINP causes adverse effects on male reproductive development and contributes to the cumulative risk from phthalates. Based on a review of this and other information, the CHAP concluded that DINP induces male developmental reproductive effects in animals and, therefore, contributes to the cumulative risk from other phthalates causing similar effects. The CHAP recommended that the interim prohibition concerning DINP be made permanent.

In the NPR, the Commission agreed that allowing the use of DINP in children's toys and child care articles would further increase the cumulative risk to male reproductive development. The Commission considered that an HI less than one was necessary "to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." Therefore, to ensure a reasonable certainty of no harm with an adequate margin of safety to children, pregnant women, or other susceptible individuals (i.e., male fetuses), the Commission proposed permanently prohibiting children's toys and child care articles containing more than 0.1 percent of DINP (79 FR 78334-78335).

In formulating the recommendation to the Commission to finalize making the prohibition on children's toys and child care articles containing more than 0.1 percent of DINP permanent, staff considered the following:

1. The CHAP found and Commission determined in the NPR that "an HI less than one is necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety."
2. In publishing the proposal in the NPR, the Commission proposed to determine that the exposures at that time (resulting in 90 percent of pregnant women and 95 percent of infants with HIs less than or equal to one) did not meet the statutory mandate of

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http://www.cpsc.gov/chap. Therefore, any estimates of current exposure and risk do not account for the contributions from unregulated use of DINP in children's toys and child care articles.

"reasonable certainty of no harm." Staff estimates that 97 percent of WORA at the time of the NPR had an HI less than one. Staff notes that the NPR did not establish which percentage of the population of susceptible individuals with an HI less than or equal than one would meet that standard of "reasonable certainty of no harm."

3. No more recent information on infant exposures is available than the 1999/2005 SFF data, which were used by the CHAP (and subsequently by CPSC in the NPR) and show that approximately 95 percent of infants have HIs less than or equal to one. Infant exposures may have changed since 2005, but staff has no infant data to quantify any change. Staff also notes that infants,' toddlers,' and children's phthalate exposures are generally greater than their parents (on a body weight basis). (See comment response 3.5.)

4. Staff has updated risk analyses using more recent NHANES data (See TAB A) that shows that approximately 99 percent of WORA in the U.S. population now have an HI less than or equal to one (up from 97 percent using the 2005/2006 data). Although the percentage of pregnant women in the U.S. population with an HI less than or equal to one may also be less than 99 percent (see TAB A, 2005/2006 NHANES and/or staff 2015 NHANES report), staff is unable to quantify the difference, due to insufficient sample sizes of pregnant women with HBM data in NHANES cycles later than 2005/2006.

5. The CPSIA does not define a "reasonable certainty of no harm with an adequate margin of safety." Staff notes that the statutory standard requires that the Commission ensure a "reasonable certainty of no harm," not a "certainty of no harm." Regarding what constitutes a "reasonable certainty of no harm with an adequate margin of safety," staff considered the CHAP recommendations, the overall weight of the evidence, the contribution of DINP to MRDE, as well as the vulnerability of children to MRDE in assessing whether exposures and risk met the statutory mandate. In addition, as noted, the staff analyzed the most recent data demonstrating WORA in each sample across the NHANES cycles with HIs exceeding one. The most recent data showed increases in exposure to DINP over time despite the interim prohibition on children's toys and child care articles containing more than 0.1 percent of DINP. Based on this review, as well as review of the comments received, staff concludes that the estimates for WORA (99 percent) and infants (95 percent) with an HI less than or equal to one do not meet the standard of "reasonable certainty of no harm . . . with an adequate margin of safety."

6. As shown by the scenario-based exposure assessment included in the CHAP report (CHAP 2014, Appendix E-1), lifting the interim prohibition on children's toys and child care articles containing more than 0.1 percent of DINP could increase exposure to DINP from these products, compared to exposures if DINP is not allowed in children's toys and child care articles. DINP exposure from children's toys and child care articles could account for up to about 29 percent of infants' total DINP exposure from all sources. Staff is unable to quantify the impact of the increased DINP exposure on the percent of WORA or infants that have an HI less than or equal to one, although staff notes that increased exposure will increase the MRDE risk to the population.

Recommendation: Staff concludes that the requirement of the CPSIA regarding *a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety* is not met. Staff thus recommends that the Commission finalize the proposed permanent prohibition on children's toys and child care articles containing more than 0.1 percent of DINP.

2. To expand the scope of products that may not contain more than 0.1 percent of DINP from "children's toys that can be placed in a child's mouth and child care articles" to "all children's toys and child care articles."

The interim prohibitions on child care articles and children's toys that can be placed in a child's mouth apply to DINP and other phthalates (CPSIA § 108 (b)(1)). This is narrower in scope than the permanent prohibition on children's toys and child care articles containing DEHP, DBP, and BBP. CPSIA § 108 (a). The CHAP recommended permanently prohibiting "children's toys and child care articles" containing DINP. After considering this CHAP recommendation and staff recommendations, in proposing to make permanent the prohibition of children's toys and child care articles containing DINP, the Commission proposed to permanently prohibit all children's toys and child care articles containing more than 0.1 percent of DINP, rather than only toys that can be placed in a child's mouth. This is consistent with the scope of the other permanently prohibited children's toys and child care articles containing phthalates, BBP, DBP, and DEHP, in CPSIA § 108 (a).

Staff notes that oral exposure to phthalates does not only occur by placing toys in the mouth. Oral exposure may also occur by any contact of the toys with the lips or mouth (EPA 2011; Greene 2002; Groot et al. 1998; Juberg et al. 2001; Kiss 2002). Thus, expanding the scope would prevent exposure from the full range of mouthing, including toys that cannot be placed in a child's mouth, that is, toys that do not have any dimension less than or equal to 5 cm.

Staff notes that a child's exposure to DINP also occurs by touching toys (CHAP 2014, Appendix E-1; ECHA 2013, Table 4.90). Expanding the scope to include all children's toys would reduce additional dermal exposures to toys not currently covered by the interim prohibition.

Therefore, staff concludes that expanding the scope of the prohibition from "toys that can be placed in a child's mouth" containing more than 0.1 percent of DINP to "all children's toys" is necessary to protect the health of children.

Staff Recommendation: Staff recommends that the Commission expand the scope of the prohibition to all children's toys containing more than 0.1 percent of DINP.

3. To prohibit children's toys and child care articles containing more than 0.1 percent diisobutyl phthalate (DIBP), di-*n*-pentyl phthalate (DPENP), di-*n*-hexyl phthalate (DHEXP), or dicyclohexyl phthalate (DCHP).

The CPSIA required the Commission to . . . "evaluate the findings and recommendations of the Chronic Hazard Advisory Panel and declare any children's product containing any phthalates to be a banned hazardous product under section 8 of the Consumer Product Safety Act (15 U.S.C. 2057), as the Commission determines necessary to protect the health of children." CPSIA §

108(b)(3)(B). Thus, the Commission proposed permanent prohibitions of children's toys and child care articles containing more than 0.1 percent of DIBP, DPENP, DHEXP, and/or DCHP, as the CHAP recommended.

Staff concludes that DIBP, DPENP, DHEXP, and DCHP cause the same constellation of effects on male reproductive development as other phthalates that cause MRDE (CHAP 2014, pp. 22-24, 105-121, Appendix A). Therefore, these phthalates are capable of contributing to the cumulative risk. Furthermore, DIBP is as toxic as DBP, which is one of the phthalates subject to permanent prohibition (CHAP 2014, pp. 15-16, 110-112), and DPENP is the most potent phthalate with respect to the phthalate syndrome (CHAP 2014, pp. 15-16, 112-113).

Staff recognizes that current exposures to DPENP, DHEXP, and DCHP are low, and these phthalates are not commonly found in children's toys and child care articles. However, the CHAP estimated that DIBP contributes up to 5 percent of the cumulative risk in infants from all products and sources (CHAP 2014, Table 2.16; CPSC 2014b, Table 7). More recent biomonitoring data show that median DIBP exposures and risks have increased 1.5-fold (TAB A, Table 6) (Zota et al. 2014). In addition, DIBP was present in some toys tested by CPSC (CPSC 2014b, TAB B). Staff notes that these four phthalates could be used as substitutes for the phthalates subject to permanent prohibition, thus, increasing human exposures from MRDE phthalates (Biedermann-Brem et al. 2008; Carlson et al. 2010; Clark 2009; CPSC 2014b; Patton 2010). All of these phthalates are capable of contributing to the cumulative risk. All are at least as potent as DEHP. In addition, they may have a greater potential for exposure than DINP because lower molecular weight plasticizers generally have higher migration rates (Dreyfus and Babich 2011). Staff concludes that permanently prohibiting children's toys and child care articles containing more than 0.1 percent of DIBP, DPENP, DHEXP, and/or DCHP is necessary to protect the health of children.

Staff Recommendation: Staff recommends that the Commission permanently prohibit children's toys and child care articles containing more than 0.1 percent of DIBP, DPENP, DHEXP, and/or DCHP.

4. Lift Interim Prohibition Involving DNOP

The CHAP concluded that DNOP does not lead to male developmental reproductive toxicity in animals and, therefore, does not contribute to the cumulative risk. However DNOP does cause other developmental (supernumerary ribs) and systemic effects (liver, thyroid, immune system, and kidney). However, because the MOEs in humans are very high, the CHAP recommended that the current prohibition involving DNOP be lifted (CHAP report, pp. 91-95). The NPR noted that DNOP levels in people are so low that they are not detectable in about 90 percent of humans, and that DNOP is not antiandrogenic, and, therefore, does not contribute to the cumulative risk. The Commission concluded that continuing the prohibition of children's toys and child care articles containing more than 0.1 percent of DNOP is not necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety, and proposed that children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DNOP should no longer be prohibited (79 FR 78334).

Staff Recommendation: Staff recommends that the Commission remove the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DNOP.

5. Lift Interim Prohibition Involving DIDP

The CHAP concluded that DIDP does not lead to male developmental reproductive toxicity in animals, and therefore, does not contribute to the cumulative risk. DIDP does cause other developmental (supernumerary ribs) and systemic effects (liver, and kidney). However, because the MOEs in humans are sufficiently high, the CHAP recommended that the interim prohibition involving DIDP be lifted (CHAP report, pp. 100-105). Staff concluded that DIDP exposure would need to increase by more than 250 times to exceed an acceptable level. The Commission concluded that continuing the prohibition on children's toys and child care articles containing more than 0.1 percent of DIDP is not necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety, and proposed that children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DIDP no longer be prohibited (79 FR 78334).

Staff Recommendation: Staff recommends that the Commission remove the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DIDP.

6. Do Not Prohibit Children's Toys and Child Care Articles Containing DIOP

The CHAP did not recommend a permanent prohibition for children's toys and child care articles containing DIOP because existing toxicology data were insufficient to support an antiandrogenic mode of action, and hence, a permanent prohibition. Although the CHAP recommended an interim prohibition, the CPSIA did not provide for an interim prohibition as an option for the Commission's rule under section 108. CPSIA section 108(b)(3). As discussed above, insufficient hazard, exposure, and risk data exists to determine that a permanent prohibition of children's toys and child care articles containing DIOP is necessary to protect the health of children. Thus, the Commission did not propose to prohibit children's toys and child care articles containing DIOP.

Staff Recommendation: Staff recommends that the Commission take no regulatory action on DIOP.

7. Do Not Expand Scope of Phthalate Regulations to Include All Children's Products

The CPSIA required the Commission to "evaluate the findings and recommendations" of the CHAP and consider whether to prohibit "any children's product containing any phthalates" if the Commission determines that this is "*necessary to protect the health of children*." CPSIA § 108 (b)(3)(B). Action by the Commission under this section could have resulted in extending the prohibition beyond children's toys and child care articles and could have been taken for any or all of the phthalates under consideration, including those involved in permanent prohibitions, subject to the interim prohibition, or proposed to be subject to a prohibition (DIBP, DPENP,

DHEXP, DCHP). A "children's product" is considered "a consumer product designed or intended primarily for children 12 years of age or younger." 15 U.S.C. § 2052(a)(2). Children's products that are not toys or child care articles and which might contain phthalates include, for example, rainwear, footwear, backpacks, some school supplies, apparel containing elastic waistbands, and printed T-shirts and sweatshirts.

In the proposed rule, the Commission did not propose expanding the scope of any phthalate regulations beyond children's toys and child care articles.

Staff has not found new information that would change the basis underlying the Commission's decision not to expand the prohibitions to all children's products containing phthalates and the rationale that there is not enough (national) information to adequately assess the health impact of children's products other than children's toys and child care articles. Additionally, few comments were received in response to the NPR that addressed expansion of the scope of the regulations to all children's products. Some commenters favored expanding the scope of the phthalate regulations to all children's products.

Staff also notes that the theoretical exposure from children's products is comparatively less than that from children's toys and childcare articles. In the NPR, the Commission noted that oral exposure (e.g., from toys) is the primary exposure pathway to phthalates, with dermal exposure adding to the overall exposure from toys. In contrast, the primary exposure route (dermal) from children's products would generally lead to lower exposures than with children's toys (CHAP, 2001, 2014; CPSC, 2001). Children's products that might contact the skin (e.g., textiles) are thought to contain lower concentrations of phthalates and so will result in lower exposures. Those children's products that might contain phthalates, such as backpacks, are also typically not in frequent contact with the skin, thus resulting in lower exposures. In addition, toys are more likely than many other children's products to be made of materials that could be plasticized with phthalates.

Staff recognizes the continued lack of reliable and nationally relevant information about children's products and the lack of information on the presence of phthalates in and exposure to phthalates from children's products in general compared to children's toys and child care articles (CPSC 2014a). Staff notes that there is less theoretical exposure from children's products compared to toys based on children's mouthing behavior. For these reasons, staff concludes that facts do not support expanding the scope of the prohibitions from all children's toys and child care articles to all children's products containing phthalates.

Staff Recommendation: Staff does not recommend expanding the scope of the regulations to include children's products other than children's toys and child care articles containing phthalates.

8. Retain the 0.1 Percent Limit

The CPSIA established the 0.1 percent limit for specified phthalates in children's toys and child care articles. The CHAP found no reason to support changing the concentration limit (CHAP 2014, p. 79). The Commission agreed with the CHAP that the 0.1 percent limit is not risk-based; rather, the limit is based on practical considerations, that is, the desire to prohibit intentional phthalate use while allowing trace levels. No comments were received in response to the NPR that addressed the 0.1 percent limit set by Congress. Therefore, staff recommends maintaining the limit at 0.1 percent, if the Commission chooses to permanently prohibit children's toys and

child care articles containing DINP, DIBP, DPENP, DHEXP, or DCHP. Staff considers the 0.1 percent limit to be a practical limit, which has already been incorporated into testing methods required of third party laboratories.

Staff recommendation: Staff recommends that the Commission retain the 0.1 percent limit for all children's toys and child care articles containing phthalates regulated under the CPSIA.

9. To make the effective date of the new requirements 180 days following publication of the final rule.

As discussed in the NPR, after considering the impact of the proposed rule on manufacturers and testing laboratories, the Commission proposed an effective date of 180 days after publication of the final rule in the *Federal Register*.

The Commission concluded that the proposed rule is expected to have a minimal impact on manufacturers, and that changes to testing procedures to include children's toys and child care articles containing the four additional prohibited phthalates would require minimal effort by testing laboratories.

Specifically, the Commission considered that firms must already comply with prohibitions on the use of phthalates in many children's products:

1) Manufacturers of children's toys and child care articles already have had to comply with mandatory prohibitions on children's toys and child care articles containing DEHP, BBP, and DBP;
2) Few manufacturers will need to reformulate products to comply with a prohibition on children's toys and child care articles containing any of the four additional phthalates (DIBP, DPENP, DHEXP, and DCHP) because these phthalates are not widely used in children's toys and child care articles;
3) No manufacturers will have to reformulate children's toys that can be placed in the mouth and child care articles for DINP because DINP concentrations greater than 0.1 percent are already prohibited in children's toys that can be placed in the mouth and in child care articles;
4) A relatively small percentage of children's toys that cannot be placed in the mouth would need to be reformulated to remove DINP; and
5) Non-regulated phthalates or plasticizer alternatives generally are available and can be substituted for regulated phthalates in children's toys and child care articles.

The Commission also recognized the impact on firms regarding the requirements for third party testing:

1) Third party testing is already required for several phthalates (DEHP, DBP, BBP) for all children's toys and child care articles;
2) The analytical test methods can be modified to consider new (DIBP, DPENP, DHEXP, DCHP) or removed (DNOP, DIDP) phthalates with little additional time, because

modifications of analytical testing equipment or sample processing will not be necessary; and

3) Third party testing for DINP is already required for children's toys that can be placed in the mouth and in child care articles;

Staff recommendation: Staff recommends an effective date of 180 days after publication of the final rule.

VIII. Summary of Staff Final Recommendations to the Commission

1) To make permanent the interim prohibition concerning DINP.
2) To expand the scope of products that may not contain more than 0.1 percent of DINP from "children's toys that can be placed in a child's mouth and child care articles" to "all children's toys and child care articles."
3) To prohibit children's toys and child care articles containing more than 0.1 percent diisobutyl phthalate (DIBP), di-*n*-pentyl phthalate (DPENP), di-*n*-hexyl phthalate (DHEXP), or dicyclohexyl phthalate (DCHP).
4) To lift the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing DNOP and/or DIDP.
5) To make the effective date of the new requirements 180 days following publication of the final rule.

As proposed in the NPR, the final rule will take no regulatory action for:

- diisooctyl phthalate (DIOP);
- acetyl tributyl citrate (ATBC);
- di(2-ethylhexyl) terephthalate (DEHT);
- diisononyl 1,2-dicyclohexanedicarboxylate (DINX);
- 2,2,4-trimethyl-1,3 pentanediol diisobutyrate (TPIB);
- di(2-ethylhexyl adipate (DEHA); and
- tris(2-ethylhexyl) trimellitate (TOTM).

In addition the NPR proposed to not change the scope of product regulation for all phthalates from "children's toys and child care articles" to "children's products," and not to modify the concentration of 0.1 percent limit for all prohibitions involving phthalates.

IX. Impact on Small Businesses

The staff evaluated the impact of the rule on small entities as required by the Regulatory Flexibility Act (RFA). The Commission certified that the proposed rule would not have a significant economic impact on a substantial number of small entities. The Commission received a number of public comments asserting that the regulation of phthalates, especially the regulation of DINP, does significantly impact small entities (TAB B). However, these commenters appeared to address the impact of the regulation of phthalates, in general, and did not appear to address specifically the projected impact of the proposed rule. Staff also notes:

- The scope of the proposal is very limited. It is limited to children's toys and child care articles that contain DINP, DPENP, DHEXP, DCHP, or DIBP;
- DINP has been prohibited in child care articles and most children's toys since 2009;
- The CHAP found that DPENP, DHEXP, DCHP are not widely used in children's toys and child care articles, and that DIBP has only limited use in children's toys and child care articles; and
- None of the public comments provided evidence that the proposed rule itself, with its limited scope, would have a significant impact on a substantial number of small entities.

Therefore, CPSC staff does not believe that the public comments or any other information that the Commission has received since the rule was proposed provides a basis for changing the Commission's certification that the rule would not have a significant impact on a substantial number of small entities.

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TAB A: CPSC Staff Analysis of NHANES Biomonitoring Data

TAB A

Estimated Phthalate Exposure and Risk to Pregnant Women and Women of Reproductive Age as Assessed Using Four NHANES Biomonitoring Data Sets (2005/2006, 2007/2008, 2009/2010, 2011/2012, 2013/2014)

May 2017

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Executive Summary

Section 108 of the CPSIA required the Commission to convene a CHAP to examine the effects on children's health of all phthalates and phthalate alternatives used in children's toys and child care articles. In July 2014, the CHAP submitted a final report to the Commission. This report included an analysis of biomonitoring data and associated estimates of phthalate exposure and risk to various populations, including pregnant women, women of reproductive age, and infants. The CHAP analysis used biomonitoring data from the 2005/2006 NHANES cycle.

Because the CHAP did not incorporate the individual-specific NHANES data cycles later than 2006 in the CHAP's report, the Commission directed staff to evaluate the NHANES data cycles that became available following 2005/2006. To do this, Health Science and Epidemiology staff first applied the CHAP's methodology for analysis of NHANES biomonitoring data and then verified that they could duplicate the results presented in the CHAP report (using NHANES 2005/2006 data). Staff then determined which portions of the later NHANES sets (2007/2008, 2009/2010, 2011/2012, 2013/2014) could be analyzed in a valid statistical manner using the CHAP's method, and then analyzed the appropriate NHANES data sets. This analysis included estimates of phthalate exposure, individual phthalate risk, and the cumulative risk (i.e., hazard index) for multiple phthalates. Staff reported the data as the median, 95th percentile, and 99th percentile and also estimated the distribution of risk estimates and variance estimates.

CPSC's staff-generated estimates for NHANES cycles 2005/2006 through 2011/2012 were reported June 2015 and published for public comment. Estimates from 2013/2014 NHANES data were reported and published for comment February 2017. This document collates both sets of estimates.

Overall, CPSC and CHAP estimations for daily intakes, hazard quotients, and hazard indices were similar when assessed using the NHANES 2005/2006 biomonitoring data. The numbers of pregnant women in the data sets after 2005/2006 were too small to generate statistical estimates for this subpopulation. Statistical estimates for women of reproductive age (non-pregnant women ages 15 through 45) indicated that daily intakes of phthalates have changed over time. Most notably, the daily intake of DEHP has decreased, while the daily intake of DINP has increased. When compared to the 2005/2006 data set, the hazard index has decreased in the more recent data sets (2009/2010, 2011/2012, 2013/2014).

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Abbreviations

ADI	acceptable daily intake
BBP	butyl benzyl phthalate
CDC	Centers for Disease Control and Prevention (U.S.)
CHAP	Chronic Hazard Advisory Panel
CI	confidence interval
CPSC	U.S. Consumer Product Safety Commission
CPSIA	Consumer Product Safety Improvement Act of 2008
DBP	dibutyl phthalate
DIBP	diisobutyl phthalate
DEHP	di(2-ethylhexyl) phthalate
DI	daily intake
DINP	diisononyl phthalate
DNOP	di-*n*-octyl phthalate
FHSA	Federal Hazardous Substances Act
HI	hazard index
HQ	hazard quotient
Log_{10}	logarithm to the base 10
MBP	monobutyl phthalate
MBzP	monobenzyl phthalate
MCPP	mono-(3-carboxypropyl) phthalate
MEHHP	mono-(2-ethyl-5-hydroxy-hexyl) phthalate
MEHP	mono(2-ethylhexyl) phthalate
MEOHP	mono-(2-ethyl-5-oxo-hexyl) phthalate
MEP	monoethyl phthalate
MIBP	monoisobutyl phthalate
MINP	mono(isononyl) phthalate
MOE	margin of exposure
N/A	not available or specified
NHANES	National Health and Nutrition Examination Survey
NPR	notice of proposed rulemaking
PEAA	potency estimates for antiandrogenicity
P-value	probability value
PW	pregnant women
WORA	women of reproductive age (non-pregnant women ages 15 through 45)

1. Introduction

1.1. Background

Section 108 of the CPSIA established regulatory and other requirements for CPSC regarding phthalates:

- Section 108(a) permanently prohibited the manufacture for sale, offer for sale, distribution in commerce, or importation in the United States of any "children's toy or child care article" that contains concentrations of more than 0.1 percent of di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), or butyl benzyl phthalate (BBP).
- Section 108(b)(1) prohibited on an interim basis (until the final rule is promulgated) the manufacture for sale, offer for sale, distribution in commerce, or importation in the United States of any "children's toy that can be placed in a child's mouth or child care article" that contains concentrations of more than 0.1 percent of diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), or di-*n*-octyl phthalate (DNOP).
- Section 108(b)(2) directed the Commission to convene a 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."
- Section 108(b)(3) of the Act requires the Commission to promulgate a final rule to: (A) determine, based on such a report, whether to continue in effect the prohibition under paragraph (1) in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety; and (B) evaluate the findings and recommendations of the CHAP and declare any children's product containing any phthalates to be a banned hazardous product under section 8 of the CPSA (15 U.S.C. 2057), as the Commission determines necessary to protect the health of children.

As required by statute, the Commission appointed a CHAP under section 108(b)(2) of the CPSIA. The CHAP held its first meeting on April 14, 2010, and met in other public sessions and teleconferences until its last meeting on January 29, 2014. After concluding its analysis, the CHAP reported the results of those examinations to CPSC on July 18, 2014. The final CHAP report included "recommendations to the Commission regarding any phthalates (or combinations of phthalates) in addition to those identified in subsection (a) or phthalate alternatives that the panel determines should be declared banned hazardous substances."

Staff delivered a briefing package for an NPR to the Commission on November 25, 2014. In the briefing package, staff presented the CHAP's recommendations on phthalates and phthalate alternatives and also staff's recommendations for a proposed rule. Staff briefed the Commission on December 5, 2014, and a decisional meeting was held on December 17, 2014. The NPR was published in the *Federal Register* on December 30, 2014. The comment period for the NPR was originally open until March 16, 2015, but the Commission voted to extend that period until April 15, 2015. A total of 91 comments were submitted on the NPR and an additional 18 comments on staff's reports on more recent NHANES data cycles. (Docket no. CPSC-2014-0033).

Consistent with the statutory directive, the CHAP's recommendations to the Commission were, in part, based on risk estimates from a cumulative assessment that considered exposures from selected phthalates. The CHAP used biomonitoring data (urinary metabolite levels) from the 2005/2006 NHANES, which is conducted by the Centers for Disease Control and Prevention (CDC).

CPSC's staff-generated estimates for NHANES cycles 2005/2006 through 2011/2012 were reported June 2015. This report was posted on CPSC's website, and the Commission published a notice of availability in the Federal Register requesting public comment. Staff also generated estimates from 2013/2014 NHANES data. This report was posted on CPSC's website, and the Commission published a notice of availability in the Federal Register requesting comment in February 2017. A total 18 comments on more recent NHANES data cycles were received. (Docket no. CPSC-2014-0033). This document collates both sets of estimates.

1.2. CPSC Staff's Approach to the NHANES Biomonitoring Analysis

Staff subdivided the project into four distinct phases to systematically replicate the CHAP analysis and report results for each data set.

- Phase 1 – Replicate the CHAP's methodology for calculating phthalate daily intakes and hazard indices.
- Phase 2 – Validate the methodology by using 2005/2006 NHANES data (i.e., compare staff results to that of the CHAP)
- Phase 3 – Examine the more recent data sets to assess which subpopulations can be analyzed in a valid statistical manner using the CHAP's methodology. Specifically, determine whether there are sufficient numbers of pregnant women in the newer data sets to support the analysis.
- Phase 4 – Analyze the more recent data sets on specific target populations using the CHAP's methodology.

2. Phase 1 - Replication of the CHAP's Methodology for Estimating Exposure and Hazard Indices Using Factors Presented in the CHAP Report on Phthalates

The CHAP estimated cumulative exposure to phthalates quantitatively by using 2005/2006 NHANES biomonitoring data (i.e., measurement of phthalate metabolites in a person's urine) that the CHAP used in their analysis (CHAP 2014). Additional NHANES data sets have been released to the public after that analysis.

2.1. Biomonitoring Data Availability

Five NHANES biomonitoring data cycles are currently publicly available for use in calculating exposure to phthalates (2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014).

2.1.1. NHANES 2005/2006 Data

The CHAP used NHANES phthalate biomonitoring data from the 2005/2006 cycle to estimate cumulative exposure. These phthalate data (PHTHTE_D 2005−2006) were originally posted online by CDC in February 2010, revised by CDC in January 2012, and updated again by CDC in February 2012. Additional data files used to calculate exposures (BMX_D 2005−2006, DEMO_D 2005−2006, ALB_CR_D 2005−2006, UCPREG_D 2005−2006) were originally posted online in November 2007. DEMO_D 2005−2006 (demographics) was subsequently updated in January and September 2009.

In response to the updates, the CHAP revised its analysis in July 2012. There have been no subsequent CDC revisions to the 2005/2006 phthalate data set since February 2012.

2.1.2. NHANES 2007/2008, 2009/2010, 2011/2012, 2013/2014 Data

Four additional NHANES phthalate data sets have been publicly released since the CHAP performed their data analysis. The release of these data sets occurred in October 2010 (PHTHTE_E 2007−2008), September 2012 (PHTHTE_F 2009−2010), November 2013 (PHTHTE_G 2011−2012), and December 2016 (PHTHTE_G 2013−2014).

2.2. Individuals Represented in the NHANES Data Sets

The five NHANES phthalate data sets contain biomonitoring and measurement data from individuals ranging from 6 to 85 years of age. For the five data sets (2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014), the number of individuals (2515, 2543, 2688, 2453, and 2663 respectively), women (1266, 1282, 1323, 1208, and 1392 respectively), and non-pregnant women of reproductive age (WORA) 15 to 45 years old (471, 473, 522, 477, and 538 respectively), and with a daily phthalate intake of > 0.0 µg/kg-day, were roughly similar. The number of women with a daily phthalate intake of > 0.0 µg/kg-day, who were pregnant (PW), as determined by self-reporting or a positive lab pregnancy test, were much smaller, however, in data cycles after 2005/2006 (130, 20, 26, 18, and 24, respectively).

2.3. Exposure and Cumulative Hazard Index Estimation

Staff estimated phthalate daily intakes, hazard quotients, and cumulative hazard indices using the data conventions and assumptions described in the CHAP report on phthalates (Appendix D).

2.3.1. Daily Intakes

Staff first estimated daily intakes (DI; µg/kg-day) for eight phthalates (BBP, DBP, DEHP, DEP, DMP, DIBP, DIDP, DINP) for each individual considering the following:

- If the measured phthalate metabolite was below the analytical limit of detection (LOD), the LOD/square root of 2 was used as the phthalate metabolite concentration.
- Creatinine excretion was estimated using formulas from Table 2 of Mage et al. (2008), heights and weights from NHANES BMX_ data files, and ages and races from NHANES DEMO_ data files. Creatinine excretion formulas used for non-Hispanic whites were also used for Mexican American, other Hispanic, and multiracial populations.
- Pregnancy status was determined by using the RIDEXPRG_ variable in the NHANES DEMO_ data file.
- Table D-1 of the CHAP report was used for parent phthalate molecular weight, phthalate metabolite molecular weight, and excretion factors (F_{ue}) for each phthalate metabolite.

2.3.2. Hazard Quotients

Staff then estimated hazard quotients (HQ) for five antiandrogenic phthalates (DBP, BBP, DINP, DIBP, DEHP) for each individual, by dividing the daily intake by potency estimates for antiandrogenicity (PEAA) developed by the CHAP (Appendix D, section 4). The PEAA is an estimate of the level of exposure at which the risk of antiandrogenic effects is considered negligible. These three PEAAs were termed “Cases”:

- Case 1 – published reference values for antiandrogenicity from a cumulative risk assessment for phthalates (Kortenkamp and Faust 2010);
- Case 2 – relative potency estimates derived by the CHAP based on comparisons across chemicals from the same study (Hannas et al. 2011b); and
- Case 3 – *De novo* determination of reproductive and developmental reference values by the CHAP from information in the published literature.

2.3.3. Hazard Indices

Finally, staff estimated hazard indices (HI) for each individual by summing the HQs for the five antiandrogenic phthalates (DBP, BBP, DINP, DIBP, and DEHP) for each PEAA Case.

3. Phase 2 - Validation of Staff's Methodology by Comparison to Selected Results from the CHAP Report on Phthalates Using 2005/2006 NHANES Data

3.1. Analyzing NHANES Data Sets

As described in Section 2, CPSC staff applied the same data conventions and methods used by the CHAP to estimate phthalate DIs and HQs/HIs for PW and WORA.

3.2. Reproduction of the CHAP's Results for NHANES 2005/2006

CPSC staff independently replicated the estimates from the CHAP report for phthalate exposures using the NHANES 2005/2006 data set, including DIs (Table 1 and 2), HQs, and HIs (Table 3). In most cases, median and 99th percentile estimates of phthalate DI were exactly as reported in Table D-2 of the CHAP report. Very minor differences in daily intakes were attributed to arithmetic rounding. Differences in DI did not substantially affect HI estimates, which were also similar to that presented in the CHAP report.

Table 1: CPSC Results Comparison to CHAP Daily Intake Estimates for Adults 15-45 Using NHANES 2005/2006 (CHAP Report Table D-2)

Daily Intake Estimates (µg/kg-day)	Phthalate (Adults 15-45)							
	BBP	DBP	DEHP	DEP	DMP	DIBP	DIDP	DINP
Median Estimate								
CHAP	0.29	0.66	3.8	3.3	0.03	0.19	1.5	1.1
CPSC	0.29	0.66	3.8	3.2	0.03	0.19	1.5	1.1
99th Percentile Estimate								
CHAP	2.5	5.5	203	118	0.80	1.9	19	35
CPSC	2.5	5.4	204	109	0.78	1.9	19	37

Table 2: CPSC Results Comparison to CHAP Daily Intake Estimates for Pregnant Women Using NHANES 2005/2006 (CHAP Report Table D-2)

Daily Intake Estimates (µg/kg-day)	Phthalate (Pregnant Women)							
	BBP	DBP	DEHP	DEP	DMP	DIBP	DIDP	DINP
Median Estimate								
CHAP	0.30	0.63	3.5	3.4	0.05	0.17	1.5	1.0
CPSC	0.28	0.63	3.5	3.3	0.05	0.17	1.5	1.0
99^{th} Percentile Estimate								
CHAP	2.7	6.4	366	357	0.68	2.0	11	27
CPSC	2.6	6.3	366	355	0.68	2.0	11	27

Table 3: CPSC Results Comparison to CHAP Hazard Index by PEAA Case for Pregnant Women Using NHANES 2005/2006 (CHAP Report Table D-9)

		Hazard Index Percentile Estimates (Pregnant Women)			
Estimated By	PEAA Case	Median	75^{th} Percentile	95^{th} Percentile	99^{th} Percentile
CHAP	Case 1	0.14	0.26	6.1	12.2
	Case 2	0.13	0.23	3.7	7.4
	Case 3	0.08	0.15	3.6	7.3
CPSC	Case 1	0.14	0.26	6.1	12.2
	Case 2	0.12	0.23	3.7	7.4
	Case 3	0.08	0.16	3.6	7.3

4. Phase 3 - Assess Which Subpopulations Can Be Appropriately Analyzed Using the CHAP's Methodology (Pregnant Women Versus Women of Reproductive Age)

Behaviorally, PW have increased consumption of fats, cheese, meat, and fruits and typically have a more health-conscious attitude when compared to non-pregnant women (Verbeke and De Bourdeaudhuij, 2007). Pregnant women also differ physiologically from non-pregnant WORA and have increased total blood volume (~30-45 percent), plasma volume (~40-60 percent), RBC volume (~25-33 percent), creatinine clearance (~21-41 percent), total plasma testosterone, and decreased metabolic clearance rate of testosterone (O'Leary et al., 1991; Picciano, 2003). The differences in these factors can result in differences in exposures to phthalates between these two populations.

Despite these differences, various publications suggest that daily phthalate or other chemical exposures are similar when comparing PW and WORA. Woodruff et al. (2011) determined that the geometric means and medians for many chemicals monitored in the NHANES 2003/2004 data set (including urinary MBzP, MIBP, MBP, and MEP) were similar for PW and WORA. Arbuckle et al. (2014) reported similar findings, in that uncorrected median concentrations of MBP, MBzP, MEHHP, MEHP, MEOHP, MCPP, and MEP in urine of PW in the MIREC study (2008−2011) were similar to WORA (20−39 years old) in a Canadian national health study (2007−2009, 2009−2011). The CHAP also concluded that the exposures to PW and WORA were not significantly different (CHAP 2014; p 36). So overall, in spite of the behavioral and physiological differences between WORA and PW, there is evidence to suggest that WORA have similar chemical exposures to PW.

4.1. Pregnant Women in NHANES 2007/2008, 2009/2010, 2011/2012, and 2013/2014 Can Not Be Used for Statistical Estimates

There are an insufficient number of pregnant women in each of the NHANES cycles following NHANES 2005/2006 to generate statistically stable estimates for daily phthalate intakes. This is because, in subsequent cycles, NHANES no longer oversampled pregnant women, leaving the sample size of pregnant women too small to use for statistical analyses in those later cycles (NCHS 2012, NCHS 2013b).

In certain circumstances, NHANES data from different cycles can be combined to increase the number of individuals in the analysis. This is not the case with NHANES phthalate data under consideration here, however. NHANES cycles 2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 cannot be combined to produce stable estimates related to phthalate DIs because all but dimethyl phthalate (DMP) evidenced a statistical trend across time when analyzing subpopulations containing sufficient numbers of individuals. The detected trend in larger subpopulations for phthalates DIs cannot be ruled out for the PW subpopulation; therefore, combining NHANES cycle data for PW was not attempted for any of the phthalates in this assessment (NCHS 2013c).

4.2. Women of Reproductive Age in NHANES 2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 Can Be Used for Statistical Estimates

There are sufficient WORA (non-pregnant women ages 15 through 45) sampled after the 2005/06 NHANES cycle to generate stable statistical estimates for daily phthalate intakes for each cycle. As noted above, NHANES cycles 2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 for any subpopulation, including WORA, were not combined because of the existence of trends in phthalate DI estimates; however, combining cycles was unnecessary to obtain stable estimates associated with phthalate exposure for WORA, in general (NCHS 2013c).

4.3. Phthalate Exposures for Pregnant Women Versus Women of Reproductive Age in NHANES 2005/2006

Staff compared their estimates from the 2005/2006 NHANES data set to determine whether WORA had similar DIs and HIs as PW. Median and 95th percentile estimates of the DIs for five phthalates were similar when comparing WORA to PW. The DIs were also similar to those in the CHAP report (CHAP, 2014; Table 2.7). Table 4 provides the median and 95th percentile estimates for daily intake estimates for five phthalates.

Table 4: Daily Intake Estimates (µg/kg-d): Comparison of Women of Reproductive Age Versus Pregnant Women Using NHANES 2005/2006

Subpopulation	BBP	DEHP	DINP	DBP	DIBP
Median					
WORA (CPSC, NHANES 2005/2006)	0.26	3.8	1.0	0.69	0.19
Pregnant Women (CPSC, NHANES 2005/2006)	0.28	3.5	1.0	0.63	0.17
95th Percentile*					
WORA (CPSC, NHANES 2005/2006)	1.1	27.7	10.5	2.6	0.82
Pregnant Women (CPSC, NHANES 2005/2006)	1.3	182	11.1	3.3	1.0

*Statistical test for comparisons cannot be performed on the 95th percentile estimates, because variance estimates are not always obtainable mathematically.

The median estimates of HIs for all three PEAA cases appeared similar for WORA and PW, although some differences existed in the upper tails of the empirical HI distributions for all three cases. Figure 1 illustrates the empirical HI distribution comparisons for PW versus WORA using PEAA Case 3. The differences in the tails of the distributions had a noticeable effect on the percentage of women with an HI greater than 1 (Table 5). Statistical significance of any differences in the upper percentile estimates could not be assessed. This was because variance estimates were unobtainable due to the limited sample size of PW in the 2005/2006 NHANES data set.

Figure 1: NHANES 2005/2006 Women of Reproductive Age Versus Pregnant Women Hazard Index, PEAA Case 3, Empirical Distribution Comparison

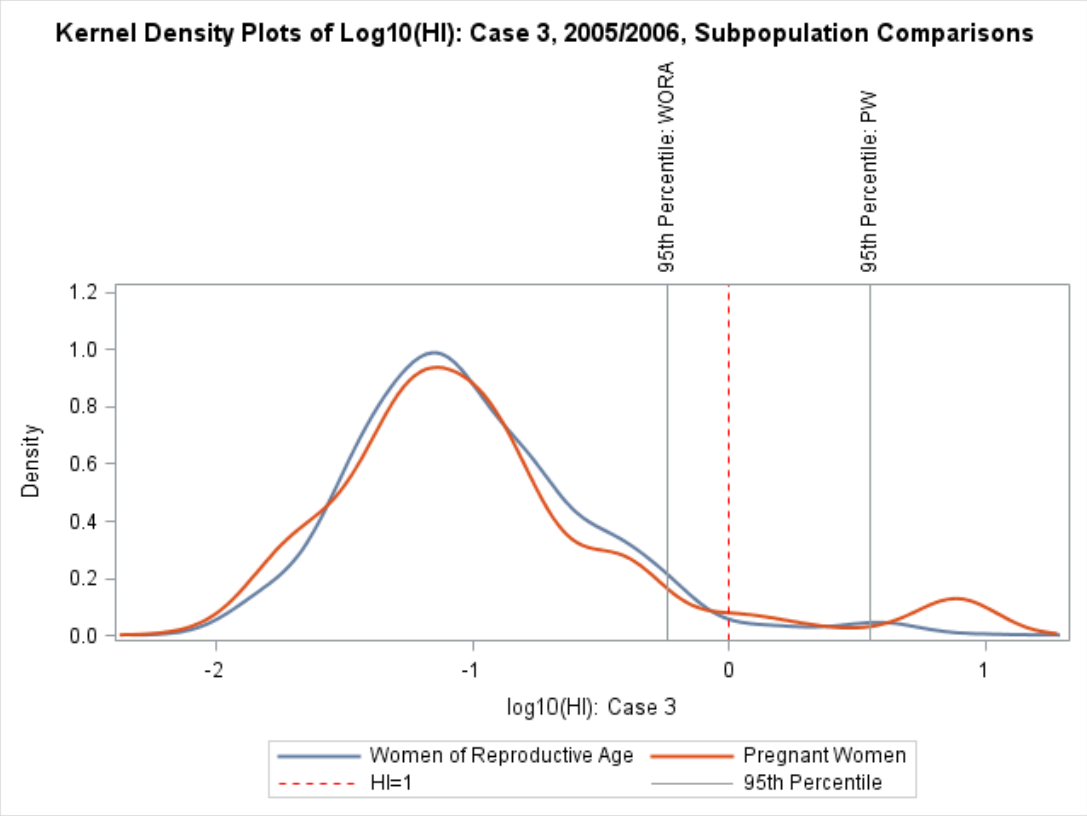


Table 5. Percentage of the population with an HI greater than one (2005/2006)

Case	Pregnant women	WORA
1	10	4.2
2	9	3.1
3	9	2.9
Pregnant women from CHAP 2014, Table 2.16. WORA from CPSC 2015, Table 7.		

5. Phase 4 – Statistical Analysis of Estimated Phthalate Exposure and Risk to Women of Reproductive Age Using 2005/2006, 2007/2008, 2009/2010, 2011/2012 and 2013/2014 NHANES Biomonitoring Data Sets

5.1. Daily Intake Estimates for Women of Reproductive Age across the 2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 NHANES Biomonitoring Data Sets

Daily Intake estimates for WORA in NHANES Cycles 2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 indicate that DIs have changed in a statistically significant manner across NHANES cycles (Table 6). For example, DINP DIs have increased, while DEHP DIs have decreased. The DIs for most other phthalates have remained fairly steady across NHANES cycles.

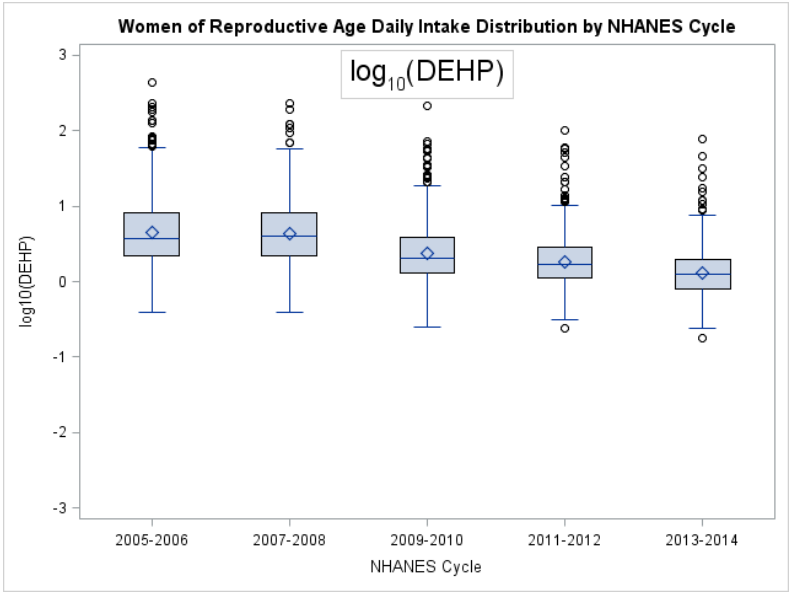
Table 6: Daily Intake Estimates (µg/kg-d) for Women of Reproductive Age Across NHANES Cycles: Median and 95th Percentile Estimates

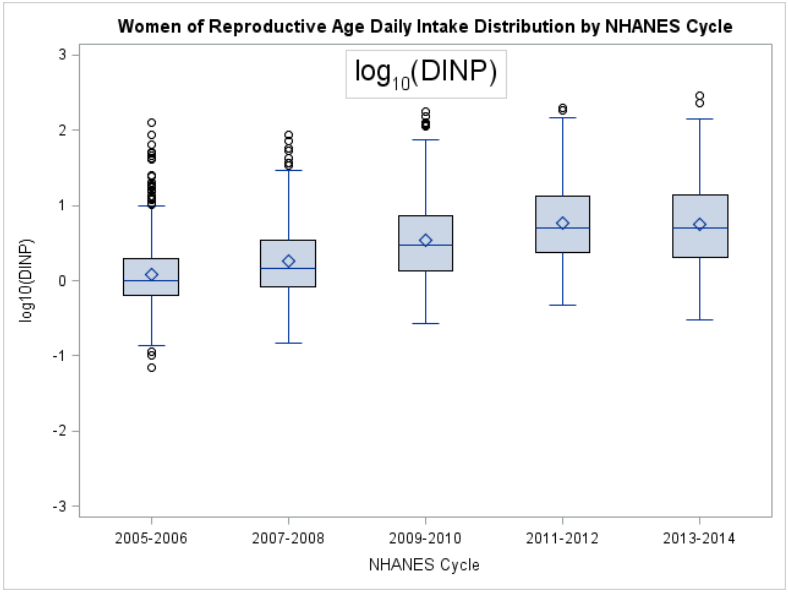
NHANES Data Set	BBP	DEHP	DINP	DBP	DIBP	Total
Median						
NHANES 2005/2006	0.26	3.8	1.0	0.69	0.19	5.9
NHANES 2007/2008	0.29	4.1	1.5	0.79	0.29	7.0
NHANES 2009/2010	0.23	2.0	3.0	0.58	0.32	6.1
NHANES 2011/2012	0.19	1.7	5.0	0.33	0.26	7.5
NHANES 2013/2014	0.15	1.3	5.0	0.33	0.29	7.0
95th Percentile						
NHANES 2005/2006	1.1	27.7	10.5	2.6	0.82*	42.7
NHANES 2007/2008	1.3	31.5	14.6	2.6	1.0	51.0
NHANES 2009/2010	1.0	10.3*	33.7	1.9*	0.98	47.9
NHANES 2011/2012	0.84	6.4*	51.7	1.3	0.94	61.2
NHANES 2013/2014	0.97	4.2	53.2	1.1	1.0	60.6

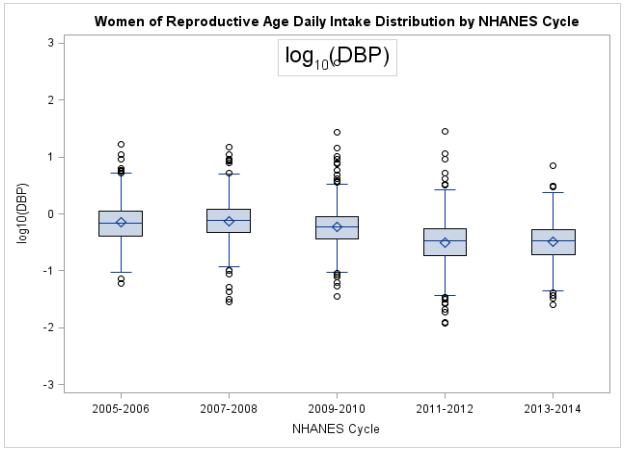
*Variance estimates can be large at the 95th percentile. Use caution when drawing conclusions using 95th percentile estimates.

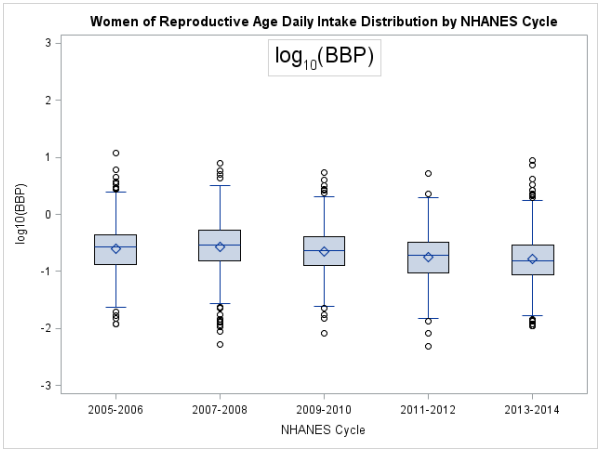
Figure 2 provides box-and-whisker plots of the empirical distributions of log_{10}-transformed DI distributions for five phthalates across NHANES cycles. There is a trend across cycles for each phthalate, including DINP and DEHP.

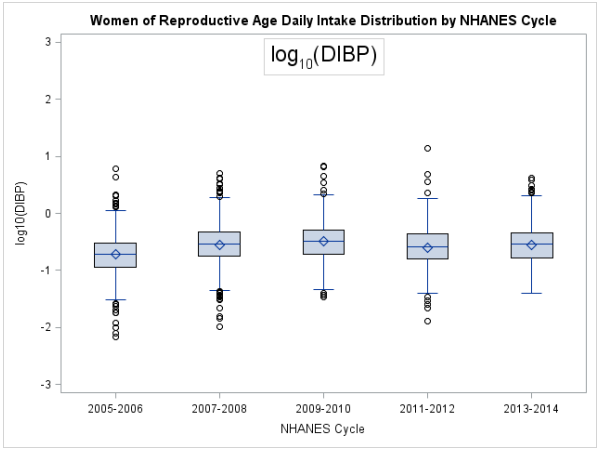
Figure 2: Log_{10}-Transformed Estimated Daily Intakes for 5 Phthalates for Women of Reproductive Age Across NHANES Cycles











5.2. Hazard Index Estimates for Women of Reproductive Age Across the 2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 NHANES Biomonitoring Data Sets

Median, 95th percentile and 99th percentile, HI estimates decreased across the NHANES data cycles (Table 7 and Figures 3-5). The log_{10}-transformed HI values were fitted to cycle in a regression model to test for trends, and cycle-to-cycle comparisons were completed within the fitted model (see Appendix A). HI estimates for Cases 1 and 3 showed a significant downward trend from the 2005/2006 cycle to the 2013/2014 cycle ($p<0.001$). When comparing HIs from 2005/2006 to 2007/2008 within the regression model, no difference was detected between Cases 1, 2, and 3 ($p=0.88$, 0.48, and 0.95, respectively). Additionally, there was not a statistically significant difference between 2009/2010 and 2011/2012 for Case 3 ($p=0.12$). For Case 2, no statistically significant differences were detected when comparing 2005/2006 to 2009/2010 or 2011/2012 ($p=0.18$ and 0.10, respectively). In addition, for Case 2, there were no statistically significant difference when comparing 2009/2010 to 2011/2012 or 2013/2014 ($p=0.84$ and 0.07, respectively) and 2011/2012 to 2013/2014 ($p=0.08$). For PEAA Case 2, however, even though the distributions of HI were roughly similar for each NHANES cycle, a trend of decreasing HIs could be detected statistically after the 2007/2008 data cycle ($p=0.0005$).

Table 7: Hazard Index Estimates for Women of Reproductive Age Across NHANES Cycles: PEAA Case 1, 2, and 3

Percentile	PEAA Case	NHANES Cycle				
		2005/2006	2007/2008	2009/2010	2011/2012	2013/2014
Median	Case 1	0.14	0.15	0.09	0.07	0.06
	Case 2	0.13	0.15	0.12	0.11	0.10
	Case 3	0.08	0.09	0.06	0.05	0.04
95th Percentile	Case 1	0.95	1.1	0.43*	0.25	0.17
	Case 2	0.69*	0.77	0.60	0.60	0.59
	Case 3	0.58*	0.65	0.30*	0.24	0.18
99th Percentile**	Case 1	6.3	1.9	1.9	0.73	0.36
	Case 2	3.8	1.6	1.7	1.3	1.19
	Case 3	3.8	1.2	0.94	0.57	0.35

*Variance estimates can be large at the 95th percentile ** and/ or unestimable for the 99th percentiles. Use caution when drawing conclusions about the 95th and 99th percentile estimates.

Figure 3: Kernel Density Plots for log_{10} Hazard Index for PEAA Case 1 by NHANES Cycle: Women of Reproductive Age

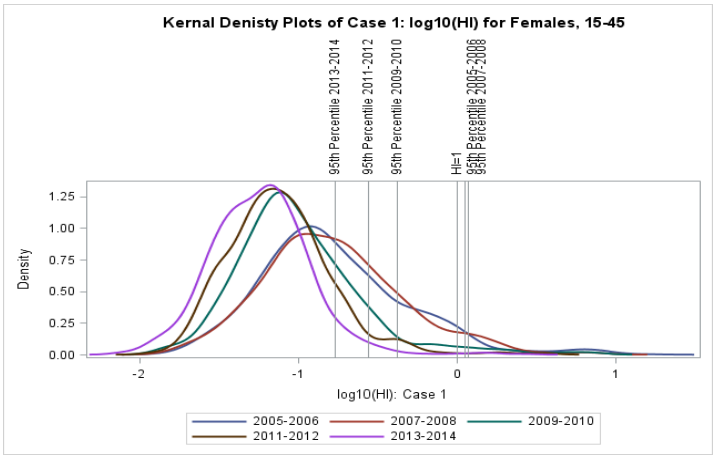


Figure 4: Kernel Density Plots for log_{10} Hazard Index for PEAA Case 2 by NHANES Cycle: Women of Reproductive Age

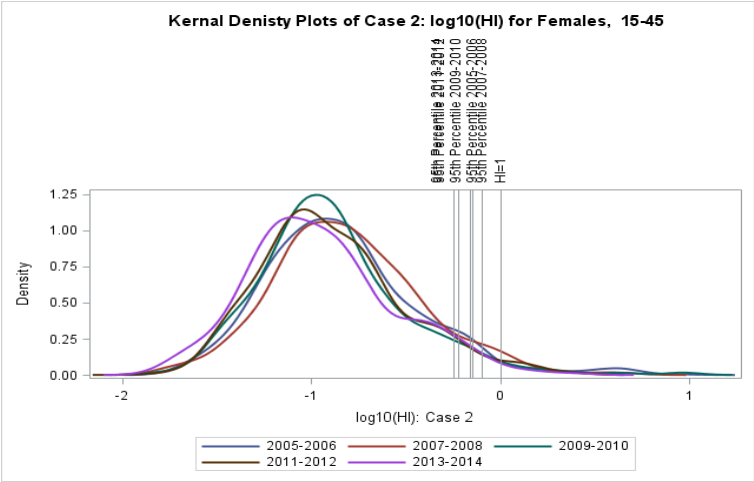
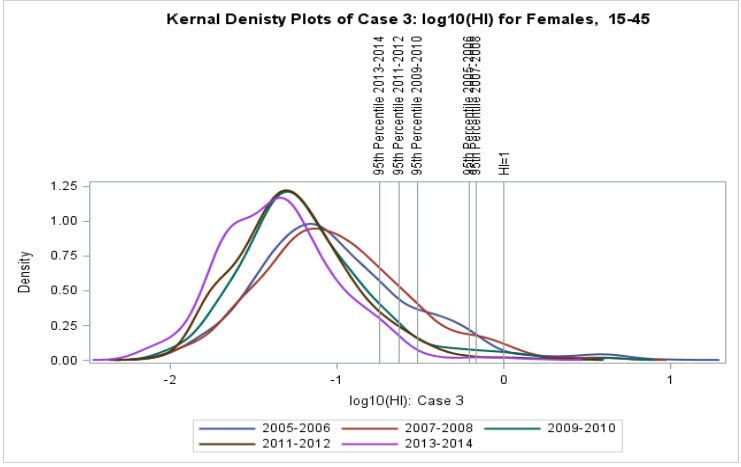


Figure 5: Kernel Density Plots for log_{10} Hazard Index for PEAA Case 3 by NHANES Cycle: Women of Reproductive Age



5.3. Percent of the Hazard Index that Phthalate Hazard Quotients Contribute

Figures 6 and 7 illustrate the impact that HQs have on the HI (sum of the HQs) across NHANES data cycles when looking at all PEAA Cases. In Figure 6, the sum of the median hazard quotients decreased in later data cycles (2009/2010, 2011/2012, and 2013/2014) when considering all PEAA Cases. As the HQ of DEHP decreased in later data cycles, the HQ of DINP increased. The contribution of DINP to the sum of the HQs (HI) depended on the PEAA Case. In PEAA Cases 1 and 3, DINP contributed a small portion to the sum of the HQs. In contrast, in PEAA Case 2, DINP contributed a large portion to the sum of the HQs, especially in later data sets (2009/2010, 2011/2012 and 2013/2014). Similar trends were repeated in Figure 7, which displayed the 95th percentile hazard quotients.

Figure 6: Median HQs for Women of Reproductive Age by NHANES Data Cycle and PEAA Case

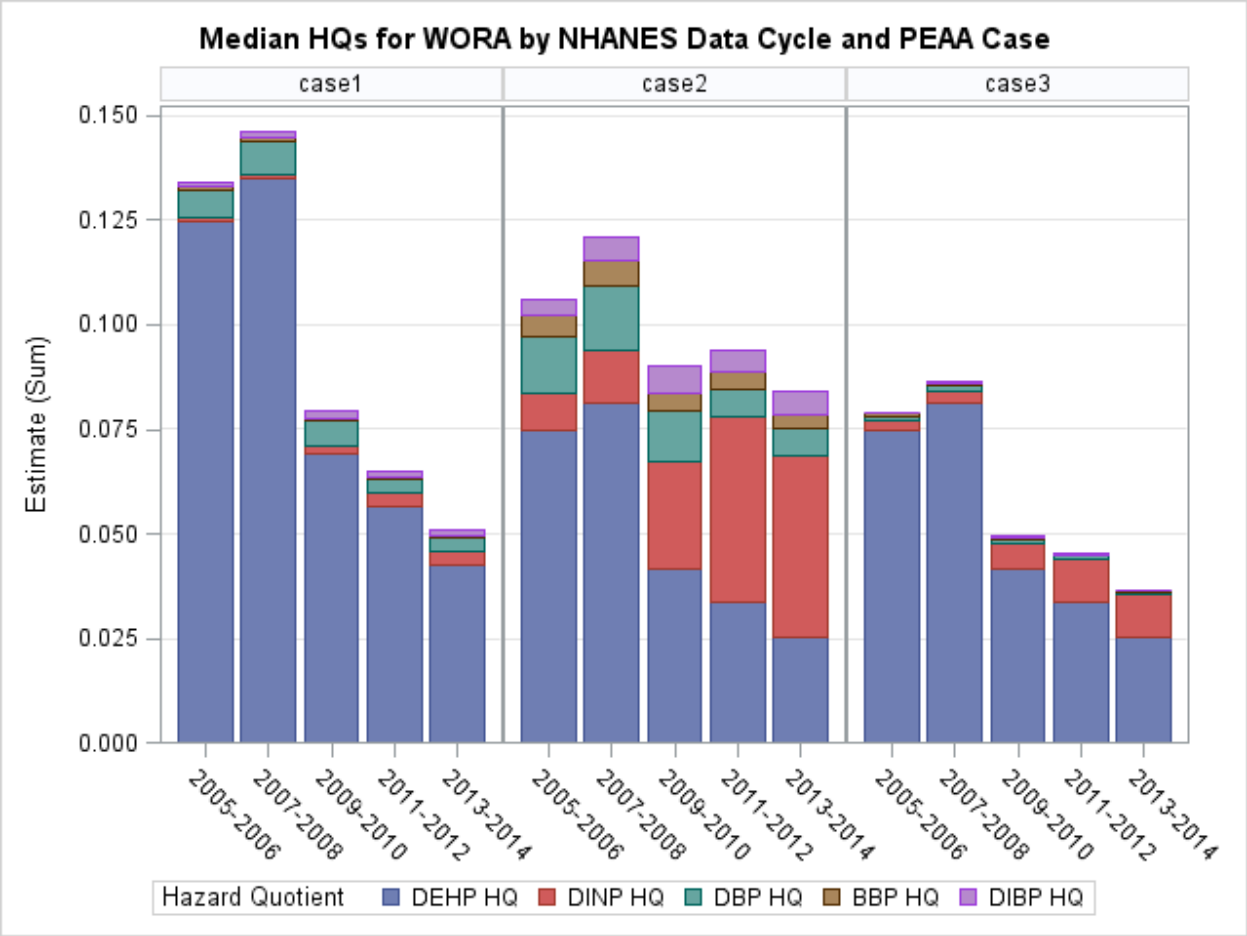
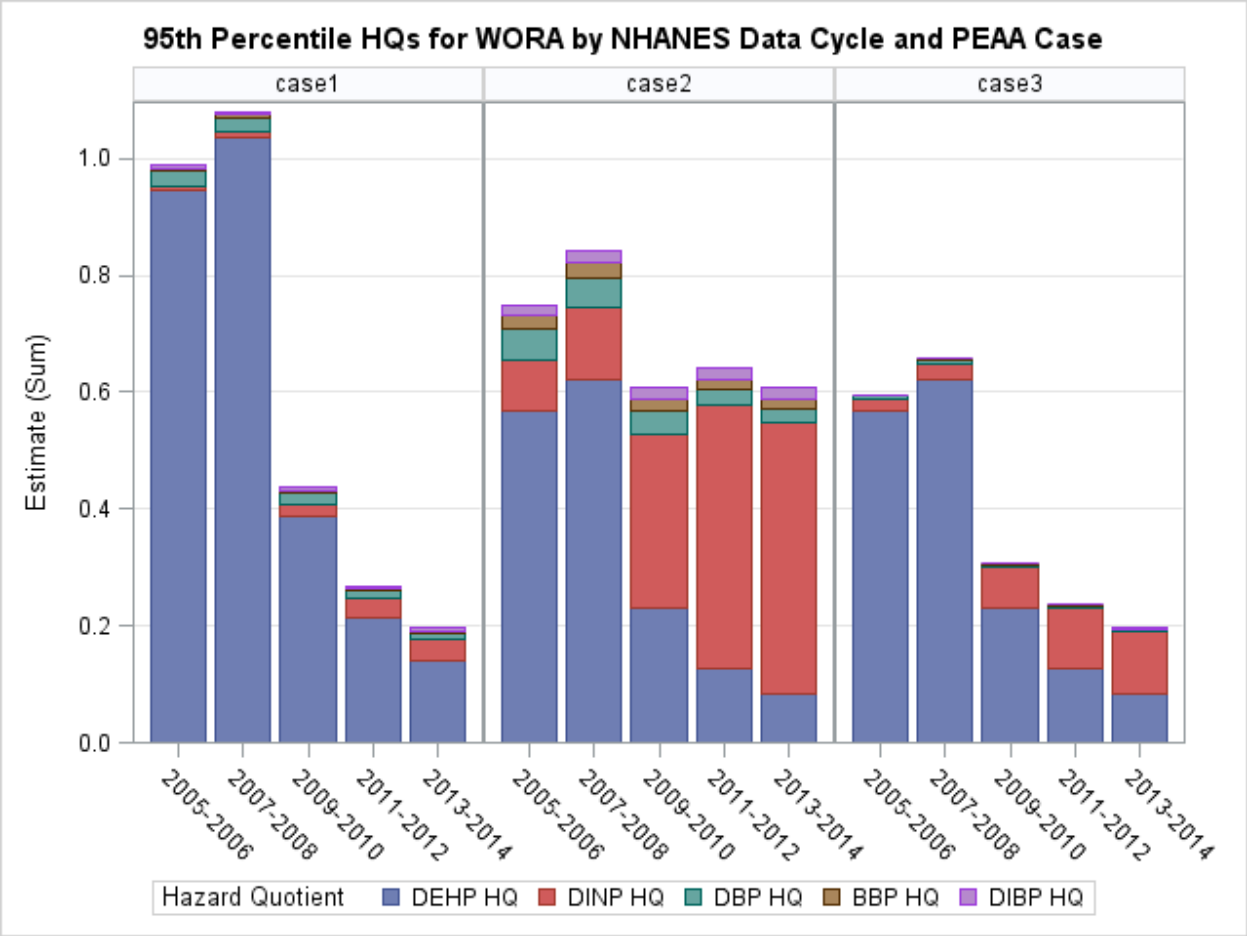


Figure 7: 95th Percentile HQs for Women of Reproductive Age by NHANES Data Cycle and PEAA Case



*95th percentile HQ estimates for DIBP in 2005/2006, DBP in 2009/2010, and DEHP in 2009/2010 have large variances. Use caution when drawing conclusions using the 95th percentile estimates.

To further illustrate the contribution of DEHP and DINP to reported HI estimates as demonstrated in Figures 6 and 7, Table 8 presents the percentage of DEHP and DINP of the HI for each PEAA Case for the median and 95th percentile estimates across NHANES cycles. While DEHP was the major contributor to the cumulative risk in 2005/2006, the relative contribution of DINP has increased since then. In 2005/2006, DINP contributed between 0.5 and 8.1 percent of the total risk (based on median HIs and HQs), depending on the PEAA case. In 2013/2014, DINP contributed between 6.5 and 51 percent of the risk (based on the median HI and HQ for Case 2). At the 95th percentile, the relative contribution of DINP was even greater, and ranged from 18 to 76 percent for Case 2. Thus, in 2013/2014, DINP contributed more to total risk than DEHP (Case 2).

Table 8. Percent Contribution to the Total Risk (HI) by NHANES Data Cycle and PEAA Case

NHANES data cycle	DEHP			DINP		
	Case 1	*Case 2*	*Case 3*	*Case 1*	*Case 2*	*Case 3*
Median						
2005/2006	93.2	70.7	94.9	0.49	8.1	2.5
2007/2008	92.4	67.0	93.8	0.68	10.6	3.4
2009/2010	86.8	45.1	83.5	2.6	29.4	12.5
2011/2012	86.9	36.5	75.1	5.1	46.7 [a]	22.1
2013/2014	83.2	30.2	69.5	6.5	51.4 [a]	27.2
95th Percentile						
2005/2006	95.8	75.3	95.0	0.73	12.4	3.6
2007/2008	95.9	73.7	94.3	0.89	14.8	4.4
2009/2010	87.4	35.7	73.6	5.7	50.8 [a]	24.1
2011/2012	79.6	20.0	54.1	12.9	70.3 [a]	43.7
2013/2014	71.9	13.8	43.1	18.1	75.9 [a]	54.3 [a]

[a] Instances where DINP contributes more to the HI than DEHP.

5.4. Estimated Proportion of Women of Reproductive Age with a Hazard Index less than or equal to one across the 2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 NHANES Biomonitoring Data Sets

The estimated proportion of the WORA with an HI less than or equal to one for each of the PEAA Cases increases across the NHANES cycles (Table 9). In the 2013/2014 cycle, 99.5 percent of WORA have an HI less than or equal to one when considering PEAA Case 1 and 99.6 percent when considering Case 3. For PEAA Case 2, an estimated 98.85 percent of WORA have an HI less than or equal to one in the same cycle. It should be noted that some WORA from each NHANES cycle demonstrated HIs greater than one for each PEAA Case. However, the national population projection for HI greater than one is not estimable at the upper percentiles of the distribution due to sampling variability.

The estimated number of WORA represented by 1 percent of the subpopulation were obtained by summing the NHANES weights for the WORA phthalate samples.

Table 9: Estimated Percent of the Women of Reproductive Age Subpopulation with Hazard Index Less than or Equal to 1 by PEAA Case and NHANES Cycle

	NHANES Cycle				
PEAA Case	2005/2006	2007/2008	2009/2010	2011/2012	2013/2014
Case 1	95.8%	93.8%	97.4%	99.2%	99.5%
Case 2	96.9%	96.7%	97.7%	97.7%	98.8%
Case 3	97.1%	98.1%	99.1%	99.4%	99.6%
1% =	540,000	586,000	576,000	602,000	604,000

5.5. Analytical Summary of the Results of Phthalate Exposure for Women of Reproductive Age Across the 2005/2006, 2007/2008, 2009/2010, 2011/2012, and 2013/2014 NHANES Biomonitoring Data Sets

The distributions of estimated HIs for WORA as characterized by the 50th percentile median, 95th percentile, and 99th percentile HIs show a decrease over later NHANES data cycles. The percentage of WORA with HIs greater than one decreases in later data cycles. The changes in HI distributions across NHANES cycles can be attributed to the changes in DEHP and DINP exposures. The decreases in HI are primarily due to decreases in DEHP exposure. The HQ for DINP is replacing the HQ for DEHP proportionally for contributions to the total HI. In each PEAA Case, DINP has less potency than DEHP; thus even though DINP's proportion of contribution to total HI is increasing, the values of HI have still decreased overall across cycles.

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Appendix 1. Statistical Methodology

NHANES includes a health examination data survey that is nationally representative of the civilian, non-institutionalized U.S. population. It is a complex, four-stage survey, which includes strata and primary sampling units (PSUs) that must be accounted for when analyzing the data. The structure of NHANES also incorporates weights for each observation. Within NHANES, there are different subsamples of the total sample for different laboratory results, which are each weighted accordingly.

Staff used SAS 9.4® survey procedures to analyze the data. The strata, PSU, and lab subsample weight NHANES variables were incorporated per NHANES documentation. Domain analysis was incorporated to maintain the full structure of the survey in generating variance estimates for the various subsamples analyzed. Variance estimates were obtained using the Taylor Series method and Woodruff's method, as appropriate.

Staff used kernel density plots in place of histograms to assist in visual comparisons of distributions across subpopulation and NHANES cycles. Kernel density plots fit a non-parametric line to estimate the probability density function. Boxplots were used to visualize the distributions of phthalate daily intake estimated distributions. The log_{10} transformation was used on daily intakes and hazard index values to deal with the extreme skewness of the distribution of the raw values.

Staff set significance of p-values at an alpha of 0.05. Adjustments to p-values to account for multiple comparisons were not incorporated in the analysis (i.e., p-values are provided in their original form). Trend across cycles was performed by linear regression, while incorporating the survey's structure and applying domain analysis techniques. The p-values for trend correspond to the test for significance variable in a simple linear regression lines fitting the cycle as a classification variable for each log_{10}-transformed value of interest, individually. P-values for cycle-to-cycle comparisons were completed within the linear regression model. Although the log_{10}-transformed values did not always create models with all the model assumptions being met absolutely, the results indicated the model assumptions were met sufficiently to draw valid conclusions.

TAB B: Staff Responses to Public Comments

TAB B

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MD 20814

Memorandum

Date: September 13, 2017

TO : Kent R. Carlson, Ph.D., Project Manager, Directorate for Health Sciences

THROUGH: Duane E. Boniface, Deputy Assistant Executive Director, Hazard Identification and Reduction
Alice M. Thaler, D.V.M., Associate Executive Director, Health Sciences
Kathleen Stralka, Associate Executive Director, Epidemiology

FROM : Michael A. Babich, Ph.D., Directorate for Health Sciences
Randy S. Butturini, Office of Hazard Identification and Reduction
Kristina M. Hatlelid, Ph.D., MPH, Directorate for Health Sciences
David M. DiMatteo, J.D., Office of the General Counsel
Robert L. Franklin, Directorate for Economic Analysis

SUBJECT : Responses to Public Comments on the Notice of Proposed Rulemaking on the Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates

This memorandum provides CPSC staff responses[1] to public comments on the Commission's NPR on the Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates.[2] The Commission received a total of 109 public comments,[3] including 91 comments on the NPR and 18 comments on CPSC staff's biomonitoring reports (CPSC 2015a; CPSC 2017a). Commenters included the general public, manufacturers of phthalates or products containing phthalates, non-governmental organizations (NGOs), and members of Congress.

Comments are organized into the following ten topics:

1. Selection of Health Endpoint and Species Differences;
2. Cumulative Risk Assessment;
3. Human Biomonitoring Data;
4. The CHAP's Three Cases (potency estimates for antiandrogenicity);
5. Relative Contributions of Phthalates and Sources of Exposure to Cumulative Risk;
6. Scope of Prohibition Involving DINP and the Four Additional Phthalates;

[1] Numerous CPSC staff contributed to this document. A complete list is available on page 45 of the briefing memorandum.
[2] 79 FR 78324-78343. Tuesday, December 30, 2014. The NPR provided for a 75-day comment period. The Commission extended the comment period for an additional 30 days. 80 FR 14880 (March 20, 2015).
[3] Public comments are available at https://www.regulations.gov/docket?D=CPSC-2014-0033.

7. Epidemiology;
8. Legal Issues, including IQA and Peer Review;
9. Economic and Compliance Issues; and
10. Other Comments.

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List of Abbreviations

ADI	acceptable daily intake
AGD	anogenital distance
AGI	anogenital index
APA	Administrative Procedures Act
BBP (BzBP)	butyl benzyl phthalate
BMD	benchmark dose
CAS	Chemical Abstracts Service
CAS RN®	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control and Prevention (U.S.)
CERHR	Center for the Evaluation of Risks to Human Reproduction
CHAP	Chronic Hazard Advisory Panel
CI	confidence interval
CNP	mono-carboxyisononyl-butyl phthalate
COP	mono-(carboxyisooctyl) phthalate
CPSC	U.S. Consumer Product Safety Commission
CPSIA	Consumer Product Safety Improvement Act of 2008
CRA	cumulative risk assessment
DBP	di-*n*-butyl phthalate
DCHP	dicyclohexyl phthalate
DEHP	di(2-ethylhexyl) phthalate
DEP	diethyl phthalate
DHEXP	dihexyl phthalate
DI	daily intake
DIBP	diisobutyl phthalate
DIDP	diisodecyl phthalate
DINP	diisononyl phthalate
DIOP	diisooctyl phthalate
DMP	dimethyl phthalate
DNOP	di-*n*-octyl phthalate
DPENP	dipentyl phthalate
ECB	European Chemicals Bureau
ECHA	European Chemicals Agency
ECP	mono(2-ethyl-5-carboxypentyl) phthalate
EFSA	European Food Safety Agency
FHSA	Federal Hazardous Substances Act
F_{UE}	fraction of the urinary metabolite(s) excreted
HBM	human biomonitoring
HI	hazard index
HQ	hazard quotient
IQA	Information Quality Act

LOAEL	lowest observed adverse effect level
MBP	mono-n-butyl phthalate
MBzP	monobenzyl phthalate
MCPP	mono(3-carboxypropyl) phthalate
MEHHP	mono(2-ethyl-5-hydroxy-hexyl) phthalate
MEHP	Mono(2-ethylhexyl) phthalate
MEOHP	Mono-(2-ethyl-5-oxo-hexyl) phthalate
MEP	monoethyl phthalate
MHH	mono(2-ethyl-5-hydroxylhexyl) phthalate
MHP	mono(2-ethylhexyl) phthalate
MIBP	monoisobutyl phthalate
MINP (MNP)	mono(isononyl) phthalate
MMP	mono-methyl phthalate
MNG	multinucleated gonocytes
MOA	mode of action
MOE	margin of exposure
MOH	mono(2-ethyl-5-oxohexyl) phthalate
MOP	mono-*n*-octyl phthalate
MRDE	male reproductive developmental effects
N/A	not available or not specified
NHANES	National Health and Nutrition Examination Survey
NOAEL	no observed adverse effect level
NPR	notice of proposed rulemaking
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
OMB	Office of Management and Budget
PE	phthalate ester
PEAA	potency estimate for antiandrogenicity
PND	postnatal day
POD	point of departure
PW	pregnant women
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RFA	Regulatory Flexibility Act
RfD	reference dose
RTM	reproductive tract malformations
SFF	Study for Future Families
T	testosterone
TBT	Technical Barriers to Trade
TDI	total daily intake
TDS	testicular dysgenesis syndrome
TEF	toxicity equivalence factors
TERA	Toxicology Excellence for Risk Assessment

TIDES	The Infant Development and the Environment Study
UF	uncertainty factor
WOE	weight of evidence
WORA	women of reproductive age (non-pregnant women ages 15 through 45)
WTO	World Trade Organization

1. Selection of Health Endpoint and Species Differences

This section includes comments on four topics: (1) selection of health endpoint, (2) selection of target populations, (3) antiandrogenicity of diisononyl phthalate (DINP), and (4) mode or mechanism of action. Health endpoint refers to the specific health effects that the CHAP selected for its cumulative risk assessment (CRA). It also includes comments on the human relevance of health effects found in animal studies. Target population refers to the subpopulations (pregnant women and infants) for which the CHAP estimated cumulative risk. Antiandrogenicity is related to the health effects caused by the phthalates, and specifically, whether DINP causes male reproductive developmental effects (MRDE). Mode of action (MOA) refers to the key steps by which phthalates cause MRDE. Mechanism of action is a more detailed description of the molecular activities by which phthalates cause MRDE.

Health Endpoint

After reviewing all health effects associated with phthalates, the CHAP selected MRDE as the critical effect for cumulative risk assessment (CRA) (CHAP 2014; pp. 13-15), which is consistent with the recommendations of the National Academy of Sciences (NAS) report on phthalates cumulative risk assessment (NRC 2008). NRC recommended, for example, that it is appropriate to perform a phthalate CRA for MRDE (phthalate syndrome), the CRA be based on all endpoints associated with MRDE or, alternatively, one sensitive endpoint such as reductions in testosterone (NRC 2008, Chapter 5) (see section 4 below). NRC also recommended using dose addition (section 2), a hazard index approach, assuming that mixture effects occur at low-doses, and including other (non-phthalate antiandrogens). Finally, NRC recommended including DINP, DEHP, DBP, DIBP, BBP, and DPENP in the CRA.[4]

In animal studies, MRDE is described by the term "phthalate syndrome." When rats are exposed to phthalates perinatally (the period ranging from late gestation to early postnatal life and lactation), male offspring exhibit a set of effects that includes reduced testosterone synthesis, reduced anogenital distance (AGD), nipple retention (normally does not occur in male rats), undescended testes, testicular atrophy, testicular histopathology, multi-nuclear gonocytes (MNGs), reduced production of insulin-like hormone 3 (insl3), underdeveloped gubernacular cords,[5] undescended testes, and genital malformations (hypospadias) (Foster 2006; Foster et al. 2001; Howdeshell et al. 2016; Howdeshell et al. 2008). These effects persist into adulthood and lead to reduced, or absent, reproductive ability. Related effects are also found in neonatal, juvenile, and adult male rats after phthalate exposure, although they are less sensitive than the fetus. A reduced rate of testosterone production and concomitant reduced insl3 gene expression are considered key events leading to the syndrome (Foster 2006; Howdeshell et al. 2016; Wilson et al. 2004). It is important to note that many, but not all, phthalates cause phthalate syndrome.[6] The CHAP identified five phthalates (DBP, BBP, DINP, DIBP, and DEHP) that cause phthalate syndrome and for which human biomonitoring data were available to assess exposure. A similar

[4] The CHAP CRA included all of these, except DPENP. NHANES does not provide biomonitoring data for DPENP.
[5] Underdeveloped gubernacular cords lead to undescended testes.
[6] The CHAP referred to phthalates which cause PS as "antiandrogenic," due to the importance of testosterone inhibition in causing phthalate syndrome. Antiandrogenic also serves to distinguish phthalates from other chemicals that act through the androgen receptor, which phthalates do not.

syndrome known as “testicular dysgenesis syndrome” (TDS) has been described in humans (Skakkebaek et al. 2001).

Species Differences

Toxicological studies are generally conducted using laboratory animals, most often rodents, such as mice and rats. Because mammals share common cellular and molecular processes, it is rare that effects observed in other mammals are not also observed in humans. Nonetheless, an evaluation of data from animal studies for use in assessment of risks to human health generally considers whether such data are relevant to humans. The observation of a particular health effect in multiple animal species, doses, routes of administration, or sexes, is generally considered (CPSC 1992; EPA 1991; IARC 2002; NTP 2016) sufficient to assume that a chemical is likely to cause the same effect in humans, in the absence of information to the contrary. The more species that are affected, the more likely it is that the effect could also occur in humans (CHAP 2014, p. 21). The public comments question whether the effects in rats also occur in humans.

Overview of Public Comments on the Selection of Health Endpoint and Species Differences

Some industry comments discussed whether MRDE was appropriate for a CRA of phthalates. Commenters asserted that: (a) humans are resistant to the adverse effects of phthalates or, at least, humans are less sensitive than animals; (b) the proposed regulations are intended to protect infants, while only the fetus is sensitive to the effects of phthalates; (c) DINP is not antiandrogenic (i.e., does not cause MRDE); and (d) the MOA of many phthalates is not well understood.

CPSC staff concludes that MRDE is the most appropriate endpoint for a CRA of phthalates. An abundance of evidence demonstrates that DEHP, BBP, DBP, DIBP, and DINP induce MRDE in animals. There is ample experimental evidence showing that the effects of these phthalates on MRDE are additive (cumulative). The National Academy of Sciences recommended MRDE (common adverse outcomes) for conducting a CRA for phthalates (NRC 2008).

(a) Staff also concludes that, while a few studies (comment response 1.3-1.6) suggest that humans may be less sensitive to phthalate effects, the majority of evidence still supports the use of the rat as an appropriate model for estimating phthalate risks in humans. In addition, a growing number of epidemiological studies have reported associations between phthalate exposure and MRDE effects in male infants and adults, supporting the relevance of rodent data to humans.

(b) The proposed regulations on children’s toys and child care articles are primarily intended to protect infants (comment response 1.11). The potency estimates derived by the CHAP (potency estimates for antiandrogenicity, PEAAs) are intended to protect the male fetus, infants, and children. Although the male fetus is considered to be the most sensitive to MRDE, MRDE affects males of all ages, including adults.

(c) Staff concludes that the overwhelming weight of the evidence demonstrates that DINP can induce MRDE (phthalate syndrome) in animals, although it is less potent than DEHP (comment response 1.14).

(d) Finally, staff concludes that the phthalates that cause MRDE share a common mechanism of action. However, staff notes that a common mechanism of action is not necessary for cumulative effects to occur (ATSDR 2004; Howdeshell et al. 2016), especially in light of experimental

evidence (Conley et al. 2017; Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008) demonstrating cumulative (i.e., dose additive) effects (comment response 1.21).

Male Reproductive Developmental Effects and Species Differences

Comment 1.1: Phthalate syndrome in other rodent species. One industry commenter stated that the effects associated with phthalate syndrome are "not very clear" in species other than the rat, that is, that there is less evidence of phthalate syndrome in species other than rats. The commenter noted that the CHAP report concluded that "guinea pigs and rabbits appear responsive to phthalates," but hamsters were resistant. The commenter went on to say that data in mice are mixed, with some studies supporting mouse susceptibility to phthalate syndrome, some demonstrating within-study susceptibility and resistance, and others demonstrating that mice are refractory (resistant) to phthalate syndrome. As discussed above, the more species that are affected by a chemical, the more likely it is that the effect could also occur in humans. Therefore, according to the commenter, due to the relative lack of evidence of phthalate syndrome in animals other than rats, it is questionable whether phthalate syndrome in rats is relevant to humans.

Response 1.1: Phthalate syndrome has been reported to occur in multiple mammalian species, including guinea pigs (Gray et al. 1982), mice, (Gray et al. 1982; Moody et al. 2013; Ward et al. 1998), rabbits (Higuchi et al. 2003), and ferrets (Lake et al. 1976). Hamsters were resistant to the effects of phthalates due to their slow metabolism to the active metabolite. However, a study by Gray et al. (1982) shows that giving the active metabolite to hamsters causes phthalate syndrome. The observation of similar effects in multiple species demonstrates that these effects are not unique to rats. Staff concludes that there is sufficient evidence that phthalates induce MRDE (phthalate syndrome) in multiple mammalian species. Therefore, based on the generally accepted toxicological practices (e.g., CPSC chronic hazard guidelines (CPSC 1992)), phthalates may be considered "probably toxic in humans," based on sufficient evidence of phthalate syndrome/MRDE in animals. Furthermore, staff notes that epidemiological studies have reported evidence of MRDE in humans associated with phthalate exposure, providing further support for the conclusion that phthalates are probably toxic to humans. See Section 7, Epidemiology.

Comment 1.2: Phthalate syndrome in mice. Two industry commenters concluded that humans are less sensitive than rats to phthalates, and that mice were a more relevant model for humans because mice, like humans, are less sensitive to phthalate induced "early key events" (Furr et al. 2014; Veeramachaneni and Klinefelter 2014). Another commenter cited multiple mouse studies (Gaido *et al.* 2007) as evidence that not all phthalate syndrome effects are observed in mice, as compared to rats.

Response 1.2: The CHAP discussed phthalate-induced effects in mice, stating:

> *In utero* exposure to phthalates in mice (as in rats) leads to disruptions in seminiferous cord formation, the appearance of multinucleated gonocytes, and suppression of insulin-like factor 3 (insl3). Unlike in rats, these effects in mice were not accompanied by suppression of fetal testosterone synthesis or by reduced expression of genes important in steroid synthesis. However, a recent study reported that phthalates suppress testosterone synthesis in prepubertal mice (Moody et al., 2013). (CHAP 2014, p. 6)

Additional details on phthalate-induced effects in mice were provided by the CHAP (CHAP 2014, p. 16-17) and the CHAP noted that in many circumstances for mice "the available data are insufficient to derive a separate set of NOAELs" (CHAP 2014, p. 71). The CHAP did not mention whether mice were a more appropriate model for investigating phthalate-induced effects.

Studies by Doyle et al. (2013) and Ge et al. (2015) published after the CHAP concluded its analysis provide additional evidence of phthalate syndrome effects in mice, including reduced testosterone levels, reduced testosterone production, testicular damage, reduced sperm count and quality, reduced AGD, delayed pubertal onset, and increased nipple retention. Additionally, *in vitro* studies by Clewell et al. (2011) and Ding et al. (2011) found that phthalates affect testosterone synthesis equally in rat and mouse cell cultures. Thus, there is now even stronger evidence of phthalate syndrome in mice than was available to the CHAP. The CHAP cautioned that differences in methodology could cloud the issue of which species is more sensitive (CHAP 2014; pp. 17, 72). Even if mice or other species are less sensitive than rats, it is not possible to make a direct comparison to humans without dose-response information in humans. Rats are the only species for which adequate dose-response data are available to support a risk assessment.

Furthermore, the most sensitive species is generally used in assessing risks to humans (Barnes and Dourson 1988; CPSC 1992; EPA 1991). The CHAP concluded that rats provide the most sensitive and most extensive studies in male developmental toxicity (CHAP 2014, pp. 1, 15, 16, 76), citing the NRC report (NRC 2008). Phthalate syndrome in rats resembles the "testicular dysgenesis syndrome" (TDS) in humans (CHAP 2014, pp. 2, 75). For these reasons, the CHAP concluded that studies in rats currently offer the best available data for assessing human risk (CHAP 2014, pp. 18, 75).

Based on evidence used by the CHAP and subsequent publications, staff concludes that the rat is the most appropriate animal model for assessing human risks, because of its sensitivity to phthalates and because adequate dose response data are available. This conclusion is consistent with the CPSC risk assessment guidelines (CPSC 1992).

Comment 1.3: Marmoset studies. Several industry commenters discussed the lack of effects of phthalates in marmosets. They argued that marmosets, being primates and having reproductive organ development that is similar to humans, were more closely related to humans than rats and, therefore, are a better model for estimating human risk.

Commenters focused on a study (McKinnell *et al.* 2009), in which pregnant marmosets were exposed to 500 mg/kg-d monobutyl phthalate (MBP)[7] from gestation weeks 7 to 15. Male offspring were evaluated on postnatal days (PND) 1 to 5. The researchers reported no effects observed for several relevant reproductive endpoints (testosterone levels, gross testicular morphology, reproductive tract development, germ cell number, and germ cell:Sertoli cell ratio). One commenter noted that in this study dosing ended 12 weeks before birth when data collection occurred, which allows the possibility of recovery from antiandrogenic effects. However, this commenter pointed out that the study authors concluded that MBP administered to pregnant marmosets did not affect steroidogenesis in the fetal testes to any significant level and that there was no evidence for testicular dysgenesis.

[7] A metabolite of dibutyl phthalate (DBP).

One commenter also summarized two studies in neonatal marmosets (Hallmark *et al.* 2007). In the first study, the researchers noted reduced serum testosterone levels after administration of a single oral dose of MBP (500 mg/kg) to 2–7 day old marmosets. The second study, in which the researchers administered to neonatal marmosets 500 mg/kg daily for 14 days, did not show reduced serum testosterone. The commenter noted that the study authors observed changes in the marmosets dosed for 14 days that were consistent with MPD-induced inhibition of steroidogenesis followed by a compensatory hormone response that would restore testosterone production to normal levels.

Response 1.3: The commenters stated that primates are a better model of human reproductive organ development than rats and mice because primates are more closely related to humans. However, it is not always true that primates are better models for humans, depending on what organ system is under investigation. For example, pigs are immunologically more similar to humans, and porcine heart valves are routinely transplanted into humans. Additionally, guinea pigs are used as models for respiratory diseases and dogs for hemophilia.

Nevertheless, while the limited data from nonhuman primates showed no effect in a study of fetal exposure to one phthalate metabolite, the published studies also show that the phthalate metabolite suppressed steroidogenesis in neonatal marmosets.

Due to the potential significance of the marmoset studies, the CHAP invited Richard Sharpe, the principal investigator of the Hallmark and McKinnell studies, to present his findings at the November 2011 CHAP meeting. Dr. Sharpe agreed with the CHAP that both studies were limited by the small numbers of animals used and the brief duration of exposure. Dr. Sharpe added that his studies were very preliminary and that it would be premature to use his studies' results to support public health decisions.

Given the limitations in primate studies, which include small number of animals and only one phthalate metabolite tested, staff considers the rat data to be the most robust data available at this time. Therefore, staff agrees with the conclusions of the CHAP that it would be premature to dismiss the data in multiple rodent species in favor of nonhuman primate data (CHAP 2014; pp. 17-18). Ultimately, staff maintains that the negative results in preliminary primate studies highlighted by commenters do not negate the growing body of positive studies in humans that parallel the results in rats (CHAP 2014; pp. 2, 27).

Comment 1.4: Fetal transplant (xenograft) studies. Some industry commenters cited studies (Heger *et al.* 2012; Mitchell *et al.* 2012), in which either rat fetal testes or human fetal testicular tissue were transplanted into rats or mice as evidence that MRDE either does not occur in humans or that humans are less sensitive than rats. The commenters noted that after exposing the host animals to phthalates, researchers examined the transplanted tissue for changes related to MRDE, such as expression of genes for steroid (testosterone) synthesis, or the presence of multinucleated gonocytes (MNGs). In these studies, the transplanted rat fetal testes responded similarly when exposed to phthalates as did rat testes *in vivo*, demonstrating that the transplanted rat fetal testes were functional. However, there was generally no effect on transplanted human fetal testicular tissue. The commenters concluded that humans are not susceptible to MRDE or, at least, that humans are less sensitive than rats.

One of these commenters noted that at the time of Dr. Boekelheide's and Dr. Sharpe's presentations to the CHAP (November 2011), they indicated that their xenograft studies were preliminary and it was premature to use them in making public health decisions. The commenter

claims, now that the research is published, that the studies are of more significance, and support the conclusion that the human fetal testis is similar to the mouse fetal testis in response to phthalates, and that both are "refractory to phthalate-induced inhibition of testosterone production." The commenter argued that this finding "highlights the need for further research but also calls into question the relevance of testosterone reduction in rats by phthalates for human health risk assessment." The same commenter also discussed review articles on species differences by Habert et al. (2014) and Johnson et al. (2012) as evidence that phthalate syndrome does not occur in humans or that humans are less sensitive than rats.

Response 1.4: The commenters cited two studies in which rat fetal testes or human fetal testicular tissue were transplanted (xenografted) into rats (Heger *et al.* 2012) or mice (Mitchell *et al.* 2012). These studies used novel methods that have not been used to support public health decisions. As discussed by the CHAP (CHAP 2014, pp. 16-17), these studies are subject to a number of limitations. Most of the human fetal tissue samples were obtained after the human window of maximum susceptibility to phthalates. This sampling time means that the tissues were less susceptible to MRDE induced by phthalates. In contrast, constant exposure to phthalates in the womb would always expose the fetal tissue to phthalates at their time of maximum sensitivity. Additionally, the studies compared intact rat fetal testes as a form of positive control, with human fetal testicular tissue. The usefulness of comparing fragmented human fetal testicular tissue with intact rat fetal testes has not been scientifically established. Furthermore, testosterone levels are highly variable in human tissue, making it difficult to compare controls with treated samples.

Due to the potential significance of the xenograft studies to the CHAP's analysis, the CHAP invited the principal investigators of the studies (Drs. Boekelheide and Sharpe) to present their findings at the November 2011 CHAP meeting. Both investigators agreed with the CHAP that it would be premature to use their results to support public health decisions, especially to dismiss the considerable body of data in rodent species and the growing number of epidemiological studies showing MRDE effects in humans that parallel the effects in animals.

Staff disagrees with the commenters' conclusion that the studies by Heger et al., and Mitchell et al., should not be considered preliminary now that they have been published. Staff concludes that publication of these studies does not mean that the scientific issues regarding xenograft studies have been resolved. The published studies contained no new data beyond what the authors presented to the CHAP. The methods used are still novel, and have not been used to support public health decisions. In addition, the significance of negative results from transplanted tissue is always difficult to assess.

Staff notes that in the review article by Habert et al. (2014), the authors expressed "concerns" about the use of rat models for human risk assessments of endocrine disruptors, and highlighted the need for additional research. The article was originally presented at the 7th Copenhagen Workshop on Endocrine Disrupters in May 2013. During the discussion at the meeting, which was documented in the review article, Dr. Habert observed that there was much greater variation in human tissue than in rodents, and that there are difficulties in obtaining and culturing human fetal tissue. He concluded that his studies do not rule out the possibility that phthalates may be active in humans, and that the rat model is still relevant for human risk assessment, at least for effects on gonocytes (e.g., MNGs). Thus, the commenter inaccurately represented Habert's research.

Staff notes that Johnson et al. is a review article that surveys and summarizes previously published studies, rather than reporting new facts or analyses. Johnson et al. (2012) acknowledged the preliminary nature and limitations of the xenograft studies by Heger et al. (2012) and Mitchell et al. (2012) and concludes that the response of human fetal testicular tissue was qualitatively more like the response seen in mice, rather than rats. Johnson et al. (2012) also highlighted data gaps in the understanding of MRDE, and noted the importance of considering epidemiological data along with xenograft data. Staff concludes that the studies by Heger et al., and Mitchell et al., are still preliminary in nature and subject to the limitations described above.

Staff concludes that the two xenograft studies with human fetal testicular tissue are essentially limited in scope, sample size, and conclusions, and have not been replicated by others. In their remarks to the CHAP, the authors of these studies said that they would not disregard the body of information from *in vivo* studies when making public health decisions. Furthermore, staff notes that *in vivo* animal studies are generally given greater weight in risk assessment (CPSC 1992; IARC 2002; NTP 2016). Staff also notes that there is a growing body of evidence in humans that shows associations between phthalate exposure and male reproductive endpoints that are consistent with the rat data. Therefore, staff concludes that the rat model remains the most appropriate choice for human risk assessment.

Comment 1.5: Newer information on xenograft models. One commenter noted that the CHAP did not have access to two additional studies that used human tissue (Habert et al. 2014; Spade et al. 2014) to support the conclusion that humans are less sensitive to phthalate effects than rodents. Specifically, the commenter stated that the Habert et al. (2014) study demonstrated that MEHP did not change testosterone levels in human fetal tissue obtained during the male programming window but decreased testosterone secretion in rat positive controls following *in vitro* exposure. They also noted that Spade et al. (2014) reported that the human xenograft model was sensitive enough to detect a reduction in testosterone. The commenter concluded that the positive results of these two studies addressed the CHAP's concerns that xenograft models were too variable to identify positive effects and that tissues were obtained outside of the male programming window. The commenter also concluded that these studies demonstrated the refractory nature of human tissue to phthalate-induced pathologies.

Response 1.5: Staff has reviewed the Habert review article (in comment response 1.4 above) and notes that the study author concluded that the studies "do not rule out possibility that phthalates may be active in humans, and that the rat model is still relevant for human risk assessment, at least for effects on gonocytes." Staff has also reviewed the Spade et al. (2014) study and noted a few inconsistencies that might affect conclusions (e.g., the use of serum testosterone versus testicular testosterone production, the use of absolute organ weights instead of relative organ weights for the seminal vesicles and anterior prostate). Staff acknowledges that the results of the paper do show a change in testosterone when treated by abiraterone and not DBP, but questions the relevance of the findings and lack of other findings for those reasons.

Staff further notes that a decrease in testosterone in one case and not another may also be related to the toxic pathways activated. Phthalate syndrome has multiple pathways operating, and a lack

of effect could be related to the lack of the pathway in the model or a true non-effect (e.g., through the CYP17A1 enzyme[8]).

Staff concludes that the two new studies (Habert et al., 2014 and Spade et al., 2014) do not clarify the issue of variability in human *ex vivo* system methods and results or conclusively demonstrate that humans are refractory to the MRDE effects of phthalates.

Comment 1.6: *In vitro* studies. Some industry commenters discussed studies (Desdoits-Lethimonier *et al.* 2012; Lambrot *et al.* 2009) in which human testicular tissue or cells were cultured *in vitro* and then exposed to phthalates. Commenters asserted that these studies raise questions about whether phthalate-induced testosterone reduction in rats is relevant to humans.

In one study, Lambrot et al. (2009) studied human fetal testicular tissue recovered during the first trimester (7–12 weeks) of gestation, when the fetus is believed to be most sensitive to the effects of phthalates. Lambrot et al., reported limited or no MRDE effects from *in vitro* exposure to MEHP, a DEHP metabolite, at the highest tested dose of 100 µM. The commenters asserted that this study showed that testosterone production in these *in vitro* fetal testes was unaffected by MEHP treatment or, in other words, that the human tissue was unresponsive to phthalates. The commenters acknowledged, however, that a major shortcoming of this study was the absence of a positive control (e.g., rat fetal testes).

One of the commenters also cited a study (Desdoits-Lethimonier *et al.* 2012) that examined the effects of DEHP and MEHP on human adult testicular tissue and a human cell line (NCI-H295R) that expresses steroidogenic enzymes. The authors found that DEHP and MEHP significantly inhibited testosterone production at concentrations of 10 µM and 100 µM, whereas no significant effect was observed at 1 µM. The authors found no effects on the other MRDE endpoints that were tested. The commenter asserted that that the antiandrogenic effects observed at 10 µM or higher are of questionable relevance because they are unlikely to be reached *in vivo*; thus, the commenter concluded that DEHP would not result in MRDE at levels to which humans would generally be exposed. The commenter noted that the experiments were conducted on adult, not fetal, testes. The commenter also acknowledged the lack of a positive control (e.g., rat fetal testes).

Response 1.6: Regarding the Lambrot et al. study cited by the commenters, staff agrees that MEHP exposure failed to reduce testosterone synthesis in human fetal testicular tissue or human cells, whereas MEHP exposure does reduce testosterone synthesis in rats. However, Lambrot et al. did report a reduction in anti-Mullerian hormone and a reduction in the number of germ cells, which are MRDE-related effects. Therefore, Lambrot et al., found that MEHP induced some of the effects associated with MRDE.

Regarding Desdoits-Lethimonier et al., one commenter asserted that the lowest concentration causing an effect in human adult testicular tissue, 10 µM, was too high to be experienced by humans.[9] However, the study authors, Desdoits-Lethimonier et al., noted that such levels have been found in men.

[8] CYP17A1 is an enzyme involved in the synthesis of testosterone, an important steroid in male development and reproduction. Some antiandrogenic compounds may act, at least in part, by inhibiting steroid synthesis.
[9] Micromolar (µM) is a concentration unit. One µM DEHP is equivalent to about 0.4 micrograms per milliliter (µg/mL).

Staff notes that *in vitro* studies are generally considered to be ancillary information that, alone, have limited value in risk assessment (CPSC 1992; IARC 2002; NTP 2016). Interpretation of *in vitro* studies is always difficult, because one can never be certain whether the *in vitro* culture conditions adequately capture *in vivo* conditions. The methods that Lambrot et al., and Desdoits-Lethimonier et al., used for culturing testicular tissue are novel and have not been validated for use by regulatory agencies. These studies are also subject to a number of limitations. In particular, as the commenters pointed out, there were no positive controls. Positive controls are necessary to determine if the differences between the study group and control group real or due to random variation.

Staff concludes that the *in vitro* studies with human fetal testicular tissue are still preliminary and are generally not sufficient, by themselves, to support public health decisions. *In vivo* animal studies are generally given greater weight in risk assessment (CPSC 1992; IARC 2002; NTP 2016). Staff also notes that there is a growing body of evidence in humans that show associations between phthalate exposure and MRDE endpoints that are consistent with the rat data (see comment response 7.1.) Therefore, staff concludes that the rat model remains the most appropriate choice for human risk assessment.

Comment 1.7: DES and finasteride. Some industry commenters asserted that studies, not cited by the CHAP, of chemicals with the same mode of action as phthalates show that humans are resistant to phthalates. The commenters cited a review article (Borgert *et al.* 2012), which noted humans are less sensitive to the antiandrogenic effect of DES and finasteride when compared to rats. The cited study concluded that basing conclusions and risk assessments using rat studies is overly conservative for any chemical, including phthalates.

Additionally, the commenters noted that the study by Yiee and Baskin (2010) concluded that no environmental exposure other than diethylstilbestrol (DES) induces testicular dysgenesis syndrome in humans.

Response 1.7: The CHAP assessed each phthalate based on the best available data for each individual chemical, and based its recommendations on those assessments, not by assuming that all phthalates will behave the same way as DES or finasteride. Staff notes that the DES and finasteride publication cited by commenters implies that humans are less sensitive than rats to these two chemicals. However, this assertion by the publication does not mean that all phthalates will produce similar biological effects as DES or finasteride because phthalates do not have a similar chemical structure, are not metabolized or detoxified in the same way, and will not have similar dose response curves to those of DES or finasteride. DES is a synthetic estrogen that binds to the estrogen receptor (Gray and Kelce 1996). Finasteride inhibits 5α-reductase (Gray et al. 1999). Phthalates do not bind to the estrogen receptor or inhibit 5α-reductase; they act by inhibiting testosterone synthesis and insl3 (see comment response 1.23 below). Phthalates indirectly inhibit testosterone synthesis by reducing expression of several genes, including StAR and Cyp11a. Therefore, for the reasons discussed above, the cited study on DES and finasteride does not predict the human response to phthalates.

Staff does not agree with the commenters' characterization of the study by Yiee and Baskin. Yiee and Baskin reviewed the literature on environmental factors that could affect genitourinary development. Their review included studies of male offspring exposed to DES *in utero*, of which one study found an effect and two did not. They did not draw any conclusions regarding any specific causes of TDS.

Comment 1.8: Interspecies uncertainty factor. Some industry commenters maintained that the CHAP's reliance on data in rats may overestimate the risk to human health because rats are more sensitive than humans. Commenters also claimed that humans may actually be nonresponsive to MRDE. Commenters recommended reducing the uncertainty factor (UF) that the CHAP applied to account for interspecies differences; the CHAP generally used a factor of 10. Commenters recommended that the interspecies uncertainty factor for these chemicals should be "0.1 (i.e., humans are 10x less sensitive than rodents) to 1 (humans are equally sensitive as rodents)." A commenter concluded that reducing the UF for interspecies differences would decrease all of the CHAP's 95th percentile Hazard Index values to less than one.

Response 1.8: Although humans are qualitatively similar to other animals with respect to health outcomes following exposures to chemicals, interspecies differences do exist (Pohl and Abadin 1995). An uncertainty factor is used in risk assessments to account for interspecies differences. Unless otherwise specified, the CHAP used a UF of 10. This is consistent with the general practice used in risk assessment to account for interspecies differences (Barnes and Dourson 1988; CPSC 1992; Dankovic et al. 2015; EPA 1991; Pohl and Abadin 1995). Humans are frequently more sensitive to reproductive and developmental effects than animals (EPA 1991), and human males are considered more vulnerable than other mammals (Klaassen 2001, p. 703). Risk assessors may use a UF value less than 10, if it is supported by quantitative data comparing animals and humans.

The commenters cited studies (Heger et al. 2012; Mitchell et al. 2012) in which human testicular tissue was transplanted into rats or mice as evidence that humans are less sensitive to the effects of phthalates than rats. As discussed above (comment response 1.4), these are preliminary studies and are subject to a number of limitations. Staff does not consider these studies to provide sufficient support for reducing the interspecies UF. Furthermore, a UF of 1 is only used in cases where the dose response assessment is based on human data (PEAA values in the CHAP's assessment). Therefore, staff disagrees with the commenters' recommendation to use a UF of 1 or lower for animal to human extrapolation.

Comment 1.9: Uncertainty factor for sensitive populations. Some industry commenters argued that the intraspecies UF of 10 used by the CHAP is overly conservative because the PEAAs are already based on a sensitive population. Commenters stated that the intraspecies UF is intended to account for variations in sensitivity among humans, as well as to protect sensitive populations. The commenters cited a report by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC 2003), which was based on analyses of human data by Hattis et al. (1999) and Renwick and Lazarus (1998). ECETOC recommended a default intraspecies factor of 5 for the general population because a factor of 5 accounts for approximately 99 percent of the variation in the human population. The commenters concluded that a reduced intraspecies factor is warranted and that such a change would reduce the Hazard Index value.

Another commenter asserted that "if there are no differences in exposure or risk between the general population and the sensitive sub-population, there is no need for additional protection and the use of an uncertainty factor to account for sensitive populations in the derivation of the POD is not warranted."

Response 1.9: Similar to the risk assessment practice of using a UF to account for interspecies differences, a UF of 10 generally is used to account for intraspecies differences (i.e., human

variability) in responses to toxic chemicals (Dankovic et al. 2015). In this case, the intraspecies UF accounts for the differences between individuals within the fetal and infant population. Staff acknowledges that in deriving PEAAs, the CHAP applied an intraspecies UF of 10 to account for differences in sensitivity among individuals (CHAP 2014; pp. 63-66). Staff still expects that the population of infants and fetuses will have a broad range of sensitivity, because, as reviewed by Pohl and Abadin (1995), age, sex, genetic composition, nutritional status, and preexisting diseases may all alter susceptibility to toxic chemicals.

Staff notes that the recommended UF of 5 by ECETOC (ECETOC 2003) was derived primarily from data on healthy adults. As such, staff notes that the ECETOC recommendation did not consider the population of concern (fetuses and infants), and therefore may not adequately account for all the sensitivities and susceptibilities of this target population.

Staff notes that multiple federal agencies use an intraspecies UF of 10 (Barnes and Dourson 1988; CPSC 1992; Dankovic et al. 2015; EPA 1991). Furthermore, to protect sensitive groups such as children, some federal agencies consider an additional UF beyond the interspecies and intraspecies UFs (EPA 2002a). The CHAP used only the interspecies UF and intraspecies UF in their analyses. The CHAP did not apply an additional UF to protect infants.

Comment 1.10: Liver toxicity is the more sensitive endpoint for DINP. One industry commenter stated that it was unclear why the CHAP did not use liver toxicity as the critical endpoint for DINP because liver toxicity has a lower point of departure (POD) than antiandrogenicity. The commenter contends that if liver toxicity were used as the endpoint for DINP, then the MOE would be well above the 100–1000 range considered adequate for public health, which would not support the CHAP recommendation to permanently prohibit children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DINP.

Response 1.10: The CHAP considered both liver toxicity and MRDE endpoints for assessing the risks of DINP. Staff notes that the CHAP provided very clear rationale for choosing MRDE instead of liver toxicity as the endpoint for the CRA. After reviewing all health effects associated with phthalates, the CHAP selected MRDE as the critical effect for cumulative risk assessment because MRDE is the most sensitive and most extensively studied endpoint common to the phthalates considered in the CRA (CHAP 2014; pp. 13-15). The CHAP noted that there are studies demonstrating that the effects of multiple phthalates on MRDE are additive (Howdeshell et al. 2007, 2008, 2016). Performing a CRA on liver toxicity, for example, would require the CHAP to assume that liver effects are additive. The CHAP also noted that the MRDE endpoint is consistent with the conclusion of the National Academy of Sciences (NAS) report on phthalates cumulative risk assessment that MRDE (phthalate syndrome) is the most appropriate endpoint for a phthalates CRA (NRC 2008).

Staff agrees that liver is the most sensitive endpoint for DINP. However, when performing a CRA, it is necessary to consider health endpoints that are common to the different chemicals used in the CRA (ATSDR 2004). However, in assessing the effects of DINP in isolation, the CHAP considered both MRDE (phthalate syndrome) effects as well as chronic liver toxicity (CHAP 2014, p. 99). Staff concludes that including DINP in the CRA using MRDE as the endpoint was appropriate, because using an endpoint in common with the other antiandrogenic phthalates was necessary to determine the health effect on the fetus, which is the most susceptible population.

Selection of Target Populations

Based on animal studies, the CHAP assumed that the human fetus was the most sensitive human population with respect to MRDE, followed by infants, children, and adults (CHAP 2014; pp. 12-14). The CHAP derived toxicological values (i.e., PEAAs) for MRDE from animal studies in which pregnant animals were fed phthalates; thus the fetus was the target population. A toxicological value that protects the most sensitive population (the fetus) will also protect infants, children, and adults. The CHAP assessed exposure and risks for pregnant women (as a surrogate for the fetus) and infants, in part because these are the most sensitive populations, and also to satisfy the CPSIA's charge to "examine the likely levels of children's, pregnant women's, and others' exposure to phthalates . . ." CPSIA §108 (b)(2)(B)(iii).

Comment 1.11: Target population. Industry commenters questioned the basis of the proposed prohibition of children's toys and child care articles containing phthalates given that a reduction in exposure to infants from children's products "would not impact the degree of cumulative risk of phthalate syndrome" because the human fetus is at risk, not the human infant because, according to the commenters, infants are not in a period of reproductive tract development. Thus, commenters asserted, the relevant population is pregnant women or women of reproductive age as a surrogate for pregnant women. Yet, commenters noted, the CHAP's analysis shows that exposures of women to DINP from children's toys and childcare articles is negligible. Commenters also pointed out that the CHAP's risk assessment was based on fetal development. One industry commenter noted that using POD based on fetal exposures to protect infants and neonates adds an additional degree of conservatism to the CHAP's risk estimates.

Response 1.11: The CHAP's risk assessment and recommendations were intended to protect infants and toddlers as well as the fetus. By applying PEAAs based on fetal exposure (the most sensitive group) to other sensitive groups (i.e., infants, toddlers, and children), the CHAP ensured the protection of all the susceptible populations.

Although fetuses are considered to be the most sensitive population, based on data from animal studies, the CHAP recognized that other populations such as infants, toddlers, and children also are susceptible to the effects of phthalates (CHAP 2014, p. 14; Foster 2006). Testosterone production and other processes involved in reproduction remain critical throughout male development in animals and humans from the prenatal period through puberty. Testosterone production is required throughout a male's lifetime to maintain the ability to reproduce (Foster 2006). As such, staff disagrees that infants are not at risk from phthalate exposure. Thus, the CHAP and staff focused on the fetus and infant as the life cycle stages of major interest.

The CHAP's toxicity assessment and derivation of potency estimates is based on consideration of fetal exposure because the fetus is the most sensitive population. CPSC, like other federal agencies, uses the most sensitive and appropriate human target population in risk assessments. Hazards associated with this target population are typically extrapolated to other less sensitive target populations to be conservative and ensure that the entire population is covered. In the case of phthalates, sensitive fetal hazard endpoints were extrapolated to other populations.

The practice of selecting the most protective endpoints and potency estimates (i.e., PODs) based on the best available studies is consistent with the statutory mandate to provide a reasonable certainty of no harm with an adequate margin of safety. Using the lowest POD also is consistent with CPSC Chronic Hazard Guidelines (CPSC 1992), and other federal agency practices (Barnes and Dourson 1988; CPSC 1992; EPA 1991).

Comment 1.12: Prohibiting children's toys and child care products that contain phthalates when population of greatest concern is pregnant women and WORA. One commenter noted that focusing on children's toys and child care articles is important, even though pregnant women might not be exposed to phthalates directly from the toys and children care articles. The commenter indicated that toys and child care articles can contribute to household dust, which can be a source of very high levels of phthalates. The commenter also indicated that focusing on toys and child care articles is not enough to protect at-risk populations, given that there are other sources of exposure to phthalates and that CPSC should work with other federal agencies to fill data gaps ensure that the uses of phthalates are safe.

Response 1.12: Staff agrees that the proposal to permanently prohibit toys and child care articles containing more than 0.1 percent of DINP and four additional phthalates would not directly reduce risks to pregnant women and WORA. However, as stated above in comment response 1.11, other sensitive groups (i.e., infants, toddlers, and children who are more likely to be exposed through contact with toys and child care articles) are also considered in the staff's analysis and recommendations. CPSC staff agrees that it is important to work with other federal agencies that have authority over products that are outside of CPSC's jurisdiction but that also contribute to the cumulative exposure to phthalates.

Comment 1.13: Exposure duration and effect. Two industry commenters expressed the opinion that the antiandrogenic effects seen in animal studies require several days of phthalate exposure (i.e., chronic exposures over time are required to induce MRDE). However, the commenters noted that CHAP relied heavily on upper percentile exposures from HBM data, which used single spot urine samples. Using upper percentile exposures (i.e., 95th percentile spot urine estimates) from HBM data means that the day-to-day variability in urinary concentration of most phthalates (in particular DEHP) for the same individual is large; this results in an overestimation of risk because upper exposure percentiles are not likely a valid measure of long-term average concentrations for individuals. One commenter concluded that long-term average individual or general population exposure levels were better represented by central tendency, rather than by upper percentile measurements. Yet, the commenter noted, the CHAP relied heavily on HI values at percentiles greater than the 95th percentile.

Response 1.13: Staff notes that longer-term exposures, as measured by average daily exposure during longitudinal studies, are not necessarily required to cause MRDE. Numerous studies in animals have demonstrated that MRDE and related effects can occur after one or a few doses (Carruthers and Foster 2005; Creasy et al. 1987; Ferrara et al. 2006; Gray et al. 1999; Hannas et al. 2011; Jobling et al. 2011; Jones et al. 1993; Li et al. 2000; Parks et al. 2000; Saillenfait et al. 1998; Saitoh et al. 1997; Spade et al. 2015; Thompson et al. 2004; Thompson et al. 2005).

Thus, either a long-term exposure or shorter-term elevated exposure could be related to adverse health outcomes in the fetus, if the exposure occurs during the window of susceptibility. Staff concludes that NHANES data indicate that measurable metabolites in the participants' urine suggest that WORA can be exposed to antiandrogenic phthalates during the window of fetal susceptibility. Staff also concludes that calculating HIs for the highest exposed individuals is necessary to assure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals, and their offspring.

Although human phthalate exposures may vary from day-to-day or during the course of a day, humans are exposed to phthalates every day. NHANES data demonstrate that all WORA are

exposed to antiandrogenic phthalates because all of the participants had measurable phthalate metabolites in their urine, and the participants were randomly sampled across the study cycle. The 95th percentile from the distribution of estimated HIs in WORA demonstrate risk from phthalate exposure.

Antiandrogenicity (MRDE) and DINP

This section addresses comments that question whether DINP is antiandrogenic, that is, whether it causes MRDE. Commenters asserted that DINP does not fit the pattern of "rat phthalate syndrome" demonstrated by other phthalates (DBP, BBP, DEHP, and DIBP). As detailed below, the commenters reviewed studies concerning various aspects of "rat phthalate syndrome" (such as decreased fetal testosterone levels, changes in anogenital distance, nipple retention, male reproductive tract malformations, decreased sperm production) and concluded that the studies demonstrate that DINP does not induce "rat phthalate syndrome."

Comment 1.14: DINP is not antiandrogenic. Some industry commenters claimed that DINP is not antiandrogenic, and that it does not cause MRDE. Commenters stated that if DINP does not cause MRDE, then it would be inappropriate to include it in the CRA. In contrast, one NGO commenter supported the inclusion of DINP in the CRA because DINP is antiandrogenic. Some commenters referred to Table A-9, *Summary of animal male developmental toxicology*, of the CHAP report, which shows either no effect or decreased testis weights, as evidence that DINP is not antiandrogenic. Commenters discussed specific issues on antiandrogenicity in detail. Those issues are addressed individually below.

Response 1.14: Staff disagrees with the commenters' claims that DINP-induced effects are not consistent with phthalate syndrome in rats. Clewell et al., found changes in testosterone, nipple retention, and AGD, among other observations, by multiple laboratories, which indicate that DINP exposure is associated with outcomes similar to the effects of other phthalates, such as DEHP and DBP, that cause MRDE; these findings support the conclusion that DINP causes phthalate syndrome (CHAP 2014; pp. 97-98). Staff's conclusion is based on consideration of the weight of the evidence from multiple studies, including the studies by Clewell et al. (Adamsson et al. 2009; Boberg et al. 2011; Clewell et al. 2013a; 2013b; Gray et al. 2000; Hannas et al. 2012; 2011; Howdeshell et al. 2016; Lee et al. 2006b; Masutomi et al. 2003). See comment responses 1.15 to 1.20 for discussions of these studies. Furthermore, studies by Hannas et al. and Howdeshell et al. (Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008) indicate that the effects of DINP and other phthalates are additive.

Staff's conclusions are also consistent with findings from a recent NAS systematic review of the DINP scientific literature (NAS, 2017). In that review study, the authors asserted with high confidence that DINP could be considered a "presumed human hazard" because of its potential to reduce testosterone in male fetal rats. A reduction in fetal testosterone is consistent with one of the adverse health effects observed in phthalate syndrome. Furthermore, the commenters cited Table A-9 of the CHAP report as evidence that DINP is not antiandrogenic because not all phthalate syndrome effects were observed in each study. Phthalate syndrome is, by definition, a group of signs or symptoms that, when considered together, characterize a disease. When rats are exposed perinatally (the period ranging from late gestation to early postnatal life and lactation), male offspring exhibit a set of effects that includes reduced testosterone synthesis, reduced anogenital distance (AGD), nipple retention (normally does not occur in male rats), undescended testes, testicular atrophy, testicular histopathology, multi-nuclear gonocytes (MNGs), reduced

production of insulin-like hormone 3 (insl3), underdeveloped gubernacular cords, and genital malformations (hypospadias) (Foster 2006; Foster et al. 2001; Howdeshell et al. 2016; Howdeshell et al. 2008). Although not all effects are always observed in the same animal or even in the same study, the large body of studies associated with phthalate exposure shows the same set of symptoms (Howdeshell et al. 2016). While the commenter cited Table A-9 of the CHAP report (a summary for multiple phthalates), staff notes that Table A-4 is specific for DINP, and identifies additional phthalate syndrome-related effects of DINP.

In summary, staff concludes that although DINP is less potent than other antiandrogenic phthalates, DINP can contribute to the cumulative risk from other phthalates. Therefore, the inclusion of DINP in the CRA is appropriate. Staff notes that DINP has similar effects as other antiandrogenic phthalates, and thus is considered antiandrogenic in the context of the CRA. Staff notes that similar findings of changes in testosterone production and nipple retention, among other observations, following exposure to DINP, which were reported by multiple laboratories, provides a body of evidence that supports the conclusion that DINP is antiandrogenic. Staff concludes that because DINP causes phthalate syndrome, it was appropriate to include DINP in the CHAP's CRA.

Comment 1.15: DINP produces inconsistent effects on testosterone production. In support of the assertion that DINP does not induce rat phthalate syndrome, some industry commenters discussed the potential for DINP to induce changes in plasma or testicular testosterone production or content. They noted that two studies (Boberg et al. 2011; Borch et al. 2004) reported effects on testosterone at either a single dose or in the mid-dose group. Two other studies (Clewell et al. 2013a; 2013b)[10] reported a dose-related decrease in testosterone two hours after dosing, but not at 24 hours, and testosterone changes in adulthood following in utero exposure. Four studies (Adamsson et al. 2009; Gray et al. 2000; Lee et al. 2006a; Lee et al. 2006b) reported no testosterone changes related to DINP exposure. The commenters noted that in some of the studies that, in the testes, testosterone content and/or production was reduced during gestation (Boberg et al. 2011; Borch et al. 2004; Clewell et al. 2013a), but not reduced in other studies (Adamsson et al. 2009). The commenters stated that Boberg et al. and Clewell et al. found no effect of DINP on testicular testosterone levels postnatally (Boberg et al. 2011; Clewell et al. 2013b).

The commenters concluded that the studies show that reductions in testosterone levels are not consistently observed following DINP exposure, therefore DINP does not induce rat phthalate syndrome, and should not be included in the CRA.

Response 1.15: Staff agrees with the commenters' assertion that some studies involving repeated measurements over time have not shown permanent or persistent changes in testosterone (e.g., Clewell et al. 2013a; 2013b). Staff notes that at least some of the apparent inconsistencies are due to differences in study design, such as exposure timing and measurement timing. However, permanent or persistent changes in testosterone are not required to have an adverse impact on male reproductive development; rather, transient reductions in the rate of testosterone synthesis at the critical period of development do have permanent effects (e.g., structural, functional) on

[10] Some commenters cite Clewell et al., 2012a and 2012b, which are pre-publication versions of the two studies by Clewell et al., which were available online. Clewell et al., 2013a and 2013b are the final print versions, as cited in this document and in the CHAP report.

male reproductive organs (Hannas et al. 2011). Furthermore, staff agrees with the study by Hannas et al., showing that the rate of testosterone synthesis, rather than plasma or testicular levels, is the most relevant measure of phthalate-induced effects on testosterone (Hannas et al. 2011). Finally, staff notes that testosterone measurements made after dosing lab animals with DINP has ended, do not account for the possible effects of ongoing exposure, as could be expected for humans with exposures occurring after birth from food, water, or contact with consumer products.

Staff also notes that other studies cited by the commenters (Boberg et al. 2011; Borch et al. 2004; Clewell et al. 2013a; 2013b) also show DINP-associated reductions in testosterone. Staff concludes that the weight of evidence of all the studies shows that reductions in testosterone levels occur following DINP exposure. Therefore DINP does induce rat phthalate syndrome, and should be included in the CRA.

Staff's conclusions are consistent with findings from a recent NAS systematic review of the DINP scientific literature (NAS, 2017). In that review study, the authors asserted with high confidence that DINP could be considered a "presumed human hazard" because of its potential to reduce testosterone in male fetal rats.

Comment 1.16. Anogenital distance. Supporting their assertion that DINP does not induce rat phthalate syndrome, several commenters cited studies reporting effects of phthalate exposure on anogenital distance (AGD). Two studies, one by Gray et al. and one by Masutomi et al. (2003), found no changes in anogenital distance (AGD) following dosing with DINP at 750 mg/kg/day (Gray *et al.* 2000), or at about 2500 mg/kg/day (Masutomi *et al.* 2003). A study by Boberg et al. (2011) reported a small (6 percent), but statistically significant, decrease in AGD on PND 13 following exposure to a 900 mg/kg-day DINP; no effect was observed on PND 90. A study by Clewell et al. (2013b) observed a statistically significant decrease in AGD following exposure to 750 mg/kg-day on PND 14, but not on PND 2 or 49. One commenter concluded that the difference in AGD on PND 14 could be attributed to pup size, and not an antiandrogenic effect. This commenter also considered a study by Lee et al. (2006b) that observed a significant decrease in AGD at all doses on PND 1 to be suspect because of the very small differences between the treated and control groups. This commenter concluded that small reductions in AGD (e.g., 2 to 3 percent) should not be considered adverse health effects.

Response 1.16: Staff notes that the AGD reductions observed by Boberg et al. (2011) (see Boberg et al. 2011, Table 3, showing a 5 to 7 percent change at PND 13 from dosing at 900 mg/kg-day) and Clewell et al. (2013b) (Clewell et al. 2013b, Table 2, showing a 7 to 16 percent change at PND 14 from dosing at approximately 750 mg/kg-day) are larger than the magnitude considered by the commenter as unlikely to be biologically significant.

Although the study results cited by the commenters appear inconsistent, staff notes that at least some of the apparent inconsistencies are due to differences in study design, (e.g., exposure timing and measurement timing.) and reporting (e.g., normalized or unnormalized AGD).

Reduced AGD is one of many effects associated with phthalate syndrome. Overall, the weight of evidence in studies cited by the commenter demonstrates that DINP causes permanent effects on male reproduction, including testicular pathology changes and reproductive function. Thus, the commenter's contention regarding a transient nature of DINP's effects on AGD conflicts with the body of evidence that DINP leads to phthalate syndrome. Furthermore, the animal studies,

which involve short term exposures, do not reflect the continuous exposures that occur in humans.

Comment 1.17: Nipple retention. Additionally supporting their assertion that DINP does not induce rat phthalate syndrome, several commenters discussed studies that reported nipple retention as an endpoint potentially related to phthalate administration. One commenter specifically questioned the "biological and/or toxicological significance of nipple retention observed in early postnatal male rats." This commenter noted that unlike rats, human males do not lose their nipples, which significantly challenges the relevance of this endpoint for use in human hazard assessment or by extension to cumulative risk assessment.

Commenters addressed three studies reporting nipple or areola observations. The commenters noted that Boberg et al. (2011) reported a significant increase in nipples in male rats exposed to DINP compared to controls on PND 13, but concluded that because the study found no difference in this endpoint on PND 90, and concluded that the utility of this endpoint for hazard assessment is questionable.

Commenters also questioned the results of the study by Gray et al. (2000). A commenter noted that the reported observation of permanent nipples (i.e., nipple retention) was only statistically significant when the permanent nipples were considered collectively with two other malformations, while the nipple retention endpoint on its own was not statistically significant. This commenter also stated that differences in reported incidence of areola retention in control animals in later studies in the same laboratory confound interpretation of the results of the earlier study.

Finally, commenters noted that Clewell et al. (2013b) reported no significant difference in nipples in male rats exposed to DINP.

Response 1.17: The CHAP specifically discussed nipple retention as a relevant endpoint for antiandrogenic activity, and concluded that nipple retention in male animals is consistent with phthalate-induced reductions in testosterone levels (CHAP 2014, p. 16; Appendix A-2). Staff notes that nipple retention is sensitive to exposure of the developing animal during key windows of susceptibility.

Furthermore, the studies cited by the commenters that indicate the dosing ends during gestation or within the early part of the postnatal period do not consider possible effects of ongoing exposure, as could be expected for humans with exposures occurring after birth, but within early life periods of vulnerability from food, water, or contact with consumer products. Additionally, Staff notes that phthalate exposure induces a continuum of adverse effects that do not have the same degree of severity, and that some of these adverse effects may precede or promote the development of others. DINP-induced nipple retention in animals is only one indicator of the antiandrogenic developmental effects of DINP. Phthalate syndrome is a spectrum of effects (Howdeshell *et al.* 2016) and thus one does not expect to observe all phthalate syndrome effects in all studies. Staff notes that while nipple retention in animals may not correspond to a specific endpoint in humans, nipple retention in animals is an indication of antiandrogenic effects, which could manifest in different ways in humans. Therefore, staff concludes that DINP-induced nipple retention is an appropriate antiandrogenic endpoint that supports including DINP in the CRA.

Comment 1.18: Reproductive tract malformations. Several commenters stated that DINP should not be included in the CRA because DINP does not induce the spectrum of effects

characteristic of the rat phthalate syndrome. Commenters noted that a number of animal studies involving DINP have not reported male reproductive tract malformations (RTM), such as cryptorchidism or hypospadias (Adamsson et al. 2009; Boberg et al. 2011; Borch et al. 2004; Gray et al. 2000; Hellwig et al. 1997; Hushka et al. 2001; Lee and Koo 2007; Lee et al. 2006a; Lee et al. 2006b; Masutomi et al. 2003; Masutomi et al. 2004; Waterman et al. 1999; Waterman et al. 2000; Won Han et al. 2009).

Several commenters focused on Gray et al. (2000), which reported that perinatal exposure to DINP induced non-dose-related malformations in 4 of 52 adult animals. Commenters noted that only by pooling all effects (a fluid filled testis; paired testicular and epididymal atrophy; bilateral testicular atrophy; and a unilateral epididymal agenesis with hypospermatogenesis and a fluid filled testis devoid of spermatids), were the results statistically significant. Commenters concluded that the significance of the changes and the statistical manipulations, including pooling the incidents, was unclear and questionable. Commenters also pointed out that the pooled incidence of DINP effects was 7.7 percent in treated animals, while the incidence was 82 percent in DEHP treated animals.

One of these commenters emphasized that general RTMs based on decreased weights of androgen sensitive tissues (levator ani/bulbocavernosus muscles, seminal vesicles, ventral prostrate, glans penis, bulbourethral gland, and epididymis) were not observed in DINP treated animals (Adamsson et al., 2009; Boberg et al., 2011; Gray et al., 2000; Clewell et al., 2013b).

Furthermore, the same commenter concluded that the positive results reported in (Lee and Koo 2007) should not be considered valid because the study does not meet OECD and EPA criteria for positive results, due to inconsistent and non-dose-related effects on androgen sensitive tissue weights (decrease in seminal vesicle weight in all dose groups, decrease in levator ani/bulbocavernosus muscle weight only in the high-dose group).

Finally, the commenter cited Clewell et al. (2013b) and noted that no evidence of rat phthalate syndrome on PND 49 following DINP administration.

Response 1.18: Staff recognizes that the same specific male reproductive tract malformations have not been consistently observed following DINP exposure. Phthalate syndrome is a spectrum of effects (Howdeshell *et al.* 2016) and thus one does not expect to observe all phthalate syndrome effects in all studies. Staff further notes that the CHAP discussed the dose-related effects of the evaluated phthalates, as well as the differences in toxicity and potency among the phthalates. Specifically in regard to observations of reproductive tract malformations, the CHAP wrote: “[t]he highest incidence of reproductive tract malformations is observed at higher phthalate dose levels whereas, changes in AGD and nipple/areolae retention are frequently observed at lower phthalate dose levels” (CHAP 2014, p. 2). Therefore, the observation of effects depends on the dose level used in each study.

Furthermore, staff notes, as discussed by (Foster et al. 2002; Foster and McIntyre 2002; Gray et al. 2000), that the three studies described by the commenter as “definitive” studies (Hellwig et al., Hushka et al., and Waterman et al.) were not designed or intended to detect phthalate syndrome effects. In fact, one of the “definitive” studies (Hushka et al.) was on DIDP, which does not cause phthalate syndrome. As such, these studies are not relevant to the consideration of DINP’s ability to cause phthalate syndrome.

Staff disagrees that the pooled results of Gray et al. (2000) are inconsistent with the credible interpretation of developmental studies. Gray et al. (2000) display pooled DINP-induced RTMs on an individual basis and on a per litter basis. Both reported results demonstrated that DINP induced a statistically significant increase in RTMs. Reporting pooled malformations and variations on a per litter basis is consistent with EPA Guidelines (EPA 1991).

Staff believes that the study of Lee and Koo (2007) is of questionable relevance for determining the spectrum of effects induced by DINP. The study used juvenile castrated male rats dosed with phthalates to determine effects. In contrast, studies designed to detect phthalate syndrome involve prenatal exposure to pregnant animals.

Staff acknowledges that the Clewell study demonstrates that DINP induces limited or no phthalate syndrome effects following dietary dosing to rats. In spite of this, the authors themselves conclude that DINP has less potency than DEHP or DBP, but more than DEP when considering effects on the male reproductive tract. They additionally state "DINP is simply less potent than DBP and DEHP, i.e., it has lower potency in causing any adverse responses". Staff also notes that this study involved oral dosing via feed, which is different than oral dosing using a tube inserted into the stomach (gavage dosing), which is used in typical developmental toxicity studies for determining phthalate syndrome effects. Different dosing strategies may account for the lack of effects seen in the Clewell study.

Comment 1.19: Effects on sperm. Several commenters asserted that there is no strong evidence that DINP adversely affects sperm production or quality. They discussed a number of studies regarding DINP effects on sperm parameters, male mating behavior, and fertility. Commenters noted that Boberg et al. (Boberg et al. 2011) reported a small but significant increase in sperm counts on PND 90 in offspring from dams exposed to 900 mg/kg/day DINP between GD 7 and PND 17, although one commenter noted that the study authors concluded that DINP may not affect testicular sperm production. One commenter also cited Kwack et al. (2009), which reported reduced sperm counts in adult males exposed to 500 mg/kg-day DINP for 4 weeks beginning at PND 28, but no other sperm effects (quality or motility). This commenter discounted the reduced sperm count findings, given the normal sperm quality and motility in Kwack et al. (2009).

Commenters further discounted the effects of DINP by noting other studies that showed no effects on development and fertility, including no effect on the age of preputial separation in male rats (Clewell et al. 2013b; Gray et al. 2000; Masutomi et al. 2003), and no effect on mating behavior in postnatal week 20 animals (Lee et al. 2006a; Lee et al. 2006b). One commenter cited the "definitive" two-generation studies showing no effect on male fertility (Hushka et al. 2001;Waterman et al. 1999; Waterman et al. 2000). This commenter concluded that there is no strong evidence DINP adversely affects sperm production or morphology and should not be included in the CRA.

Response 1.19: Staff notes that the three studies described by a commenter as "definitive" studies—Hellwig et al., Hushka et al., and Waterman et al.— were not designed or intended to detect phthalate syndrome effects, as discussed by Gray et al. (2000), Foster and McIntyre (2002), and Foster et al. (2002). In fact, one of the "definitive" studies—Hushka et al.— was on DIDP, which does not cause phthalate syndrome.

Staff notes that inconsistent findings for sperm effects could be due to study parameters, such as timing of exposure or dose-selection, or may be a function of the lower potency of DINP

compared to other phthalates that have more consistent effects on sperm and fertility. Finally, as noted, phthalate syndrome is a spectrum of effects (Howdeshell *et al.* 2016) and thus one does not expect to observe all phthalate syndrome effects in all studies.

Comment 1.20: Multi-nucleated Gonocytes (MNGs). Several commenters disagreed with the CHAP's use of MNG as a phthalate syndrome endpoint, and asserted that MNG formation is not a consequence of reduced testosterone synthesis (an effect of phthalate exposure). Commenters indicated that mice produce MNGs after phthalate exposure, but do not show the same antiandrogenic effects as rats. Commenters cited the studies Scott et al. (2007), which indicated that MNG induction was mechanistically separated from intratesticular testosterone reduction, and Johnson et al., (2012), which concluded that MNG induction is not considered an adverse effect, because the MNGs are eliminated from the testis within a few weeks after birth.

Response 1.20: Although MNG formation is not directly linked to changes in testosterone production, and not necessarily a direct antiandrogenic effect of phthalate exposure, MNGs are a characteristic effect routinely observed after dosing with phthalates (Spade et al. 2015). Therefore, the observation of MNGs formed after DINP exposure is consistent with the occurrence of MNGs associated with exposure to other active phthalates, such as DBP, and is a marker of phthalates' effects in the developing male reproductive system. While MNGs might not be an adverse effect, finding MNGs following DINP exposure supports that DINP has a biological effect similar to the other active phthalates. Furthermore, it has been suggested that the presence of MNGs may be linked to reduced fertility or testicular germ cell cancer in humans (Ferrara et al. 2006).

Mode or Mechanism of Action

The "mode of action" (MOA) is a description of the key cellular and molecular events by which a chemical exerts its effects on organisms. The "mechanism of action" is a more-detailed description of how a chemical alters normal cellular biochemistry and physiology, especially the chemical's interactions s with receptors. Knowledge of the mechanism/mode of action can inform risk assessments in several ways, such as to inform the selection of dose response models in a cancer risk assessment (CPSC 1992; Klaunig et al. 2003), as support for performing a CRA (ATSDR 2004), or to assess human relevance of a particular mode or mechanism of action (Cohen et al. 2003).

Public comments address mode/mechanism of action in several contexts. (See comment/response 2.4 on CRA). Commenters used both terms to describe how phthalates exert their effects on reproductive development.

Comment 1.21: MRDE mechanism of action not well understood. Some industry commenters concluded that the mode/mechanism of action for MRDE is not well understood, and that multiple modes/mechanisms of action may exist. Some commenters argued that DINP should not be included in the CRA because it has a different mechanism of action. The commenters state that grouping multiple endpoints into a CRA results in "a highly conservative, potentially speculative, assessment."

One industry commenter noted that the CHAP provided "a thorough review of… studies of phthalate mechanisms." The commenter then noted that the reviewed studies only provide a superficial assessment of study quality limited to number of animals used, number of dose groups, and routes of administration. If the relevant mechanism of action is androgen

suppression, then diets rich in phytoestrogens may confound the results and bias the results toward showing greater effect. If this was the case, then the high MOEs for phthalates show that the risks to humans are low.

Response 1.21: As noted above, knowledge of the MOA or mechanism of action can be informative to the risk assessment process. However, a detailed understanding of the mode/mechanism of action is never required to perform a risk assessment (e.g., the CHAP CRA), as noted in the CPSC Chronic Hazards Guideline (CPSC 1992; EPA 1991; EPA 2005; IARC 2002; NTP 2016). By applying the criteria in the CPSC Chronic Hazard Guidelines, staff concludes that there is sufficient evidence from animal studies that phthalates cause adverse effects in animals and that phthalates are probably toxic to humans. That evidence alone is sufficient justification to perform a risk assessment and, where appropriate, to support a risk management decision (CPSC 1992).

Staff agrees with the CHAP (CHAP 2014, p. 14) and other authors (Howdeshell et al. 2016; NRC 2008) that concluded that much is known about the mechanism of action for phthalate syndrome. However, while much is known, this does not mean everything about the mechanism of action for phthalates is known. As the commenters note, the specific molecular receptor to which phthalates presumably bind, leading to phthalate syndrome has not been identified. However, because the adverse health effects of phthalates are well established, it is scientifically unnecessary to wait for a full understanding of the mechanism of action before proceeding with the current rulemaking process, as required by the CPSIA. Further discussion of the relevance of the mechanism of action to the CRA may be found in comment response 2.4.

Comment 1.22: Need for a common mechanism of action. Some industry commenters stated that all chemicals considered in the CRA should have the same mechanism of action or "pattern of effects."

Response 1.22: This comment is addressed in more detail in comment response 2.4 regarding the CRA. Based on the ATSDR guidelines (ATSDR 2004), the strongest justification for performing a CRA are scientific data demonstrating that mixtures of the chemicals of interest act in concert, such as in an additive fashion. In the absence of mixtures studies, performing a CRA may be justified if the chemicals of interest act by a common mechanism of action or act on the same target organ. Because mixtures studies (Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008) demonstrating the additive effects of phthalates are available, establishing a common mechanism of action is not necessary. There are examples (see comment response 2.4) of other chemicals that do not share a common mechanism, but still have additive effects in mixtures (Howdeshell et al. 2016). Therefore, a common mechanism of action is not needed to conduct a CRA with multiple chemicals.

Comment 1.23: Lack of a common mechanism of action. Some industry commenters claimed that there is a lack of evidence that the phthalates in the CHAP's CRA share a common MOA or mechanism of action.

Response 1.23: As noted above (comment response 1.22), a common mechanism of action is not required to perform a CRA. Nonetheless, the CPSC staff considers that the phthalates in the CRA do share a common mechanism. This comment is addressed in more detail in comment response 2.4.

The commenters claim that the phthalates in the CHAP's CRA do not share a common mechanism of action, because they cause a different "pattern of effects." The mechanism of action for phthalate syndrome was discussed by the National Academy of Sciences (NRC 2008; pp. 48-55), and others (Foster 2005; Howdeshell et al. 2016; Howdeshell et al. 2008). Several studies have shown that the phthalates act by inhibiting testosterone production in the testis during any critical period in development (Foster et al. 2001; Gray et al. 2000; Mylchreest et al. 1998; Parks et al. 2000) by decreasing expression of genes involved in steroid synthesis, including StAR and Cyp11a. As reported byFoster (2005), Howdeshell et al. (2016), NRC (2008), and Wilson et al. (2004), reduced expression of insulin-like hormone 3 gene (insl3) is an additional pathway.

Furthermore, all of the phthalates in the CRA induce a similar spectrum of effects, known as the "phthalate syndrome," and which is also described as "antiandrogenic" effects. DINP has been clearly established by multiple studies (Adamsson et al. 2009; Boberg et al. 2011; Clewell et al. 2013b; Gray et al. 2000; Hannas et al. 2011; Masutomi et al. 2003) as causing the same pattern of effects (phthalate syndrome) and by other studies (Gray et al. 2000; Hannas et al. 2011) as acting by the same MOA as other phthalates in the CRA. Other experts (Foster 2005; Howdeshell et al. 2016; NRC 2008) agree that the phthalates in the CHAP's CRA act by the same mechanism of action.

Comment 1.24: Phthalate syndrome has multiple mechanisms of action. An industry commenter stated that different mechanism of action should be treated independently in a CRA, not under the broad heading of "antiandrogenicity." The commenter stated that phthalates act through three different mechanisms, and that each phthalate must be evaluated for potential activity by each mechanism if a CRA is done because each phthalate can act differently by each mechanism. According to the commenter, DEHP can affect all three mechanisms of action, but it has not been reported that DINP can affect any of these mechanisms of action.

Response 1.24: Some investigators divide the mechanism of action or MOA for phthalate syndrome into antiandrogenic (reduced testosterone production) and insl3-dependent pathways (e.g., Lehraiki et al. 2009), or alternatively, by effects on Leydig cells and Sertoli cells (testicular cells) (Howdeshell et al. 2016). These pathways, referred to by the commenters, may or may not be independent or share a common step. Nonetheless, the phthalate syndrome effects are common to all the phthalates in the CRA, regardless of the mode or modes of action. Because mixtures studies (Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008) showed that the effects of phthalates are additive, the commenters' concerns that phthalate syndrome may have multiple mechanisms of action are moot.

Comment 1.25: DINP has a different mechanism of action than other phthalates. Some industry commenters claimed that DINP does not act by the same mechanism of action as the other phthalates in the CRA. As evidence, the commenters reviewed various studies on DINP, concluding that the phthalate syndrome effects are not consistently observed with DINP, and that DINP is less potent than the other phthalates.

As part of the assertion that DINP should not be included in a CRA that is based on the "rat phthalate syndrome, one commenter stated that the mechanism leading to the observed effects of "rat phthalate syndrome" is not known, but that a reduction of fetal testosterone and/or reduction in the insl3 gene have been hypothesized to be key events in predicting "rat phthalate syndrome." The commenter reviewed DINP effects on the insl3 gene. Other phthalates reduce insl3

expression, which results in cryptorchidism (undescended testes), one of the effects associated with phthalate syndrome. The commenter continued that DINP has been shown to increase insl3 mRNA two days after the last DINP dose, possibly due to a rebound effect from low testosterone production (Adamsson et al. 2009). The commenter cited another study showing no DINP effect on insl3 mRNA levels (Lambright et al. 2011). Furthermore, the commenter claims that cryptorchidism has not been reported for DINP, suggesting that DINP probably does not affect the insl3 gene.

Thus, according to the commenters, because the studies show that DINP does not have the same MOA as other phthalates, DINP should not be included in the CRA.

Response 1.25: Staff notes that mixtures studies including DINP (Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008) show that the effects of DINP and other phthalates are additive. Therefore, a common mechanism of action is not necessary to include DINP in the CRA. See comment response 2.4 for further discussion of the relevance of MOA to CRA.

In response to the commenter's review of DINP, staff notes that not all effects of phthalate syndrome are always observed in the same animal or even in the same study. Furthermore, while the study results cited by the commenters appear inconsistent, staff notes that at least some of the apparent inconsistencies are due to differences in study design, (e.g., exposure timing and measurement timing) and reporting. The time when measurements are made, i.e., postnatal day (PND), will affect the results. Measurements made on different PNDs make it difficult to compare studies. A review of the body of studies as a whole shows that DINP exposure causes phthalate syndrome.

The CHAP's review focused on the mechanism of action for phthalates in general, not on individual phthalates. However, the CHAP did cite studies indicating that DINP does induce antiandrogenic effects in animals, although with lesser potency than other active phthalates, and therefore does contribute to the cumulative risk from other antiandrogenic phthalates (CHAP 2014,Appendix A, Table A-4). Studies show that DINP exposure in rats during the perinatal period is associated with increased incidence of male pups with areolae and other malformations of androgen-dependent organs and testes (Gray et al. 2000), reduced testis weights before puberty (Masutomi et al. 2003), reduced AGD (Lee et al. 2006b), increased incidence of multinucleated gonocytes, increased nipple retention, decreased sperm motility, decreased male AGD, decreased testicular testosterone (Boberg et al. 2011), reduced fetal testicular testosterone production and decreased StAR and Cyp11a mRNA levels (Adamsson et al. 2009; Hannas et al. 2012; Hannas et al. 2011). Hannas et al. (2011) found that DINP reduced fetal testicular testosterone production. The CHAP cited studies indicating that phthalates can reduce insl3 expression, resulting in lower testosterone levels. The CHAP only indicated an association between DINP and increased insl3 expression, but did not discuss the degree or the implications of this increase. Overall, the weight of the evidence confirms the CHAP's conclusion that DINP does induce antiandrogenic effects in animals, and thus should be included in their CRA.

Comment 1.26: Role of developmental testosterone. One industry commenter asserted that because humans differ from rats in aspects of testicular steroidogenesis, rat studies should not be extrapolated to human hazard characterization and risk assessment, and DINP should not be included in the CRA. The commenter reviewed the development of fetal testosterone (steroidogenesis) in an attempt to determine if it was a "critical contributor or common key event predictive of the rat phthalate syndrome." The commenter cited a study by Scott et al. (2009),

which reported that testicular testosterone production in the rat starts around gestation day (GD) 15 and luteinizing hormone (LH) secretion starts on GD 17.5, suggesting that "testosterone production is largely regulated either autonomously or by paracrine[11] factors during embryonic days 15.5–17.5." This period of time is the "critical window for androgen influence necessary for morphological differentiation of the male genitalia (e.g., epididymis, vas deferens, seminal vesicles, prostate, penis, scrotum and perineum)."

Response 1.26: Staff concurs that there are differences in the timing and development of the fetus when comparing rats and humans. As noted by Foster, "the critical enzymes involved in steroidogenesis are identical in rats and humans, and all mammals are believed to have parallel activation mechanisms for androgen dependent processes" (Foster 2006), contradicting the commenter's assertions. The precise mechanisms of actions in animals and humans does not need to be identical (EPA 1991, p.2). Therefore, staff agrees with the CHAP's use of rat data in the CRA to estimate the risk in humans.

Comment 1.27: Role of decreased testosterone concentration. An industry commenter noted that circulating and intratesticular T (testosterone) are reduced in fetal or juvenile animals following exposure to phthalates at concentrations that are higher than that needed to induce nipple retention, reduce AGD, and decrease semen quality. The commenter suggested that these observations "call into question the role of decreased T concentration as the central mechanism in developmental abnormalities of the male reproductive tract," suggested that an alternative mechanism(s) might be of primary importance, and asked CPSC to "discuss this issue and clarify the rational for the heavy reliance on this mechanism in the risk estimations."

Another industry commenter agreed that the physical manifestations of phthalate exposure occur at lower doses than doses that reduce testosterone. The commenter added, "it may be reasonable to rely on them for the purposes of risk assessment and regulatory decision making, but it should be recognized that these effects do not represent the same degree of toxic severity." The commenter concluded that while antiandrogenicity may be a part of phthalate syndrome, the commenter argued that antiandrogenicity was not a primary part of the mechanism of action for phthalate syndrome. The commenter also stated that reduced fetal testosterone production, Leydig cell aggregation, and induction of multinucleate giant cells, are transient or adaptive changes that are less severe than other adverse effects associated with as adverse phthalate syndrome.

In summary, both commenters questioned the role of reduced testosterone in causing phthalate syndrome.

Response 1.27: Staff agrees with the commenters' assertion that some studies involving repeated measurements over time have not shown permanent or persistent changes in testosterone concentrations (e.g., Clewell et al. 2013a; 2013b). However permanent or persistent changes in testosterone concentrations are not required to have an adverse impact on male reproductive development; rather, transient reductions in the rate of testosterone synthesis at the critical period of development do have permanent effects (e.g., structural, functional) on male reproductive organs (Hannas et al. 2011). Furthermore, staff agrees with the study by Hannas et al., showing

[11] Of, relating to, or denoting a hormone that has effect only in the vicinity of the gland secreting it.

that the rate of testosterone synthesis, rather than plasma or testicular levels, is the most relevant measure of phthalate-induced effects on testosterone (Hannas et al. 2011).

Staff concurs with the CHAP and the National Academy of Sciences that a reduction in testosterone plays a critical role in the phthalate syndrome mechanism of action, along with insl3 suppression and possibly other effects (CHAP 2014; NRC 2008). In contrast to the commenter's statement, staff considers that phthalate doses lower than the doses that cause morphological effects can inhibit the production of testosterone and initiate detrimental changes in testicular gene expression (Lehmann et al., 2004).

Staff disagrees with the commenter's conclusion that MNGs, reductions in fetal testosterone production, and Leydig cell effects are not adverse changes. Phthalates induce a continuum of adverse effects, which do not have the same degree of severity, and that some of these adverse effects may precede or promote the development of others. Phthalate-induced decrements in fetal Leydig cell testosterone have been hypothesized to result in abnormal development of the Wolffian duct system and subsequent development of the vas deferens, epididymides, and seminal vesicles. Similarly, decrements in fetal testosterone influence levels of dihydrotestosterone, which contributes to development of the prostate and external genitalia, and also affects nipple development and growth of the perineum (AGD) (Foster, 2006). Furthermore, it has been suggested that the presence of MNGs may be linked to reduced fertility or testicular germ cell cancer in humans (Ferrara et al. 2006).

The commenters suggest that antiandrogenicity (reduced testosterone) is not sufficient justification for conducting a CRA. As discussed above, staff concludes that the mechanism of action is not the only justification for conducting a CRA, because empirical data demonstrating additive effects of phthalates are available. Commenters also questioned the role of reduced testosterone levels in causing phthalate syndrome. As discussed above, staff concludes that the rate of testosterone synthesis, and not the level, is the most sensitive measure of antiandrogenic effects, and transient reductions in testosterone synthesis during critical periods may lead to permanent adverse effects (Hannas et al. 2011a).

Section 1 Summary

The CPSC staff concludes that MRDE is the most appropriate endpoint for a CRA of phthalates. The phthalates in the CHAP's CRA induce MRDE and there is experimental evidence that their effects are additive. The National Academy of Sciences recommended MRDE for conducting a CRA for phthalates (NRC 2008). Staff also concludes that the weight of the evidence suggests that the rat is an appropriate model for estimating phthalate risks in humans. Although a limited number of experiments with human tissue have not replicated the effects in animals, it would be premature to conclude that humans are less sensitive to phthalates than animals, especially considering the growing number of epidemiological studies demonstrating associations between phthalate exposure and MRDE effects in male infants and adults (Section 7). Staff concludes further that the overwhelming weight of the evidence demonstrates that DINP produces MRDE (phthalate syndrome) in animals, although it is less potent than DEHP. Finally, staff concludes that the phthalates that cause MRDE share a common mode or mechanism of action. However, staff notes that a common mechanism of action is not a requirement for cumulative effects (ATSDR 2004; Howdeshell et al. 2016), especially in light of experimental evidence (Conley et al. 2017; Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008) demonstrating cumulative (i.e., dose additive) effects.

2. Cumulative Risk Assessment

A cumulative risk assessment (CRA) estimates the potential risk following exposure to multiple "stressors," in this case, multiple phthalates. The CPSIA required the CHAP to assess the risk from phthalates "both in isolation and in combination with other phthalates." CPSIA § 108(b)(2). The CHAP assessed phthalate risks in combination with other phthalates by performing a CRA. The CHAP performed a CRA limited to phthalates that were: (1) known to cause certain male reproductive developmental effects (MRDE) in laboratory animals, also known as the "phthalate syndrome," and (2) measured in human biomonitoring (HBM) studies (DEHP, BBP, DBP, DIBP, DINP). To perform their CRA, the CHAP used animal data to assess the dose response (potency) of phthalates and HBM from the National Health and Nutrition Examination Survey (NHANES) and Studies for Future Families (SFF) to estimate exposure.

Overview of Public Comments on CRA

The CHAP decided that the hazard index approach to CRA was appropriate to use for determining the risk to sensitive populations. (a) Several industry and other commenters claimed that CRA is not widely used and is not generally accepted for use in human health risk assessment. They added that federal agencies, including CPSC, have little experience with CRA and have not used CRA to support regulations. (b) Some commenters criticized the CHAP's use of a "novel" method in their CRA. (c) Some commenters also asserted that it is not appropriate to perform a CRA for phthalates, because they do not share a common MOA or mechanism of action.

(a) The CPSC staff concludes that the hazard index approach to a CRA used by the CHAP is appropriate to use for determining the risk of phthalates. The CPSC staff notes that CRA of chemical mixtures has been an established practice since the 1980s (EPA 1986) and has been used to support federal regulations (ATSDR 2017; 2002a; EPA 2002b; 2006; 2015b; 2015c). The CHAP's CRA was consistent with the recommendations of a National Academy of Sciences report on cumulative risk assessment of phthalates (NRC 2008) (comment response 2.1).

(b) To avoid overestimating risk, the CHAP introduced a minor variation into the standard CRA methodology. This minor variation was accepted by the peer review panel and has been adopted by other authors (Christensen et al. 2014) (comment response 2.2).

(c) Finally, staff concludes that there is adequate experimental support for the cumulative (i.e., dose additive) effects of phthalates (Conley et al. 2017; Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008), even at low doses. Although a common MOA is not necessary for additivity to occur (ATSDR 2004; Howdeshell et al. 2016), staff concludes that the phthalates in the CRA act through a common mechanism of action (comment response 2.4-2.8).

Staff concludes that CRA of chemical mixtures has been in use for many years, it is used by federal agencies to regulate chemicals, and that the CHAP followed the recommendations of the National Academy of Sciences.

Comment 2.1: General acceptance of CRA. Some commenters argued that CRA is not a generally accepted approach for assessing risks associated with mixtures of related chemicals. They considered CRA to be an approach that is still under development, and that CRA should not be used for regulatory purposes. Therefore, these commenters did not agree with the CHAP's use of CRA to determine the combined risk of phthalate exposure from all sources. However,

another commenter noted that "when multiple phthalates act on a similar biologic target, it is critical to understand and regulate based on their combined effect on human health."

Response 2.1: Several agencies have concluded that a cumulative risk assessment of phthalates is needed. In the late 1990s, the Dutch National Institute for Public Health and the Environment was the first to recognize the need to consider the cumulative risks of phthalates (RIVM 1998). In 2000, the Commission convened a CHAP on DINP to consider the potential risks from DINP in children's toys and child care articles in isolation from other phthalates and other DINP exposure. In the final report, the CHAP on DINP discussed the need to consider exposures to multiple phthalates from multiple sources, but concluded that there were insufficient data on the health effects of phthalate mixtures, phthalate pharmacokinetics, and phthalate biomonitoring data to undertake such an assessment at that time (CHAP 2001; pp. 123-124). In the 2002 staff briefing package responding to a petition to ban PVC in children's products, the CPSC staff emphasized the need to consider the effects of exposure to multiple phthalates from multiple sources (CPSC 2002; TAB L, pp. 385-388). Since then, the needed studies have been published.

In 2008, a report by the National Research Council (NRC) of the National Academy of Sciences (NAS) outlined a process for performing a CRA for phthalates (NRC 2008). A 2009 NAS report reiterated the need for a CRA of phthalates (NRC 2009: pp. 10, 133, 267). NRC recommended, for example, that it is appropriate to perform a phthalate CRA for MRDE (phthalate syndrome). The NRC also recommended that the CRA should consider all endpoints associated with MRDE or, alternatively, one sensitive endpoint such as reductions in testosterone (NRC 2008, Chapter 5) (see section 4 below). NRC further recommended using dose addition (section 2), a hazard index approach, assuming that mixture effects occur at low-doses, and recommended including other (non-phthalate) antiandrogens in the CRA.

The CPSC staff does not consider CRA to be a new, untested approach for assessing risks associated with chemical mixtures. EPA first issued guidelines for the risk assessment (RA) of chemical mixtures in 1986 (EPA 1986). EPA (2000), ATSDR (2004), and the World Health Organization (WHO) (Meek et al. 2011) have since issued guidance for CRA of chemical mixtures. EPA routinely uses CRA to assess risks from pesticides, as required by the Food Quality Protection Act of 1996 (EPA 2002b; 2006). In addition, EPA has used CRA to regulate organophosphates, N-methyl carbamates, triazines, chloroacetanilides, pyrethrins, and pyrethroids (EPA 2015b). The EPA Office of Pesticide Programs also used CRA in regulatory proceeding when it examined thiocarbamates and dithiocarbamates and concluded that these chemicals do not share a common mechanism of toxicity at the organ (neuropathy) or molecular (acetylcholinesterase inhibition) level with other carbamates (EPA 2015c). EPA and ATSDR use CRA to assess risks under Superfund (ATSDR 2017; EPA 2017; Howdeshell et al. 2016). ATSDR has published 11 final and three draft CRAs, called "Interaction Profiles," that are relevant to Superfund sites (ATSDR 2017). EPA has performed a number of CRAs for various purposes, including phthalates (Christensen et al. 2014; Gallagher et al. 2015).

In conducting its CRA, the CHAP followed the general approach for performing a CRA outlined in a NAS report on performing a CRA for phthalates (NRC 2008). Mixtures RA and CRA are so widely used that the Society of Toxicology (SOT) and the Society for Risk Analysis (SRA) offer continuing education classes on this topic.

CPSC staff concludes that CRA is a generally accepted approach because CRA of mixtures has been conducted for many years for assessing risk from chemical exposures. As discussed, above,

federal agencies such as ATSDR and EPA use CRA for regulatory purposes. The need to perform a CRA for phthalates has been apparent for many years. There is a firm scientific basis to support the CHAP's CRA, including studies on phthalate mixtures (Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008) and the guidance of multiple agencies (ATSDR 2004; EPA 2000; 2002b; NRC 2008). The CHAP's CRA approach was consistent with the recommendations of the NAS. Therefore, the CHAP's CRA was an appropriate approach for assessing the cumulative risk of multiple phthalates from all sources, including consumer products, to inform the CPSC determination of reasonable certainty of no harm.

Comment 2.2: CHAP CRA used novel approach. Some commenters stated that the CHAP used a novel approach in conducting the CRA, which was different from the "typical and scientifically accepted method to develop the hazard index of cumulative effect of phthalates." However, another commenter stated that the CHAP's CRA methodology was not new, but "is a well understood and science-based approach also used by other regulatory agencies."

Response 2.2: The CHAP followed the NAS guidance for conducting the CRA (NRC 2008), with one modification. The calculation of hazard indices (HIs) for each individual sampled in NHANES was the only new method used by the CHAP. Because NHANES and SFF bio-monitoring data reported individual-level data on exposures, the CHAP observed that each individual was exposed to different phthalates in unique proportions. Thus, the CHAP used a novel approach to calculate the HI for each individual person sampled in NHANES based on his or her particular urinary concentrations of multiple phthalates (in our case, for each pregnant woman and infant). This method is in contrast to the more common HI approach of using population percentiles from exposure studies on a per chemical basis. (CHAP 2014; p. 63). This allowed the CHAP to calculate hazard quotients (HQs) for each phthalate and an HI for each individual in each study. Using the individual HQs and HIs avoids overestimating the risk for individuals with higher than average exposures, such as those at the 90^{th} and 95^{th} percentiles. It also takes into account the fact that each individual is exposed to phthalates in different proportions. The CHAP specifically asked the peer reviewers to consider the CHAP's use of individual-level HIs; the peer reviewers agreed that the CHAP's approach was appropriate (TERA 2013). One reviewer commented that "The novel approach to calculating HIs is defensible in that it provides a sound basis for evaluating actual rather than hypothetical phthalate mixtures to which individual members of the U.S. general population are exposed." The CHAP's approach was adopted by EPA staff in a CRA of phthalates (Christensen et al. 2014).

CPSC staff concludes that the CHAP's modification to the usual CRA methodology was appropriate and was done to avoid overestimating risk and to account for exposure to different proportions of phthalates by different individuals.

Comment 2.3: CRA level of assessment. Commenters argued that, even if CRA were a generally accepted approach, the CHAP's CRA only provides screening level information, which some commenters argued is not sufficient to support rulemaking. Some commenters cited the World Health Organization (WHO) framework to support their argument that the CHAP CRA was only a screening level assessment. However, one industry commenter, acknowledged that part of the CHAP's CRA—biomonitoring-based exposure assessment—could be considered WHO Tier 3 information (tier 3 is the highest level of assessment).

Response 2.3: As described in the WHO framework (Meek et al. 2011), Tier 0 (screening level) CRA uses semi-quantitative exposure estimates and assumes additivity as a default. Tier 1 uses conservative point estimates of exposure and dose-response estimates based on points of departure (PODs). Tier 2, uses refined exposure estimates including empirical data and takes mode of action into account. Tier 3, the highest tier, includes probabilistic measurements of exposure and risk. CPSC staff concludes that the CHAP's risk assessment is not a "screening level risk assessment" by the WHO definition, because it satisfies conditions for WHO Tier levels higher than 0 (screening level). The CHAP's CRA exceeds Tier 0 (screening level), because it uses quantitative exposure estimates (not semi-quantitative) and does not merely assume additivity. Additivity is supported by experimental data. The CHAP's assessment exceeds Tier 1, because it uses distributions for exposure estimates, rather than point estimates (single values), although the risk estimates are derived from PODs. The CHAP's CRA is at least Tier 2, because it uses refined exposure estimates. Staff considers that the CHAP's exposure assessment, based on human biomonitoring data, exceeds what the WHO framework considers a "refined" exposure assessment, because it is based on exposure measurements in actual people. It exceeds the Tier 2 requirement for considering the mode of action (MOA) because the CHAP's use of dose additivity is based on experimental data (see the response to the following comment). Staff concludes that the CHAP's CRA could be considered Tier 3, the highest tier, because it includes probabilistic estimates of exposure and risk. The CHAP CRA began with a comprehensive review of the toxicology and exposure literature. The primary exposure assessment for the CHAP report was based on measurements of phthalate metabolites in a statistically representative population (NHANES study) of real people.

CPSC staff concludes that the CHAP's CRA was a high level assessment, not merely a screening level assessment, because exposure and risk estimates are based on distributions of phthalate measurements from participants in NHANES, rather than assumption-based simulated exposures.

Comment 2.4: Need for common MOA or mechanism of action. Some industry commenters argued that the phthalates included in the CRA should have the same mode of action (MOA), which they describe as the same "pattern of effects." They claimed that a similar MOA is necessary to support the assumption that phthalate effects are cumulative (i.e., additive). They also claimed that there was insufficient evidence that the phthalates in the CHAP's CRA share a common MOA. More specifically, some commenters asserted that DINP does not act by the same MOA as other phthalates and should not be included in a CRA.

Response 2.4: Under CRA guidelines such as ATSDR's, experimental data on the health effects of the chemical mixtures under consideration are the strongest justification for performing a CRA (ATSDR 2004). In the absence of experimental data, one may assume dose additivity when the substances have a common MOA or act on the same target organ.

The CHAP did not need to present evidence of a common MOA or mechanism of action to justify performing a CRA because there are data from laboratory studies showing that phthalate mixtures, in fact, act in a cumulative, additive fashion (Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008). As described in the ATSDR guidelines (ATSDR 2004), because the CHAP had actual data demonstrating the additive effects on the male reproductive system, the CHAP did not have to make assumptions about whether the effects were additive. One of the reasons that the CHAP chose MRDE as the health effect for its CRA is that MRDE is the only health endpoint that was extensively studied in phthalate mixtures (CHAP 2014; p. 2).

Furthermore, a common mechanism of action is not required to observe cumulative, dose-additive effects. There are numerous examples of chemicals that act through different mechanisms of action and still have cumulative effects in mixtures (Axelstad et al. 2014; Christiansen et al. 2009; Howdeshell et al. 2016; Levin et al. 1987; Rider et al. 2008; 2010; 2009). For example, androgen receptor antagonists such as flutamide and linuron act in a dose-additive manner in mixtures with phthalates, even though they act by binding to the androgen receptor, whereas phthalates act, in part, by reducing testosterone synthesis (Howdeshell et al. 2016; Rider et al. 2008; Rider et al. 2010; Rider et al. 2009). As another example, carbon monoxide, cyanide, carbon dioxide, and oxygen deprivation all act in an additive fashion to produce lethality, even though their mechanisms of action differ (Levin et al. 1987). Carbon monoxide acts primarily by binding to hemoglobin, cyanide inhibits oxidative phosphorylation, and carbon dioxide increases the inhalation rate, leading to increase carbon monoxide and cyanide uptake. All four substances act on the same process, respiration, but in different ways to produce additive effects. These examples demonstrate that a common MOA is not needed to observe cumulative, additive effects.

Although a common mechanism of action is not required, the CPSC staff considers that the phthalates in the CRA do have a common mechanism of action. The commenters claim that the phthalates in the CHAP's CRA do not share a common mechanism of action, because they cause a different "pattern of effects." The MOA is the cellular and molecular processes by which a chemical exerts its pattern of effects, not the pattern of effects itself. The MOA for MRDEs was discussed by the National Academy of Sciences (NRC 2008; pp. 48-55), and others (Foster 2005; Howdeshell et al. 2016; Howdeshell et al. 2008). The phthalates act by inhibiting testosterone production in the testis during a critical period in development (Foster et al. 2001; Gray et al. 2000; Mylchreest et al. 1998; Parks et al. 2000), by decreasing expression of genes involved in steroid synthesis, including StAR and Cyp11a. There are additional factors, such as reduced expression of insulin-like hormone 3 gene (insl3) (Foster 2005; Howdeshell et al. 2016; NRC 2008; Wilson et al. 2004). Furthermore, all of the phthalates in the CRA induce a similar spectrum of effects, known as the "phthalate syndrome," and which is also described as "antiandrogenic" effects. DINP clearly causes the same pattern of effects (phthalate syndrome) (Adamsson et al. 2009; Boberg et al. 2011; Clewell et al. 2013b; Gray et al. 2000; Hannas et al. 2011; Masutomi et al. 2003) and acts by the same mechanism of action (Gray et al. 2000; Hannas et al. 2011) as other phthalates in the CRA. Other experts agree that the phthalates in the CHAP's CRA act by the same mechanism of action (Foster 2005; Howdeshell et al. 2016; NRC 2008). (See also comment response 1.20, above.)

Furthermore, the phthalates all act on the male reproductive system. Specifically, as discussed in the preceding paragraph, the phthalates act on the testis, inhibiting testosterone production by decreasing expression of genes involved in steroid synthesis. This common effect on the male testis further supports the CHAP's CRA.

Performing a CRA based on additive effects may be justified by having either a common mechanism of action, a common target organ, or experimental data showing an additive effect (ATSDR 2004) . Of these three justifications, experimental data are given greater weight (ATSDR 2004). The CHAP not only had experimental studies showing the additive effect of phthalates, but also demonstrated that the phthalates included in the CHAP's CRA share a common MOA (primarily antiandrogenicity) and affect the same target organ (primarily the

testes). Therefore, the CHAP's use of a dose-additive model for its CRA is supported by experimental evidence and consistent with the recommendations of the NAS (NRC 2008).

Comment 2.5: Low dose additivity. Some commenters claimed that the CHAP inappropriately assumed that the cumulative effects of phthalates are additive (cumulative) at low doses (doses to which humans are exposed). Rather, they claimed that the CHAP should have assumed that phthalate effects are not additive (i.e., are independent) at low doses. Specifically, they argued that cumulative effects cannot be additive at low doses when there is a threshold dose (dose below which there is no effect). In support of this claim, commenters cited articles by Borgert et al. (2013; 2012) and Rhomberg et al. (2011). They also cited an EPA guidance document (EPA 2000).

Response 2.5: The CHAP did not simply assume that the cumulative effects of phthalates were additive. Rather, the CHAP cited published studies demonstrating that the cumulative effects of phthalates on MRDE are, in fact, additive (Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008). One of the reasons why the CHAP focused on MRDE is that it is the only phthalate endpoint for which mixtures of phthalates have been extensively studied (CHAP 2014; p. 2).

To support their position, the commenters cited articles which were funded by phthalate manufacturers (Borgert et al. 2013; 2012; Rhomberg et al. 2011). The articles by Borgert et al. present a theoretical argument that additivity might not occur at low doses, that is, doses at which humans are typically exposed. The theory is based on the assumption that there is a threshold, that is, a dose below which phthalates have no effect. However, the commenter did not cite or provide any empirical evidence to support his theory. Rhomberg et al. present a theoretical analysis which argues that most non-cancer health effects have thresholds. If true, this means that Borgert's theory (if true) would apply in most cases. However, neither Rhomberg's, nor Borgert's theories can be verified by experiment. As discussed below, there is a considerable body of experimental data demonstrating that the effects of phthalates are, in fact, additive, even at the lowest doses that can be tested.

The commenters also cited an EPA guidance document (EPA 2000) in support of their argument. The EPA document, on risk assessment of chemical mixtures, merely states that, in the absence of mixtures data one may apply "dose addition for similarly acting chemicals and response addition for independently acting chemicals" (EPA 2000, p. 6). Staff considers that this statement is moot because of empirical data showing that phthalates are additive, even at doses well below the NOAEL.

As other experts on mixtures have pointed out, studies of phthalate mixtures at low doses do not exist (Christiansen et al. 2010; Howdeshell et al. 2016). Such studies would require extraordinarily large numbers of animals. The commenters did not present any evidence of a threshold for phthalate-induced MRDE. Even with studies at low doses, it is virtually impossible to prove that a threshold exists, because of statistical uncertainty in the estimate of the threshold dose (Crump 2014). In short, the commenters cited a theory that cannot practically be verified experimentally. On the other hand, a well-established theory argues that when chemicals act through similar processes (mechanisms of action), their dose responses do not have thresholds (Crump et al. 1976), contrary to the papers cited by the commenter. The paper by Crump et al. is still cited as support for the methods by which federal agencies assess cancer risk (CPSC 1992; Krewski et al. 1995; Lutz 1990; Lutz 2001; NRC 2009; pp. 129-130) (see also White et al. 2011).

Although mixtures studies at low (environmental) doses have not been performed, there are published studies in which the doses of the individual phthalates produced little or no effect, but the mixtures produced significant cumulative effects (Axelstad et al. 2014; Christiansen et al. 2010; Hotchkiss et al. 2004; Howdeshell et al. 2007; 2016; Rider et al. 2010). In a recent study, (Conley et al. 2017) rats were exposed to phthalates and other antiandrogens at doses well below the NOAEL. Although the individual phthalates had no observable effect, the mixture induced MRDE-related effects. Thus, additivity occurs even at doses where individual phthalates have no observable effect.

CPSC staff concludes that there is overwhelming evidence to conclude that phthalate mixtures act in a cumulative, dose-additive fashion (Howdeshell et al. 2016; NRC 2008), even at doses well below the NOAEL. There is no empirical evidence to the contrary. The CHAP, which followed the recommendations of the National Academy of Sciences (NRC 2008), used appropriate, scientifically defensible methods to perform its CRA. Therefore, the results of the CHAP's CRA are an appropriate basis for the CPSC's phthalates rulemaking.

Comment 2.6: Articles on low dose additivity. Industry commenters asserted that the CHAP did not appropriately consider papers by Borgert et al. (2013; 2012) on additivity at low doses.

Response 2.6: Staff disagrees with the commenter's assertion that the CHAP did not appropriately consider Dr. Borgert's papers. As the commenters noted, Dr. Borgert presented his work to the CHAP at the July 2010 CHAP meeting.[12] Copies of his papers were submitted to the CHAP between March 2011 and February 2012. Some CHAP members saw Dr. Borgert's presentation at the Society of Toxicology meeting in March 2011. As discussed above (comment response 2.5), Dr. Borgert cited theoretical arguments that dose addition cannot occur when a threshold exists, i.e., a dose below which no adverse effects occur. Dr. Borgert and colleagues rejected the National Research Council approach, and presented an alternative method, described by the authors as a "proposed approach." The first paper, only recently published and publicly available at the time of the CHAP meeting, presented a novel but not yet validated approach by a single group, which was funded in part by industry. In contrast, the CHAP and the National Research Council relied on empirical data showing that dose addition adequately describes the combined effects of phthalates. Staff agrees with the CHAP's decision to rely on the established approaches available at the time, especially the recommendations of the National Research Council, and not on a single, new, unvalidated theory.

Comment 2.7: Dose addition. One commenter also cited a paper by Howdeshell et al. (2008) as evidence that "use of the dose addition model needs to be verified due to violated assumptions, great uncertainty, and poor model fit."

Response 2.7: The CHAP's risk assessment is based on empirical data showing that dose addition adequately describes the combined effects of phthalates (Howdeshell *et al*. 2007; Howdeshell et al. 2008). In other words, studies by Howdeshell et al., upon which the CHAP relied, predicted what effect a phthalate mixture would have if the phthalates are additive and then compared the prediction to the results from an experiment with laboratory animals. The prediction, based on an additive assumption, compared favorably, but not perfectly, with the experimental results. Although the agreement between the prediction and experimental results

[12] https://www.cpsc.gov/s3fs-public/borgert.pdf

was not perfect, assuming dose addition was much better than any of the alternatives, such as assuming the lack of additivity. Further supporting an additive assumption and contrary to the commenters assertions, the NRC report on phthalates cumulative risk (NRC 2008, p. 10) and other reports (Benson 2009b; Christensen et al. 2014; Kortenkamp and Faust 2010) concluded after reviewing the empirical evidence that dose addition is appropriate for assessing the cumulative effects of phthalates and other antiandrogens.

Comment 2.8: Dose response curves and additivity. One industry commenter stated that dose additivity does not apply, unless the dose response curves of the components of the mixture are parallel. Specifically, the commenter stated that "…the use of fractions of effect doses (the HQs) for different agents implies that the dose-response curves among agents are parallel. For phthalates, the basis for this assumption is limited and can have substantial consequences for the validity of the computed HI." They went on to explain that if the dose responses are not parallel, then the relative potencies of different phthalates would change at different dose levels.

Response 2.8: The CHAP's risk assessment is based on empirical data showing that dose addition appropriately describes the combined effects of phthalate exposure (Howdeshell et al. 2007; Howdeshell et al. 2008). The NRC report (2008) on phthalates cumulative risk was written at the request of EPA to recommend methodology for the CRA of phthalates. As discussed in the NRC report on cumulative risk, dose addition does not require parallel dose response curves (NRC 2008). The NRC report further concluded that EPA stipulations for requiring parallel dose response curves to assume additivity were too restrictive in general, but might be required for more specific applications, such as the estimation of relative potency(NRC 2008, p. 9). The NRC committee then strongly recommended that EPA group chemicals that cause common adverse outcomes, rather than focus exclusively on structural similarity or similar mechanisms of action (either of which would generate parallel dose response curves). The NRC report and other authors (Benson 2009b; Christensen et al. 2014; Kortenkamp and Faust 2010) concluded that dose addition is appropriate for assessing the cumulative effects of phthalates. CPSC staff concludes that the CHAP used methodology that was consistent with the recommendations of the NRC report on phthalates CRA.

Comment 2.9: Inclusion of prohibited children's toys and child care articles containing DEHP. One industry commenter asserted that the CHAP's cumulative risk assessment depends on the unrealistic inclusion of prohibited children's toys and child care articles that contain DEHP. The commenter claimed that the CHAP did not attempt to assess risk with a CRA excluding DEHP. The commenter claimed that the value of CRA is in situations in which exposure to each single substance is below the level of concern, but that exposures to multiple chemicals with the same mechanism of action (or that affect the same endpoint) at the same time rise to levels of concern. The commenter asserted that, in this case, only one chemical (DEHP) poses a risk in isolation.

Response 2.9: The CHAP did not model the CRA in the absence of DEHP because the CPSIA directed the CHAP to complete an examination of the full range of phthalates that are used in products for children, to consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates, and to consider the cumulative effect of total exposure to phthalates, both from children's products and from other sources. Thus, the CHAP performed the CRA to examine the risks from all phthalates to which humans are exposed.

Staff notes that it would be arbitrary to exclude a phthalate that is regulated only in toys and child care articles, but allowed in other products (i.e., DEHP). The fact that DEHP is a significant contributor to the cumulative risk provides evidence for the widespread human exposure to DEHP. DEHP is found in drinking water, surface water, storm water, soil, and wildlife (Clark 2009; Versar 2010). It is found in indoor and outdoor air, household dust, and indoor surfaces. DEHP has been found in gloves, footwear, personal care products, medical devices, and food. It is found in paints, adhesives, sealants, wallpaper, and flooring. Thus, given the number and variety of sources of exposure, DEHP should be included in the CRA.

Although the CHAP did not model cumulative risk in the absence of DEHP, the CHAP provided results for each phthalate, presented as the HQ at the medians and 95th percentiles of the risk distribution (CHAP 2014, Table 2-16). The relative contributions of each phthalate are also presented in staff biomonitoring analyses using current NHANES data (CPSC, 2015, CPSC, 2017). Thus, the relative contribution of each phthalate is readily apparent.

The commenter asserts that CRA is most valuable when exposure to any single substance is below level of concern, but exposures to multiple chemicals with the same mechanism of action (or that affect the same endpoint) do rise to levels of concern. In the CHAP's risk assessment, no single phthalate had an HQ greater than one, not even DEHP (CHAP 2014, Table 2.16). Therefore, the CHAP's CRA meets the commenter's definition of a valuable assessment.

Staff concludes that the CHAP was correct to include in the CRA phthalates included in the permanent prohibition in the CRA, not only because it was required by the CPSIA, but also because the reason for performing a CRA is to include all phthalates and all sources of exposure.

Comment 2.10: Human experience and clinical evidence. One commenter concluded that the CHAP "failed to recognize obvious inconsistencies with human experience and clinical evidence." The commenter argues that there are many other antiandrogenic compounds, perhaps hundreds or thousands, which also may contribute to the cumulative risk. He concludes that, if the CHAP's CRA is valid, then the risk would then be so high that no male could be born without MRDE.

Response 2.10: The commenter provides little in the way of data, methods, or literature citations to support his risk estimates. The commenter made unsupported assumptions about the risks posed by the other antiandrogenic compounds, with no mention of exposure or potency. Therefore, it is not possible to evaluate his claims.

Regarding the commenter's claim that the CRA predicts high incidence of MRDE, staff notes that the mean incidence rate in the United States for hypospadias is around 6.5 per 1000 live births (Mai et al. 2015), or approximately 13,000 new hypospadias per year. Cryptorchidism occurs in about 5 percent of male live births (Kolon et al. 2014), or about 95,000 newborns per year. It is estimated that young men with cryptorchidism have a 4-fold increased risk for testicular germ cell cancer (Banks et al. 2012). Impaired male fertility has been reported in about 12 percent of males age 25–44 (Chandra et al. 2013). While we cannot attribute the observed cases to phthalates or any other specific exposure, staff concludes that the incidence of MRDE-related effects in the United States is indeed high. (See section 7 introduction for additional discussion.)

Comment 2.11: CRA methodology. Three industry commenters, two NGOs, and one commenter from the public claimed that the CHAP used flawed or faulty methodology for their

CRA. The commenters cited several examples supporting their belief that the CHAP CRA was flawed, including:

1) Improper inclusion of the non-phthalate, syndrome-inducing DINP;
2) Inappropriate choice of uncertainty factors;
3) Overly conservative factors were used throughout the CRA;
4) Older NHANES data were used to estimate exposures;
5) The epidemiology data were equivocal (especially the data relating to DINP); and
6) Species differences in toxicity suggested that humans are less sensitive to phthalate effects.

In contrast, comments from three NGOs and one from industry agreed with the CHAP's methodology, describing it as state of the art and saying that the CHAP report was consistent with the NRC report on phthalates cumulative risk or consistent with recommendations from the report regarding the use of reproductive developmental endpoints as the hazard endpoint. The American Chemistry Council (ACC) convened a panel of six individuals to "peer review" the CHAP's report; their comments are compiled in one submission. The ACC panel scientists differed in their characterization of the CHAP report. As mentioned above, one panel scientist stated, for example, that the CHAP report "with few exceptions represents state of the art methodology drawing maximally on multiple sources of relevant data." Others on that industry-sponsored panel espoused more critical views of the CHAP process and report.

Response 2.11: Specific comments on the CHAP's methodology are addressed in more detail elsewhere in this document. They are addressed briefly here.

1) Improper inclusion of the non-phthalate syndrome-inducing DINP. Staff concludes that there is adequate evidence showing that DINP induces the phthalate syndrome. See comment response 1.3 above.
2) An inappropriate choice of uncertainty factors. The CHAP used the default values that are most commonly used in risk assessment. See Sections 1, 4, and 10.
3) Overly conservative factors were used throughout the CRA. Staff concludes that the CHAP used appropriate "factors" in its CRA. See Sections 1, 4, and 10.
4) Older NHANES data were used to estimate exposures. Staff incorporated more recent NHANES data published since the CHAP completed its analysis. See Section 3.
5) The epidemiology data were equivocal (especially the data relating to DINP). There is a growing body of epidemiological studies reporting associations between phthalate exposure and human health effects that are consistent with effects seen in animals. Staff also concludes that the epidemiological data, in combination with animal studies, provide additional support to conclude that the phthalates considered in the CHAP's CRA are "probably toxic to humans." See comment response 7.1.
6) Species' differences in toxicity suggested that humans are less sensitive to phthalate effects. Staff concludes that there is insufficient information to conclude that humans are less sensitive than animals. See comment response 1.1.

Comment 2.12: CRA requires chemicals with similar exposure potential. One commenter advocated for a change in the CPSC analysis approach away from the CRA because the primary risk drivers, DEHP and DINP are not in the same products at the same time and differ in physical properties. The commenter specifically noted that DEHP and DINP are not used together in products, have different vapor pressures and potencies, and have different aging characteristics, so they have different exposure potential. This difference in exposure potential would obviate their use in the CRA together. They recommended that DINP be dropped from the CRA because of these differences.

Response 2.12: Staff concurs that some of the physical properties for DINP and DEHP differ and that they might theoretically have different exposure potentials. However, staff does not agree with the commenter's assertion that these two phthalates do not co-occur. Staff notes that NHANES metabolite data demonstrate that many individuals are co-exposed to both DINP and DEHP. CPSC and The European Union (EU) RAPEX analytical monitoring data on phthalate residues in toys and childcare articles also demonstrates that some products contain both DEHP and DINP simultaneously. For these reasons, staff disagrees with the commenters assertions that both should not be considered in the CRA.

Comment 2.13: CPSC's proposal's consistency with the EU regulatory actions on phthalates. One commenter stated that CPSC's proposal is consistent with EU regulatory actions on phthalates. The commenter noted that the ECHA review of DINP and DIDP concluded that risk from these chemicals "cannot be excluded if the existing restrictions were lifted" and also that "DINP has antiandrogenic properties and it could be appropriate to include this substance in a combined risk assessment of phthalates with antiandrogenic properties." The commenter stated that this approach "is in agreement with the CHAP approach to cumulative risk assessment by grouping DEHP, DBP, DIBP, and DINP based on their antiandrogenic properties."

Response 2.13: Regarding DINP, staff agrees that the CHAP's approach, the Commission's proposed rule, and staff's conclusions about the most recent human biomonitoring data are consistent with the ECHA conclusions about the potential for increased exposure to DINP and the appropriateness of a combined risk assessment based on antiandrogenic properties. On the other hand, the CHAP concluded that DIDP does not appear to possess antiandrogenic potential. Because the CHAP calculated MOEs that indicated low concern for other health effects, the CHAP could not justify maintaining the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing DIDP. The Commission agreed with the CHAP's findings and concluded that continuing the prohibition on children's toys that can be placed in a child's mouth and child care articles containing DIDP is not necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals. Staff has not found any additional information that would change the conclusions about DINP or DIDP.

Section 2 Summary

The CPSC staff concludes that CRA, specifically CRA of chemical mixtures, has been an established practice since the 1980s (EPA 1986) and has been used to support federal regulations (ATSDR 2017; EPA 2002b; 2006; 2015b; 2015c). The CHAP's CRA was consistent with the recommendations of the National Academy of Sciences (NRC 2008), which included using dose addition, a hazard index approach, and assuming that mixture effects occur at low-doses. To

avoid overestimating risk, the CHAP introduced a minor variation into the standard CRA methodology. This minor variation was accepted by the peer review panel and subsequently has been adopted by other authors (Christensen et al. 2014). After reviewing WHO guidance documents (Meek et al. 2011), staff concludes that the CHAP produced a high level risk assessment that is more than adequate for regulatory purposes. Finally, staff concludes that there is adequate experimental support for the cumulative (i.e., dose additive) effects of phthalates (Conley et al. 2017; Hannas et al. 2012; 2011; Howdeshell et al. 2007; 2016; 2008), even at low doses. Although a common mechanism of action is not required for additivity (ATSDR 2004; Howdeshell et al. 2016), staff concludes that the phthalates in the CRA act through a common mechanism of action.

3. Human Biomonitoring Data

Human biomonitoring (HBM) is the measurement of a chemical or its metabolites in biological samples, such as blood or urine. Phthalate exposure can be estimated from concentrations of urinary metabolites. To understand human exposures to phthalates, the CHAP analyzed biomonitoring data from the National Health and Nutrition Examination Survey (NHANES), a national, statistically representative sample of the U.S. population. Because NHANES does not include children under six years old, the CHAP analyzed data from the Study for Future Families (SFF) to estimate exposure to children from 2 to 36 months old, as well as to estimate prenatal and postnatal measurements of their mothers.

Overview of Public Comments on HBM

In conducting its CRA, the CHAP used HBM data from NHANES (CDC 2012) to estimate phthalate exposures to pregnant women (2005/2006). The CHAP also used HBM data from the SFF study (Sathyanarayana et al. 2008a; 2008b) to estimate exposures to infants and their mothers (1999-2008), because NHANES does not collect data on children under 6 years old. The primary criticism raised by phthalate manufacturers is that the CHAP's analysis was based on 2005/2006 data, while more recent NHANES data have become available. The more recent data show that phthalate exposures in adults have changed, and commenters asserted that the population is no longer at risk for phthalate-induced MRDE. Other comments criticized the use of "spot urine samples" by NHANES, claiming that spot sampling does not accurately reflect human exposure.

In response to concerns that the CHAP's analysis was based on old data, staff analyzed NHANES data for women of reproductive age (WORA), from 2007 through 2014 (TAB A). Staff notes that the 2005/2006 data cycle was the last to sample with a sufficient number of pregnant women to make reliable exposure estimates for pregnant women. Thus, all subsequent analyses are for women of reproductive age (WORA). Staff analysis (TAB A) found that that total phthalate exposures in WORA have increased over time. Although DEHP exposure has declined, exposure to DINP has increased roughly 5-fold since 2005/2006. Although DEHP was the major contributor to the cumulative risk in 2005/2006, DINP now contributes about as much to the cumulative risk as DEHP. Although the net exposures have increased, the risk to WORA, as indicated by HI, has decreased. Median and 95th percentile HIs for WORA are all less than one. Staff estimates that between 98.8 and 99.6 percent of WORA have HIs less than or equal to one. In a sample of 538 WORA, there were from two to nine individuals with a HI greater than one (i.e., at risk), depending on the PEAA case. As described in section 5.4 of TAB A, the 2013/2014 NHANES data cannot be used to estimate how many WORA in the U.S. population have HIs greater than one. Furthermore, there are six individual WORA in the NHANES data set in which DINP exposure alone results in an HQ greater than one (Case 2, comment response 3.1, 3.2).

No new biomonitoring data on pregnant women or infants have become available since the CHAP report was published. The CHAP report, (CHAP 2014, Table 2.16), showed that about 90 percent of pregnant women and 95 percent of infants had an HI of less than or equal to one. Thus, 10 percent of pregnant women and 5 percent of infants were at risk. If the overall phthalate exposure and risk to WORA have declined since 2005/2006, it is possible that exposure and risk to pregnant women and infants have also declined. Staff concludes that WORA are a reasonable

surrogate for pregnant women (TAB A). However, Staff notes that infants' and children's exposures tend to be greater than in adults, generally by 2- to 3-fold (CHAP 2014; Koch et al. 2004; Sathyanarayana et al. 2008a; Swan 2008; Swan et al. 2005). Therefore, the exposures and risks to WORA may underestimate the exposures and risks to infants.

In summary, staff estimates that between 98.8 and 99.6 percent of WORA have HIs less than or equal to one. The only available data showed that 5 percent of infants had HIs greater than one (CHAP 2014, Table 2.16). Even if infants' exposures have declined, their exposures are likely to be 2- to 3-fold greater than those of WORA. Although staff is unable to estimate the percentages, staff concludes that a portion of pregnant women and infants remain at risk for the effects of MRDE. Furthermore, lifting the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DINP could increase exposure to DINP from these products, compared to exposures if DINP is not allowed in children's toys and child care articles. DINP exposure from children's toys and child care articles could account for up to about 29 percent of infants' total DINP exposure from all sources (CHAP 2014; Appendix E1, Table E1-21)(CHAP 2014; Appendix E1, Table E1-21)(CHAP 2014; Appendix E1, Table E1-21).

Comment 3.1: Date of NHANES data. One primary criticism raised by phthalate manufacturers focused on the dates of the NHANES data, noting that the CHAP used 2005/2006 data even though more recent data were available. The CHAP report states (p. 12) that "the stopping point for CHAP analysis and interpretation was information available by the end of 2012." However, commenters stated, that both 2007/2008 data and 2009/2010 data were available by then. One commenter stated that the 2007/2008 data set was available in October 2010, when the CHAP was still getting started, citing a CPSC report as their source (CPSC 2015a, p. 3). The commenter noted that the 2009/2010 data set was available in September 2012, nearly two full years before the final CHAP report was issued and before the CHAP cutoff date for consideration of new information (end of 2012). The commenter noted that the 2011/2012 data set was available in November 2013, ahead of the January 2014 meeting at which the CHAP discussed the peer review of its report. The commenter concluded that the CHAP was disingenuous in stating that the CHAP used the latest NHANES data available.

Another commenter said that the NPR "incorrectly states that phthalate exposures have remained essentially constant for a ten year period ending in 2012 or 2013."

Response 3.1: The CHAP used 2005/2006 NHANES data on pregnant women to assess phthalate exposure as part of the CRA, to satisfy the CPSIA's charge to "examine the likely levels of children's, *pregnant women's,* and others' exposure to phthalates…" CPSIA §108 (b)(2)(B)(iii) (emphasis added). This data set was the most recent data on pregnant women available at the time the CHAP completed its analysis in July 2012 (CHAP 2014, p. 35). (emphasis added). The 2005/2006 NHANES study was the last data cycle to include a large sample of pregnant women. The CHAP included summary phthalate metabolite data from the 2007/2008 data cycle in its report (CHAP 2014, Tables 2.5, 2.6), but did not calculate exposure and risk, because this data set did not have sufficient numbers of pregnant women. Staff analyses of more recent NHANES data cycles may be found in TAB A.

The commenters stated that NHANES data from 2007/2008, 2009/2010, and 2011/2012 were available before the final CHAP report was released. However, these data sets did not include adequate numbers of pregnant women. Partial data for 2009/2010 were first released in

September 2012, after the CHAP completed its analysis in July 2012. The commenter stated correctly that the 2011/2012 data on phthalate metabolites were initially released in November 2013, but the commenter failed to mention that the data were revised in October 2014, and other demographics data needed to calculate exposure and risk were revised in January 2015[13], well after publication of the final CHAP report. The CPSC staff subsequently analyzed NHANES WORA data from 2007/2008 through 2013/2014 (see below, comment response 3.2).

Commenters also stated that the 2009/2010 data set was available before the CHAP cutoff date for consideration of new information (end of 2012). The commenters quoted one sentence from a paragraph describing the CHAP's literature search process. In context, the cutoff date clearly refers to the final update of the CHAP's search of the biomedical literature for new peer-review publications in biomedical journals, specifically, National Library of Medicine databases. The CHAP was also explicit in noting that the 2005/2006 data were "the most recent version in which phthalate data were available at the time of our analyses" (CHAP 2014, p. 35).

Another commenter said that the NPR "incorrectly states that phthalate exposures have remained essentially constant for a ten year period ending in 2012 or 2013." On page 27, the NPR stated, "Phthalate exposures in the U.S. population, as measured by biomonitoring, have remained essentially constant for about a 10-year period (CDC 2017; EPA 2013)." The dates 2012 and 2013 refer to the publication dates, not the NHANES data sets. EPA reviewed phthalate exposure from the first NHANES data set in 1999/2000 through 2007/2008 (EPA 2013). EPA reviewed five data sets covering a 10-year period. EPA concluded that phthalate metabolite concentrations were relatively stable during this time period, with no evidence of change over time, except for some lower molecular weight phthalates. Dr. Clarke made a similar observation in her presentation to the CHAP (July 2010). Thus, when the CHAP performed its analysis, there was no evidence that phthalate exposures were changing.

The CHAP exercised their professional judgment in focusing on data on pregnant women for their CRA. The CHAP completed its analysis in July 2012. CPSC staff has since determined that WORA are a surrogate for pregnant women. Staff concludes that the CHAP was not disingenuous in stating that they used the latest NHANES data available at the time of their analysis.

Comment 3.2: Impact of new data. The same industry commenters (see comment response 3.1) requested that CPSC analyze more recent data and make the results public. They stated that the risk from phthalates has declined, and argued that due to this decline, the permanent prohibition on children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DINP is no longer justified. However, some commenters supported the CHAP's choice of NHANES biomonitoring datasets and methods. One of these commenters, in response to staff's analysis of the 2013/2014 NHANES data cycle, noted for all three cases, the median HI for WORA is far less than one. The commenter also noted that even at the 95th percentile, the HI is uniformly less than one and has decreased further from the HI values calculated for the 2011/2012 data cycle. The commenter concluded, therefore, that these data show less risk than previous years.

[13] https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Demographics&CycleBeginYear=2011.

Response 3.2: Staff notes that the CHAP established an HI greater than one as defining excess exposure, relative to the acceptable exposure level. In contrast, an alternative approach is to establish an acceptable percentile of the population to protect, and then consider the exposure level associated with that percentile. The CHAP did not indicate that the 95th percentile, or any other part of the cumulative risk distribution, should be used to establish unacceptable risk. Therefore, discussions of acceptable risk should not be limited to the 95th or other percentile. Staff agrees with the CHAP's focus on an HI greater than one as an unacceptable exposure. Staff concurs with commenters that through the NHANES cycles, the population of WORA with an HI greater than one has decreased. In the 2013/14 NHANES sample of 538 WORA, there were from two to nine individuals with a HI greater than one (i.e., at risk), depending on the PEAA case. As described in section 5.4 of TAB A, the 2013/2014 NHANES data cannot be used to estimate how many WORA in the U.S. population have HIs greater than one.

CPSC staff analyzed NHANES data from 2005/2006, 2007/2008, 2009/2010, and 2011/2012 (CPSC 2015a) and subsequently analyzed data from 2013/2014 (CPSC 2017) using the same methodology used by the CHAP.

There are an insufficient number of pregnant women in each of the NHANES cycles following NHANES 2005/2006 to generate statistically stable estimates for daily phthalate intakes. This is because, in subsequent cycles, NHANES no longer oversampled pregnant women, leaving the sample size of pregnant women too small to use for statistical analyses in those later cycles (NCHS 2013a; 2013b). As a result, staff was unable to estimate phthalate exposures for pregnant women for the subsequent data, but instead used women of reproductive age (WORA) as a surrogate.

In the analysis of the later NHANES data, staff found that the percentage of WORA with an HI less than or equal to one increased from approximately 97 percent in the NHANES 2005/2006 cycle to approximately 99 percent in the NHANES 2013/2014 cycle (TAB A, Table 9). Over this period, the median and 95th percentile HIs show a net decrease. (CPSC 2015a; Table 6). Staff concurs that the median and 95th percentile HIs for WORA in the 2013/2014 data are both below one.

However, staff's analysis of the most recent two-year data collection cycle (NHANES 2013/2014) shows some HIs greater than one in the WORA participants, but the number is too small to project to the national population. While only a percentage of WORA are pregnant, male fetuses of WORA with an HI greater than one are potentially at risk for MRDE. The CPSIA required the Commission to consider whether making the interim prohibitions on children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DINP, DNOP, and DIDP permanent is necessary "in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." CPSIA § 108(b)(3)(A). As described in the briefing memorandum in Sections VI and VII, in part because a portion of the potentially sensitive population is still at risk, staff concludes the standard of "reasonable certainty of no harm with an adequate margin of safety" has not been satisfied. Lifting the prohibition on children's toys that can be placed in a child's mouth and child care articles containing DINP could only increase the portion of the population at risk. Therefore, staff concludes that lifting the prohibition on children's toys that can be placed in a child's mouth and child care articles containing DINP would be inconsistent with the statutory directive to "ensure a reasonable certainty of no harm" to children and pregnant women with an "adequate margin of safety."

Comment 3.3: Phthalate trends. One commenter asserted that risk trends would continue going down into the future, given that there are no new market changes or regulations, and faulted the CHAP for not considering future trends. The commenter further asserted that there would be an "inconsequential effect" on cumulative risk from lifting the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing DINP.

Response 3.3: Staff concurs that analyses of more recent NHANES data cycles have shown a limited decrease in HI (see TAB A), which is likely affected by the consistencies in the market and regulatory framework noted by the commenter. However, staff disagrees that the CHAP did not consider future trends. In fact, as discussed by the CHAP in its report (CHAP 2014, Appendix E1, Table E1-21), and CPSC in the NPR, based on the scenario-based exposure assessment lifting the interim prohibition on children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DINP could result in children's toys and child care articles accounting for up to about 29 percent of total DINP exposure to infants. Whereas, if DINP is not allowed in children's toys and child care articles, such products would not contribute to total DINP exposure. Staff is unable to quantify the impact of changes in DINP exposure on the percent of WORA or infants that have an HI less than or equal to one, although staff notes that an increased exposure will increase the MRDE risk to the population. Staff does not consider that increasing MRDE risk to the population is "inconsequential," particularly to those affected.

Comment 3.4: Substitution of all phthalates with DINP. One industry commenter provided an analysis of NHANES data on WORA (using PEAA Cases 1 and 3) in which all phthalate exposures were assumed to be from DINP. By this methodology, the commenter concluded that the 95th percentile HI would be less than 0.2. The commenter pointed out that even "if DINP replaced all of the other phthalates (which is unlikely because, among other things, DINP is not suited for all of the technical applications of all of the other phthalates), the overall HI would be far below one." Similar conclusions were reached by another industry commenter.

Response 3.4: CPSC staff agrees that the median and 95th percentile HIs would be less than one if all CRA phthalate exposures were considered to be from DINP. Staff points out, however, that a certain number of WORA in the 2013/2014 NHANES sample have HIs and DINP HQs greater than one. Any increase in DINP exposure could increase these individual's risk. In addition, there are a number of individuals that have HIs and DINP HQs near one. Additional DINP exposure to these individuals could increase the risk to greater than an HI of one (see comment response 3.2 and TAB A).

In addition, as the commenter points out, the technical reality is that DINP will not replace all of the other phthalates. In fact, as industry representatives have frequently noted, it is unlikely that DINP would replace all DEHP, let alone all phthalates. Thus, the argument posed by the commenter does not reflect expected exposures. As noted in comment response 5.5, current analysis suggests that the DINP margin of exposure (MOE), in isolation, (e.g., the MOE is 220 for Case 2) is below the upper limit and nearing the lower limit considered adequate for protecting public health.

Comment 3.5: SFF data. Some commenters stated that they were unable to replicate the CHAP's analysis of the SFF data. Commenters also pointed out that a more recent study, The Infant Development and Environment Study (TIDES), indicates that DEHP metabolite concentrations are 50 percent lower than those in the SFF study. One commenter agreed with the

CHAP's using multiple databases, including the SFF, and noted that the SFF data show a large proportion of mothers and infants are at risk of adverse health effects.

A commenter noted that SFF data were collected before the CPSIA was implemented, and before an asserted sharp decline in DEHP exposure. Thus, according to the commenter, basing the NPR on five percent of infants with an HI greater than one is not supportable.

Response 3.5: Regarding SFF, CPSC staff re-analyzed the SFF data provided online with the same methodology used by the CHAP. Staff results were consistent those reported by the CHAP (Table 2.16). It is unclear why the commenters estimated substantially different results from those of the CHAP for the infant SFF data.

TIDES is a study that measured phthalate exposure in pregnant women, but not their infant children. The TIDES study evaluated if the prenatal phthalate exposure was associated with changes in infant genital morphology (visible appearance of male genitals) (Swan et al. 2015). The TIDES study's authors reported that DEHP exposures were about 50 percent lower than in the SFF study, but the publication provided insufficient details on phthalate exposure to analyze cumulative risk. Because TIDES did not measure metabolites in infants, there is no direct comparison to the SFF.

Staff notes that infants' and children's phthalate exposures tend to be greater than in adults (CHAP 2014; Sathyanarayana et al. 2008a; Swan 2008; Swan et al. 2005). For the phthalates in the CHAP's CRA (DBP, DIBP, BBP, DEHP, and DINP), daily intakes were generally 2- to 3-fold greater in SFF infants than in their mothers (CHAP 2014, Table 2.7). In the scenario-based exposure assessment considered by the CHAP, estimated daily intakes were 2- to 5-fold greater in infants than in women (CHAP 2014, Appendix E1, Table E1-18). In Germany, nursery school children had roughly twice the DEHP exposure as their parents (Koch et al. 2004).

No more recent information on infant exposures is available than the 1999/2005 SFF data, which was used by the CHAP (and subsequently by CPSC in the NPR) and shows that approximately 95 percent of infants have HIs less than or equal to one. Infant exposures may have changed since 2005, but staff has no infant data to quantify any change.

Comment 3.6: **Fasting time differences.** One industry commenter noted that CPSC staff posited (December 17th briefing) that a change in fasting protocol in NHANES datasets after 2005/2006 (related to fasting before sampling) may have "reduced measured phthalate exposures" and might have been a reason for the CHAP using the 2005/2006 cycle. The commenters refuted this position and noted that there has not been a change in NHANES fasting protocols after this date (plasma fasting glucose and insulin required in data cycles up through 2012), that the CHAP took this into consideration when not including earlier data cycles in the analysis because they had noted " 'study design changes associated with fasting requirements.' (CHAP 2014, pg. 35)," and that the methodology for "fasting participants has been substantively the same since 1999." They also added that the current directions to "fast after 11 pm for a first-in-the-morning sample actually would inflate phthalate exposures" because "phthalate metabolites are observed to peak when fasting times are less than 12 hours long." The commenters cited papers by Aylward et al. and Koch et al. (Aylward et al. 2011; Koch and Angerer 2007; Koch et al. 2005; Koch et al. 2013) as showing "that phthalate metabolite levels actually rise in the first hours after fasting" and therefore, morning samples would be higher, and this would not provide a reason to exclude analysis of more recent NHANES data.

Another industry commenter refuted a suggestion in the CHAP report (p. 4) that urinary concentrations might be affected by fasting. The commenter provided box and whisker plots of fasting time by NHANES data cycle, which demonstrated that early NHANES data cycles (2001/2002, 2003/2004; median ~ 11–12 hours, lower/upper quartiles ~7.5/14 hours, lower/upper values ~ 2.5/19 hours) were substantially different than the 2005/2006 and later data cycles (median ~5–7 hours, lower/upper quartiles ~2.5/12 hours, lower/upper values ~ 0.5/15 hours). The graphs suggested that the quartiles, minimum, and maximum values for later datasets were not different; the medians appeared to decrease slightly over time (from 7 to 5 hours). The commenter also provided a figure demonstrating the concentration of urinary MEHHP or MCOP in each data cycle, but grouped by fasting time into four bins (less than 6, 6 to less than 10, 10 to less than 24, and all less than 24 hours). The decrease in MEHHP or increase in MCOP over time was visually similar for all groups, suggesting that fasting time did not influence urinary metabolite levels.

Response 3.6: The CHAP paid special attention to the possible effects of fasting on NHANES data, and invited experts to the December 2010 meeting to address this issue. The CHAP finally chose the 2005/2006 NHANES data because this data set contained the best available data for pregnant woman. Staff reviewed NHANES documentation[14,15] and spoke with CDC staff regarding fasting protocol changes between cycles. No fasting requirements changed. Therefore, fasting requirements were not a factor in the decision not to combine data from subsequent NHANES cycles with the 2005/2006 data. Fasting may have an impact on food-borne phthalates and result in underestimation. However, it is difficult to give a factor to correct the influence of fasting, which is likely less than 2-fold. Fasting is not an issue in the SFF samples (CHAP 2014, pp. 74). The daily intake for pregnant woman derived from the 2005/2006 NHANES data was comparable to that of the SFF data (CHAP 2014, pp. 45). Therefore, the CPSC staff concludes the major conclusion or the recommendation of the CHAP report would not change whether the CHAP included the early NHANES data or not.

Comment 3.7: Pregnant women and women of reproductive age. One commenter supported the CHAP's decision to base its analyses on the 2005/2006 data that focused on pregnant women.

Industry commenters argued that the 2005/2006 NHANES data on WORA were a reasonable surrogate for pregnant women data, and that the CHAP should have used WORA in its cumulative assessment. Commenters explained that that WORA have an increased sample size in most NHANES datasets and also stated that phthalates exposures for both are statistically similar. Commenters referred to a report by Woodruff et al. (2011), in which phthalate exposures were estimated for pregnant women and WORA using the NHANES 2003/2004 database, concluding that the differences between pregnant women and WORA were not statistically significant. The commenter also cited the CHAP report, "In NHANES 2005/2006, comparing pregnant women to non-pregnant women in this age range, the exposures were not found to be significantly different" (CHAP 2014, p. 36). The commenters thought it was unclear as to why

[14] National Health and Nutrition Examination Survey, 2005 - 2006 Data Documentation, Codebook, and Frequencies. Available at: https://wwwn.cdc.gov/Nchs/Nhanes/2005-2006/FASTQX_D.htm.
[15] National Health and Nutrition Examination Survey, 2003 - 2004 Data Documentation, Codebook, and Frequencies. Available at: http://wwwn.cdc.gov/nchs/nhanes/2003-2004/PH_C.htm.

the CHAP used 2005/2006 pregnant women data instead of WORA, given the similarities and larger sample size.

Response 3.7: Regarding the use of pregnant women versus WORA, the CHAP specifically chose to study pregnant women (as a surrogate for the fetus), rather than WORA, to satisfy the CPSIA mandate to "examine the likely levels of children's, *pregnant women's*, and others' exposure to phthalates…" CPSIA §108 (b)(2)(iii) (emphasis added)(CHAP 2014, pp. 13-14, 34-37). Although there are similarities in exposure between pregnant women and WORA, there are differences in the distributions, especially at the 95th percentile exposures (CHAP 2014, Table 2.7). The CHAP reported, "In the upper percentiles, as well as with weighted analyses, there are indications that exposures might be higher in pregnant women than in women in general or in the rest of the NHANES population." (CPSC 2014, p. 36). Staff notes that Woodruff et al. compared phthalate concentrates in urine, not daily intakes, and did not include DEHP or DINP in their analysis.

Although the CHAP did not assess cumulative risks for WORA, CPSC staff completed an exposure and risk assessment of both pregnant women and women of reproductive age in June 2015. Staff compared estimates from the 2005/2006 NHANES data set to determine whether WORA had similar daily intake (DI) and Hazard Index as Pregnant Women. Median and 95th percentile estimates of the DI for five phthalates were generally similar when comparing WORA to pregnant women. CPSC staff had to rely on data for WORA to analyze NHANES data from 2007/2008 and later (CPSC 2015a; CPSC 2017a), because of insufficient sample sizes for pregnant women in the later NHANES data.

Comment 3.8: NHANES and TIDES data on pregnant women. One commenter remarked that it was unclear why CPSC did not include pregnant women in the WORA population in the two recent biomonitoring analyses (CPSC 2015; CPSC 2017) to increase the population size. The commenter noted that inclusion of pregnant women did not significantly affect the outcome of estimated risk, but encouraged staff to add pregnant women into the analysis anyway. The commenter also provided information on first trimester pregnant women in the TIDES analysis (2010-2012) demonstrating that exposures were similar or lower than NHANES 2011/2012 women. The commenter extrapolated that because trends in pregnant women and WORA were similar, the current risk to pregnant women would be the same as WORA, and therefore the risk to pregnant women from phthalates would have declined similar to WORA.

Response 3.8: Staff acknowledges that pregnant women were not included in either staff biomonitoring analysis (CPSC 2015; CPSC 2017). This was stated in the 2017 staff analysis (CPSC 2017a, p.2). Staff omitted pregnant women in these analyses to be consistent with the CHAP methodology, which intentionally separated pregnant women from WORA.

Staff notes that the TIDES study had not been designed to be nationally representative and therefore, TIDES urinary metabolites may not be similar to the sampled population in NHANES. Also, when comparing female 2011/2012 metabolite concentrations (µg/L) in the CDC 4th National report (CDC 2017) to TIDES specific gravity adjusted metabolite data in pregnant women (Sathyanarayana et al. 2016), staff notes that the similarity between pregnant women and WORA depends on the phthalate metabolite and the percentile examined. When examining some metabolites (e.g., 75th percentile MECPP, MEOHP, and MEHHP) NHANES females have higher values than TIDES pregnant women, and the converse relationship is true when investigating other metabolites (e.g., 75th percentile MCOP and MEHP). A recent paper by

James-Todd et al. (2017) also demonstrates that levels of urinary phthalate metabolites vary over the course of pregnancy for different races and ethnicities, making extrapolation from WORA to pregnant women even more uncertain.

Although it is reasonable to assume that changes in exposure for WORA and pregnant women are likely to be similar in direction, human biomonitoring data does not exist to support quantitative extrapolations from WORA to pregnant women.

Comment 3.9: Exposure impact. A commenter noted that the most recent NHANES data (2013/2014) demonstrated that the non-white and young children populations had creatinine corrected levels of DEHP (MEHHP) that were disproportionately higher than other populations and that it was CPSC's obligation to consider these disproportionate exposures. The commenter also contended that DINP and DIBP exposures were increasing and that the CPSC must finalize prohibitions "to protect vulnerable populations including children, women of reproductive age, and particularly women of color."

Response 3.9: Section 108 of the CPSIA permanently prohibited children's toys and child care articles containing DEHP in concentrations greater than 0.1 percent.

The CHAP and staff considered the most MRDE-sensitive subpopulations when performing risk analyses to support the NPR and subsequent analyses. WORA were selected because they represented the best surrogate for pregnant women, which in turn were a surrogate for fetuses, the population most sensitive to phthalate MRDE effects. By protecting the population most sensitive to phthalate exposure, the draft final rule also protects other populations, irrespective of ethnic or racial composition.

The draft final rule prohibits children's toys and child care articles containing DINP and DIBP in concentrations above 0.1 percent.

Staff concurs with the commenter that the 95th percentile creatinine corrected metabolites for children 6-11 years old and Mexican Americans, Non-Hispanic blacks, All Hispanics, and Asians for DEHP (MEHP, MEHHP, MEOHP, MECPP) are higher than those for Non-Hispanic whites (CDC 2017). Staff also notes that creatinine corrected levels of DIBP (MIBP) have increased in Mexican Americans, non-Hispanic black, and Asian individuals when compared to 2005/2006 levels and that these levels are higher than in non-Hispanic whites (CDC 2017). Staff notes that the same analysis shows that the levels of DINP (MINP or MCOP) have also increased over time when compared to 2005/2006, but are highest in non-Hispanic whites when compared to other populations.

Staff notes that the CDC demographically focused results include all individuals within the ethnic demographic and do not necessarily reflect phthalate concentrations in the populations most sensitive to phthalate MRDE (pregnant women, WORA 15-45, male infants). Staff also is aware of the publication by (James-Todd et al. 2017) in which phthalate metabolite concentrations are associated with racial/ethnic disparities in pregnant women that had term births. In the study, the authors determined that MBP, MIBP, MEP, MBzP concentrations were highest in Hispanics and MCPP, MEHP, sum of four DEHP metabolites, sum of three DEHP oxidative metabolites highest in non-Hispanic blacks (when compared to non-Hispanic whites). The author stated that "Reasons for racial/ethnic variations in urinary phthalate metabolite concentrations are likely due to differences in exposure to phthalate containing consumer products."

Most recently, CPSC assessed exposure and risks to WORA in five NHANES biomonitoring data cycles (2005/2006, 2007/2008, 2009/2010, 2011/2012, 2013/2014; CPSC 2015, 2017). Pregnant women in NHANES were not selected for exposure analysis in years later than 2005/2006 because their numbers were not sufficient to use for statistical analysis (approximately 20 pregnant women in each data cycle after 2005/2006).

Staff would like to note that conservative assumptions used for assessing the potential risks to the most sensitive target population (WORA) will also encompass risks to other populations and demographics. Statistics such as the proportion of the population with an HI greater than one naturally include these individuals. Staff recommendations for mitigating the potential risks from phthalate exposure would also apply to these more sensitive demographics.

Comment 3.10: Sample size for pregnant women. Some industry commenters said that sample size for pregnant women in the CHAP's analysis was too small to yield reliable risk estimates. One commenter noted that a "minimum sample size of 150 would be required to meet NHANES guidelines for statistical reliability. Another observed that, at the very least, working with small sample sizes would require consideration of the "increased uncertainty in the estimation of the upper exposure limits."

Response 3.10: The sample size necessary for statistical analysis of NHANES data was calculated by CDC.[16] The estimated sample size needed for analysis of NHANES was determined assuming a design effect of 1.5 and considering two conditions: 1) "An estimated prevalence statistic on the order of 10 percent in the sex-age domain should have a relative standard error of 30 percent or less; and 2) "Estimated (absolute) differences between domains of at least 10 percent should be detectable with a Type I error rate (α) of less than or equal to 0.05 and a Type II error rate (β) of 0.10." To fulfill the first condition a sample size of approximately 150 persons is needed. To fulfill the second more stringent condition a sample of approximately 420 individuals is needed.

The 2005/2006 NHANES biomonitoring cycle is the most current cycle designed to over-sample pregnant women. The number of pregnant women from which urine phthalate metabolites were measured is 130. This is the largest publicly available set of biomonitoring data from pregnant women to date. For later NHANES data sets, CPSC staff used WORA to estimate phthalate exposures from later NHANES cycles because the numbers of pregnant women with urine measurements of phthalate metabolites were much smaller. CPSC does not present any tests of differences between domain means, thus, the higher recommended sample size is not applicable.

Comment 3.11: Urinary spot sampling. Several industry commenters noted that HBM studies typically take one spot urine sample as opposed to averaging urine samples collected over a longer period of time. Commenters suggested, based on a study by Preau et al. (2010), that exposures calculated using spot samples will have a larger variance than the distribution of average daily intake estimated from repeated measures from each individual, and will therefore overestimate exposure and result in conservative risk estimates. Industry commenters explained that a spot urine sample bases the entire exposure on that one day and time, even though the individual's exposure fluctuates over time (hour to hour, day to day). These commenters stated that when calculating risk, the exposure information should match the exposure scenario of that

[16] National Health and Nutrition Examination Survey: Sample design, 2007–2010. Available at: https://www.cdc.gov/nchs/data/series/sr_02/sr02_160.pdf.

hazard data to which it is compared (e.g., chronic exposure to chronic hazard). The commenters further noted that the exposed individual would need to have exposures greater than an HI of one day after day to have a risk to her fetus and that this was very unlikely.

However, another industry commenter stated that spot samples are as predictive of urinary concentration as 24-hour urinary samples and provided a graph of cumulative probability and log urinary concentration of MEHHP (a DEHP metabolite) for spot, 24-hour, and 7-day average samples. The commenter stated that trend lines for concentrations based on 24-hour and 7-day average sampling overlapped substantially. Concentrations from spot sampling were similar, but lower than 24-hour and 7-day average sampling methods. Fit of the data to the trend lines was visually very good for all sampling methods. This commenter also referred to Preau et al. (2010) results for MEHHP and stated that the 95th percentile concentrations from spot samples "are a conservative estimate of average exposure over time and appropriate for derivation of HQ's/HI's for determination of risk" but that the 95th percentile also overestimated the 7-day average of the individuals.

Response 3.11: Regarding spot urine samples versus average daily samples, the CHAP and CPSC staff estimated daily intake of each phthalate by modeling creatinine-related metabolite measurements across participants in NHANES. NHANES measured metabolites from one spot urine sample per individual in the study. Spot urine samples were collected at different sites and at various times of the day and days of the week. Additionally, because participants for each NHANES study cycle were randomly selected from civilian, non-institutionalized individuals in the United States according to a probability-based complex, multi-stage sample design, the estimated daily intakes are representative of the U.S. population. The estimated daily intakes and the resulting HQs and HIs represent estimated population per capita phthalate exposure across the 2-year NHANES cycle, not average daily estimates of an individual's exposure across time. Thus, an estimated proportion of the population with an HI less than one using HBM from NHANES represents the estimated proportion of population within that cycle that would have an HI less than one at any one given time of that cycle. Estimates based on NHANES HBM do not imply that individuals with HI less than one at given time will continue to have HI less than one for all 2 years of a NHANES study cycle.

The commenters point to Preau et al.'s small sample observational study to conclude that the concentrations of phthalate metabolites can vary considerably throughout a day for a given person, and thus spot sampling is not representative of a person's average exposure over time. Staff notes that longer-term exposures, as measured by average daily exposure during longitudinal studies, are not necessarily required to cause MRDE. Numerous studies in animals have demonstrated that MRDE and related effects can occur after one or a few doses (Carruthers and Foster 2005; Creasy et al. 1987; Ferrara et al. 2006; Gray et al. 1999; Hannas et al. 2011; Jobling et al. 2011; Jones et al. 1993; Li et al. 2000; Parks et al. 2000; Saillenfait et al. 1998; Saitoh et al. 1997; Spade et al. 2015; Thompson et al. 2004; Thompson et al. 2005). Thus, shorter-term elevated exposures could be related to adverse health outcomes in the fetus, if the exposure occurs during the window of susceptibility.

The CHAP noted that sources of variability and uncertainty qualitatively discussed in comment response 4.1.3 of the CHAP report are: measurement; individual metabolism; temporal; fasting; and elimination kinetics and spot samples. The CHAP concludes that when using HBM and dose extrapolations based on them "…certain factors for the possibility of overestimates of the daily

intake (and therefore the HI) seem to be balanced by factors for the underestimation of the DI/HI." (CHAP 2014, p. 75).

Staff agrees with the CHAP that the HBM represent the best available estimate of exposure and that any errors in daily intake estimates are unbiased, that is, they are equally as likely to underestimate exposure as they are to overestimate it (CHAP 2014, pp. 73–75). HBM data are a direct measure of human exposure and, therefore, superior to alternatives such as modeled exposures. NHANES is a high quality study and provided exposure data that are representative of the U.S. population. Similar data with 24-hour or longer sampling times are not available.

Comment 3.12: Individual risk. Commenters stated that individual phthalate risk cannot be determined using NHANES spot samples, and it is inappropriate and not scientifically supportable to report results as a proportion of the population with an HI over one. The commenters continued that the individual spot urine samples are too variable and do not represent chronic exposures over time and that chronic exposures over time are needed to induce MRDE. The commenter ended with the conclusion that the upper tails of the spot urine distribution over-predicted longer term exposures.

Response 3.12: Staff disagrees that the estimation of individual phthalate risk from NHANES biomonitoring data is inappropriate. Staff concurs that spot urine samples are variable and are not representative of long-term exposures, but also notes that numerous studies in animals have demonstrated that MRDE and related effects can occur after one or a few doses (Creasy et al., 1987, Jones et al., 1993; Saitoh et al., 1997; Saillenfait et al., 1998; Gray et al., 1999; Parks et al., 2000; Li et al, 2000; Thompson et al., 2004; Carruthers and Foster, 2005; Thompson et al 2005; Ferrara et al., 2006; Hannas et al., 2011; Jobling et al 2011; Spade et al., 2015). These studies refute the commenters' assertion that a long-term chronic exposure is necessary to induce MRDE. Staff therefore notes that exposures resulting in an HI greater than one (as demonstrated by a sufficiently high NHANES metabolite concentration) have the potential for inducing MRDE. Staff also notes that it is impossible to know whether a particular spot urine sample is over predicting or under-predicting the actual exposure, so asserting that a spot urine sample is an overly conservative estimation of risk is inappropriate.

Because the sample size is sufficient to estimate the proportion of the U.S. population of WORA with HIs less than one, staff concludes that it is appropriate to use the individual NHANES HI values to estimate risk. Contrary to the commenter's claims, chronic exposure is not needed to induce MRDE, and any uncertainties in the measurements are unbiased, that is, they do not necessarily over-predict risk. Staff notes that in the 2013/2014 NHANES sample of 538 WORA (of approximately 60 million WORA in the U.S. population), there were from two to nine individuals with a HI greater than one (i.e., at risk), depending on the PEAA case. As described in section 5.4 of TAB A, the 2013/2014 NHANES data set cannot be used to estimate how many WORA in the U.S. population have HIs greater than one.

Comment 3.13: Proportion of the individuals with an HI greater than one and regulatory thresholds. A commenter discussed the implications of the CHAP and CPSC staff presenting risks as the proportion of individuals with an HI greater than one. The commenter thought that portrayal of information in this manner was misleading and a misuse of statistics. The commenter continued that no WORA had a cumulative risk of concern and that WORA with a spot sample above the 95th percentile were not at risk because the adverse effect is caused by a high level of phthalates day after day over the first trimester (humans; repeat dose) and not a

peak one time hit, which is what a (variable) NHANES spot urine sample represents. The commenter adds that an individual's HI from a spot urine sample "has essentially no bearing on risk to the individual" because it does not represent a repeat dose, longer term exposure necessary to induce the adverse effects (phthalate syndrome) and that a few HIs (or HQs such as DINP) above one also are not representative of the population risk.

The commenter concluded that using the "95th percentile of the HIs calculated from single spot samples of multiple individuals will encompass the longer-term exposures experienced by all individuals in the population," provide a conservative worst case scenario, be most supportable scientifically, and has been used by EPA (Christiansen et al, 2014), the CHAP, and CPSC in the proposed rule. The commenter also asserted that 99th percentile exposures "are too unstable to provide a reliable basis for decision-making and do not reflect true risk." The commenter made similar arguments in support of the DINP, concluding that the DINP 95th percentile HQs (and HIs) were less than one, so WORA and their fetuses "do not have risks of concern."

Response 3.13: CPSC staff disagrees with the commenter and emphasizes that it is statistically appropriate to portray the individual NHANES data as a proportion of the NHANES sample population with an HI of greater than one. Staff notes that in both biomonitoring analyses (CPSC 2015, 2017) the statistical stability of this number was reported so that readers could assess whether extrapolation from this number to the national population could be performed with statistical reliability.

Comment 3.14: Biomonitoring exposure. One industry commenter stated that the CPSC staff biomonitoring exposure and risk analysis overestimated exposures when using the 2009/2010 and 2011/2012 NHANES data sets, because it did not consider urinary excretion rates, and instead used normalization to creatinine excretion. This criticism was noted after the commenter stated that "most of the Staff Analysis was conducted correctly."

Response 3.14: Regarding use of direct urinary extraction rates versus extrapolation, the submitter's comments pertain to CPSC staff's June 2015 report (CPSC 2015a). Staff estimated exposure and risk from each of the four NHANES data sets using the extrapolation method applied by the CHAP (pp. 35–36). Because the 2005/2006 NHANES study oversampled pregnant women, the CHAP presented its exposure and risk estimates based on the BMD collected during that NHANES cycle. The additional information necessary to directly calculate urinary mass excretion rates was not collected during the 2005/2006 or 2007/2008 NHANES studies. Therefore, the extrapolation method was the only option available to the CHAP. Staff replicated the CHAP's reported exposure and risk estimates using the 2005/2006 NHANES data and applied the same methods to calculate estimates from the later NHANES studies. The Commission directed staff to conduct its analyses to evaluate changes in phthalate exposures across NHANES studies, which required avoiding the introduction of additional uncertainties. Staff chose not to produce daily intake estimates from the 2009/2010 and 2011/2012 NHANES studies using directly estimated urinary mass excretion rates. Doing so would have unnecessarily introduced another uncertainty factor that would confound the suggested changes in exposure to each phthalate ester over time.

Comment 3.15: Metabolites and fraction excreted in the urine. A commenter remarked that using the hydrolytic metabolites for DINP and DIDP (10 percent of total urinary metabolites) for estimating exposures could lead to underestimation of phthalate risk when compared to other

phthalates such as DEP, DBP, DIBP, and BBP which have a higher proportion of total metabolites excreted and considered (70 – 80 percent).

Response 3.15: Staff notes that the estimation of daily intake (mg/kg-day) from NHANES urinary phthalate metabolite concentrations considers the specific metabolite AND its molar fraction excreted in the urine (F_{UE}; from published papers). In this way, the algorithm compensates for any lapse in information regarding important metabolites or their fraction in the urine. The CHAP considered many combinations of metabolites and their urinary fractions (CHAP report, Table 2.4), before selecting on the ones they used in exposure estimations (CHAP report, Table D-1).

Comment 3.16: Metabolite biomarkers. Five commenters; two industry, two NGO, and one government asked CPSC to re-evaluate exposure using additional metabolite biomarkers for DINP, DNOP, and other phthalates and also re-evaluate using later NHANES data. In particular, the government commenter noted that MINP was previously used as a DINP biomarker in the CHAP report and that CPSC should also consider the other DINP biomarker MCOP. This is because MCOP is detected more frequently and at higher concentrations in the 2011/2012 data (median and 95th percentile levels in females have tripled and quadrupled, respectively since 2005/2006). Commenters suggested that staff consider the DNOP metabolite MCPP when re-assessing exposure because MCPP appears to be increasing in U.S. females (a doubling from 2005/2006 to 2011/2012), was "detected widely" in the later NHANES data cycle (2011/2012), and was highest in children and Asian-Americans. A commenter noted that exposure to MCNP, the metabolite for DIBP, has also increased in women from NHANES 2001/2010, but declined slightly in 2011/2012, and that CPSC should also re-evaluate exposure to this metabolite. One NGO commenter noted similarly that the exposures to DINP are increasing and are concerning.

One of the commenters asserted that the quantitative estimates of DINP risk from the 2017 analysis provided by CPSC staff were calculated incorrectly and were 17 percent too high. The commenter requested that staff use multiple metabolites (e.g. MINP and MCOP) to estimate DINP exposure instead of just one (MCOP). The commenter noted that exposure estimated for DEHP used 4 metabolites.

Response 3.16: CPSC used MCOP to analyze phthalate exposure, as did the CHAP. Staff concurs that MCOP is the most appropriate metabolite to use for DINP exposure because for exposed individuals, MCOP will be detected more frequently and at higher levels than other DINP metabolites (e.g., for the 2005/2006 NHANES data, MCOP was detected in 95.2 percent of the samples, and MINP was detected in 12.9 percent of the samples; (Calafat et al. 2011)). Staff is also concerned about the increase in DINP exposure.

Staff acknowledges that the creatinine corrected urinary metabolite data for MCPP (CDC 2017) demonstrate that children 12-19 years old and Asian-Americans have higher exposures than other populations and that the MCPP metabolite has been increasing in some populations. Staff and CHAP did not use MCPP to estimate DNOP exposure, however because MCPP is not a specific metabolite for DNOP and can be created from the metabolism of other phthalates. Therefore, trends regarding MCPP exposure in some populations are less relevant to estimating national risk from DNOP. Furthermore, DNOP does not induce MRDE, and was not included in the CRA.

Regarding MCNP, the commenter's reference to MCNP is inaccurate because MCNP is a metabolite of DIDP, and not DIBP (CDC 2017). Staff analysis of later NHANES data included

the DIBP metabolite MIBP. Nonetheless, staff agrees that exposure to DIBP has increased, which is of concern because DIBP is similar in toxicity to DBP. Furthermore, staff has assessed DIBP risks to WORA in two recent biomonitoring analyses (CPSC 2015a; 2017a).

Regarding the use of both MINP and MCOP to estimate DINP exposures, staff does not agree that the estimated exposures for DINP in the 2015 and 2017 analyses were incorrect. CPSC staff acknowledges that using different metabolites and F_{UE}s will change exposure and risk estimates. CPSC staff used one metabolite, MCOP, to estimate DINP exposure to be consistent with the CHAP methodology and a previous staff exposure and risk documents (CPSC 2015a)(TAB A).

The CHAP recognized that there are multiple ways to estimate phthalate exposure using individual and combined phthalate metabolites and provided a table of potential metabolites and associated fraction of the urinary metabolite excreted factors (F_{UE}s; Table 2.4, CHAP report). Ultimately the CHAP selected only one F_{UE} and metabolite pair for each phthalate (CHAP 2014, Table D-1)(Table D-1, CHAP report).

Staff also notes that the information provided by the commenter was incomplete as to the factors necessary to estimate DINP exposure from the combination of MINP and MCOP metabolites. The commenter did not provide an F_{UE} for this combination of metabolites and therefore, there is not enough information to appropriately estimate exposure.

Comment 3.17: Multiple metabolite biomarkers for DINP. One industry commenter argued that the CHAP and staff inappropriately used only one metabolite (MCOP) instead of two (MCOP and MINP) when estimating exposures for DINP from extant NHANES biomonitoring data. The commenter noted that multiple metabolites were used in combination to estimate exposures for DEHP and concluded that the DINP DI for WORA would be 17 percent less if both metabolites were used to estimate exposure. The commenter thought that staff should be using this approach for estimating DINP exposures from the NHANES data sets.

Response 3.17: CPSC staff acknowledges that using different metabolites and F_{UE}s will change exposure and risk estimates. CPSC staff used one metabolite, MCOP, to estimate DINP exposure to be consistent with the CHAP methodology and a previous staff exposure and risk documents (CPSC, 2015, TAB A).

The CHAP recognized that there are multiple ways to estimate phthalate exposure using individual and combined phthalate metabolites and provided a table of potential metabolites and associated fraction of the urinary metabolite excreted factors (F_{UE}s; Table 2.4, CHAP report). Ultimately the CHAP selected only one F_{UE} and metabolite pair for each phthalate and specifically, MCOP for estimating exposures to DINP (Table D-1, CHAP report).

Staff also notes that the information provided by the commenter was incomplete as to the factors necessary to estimate DINP exposure from the combination of MINP and MCOP metabolites. The commenter did not provide a urinary excretion factor (F_{UE}) for this combination of metabolites.

Comment 3.18: Staff analyses of post-CHAP NHANES data. One industry commenter stated that it was unclear whether staff included pregnant women in the WORA population in staff's NHANES Biomonitoring Analysis (CPSC 2015) and, if staff did not include pregnant women in the analysis, why the pregnant women would have been left out after determining there was no difference in exposure. The commenter concluded that it would not have made a difference, because the commenter's reanalysis for both possible populations found HIs less than one at the

95th percentile when considering both 2009/2010 and 2011/2012 data sets. The commenter also noted that all pregnant women had an HI less than one in these data sets.

Response 3.18: In staff's 2015 NHANES Biomonitoring Analysis, the CPSC staff did not include pregnant women in the WORA population (CPSC 2015a, p.8). In addition, the sample size of pregnant woman was too small in each of the later NHANES cycles to use for statistical analyses. Even if all pregnant women had an HI less than one in these data sets, no conclusion could be drawn, because the sample size of pregnant women is too small for statistical tests of differences.

Comment 3.19: Bright line: Regarding the biomonitoring data and the CRA, one commenter noted that CPSC had established a "bright-line" "for determining whether there is potential for harm," "for determining when there is a reasonable certainty of no harm," and for making "recommendations about risk management" or "decisions for rulemaking," and that the "bright-line" chosen was not appropriate.

Response 3.19: Regarding the establishment of a "bright-line" for determining potential for harm, a reasonable certainty of no harm, risk management decision or rulemaking decision, CPSC did not establish such a bright line in the NPR. In the context of the phthalate rulemaking, such a "bright-line" would establish: 1) a metric (i.e., hazard index greater than one), and 2) acceptable levels of the population exposed (e.g., less than some percentage). The Commission stated that an HI less than one is necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." 79 FR 78334. However, the Commission did not set an acceptable level of population exposed. Instead, the Commission determined that the 10 percent of pregnant females and 5 percent of infants with hazard indices greater than one was not acceptable. The Commission did not establish what bright line level would meet the statutory requirement of "reasonable certainty of no harm with an adequate margin of safety." In Section VII, staff discusses the results of the later NHANES data in regards to the statutory requirement of "reasonable certainty of no harm."

Comment 3.20: NHANES data and "reasonable certainty of no harm." Commenters asserted that CPSC staff's reanalysis of the CHAP's analysis using more recent NHANES data clearly demonstrates that the interim prohibition involving DINP, DIDP, and DNOP can be lifted while meeting the "reasonable certainty of no harm" standard set forth in the CPSIA. For example, in response to staff's 2015 update, one commenter stated: "For all three Cases and all four data sets the median HI for WORA (women of reproductive age) is far less than 1. Even at the 95th percentile, the HI is uniformly less than one, except for Case 1 in 2007/2008 where the HI is only slightly above 1 (HI is 1.1)." The commenter stated further that "under any reasonably foreseeable scenario," the cumulative risk cannot be expected to increase above an HI of 1 because, although DINP is replacing DEHP (children's toys and child care articles with DEHP were prohibited after the 2005/2006 NHANES sample data was obtained by CDC and used by the CHAP), DINP's potency is much lower than DEHP's potency. Some of these commenters also noted that SFF data does not support continuing the prohibitions because that data was collected before the CPSIA's permanent prohibition involving DEHP and the sharp decline observed for DEHP. Comments on staff's 2017 update reiterated these points, noting that the NHANES 2013/2014 data show that cumulative risk for WORA continues to decline with the HI consistently below one for the 50th and 95th percentiles.

Response 3.20: The CPSIA required the Commission to consider whether making the interim prohibitions involving DINP, DNOP, and DIDP permanent is necessary "in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." CPSIA § 108(b)(3)(A).

For DNOP and DIDP, the Commission proposed lifting the prohibition concerning their use because they do not contribute to the cumulative risk and their risks in isolation are low.

The CHAP's and staff's recommendations on DINP are based primarily on cumulative risk. As noted in the response to comment 3.2, the CRA demonstrates that HIs greater than one were observed in WORA, in all NHANES data cycles, including the most recent (2013/2014). Male children for these women would be at risk for MRDE. The NHANES 2013/2014 data set shows some HIs greater than one among the WORA participants, but the number is too small to project to the national population.

Staff concludes that, because a portion of the potentially sensitive population is still near the level of concern (HI greater than 1), permanent prohibition of children's toys and child care articles containing more than 0.1 percent of DINP is still necessary to "ensure a reasonable certainty of no harm" to children and pregnant women with an "adequate margin of safety."

Comment 3.21: Use of values above the 95th percentile. A commenter on the 2017 staff report asserted that it is "scientifically inappropriate to go above the 95th percentile in evaluating either individual or cumulative risks to the fetuses of women of reproductive age as indicated by the CRA." The commenter stated that going above the 95th percentile values are too unstable to provide a basis for regulatory decisions. The commenter noted that EPA's 2014 paper on five phthalates reported the 95th percentile from the calculations of HIs for three of the five phthalates (and the CHAP and CPSC's previous analyses used the 95th percentile).

Response 3.21: Staff notes the utility of the 95th percentile in describing risk. Staff considers that the 95th percentile, as well as other measures such as the average, median, or 99th percentile, is a commonly used metric, included by the CHAP, to help characterize the distribution of exposure and risk in a population.

The CHAP did not indicate that the 95th percentile, or any other part of the cumulative risk distribution (e.g. median, 99th percentile), should be used to establish acceptable risk for risk management purposes. Rather, the CHAP, having determined that an HI greater than one was necessary to identify the population at risk, then used the distribution of HIs to characterize the percentage of the population with an estimated HI greater than one. In this proceeding, staff did not base its recommendations on any particular percentile; staff's recommendation is based on the observation that people in the NHANES sample have HIs greater than one.

Staff disagrees with the blanket statement that it is scientifically inappropriate to go above the 95th percentile in interpreting a cumulative risk assessment. There is no scientific basis for an assertion that the 95th percentile of a distribution is the largest value that can be considered. The commenter specified that the values above the 95th percentile are unstable. In this case, staff agrees that the values associated with the upper tail of the distribution of HIs (e.g., above the 95th percentile) have large variance estimates, due to sample size (i.e., statistically unstable). The large variances mean that we may be precluded from estimating the precise number of WORA with HIs greater than one in the larger population from which the sample was selected. Individuals with HIs greater than one were observed in every NHANES data cycle analyzed.

As the commenter mentioned, EPA's paper (Christensen et al. 2014) states, "we present findings for the 95th percentile of estimated phthalate intake recognizing that there may be more variability in these values, because this information provides insight into the potential risk at the highest levels of exposure in a general population setting." Staff considers EPA's discussion to be consistent with the CHAP's and staff's presentation of results, because the goal is to provide insight into the risks among the most highly exposed individuals.

Staff considers that risk managers should take into account all of the information and results of an analysis, including the entire distribution of exposure and risk in the sample. Even if one considers only the biomonitoring study sample, rather than the larger population, some WORA from each NHANES cycle show HIs greater than one.

Staff re-emphasizes that the CHAP's and staff's analyses are based on human biomonitoring, i.e., actual observations of people. These observations should be considered in risk management and decision-making.

Section 3 Summary

Staff concludes that the data used and analyses performed by the CHAP were appropriate and support the phthalate rulemaking. In the analysis of NHANES data published following the CHAP's analysis, staff found that that total phthalate exposures in WORA have changed. Although DEHP exposure has declined, exposure to DINP has increased roughly 5-fold since 2005/2006. Although DEHP was the major contributor to the cumulative risk in 2005/2006, DINP now contributes about as much as DEHP (see TAB A, Figures 6 and 7, and Table 8). As a result of changing phthalate exposures, the percentage of WORA with HI equal to or less than one has increased from about 97 percent (95.8 to 97.1, depending on the PEAA case) in 2005/2006 to about 99 percent (98.9 to 99.6 percent) in 2013/2014 (TAB A, Table 7). Although the percentage of WORA with HI less than or equal to one has increased, there are still some WORA with an HI greater than one in the 2013/2014 data sample. In a sample of 538 WORA, there were from two to nine individuals with a HI greater than one (i.e., at risk), depending on the PEAA case. As described in section 5.4 of TAB A, the 2013/2014 NHANES data cannot be used to estimate how many WORA in the U.S. population have HIs greater than one. Furthermore, there are also now individual WORA in the 2013/2014 NHANES sample in which DINP exposure alone leads an HI greater than one, although we cannot calculate a national percentage.

If the overall phthalate exposure and risk to WORA have declined since 2005/2006, it is likely that exposures and risks to infants and pregnant women have also declined. However, no new data on infants or pregnant women are available to quantify the effects of changing exposures. Staff notes that infants' and children's exposures tend to be greater than in adults (CHAP 2014; Sathyanarayana et al. 2008a; Swan 2008; Swan et al. 2005). For the phthalates in the CHAP's CRA (DBP, DIBP, BBP, DEHP, and DINP), daily intakes were generally 2- to 3-fold greater in SFF infants than in their mothers (CHAP 2014, Table 2.7). In the scenario-based exposure assessment considered by the CHAP, estimated daily intakes were 2- to 5-fold greater in infants than in women (CHAP 2014, Appendix E1, Table E1-18). In Germany, nursery school children had roughly twice the DEHP exposure as their parents (Koch et al. 2004).

The most recent available data for pregnant women (2005/2006 NHANES) and infants (Sathyanarayana et al. 2008a; 2008b) show that in the United States, 10 percent of pregnant

women and 5 percent of infants had HIs greater than one. Even if pregnant women and infants' exposures have declined since those data were obtained, their exposures are likely to be at least as much as those of WORA, and infant exposures are likely to be greater than that of WORA.

4. The CHAP's Three Cases

This introduction addresses specific terminology including PEAA, POD, and uncertainty factors, and the three cases discussed in the following comments and responses. Comments common to all three cases are addressed first, followed by comments focused on specific cases.

Potency Estimate for Antiandrogenicity (PEAA)

PEAA is an acronym for potency estimate for antiandrogenicity. This term was first described in the CHAP report (2014). The CHAP coined the term PEAA solely for the antiandrogenic cumulative risk assessment, differentiating this hazard term from the regulatory terms Acceptable Daily Intake (ADI) or Reference Dose (RfD), which may have been estimated using other non-antiandrogenic (lower) toxicity endpoints. A PEAA for each phthalate is estimated by dividing the MRDE "antiandrogenic" point of departure (POD; toxicity endpoint) by an uncertainty factor (UF) that is a quantitative estimate of interspecies, intraspecies, database, and toxicity uncertainties

Point of Departure

A point of departure (POD) is a dose on a dose-response curve used to derive an ADI, RfD, or PEAA. Traditionally, a POD represents the highest dose level at which the adverse effect is not seen or is not statistically significant; this is known as the no observed adverse effect level (NOAEL). In some cases, the POD is the lowest dose level at which an adverse effect was seen; this is known as the lowest observed adverse effect level (LOAEL). Typically a LOAEL is only used in risk assessment when a NOAEL is not available, which occurs when the lowest dose level tested showed the adverse effect. Another method for determining POD is benchmark dose (BMD) analysis, which may be used to estimate the dose at which, for example, 10 percent of animals are affected.

Uncertainty Factor (UF)

An uncertainty factor (UF, also called a safety factor) is a quantitative factor that is used to account for uncertainties associated with available data. Such factors are used to derive acceptable dose or exposure levels, such as an acceptable daily intake (ADI or PEAA).

Typically, an interspecies UF is applied to account for potential differences in sensitivity between humans and the animals used to study particular chemical hazards. Differences between humans and animals may include the rate and extent of absorption of a chemical into the body, metabolism, elimination of the chemical from the body, and the specific interactions of the chemical with the tissues of the body that cause adverse health effects. In addition, the conditions of exposure to a chemical in experimental animal studies may differ from typical human exposures.

A second intraspecies UF is applied to account for differences in sensitivity among humans. Conditions that may contribute to differences in sensitivity to adverse health effects among human include age, sex, genetics, nutritional status, and health status. Additional UFs may be applied to account for limitations in the available data. Generally, a factor of 10 has been considered to be adequate to account for the range of possible differences that each UF addresses (Barnes and Dourson 1988; CPSC 1992; Dankovic et al. 2015). If sufficient information is

available, assessment-specific factors, with values other than 10, may be derived. The CHAP generally applied UFs of 10 for the animal studies to human extrapolation and to account for human sensitivity, and applied additional factors in specific cases for other data limitations. Uncertainty is also considered in assessments in which an acceptable dose level is not derived, such as margin of exposure analysis (MOE), although the MOE approach does not use the same quantitative process as for derivation of an ADI.

Three Cases

The CHAP derived three sets of PEAA values (cases) to explore the effect of different methodology (e.g., different uncertainty factors and PODs) on cumulative risk estimates to "determine the sensitivity of the results to the assumptions for PEAAs and the total impact on the HI approach" (CHAP 2014, p. 4) The three cases were explained in the CHAP report (CHAP 2014, pp. 63-64). This explanation included a description of the uncertainties involved. Case 1 was based on published, peer-reviewed values (Kortenkamp and Faust 2010). Case 2 was based on a relative potency method, using multiple-dose studies of *in-vitro* fetal testosterone production (Hannas et al. 2011). For Case 3, the CHAP derived new PEAA values after considering all the available literature, including studies such as Boberg et al. (2011). The results of all three cases are important for understanding the potential risks, as the cases bring different perspectives to the risk assessment. As such, all three cases must be considered.

Overview of Public Comments on the CHAP's Three Cases (PEAAs)

Some commenters noted that Case 1, which was based on PEAA values published in 2010, was out of date. However, the source of the published PEAA values (Kortenkamp and Faust 2010) was new when the CHAP began its deliberations in April 2010 (comment response 4.7). Case 2, the subject of numerous comments, was based on a comparison of the relative potencies of the different phthalates. Some commenters claimed that Case 2 was based on an *in vitro* study. Staff notes that Case 2 was based on a study (Hannas et al. 2011) in which animals were exposed *in vivo*, although the rate of testosterone synthesis, by necessity, was measured *in vitro*. Other commenters criticized the method for estimating the relative potency of DINP to DEHP. Staff concludes that the CHAP used generally accepted methods for estimating relative potency (comment response 4.9-4.14). Comments on Case 3 were minor and limited to technical details.

Staff concurs with the CHAP's use of three Cases, in part, because different regulatory agencies often derive slightly different toxicity values (PEAAs). Furthermore, the risks resulting from the three Cases are remarkably similar. Staff concludes that each of the three Cases has certain advantages, as noted above, and that all three are appropriate for estimating human risk. Case 1 and Case 3 were developed by assessing each phthalate individually, using conventional risk assessment methods. Case 1 was from published PEAA values, while Case 3 was derived *de novo* by the CHAP. Case 2 has the advantage that most of the phthalates were assayed in the same laboratory using the same methodology. Thus, Case 2 is ideal for comparing the potencies of individual phthalates. Staff concludes that the CHAP's approach of using three Cases is not only appropriate, but provides an additional degree of reliability to its CRA. Staff further concludes that all three Cases are useful for human health risk assessment.

Comments on All Three Cases

Comment 4.1: Independence of the three cases. One industry commenter expressed concerns with the CHAP's methodology regarding the selection of PODs and the derivation of potency estimates saying that the selection of cases "is misleading because they do not represent independent research, but rather the selection of different PODs," and as such did not truly evaluate the impact of assumptions used in the selection of PODs. The commenter also specified that the original information for both Cases 1 and 2 was the same and primarily based on Howdeshell et al. (2008). The commenter concluded that "there are insufficient data to support the use of these three scenarios to derive HQs and HIs." Thus, the commenter states that this is a limitation of the CHAP report and does not support the prohibition of children's toys that can be placed in a child's mouth and child care articles containing DINP.

Response 4.1: The three Cases are based on three different approaches, as described by the CHAP (CHAP 2014, p. 64, Appendix D, pp. D19–D20). Contrary to the commenter's assertion, staff considers the three Cases to represent independent evaluations using different risk assessment approaches to selecting PODs and deriving PEAAs, rather than just the selection of different PODs. In addition, the CHAP's rationale for Case 1 was that the PEAAs were published values that were specific for phthalate syndrome. In contrast, Case 2 used a relative potency approach, which is an alternative method for assessing the effects of mixtures.

The commenter asserted that Case 1 and Case 2 were both based primarily on Howdeshell et al. (2008). Staff notes that Case 1 PEAAs are from Kortenkamp and Faust (2010). Kortenkamp and Faust derived PEAAs in Case 1 from PODs in Howdeshell et al. (2008), Christiansen et al. (2009), Gray et al. (2000), and Borch et al. (2004). Case 2 PEAAs were based on Hannas et al. (2011). Staff concludes that Cases 1 and 2 are based on different references.

Staff concludes that the three cases used by the CHAP as independent approaches to POD selection are useful in understanding the potential effects of POD and UF selection on risk. The CHAP stated: "We considered these three cases to determine the sensitivity of the results to the assumptions for PEAAs and the total impact on the HI approach." (CHAP 2014, p. 4).

Comment 4.2: Three Cases—Case 1 and 3 PODs vs. Case 2. Among the industry commenters responding to the three cases, one commenter noted that Case 1 and 3 PEAAs "have flaws and quite arguably are too conservative, they nevertheless have a degree of scientific credibility" when compared to Case 2. This commenter also noted that Cases 1 and 3 are based on "real world data and therefore provide a more realistic estimate of the no effect 'ceiling.' " The commenter asserted that case 2 was a model and "it is not scientifically tenable to rely on modeled data when more accurate and reliable data exist" (e.g., NOAELs or LOAELs), which requires Case 2 to be eliminated as a basis to determine risk. Another commenter also suggested that case 2 modeling results were more uncertain than case 3 and for this reason it should be disregarded.

Response 4.2: Staff notes all three cases were based on published, peer-reviewed studies. Dose-response data in Case 2 were analyzed statistically using a dose-response model, which is common practice in toxicology and risk assessment. Dose-response modeling provides a precise, objective means to analyze the data and compare different phthalates.

Staff notes that the CHAP's rationales for each case have certain advantages. The principal advantage of Case 2 is that the PODs are from a study (Hannas et al. 2011) in which multiple

phthalates were tested in the same laboratory using the same methodology. In addition, the study was designed to assess potency, that is, it included multiple doses. Finally, the PODs are based on the rate of testosterone production, which is a key, early step in the mechanism of action that correlates well with reproductive tract malformations (Hannas et al. 2011; Howdeshell et al. 2016). Staff concludes that the uncertainties in Case 2 have been minimized by the use of an appropriate study method and study endpoints to assess DINP potency. Staff considered the results from each case independently and with equal weight when drawing conclusions and crafting recommendations. Staff also concludes that because Case 2 is based on published, peer-reviewed, "real world" data, staff declines the commenter's suggestion to eliminate Case 2 as a basis for determining risk. Further details on Case 2 are discussed in comment responses 4.9 to 4.14.

Comment 4.3: Differences between cases. Some industry commenters criticized the rationales for all three Cases, although they preferred Case 3. One industry commenter noted that while the PEAAs are relatively consistent for DEHP, the PEAAs for some of the phthalates varied considerably (e.g., 13-fold for DINP) and that this variation resulted in "large uncertainties regarding comparative potency assessment and conclusions regarding cumulative risk." The commenter asserted that the reason for this large variation was the "inconsistent use of studies and extrapolation factors" for Case 1, which was taken from a publication by Kortenkamp and Faust (2010). Specifically, the commenter noted that the supporting studies for Case 1 were not designed to estimate potency. The commenter asserted that the Kortenkamp and Faust ignored newer publications by the European Food Safety Agency (EFSA), the European Chemicals Bureau (ECB),[17] and the U.S. National Toxicology Program's (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR).[18]

The commenter criticized Case 2 primarily for its "reliance on biochemical endpoints for assessing relative potency, "where "biochemical assay" refers to the rate of testosterone synthesis (Hannas et al. 2011). The commenter also asserted that "a reduction of testosterone" was not an adverse effect and, therefore, should not be used as the basis of the risk assessment.

The commenter concluded that the use of only one "well justified POD and PEAA as defined in Case 3 will significantly reduce confusion generated by the use of widely differing PODs in table 2.15." in the CHAP report. Thus, the commenter concluded that only the PODs derived for Case 3 are sufficiently supported.

Response 4.3: The CHAP derived three sets of PEAA values (cases) to explore the effect of different methodology (e.g., different uncertainty factors and PODs) on cumulative risk estimates to "determine the sensitivity of the results to the assumptions for PEAAs and the total impact on the HI approach."

As the CHAP explained, they applied three cases to evaluate the impact of using different assumptions to estimate PEAAs (CHAP 2014, pp. 63-66). The commenter criticized Case 1 for inconsistent use of studies and extrapolation factors. Specifically, the commenter notes that the studies cited by Kortenkamp and Faust (the source of Case 1) were not designed to estimate potency. Staff agrees that some of the studies cited in Case 1 were not designed to evaluate potency. However, Kortenkamp and Faust cited the most recent studies available at the time they

[17] Now the European Chemicals Agency (ECHA).
[18] Now the Office of Health Assessment and Translation (OHAT).

performed their analysis. In addition, Kortenkamp and Faust, published in 2010, was the most recent available analysis of PEAAs available when the CHAP convened in 2010.

The commenter also asserted that Kortenkamp and Faust ignored recent studies by the EFSA, ECB, and CERHR, but did not provide references to the reports, and did not specify what specific information Kortenkamp overlooked. Staff notes that the European Food Safety Authority (EFSA), European Chemicals Bureau (ECB), and the U.S. Center for the Evaluation of Risks to Human Reproduction (CERHR) reports are evaluations of published literature, but do not provide new experimental data. In addition, the EFSA, ECB, and CERHR reports generally focus on chemicals in isolation, rather than CRA, which was the purpose of Kortenkamp and Faust's publication.

The commenter criticized Case 2 because it was based on a "biochemical assay," the rate of testosterone synthesis, which he did not consider an adverse health effect. Staff asserts that the rate of testosterone synthesis, and not the level, is the most sensitive measure of antiandrogenic effects and transient reductions in testosterone synthesis during critical periods may lead to permanent adverse effects (Hannas et al. 2011a).

Finally, the commenter concluded that Case 3 was the most defensible of the three cases. Staff agrees that Case 3 is scientifically defensible. However, staff notes that Case 3 is based on multiple phthalate syndrome-related effects in multiple studies, whereas Case 2 is based on one phthalate syndrome-related effect in a single study of multiple phthalates.

Staff concludes that the CHAP's alternate approaches to POD selection are useful in that they demonstrate the impact of different sets of PEAAs on risk estimates. The CHAP concluded that all three cases yielded comparable results. Staff considered the PODs and PEAAs derived for each of the three cases when developing its recommendations to the Commission.

Comment 4.4: Sensitivity analysis. One commenter noted that the CHAP's rationale for using three cases was to "determine the sensitivity of the results to the assumptions for PEAAs and the total impact on the HI approach" and suggested that, as presented, the cases did not thoroughly quantify the impact of the assumptions because they did not transparently provide a range of results, discussions of uncertainty inherent to the cases, and the potential impacts of those uncertainties. For these reasons, the commenter suggested that the decisions made were not well informed, nor science-based. Another commenter noted that the CHAP understood many of the limitations of their methods but failed to discuss them, so the commenter suggested that to "understand the impact of these assumptions and uncertainties embedded in these approaches, alternative plausible assumptions should be evaluated to enable a transparent, side by side comparison."

Response 4.4: The CHAP considered all Cases independently when discussing estimated potential risks to pregnant women and infants (CHAP report Appendix D, 21–40) but also displayed Case results together (e.g., Table 2.16, Table D-9, Table S-1). The CHAP also presented a side-by-side comparison of the PODs, UFs, and PEAAs in Table 2.15 and Table D-8 of the CHAP report. The CHAP concluded that, "The results were roughly similar for all 3 cases (sets of PEAAs) considered." (CHAP 2014, p. 4). Staff considers that because the results were similar, further discussion relating to Case sensitivities is unnecessary. Staff concludes that the CHAP adequately described the differences between the Cases and illustrated the effects of the differences on cumulative risk.

Comment 4.5: Weighting PEAA cases. One industry commenter noted that staff should not have considered each PEAA case in the staff reanalysis as equally weighted and of equal confidence, because, according to the commenter, there are fundamental flaws associated with Case 2's underlying base study and calculated potency estimates, which make the results "not scientifically defensible." The commenter stated that CPSC should eliminate Case 2 from consideration, or at least indicate that Case 2 HIs are not as reliable as HIs in Cases 1 and 3.

Response 4.5: As mentioned in the introduction to this section, the CHAP considered three Cases to assess the effect of different PODs and UFs on risk. Each Case has certain advantages (see introductions for each case). However; the CHAP did not state or imply that any one Case was superior to another. Therefore, staff concludes that each Case should be considered equally. Staff disagrees with the commenter's conclusion that Case 2 is flawed, as explained in comment response 4.4. The CHAP concluded that, "The results were roughly similar for all 3 Cases (sets of PEAAs) considered." (CHAP 2014, p. 4).

Comment 4.6: Biomarkers vs. adverse effects. A commenter noted the inappropriateness of using PODs for different types of endpoints (e.g., MNGs, reduced testosterone production, and retained nipples) and using different effect measures (NOAELs, LOAELs, BMDLs). The commenter continued that because reduced testosterone probably occurs at a lower dose than retained nipples, the PODs could "overestimate the relative potency for DEHP."

Another commenter noted that for Case 1, the PODs for BBP, DBP, and DIBP were based on BMDs for decreased fetal testosterone and that DINP's POD was based on a LOEL for nipple retention. The commenter also noted that changes in fetal testosterone (T) were transient, non-adverse and "should not be combined with other biomarkers or true adverse effects." Another commenter wrote that for Case 1, the use of reductions in fetal testosterone for DINP (DINP NOEL = 900 mg/kg-day; Boberg et al 2011) would be more appropriate to use, because it is same toxic endpoint and potential mode of action as other phthalates.

One industry commenter noted that the key study for Case 2, Hannas et al. (2011), did not quantify adverse effects, but used a reduction in testosterone production (a biochemical marker of phthalate syndrome) in a small number of animals/groups to estimate potency. The commenter concluded that because adverse effects are used in risk characterization, Case 2 was "unsuited and should not serve as a basis for comparative potency assessment."

A commenter noted that because rat phthalate syndrome was very complex, the selection of CRA endpoints is difficult, and the selection of earlier "biomarker" events (Case 3) is highly conservative, and potentially speculative. Another commenter made a similar argument for Case 3, noting that only the lowest LOAELs were chosen for Case 3 regardless of their type of toxicity (including biomarkers and transient non-adverse effects). The commenter asserted that the combination of differing toxicities was inappropriate without a consistent mechanism of action. The commenter continued that reversible and non-adverse induction of MNGs following DINP exposure (NOEL = 50 mg/kg-day) should not be combined with other PODs with more significant toxicity, and instead, a NOAEL of 600 mg/kg-day should be considered.

Response 4.6: Staff notes that a wide variety of effects of different types and severities are included under the umbrella of phthalate syndrome. Phthalate syndrome, by definition, is a constellation of related changes consisting of biochemical (changes in testosterone, dihydrotestosterone, StAR, insl3, cholesterol transport – CYP11a), cellular (function and development of Leydig or Sertoli cells) and structural (malformed epididymis, vas deferens,

seminal vesicle, prostate, hypospadias, cryptorchidism) effects on the male reproductive system induced by phthalates (Foster 2006; Foster et al. 2001). Staff notes that transient reductions in the rate of testosterone synthesis at the critical period of development do have permanent effects (e.g., structural, functional) on male reproductive organs (Hannas et al. 2011).

Staff disagrees with commenter's assertions that these effects cannot be considered equal when selecting PODs. As shown by Foster, the effects associated with phthalate syndrome are mechanistically related (Foster 2005). The observation of one or more of the specific effects generally associated with phthalate syndrome after exposure to the phthalates indicates perturbation in common or overlapping pathways affecting the male reproductive system. While the interconnections of biochemical pathways and end pathologies involved in phthalate syndrome have not been thoroughly elucidated for each phthalate, any observed effects related to the male reproductive system is a marker of biological activity that could lead to a broad range of effects in the organism. Thus, such markers should be given equal weight in quantifying the biological activity.

Staff notes that although MNG formation is not directly linked to changes in testosterone production, and not necessarily a direct antiandrogenic effect of phthalate exposure, MNGs are a characteristic effect routinely observed in phthalate syndrome. Therefore, the observation of MNGs formed after DINP exposure is consistent with the occurrence of MNGs associated with exposure to other active phthalates, such as DBP, and is a marker of phthalates' effects in the developing male reproductive system. While the induction of MNGs might not be an adverse effect, finding MNGs following DINP exposure supports that DINP has a biological effect similar to the other active phthalates. Furthermore, it has been suggested that the presence of MNGs may be linked to reduced fertility or testicular germ cell cancer in humans (Ferrara et al. 2006). Staff notes that the CHAP also considered each of these endpoints as equally indicative of phthalate syndrome.

Staff also concludes that it is appropriate to use reductions in the rate of testosterone production as a basis for comparative potency because reduced testosterone production is an early step in the mechanism of action for phthalate syndrome. Reduction in testosterone production at a critical point in development can lead to reproductive tract malformations. Staff would also like to note that Hannas et al. (2011) supported this view and concluded "The congruency between the potency of DINP for inhibiting T production and producing postnatal malformations in androgen-dependent tissues further supports the connection between these two toxicity endpoints."

Therefore, staff concludes considering PODs based on different but equal phthalate syndrome endpoints for each phthalate is appropriate to assure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety.

Comments on Case 1

For Case 1, the CHAP used published PEAA values from (CHAP 2014, pp. 64, Appendix D, pp. D19-D20). The CHAP chose Kortenkamp and Faust instead of a published phthalate CRA performed by Benson (2009) primarily because Kortenkamp and Faust focused "on *in vivo* antiandrogenicity" (CHAP Report, p 64). Using the Kortenkamp and Faust study provided additional benefits because it addressed antiandrogenic phthalates to be investigated in the future CHAP report, it was peer-reviewed (meaning that the selection of PODs, UFs, and HI

methodology were rigorously vetted in the scientific publication process), and the data and results were also current when the CHAP convened in 2010.

Other published toxicological values (ADIs, RfDs) were based on the most sensitive endpoint for each phthalate, which would not necessarily include phthalate syndrome. In conducting a CRA, it is necessary to have toxicological values for a common endpoint (or endpoints) (ATSDR 2004).

Comment 4.7: PODs from newer studies. One industry commenter concludes that the derived PODs and PEAAs applied by the CHAP, as derived by Kortenkamp and Faust for Case 1 are based "on inappropriate data" and "have little validity and should not be used for risk characterization." The commenter asserts that the study cited as support for case 1, Kortenkamp and Faust (2010), did not consider several high quality studies that were available at the time (EFSA, CERHR). The commenter also asserts that the Kortenkamp and Faust integrated studies that were inappropriate for risk characterization (e.g., single dose studies) when deriving PODs for DINP, DIBP, DBP, and BBP and that, because of this, UFs to compensate for these studies were inappropriately high (500 for DINP, 200 for DIBP, DBP, and BBP) and hence PEAAs were inappropriately low.

Another industry commenter objected to the CHAP's use of the DINP POD from Kortenkamp and Faust (2010), which was based on Gray et al. (2000), and concluded that "there was no reason for the CHAP to even consider a point of departure based on Gray et al. or Kortenkamp & Faust's analysis of it." The commenter noted that additional studies published since 2010 were more robust (Boberg et al., 2011) and included NOAELs which would eliminate the need for an uncertainty factor for LOAEL to NOAEL extrapolation. Overall, the commenter thought that low potency estimates for DINP artificially lowered the lower bound for MOE estimation.

The same commenter noted that the POD (LOAEL) for Case 1 is "outdated." The commenter stated that it was unclear why the CHAP did not use a NOAEL from Boberg et al. (2011) since it (and other studies) was available to the CHAP. The commenter also stated that using a LOAEL was unacceptable when a NOAEL existed in a high quality study and provided the example that if the CHAP had used a NOAEL of 600 mg/kg-day for retained nipples or 300 mg/kg-day for other endpoints as reported n Boberg et al. (2011), and divided by UF = 100, the PEAA would have been 2–4-fold higher than when using the Gray et al. (2000) study (1500 µg/kg-day), and hence the current contribution of DINP to the potential risk was over-estimated.

Another commenter provided similar language supporting the use of Boberg et al. (2011), concluding that the PEAA was overestimated by a factor of 4 (6000 versus 1500 µg/kg-day). The commenter understood that the CHAP's idea was to use PODs from Kortenkamp and Faust (2010), but stated that once shown to be scientifically inappropriate (outdated), the CHAP should have discontinued their use in favor of the more recent data.

Response 4.7: Staff agrees that more recent literature has been published regarding the selection of PODs and UFs for phthalates that cause phthalate syndrome. Staff does not agree that excluding Case 1 and the use of Kortenkamp and Faust (2010) is appropriate, because alternate approaches (such as Case 1) to POD selection are useful to understand the potential effects of POD and UF selection on risk. The CHAP stated: "We considered these three cases to determine the sensitivity of the results to the assumptions for PEAAs and the total impact on the HI approach." (CHAP 2014, p. 4). The Kortenkamp and Faust publication also discussed elements

of POD selection and cumulative risk estimation that made it invaluable to the CHAP's overall CRA process (see the introduction for Case 1 comments and responses).

Staff notes that independent consideration of all relevant hazard studies (including those cited by the commenters) was considered in the CHAP's *de novo* review of the literature for Case 3. Elements discussed by the commenters regarding outdated and inappropriate PODs were considered in that review.

Comment 4.8: Consistency of UFs. A commenter noted that the CHAP's use of larger UFs for some phthalates (e.g., DINP) could "overestimate potency relative to phthalates with smaller UFs." The commenter assumed that Kortenkamp and Faust (2010) included an additional and unnecessary uncertainty factor of 2 for study size (for DBP, DIBP, and BBP) and thus overestimated toxicity because these phthalates had BMDL[19] estimates for PODs. The commenter asserts that the BMDL methodology already considers study size and dose selection (EPA 2012a), so essentially the UF for study size was already accounted for.

Response 4.8: Staff notes that the use of independent UFs for each phthalate normalizes the resultant hazard estimates such that the phthalate effects can be compared from study to study. Staff understands that without normalization by uncertainty factors, hazard values for phthalates would need to originate from studies performed under very similar conditions. Therefore, staff concludes that the CHAP's selection of UFs was appropriate and does not overestimate risk.

Staff agrees that BMD strategies provide a more quantitative approach to dose-response assessment and also consider dose selection and sample group size. However, staff notes that the BMDL methodology accounts for the effect of experimental variation within in a bioassay on the POD estimate (EPA 2012a). Study size (number of animals per dose) is one of many factors that may influence experimental variation; a larger study size may lead to less experimental variation. Staff also agrees that the UF=200 in Kortenkamp and Faust (2010) involved "study size" (as was identified in the publication). Overall, staff disagrees that the UFs as presented in the Kortenkamp and Faust paper should be changed, because "study size" was not defined or described in the publication. The UF could have included mixes of other elements (e.g., interspecies, intraspecies, non-robust database).

Comments on Case 2

Case 2 uses a "relative potency" approach. In relative potency methods, the members of a class of chemicals (e.g., antiandrogenic phthalates) are scaled to an "index or reference" chemical within the same chemical class (in this instance, DEHP). Relative potency and other similar toxicity scaling methods such as toxicity equivalence factors (TEFs) are well accepted in the regulatory community and have been used in risk assessments for mixtures of related chemicals, such as dioxin-like compounds (EPA 2010) and polycyclic aromatic hydrocarbons (CPSC 1995; EPA 1993).

In Case 2, DEHP was the reference phthalate for all antiandrogenic phthalates when estimating relative potency, and therefore the toxicities of DBP, DIBP, BBP, and DINP were scaled to DEHP. The CHAP obtained relative potency estimates from a dose response study of multiple phthalates (Hannas et al. 2011). The CHAP then applied these relative potency estimates to an *in*

[19] BMDL refers to lower bound statistical estimate of the dose at which a given fraction of animals are affected.

vivo NOAEL for phthalate-induced reproductive tract effects for the reference chemical DEHP (5 mg/kg-day) to derive PEAA values for each of the phthalates.

There are a number of advantages to Case 2. Most importantly, the Hannas et al. study (2011) was ideally suited for a direct comparison of the relative potencies of different phthalates, because multiple phthalates were tested in the same laboratory using the same methods. In other words, the phthalates are all compared using the same criteria. Another advantage of Case 2 is that Hannas et al. tested phthalates at multiple doses, which improves the quality of dose response assessments and, therefore, improves the quality of comparisons among phthalates. Finally, Hannas et al. measured the effect of phthalates on the rate of testosterone synthesis, which is a critical, early step in the phthalate syndrome mechanism of action, and which leads to the development of other phthalate syndrome effects, such as reproductive tract malformations (see comment response 1.4 above). Hannas et al. (2011) concluded, "The congruency between the potency of DINP for inhibiting testosterone production and producing postnatal malformations in androgen-dependent tissues further supports the connection between these two toxicity endpoints. Thus, basing Case 2 on the rate of testosterone synthesis ensures that the PEAAs are appropriate to phthalate's mode of action.

Comment 4.9: Case 2 – the Hannas et al. (2011) study. One commenter recommended that the CPSC remove Case 2 for HI calculations for DINP, because the key study used to support Case 2 (Hannas et al. 2011) contained flaws and limitations.

The commenter stated that the Hannas et al. (2011) study had several limitations, such as: the "study rats for DEHP and DINP were obtained from different laboratories, resulting in significantly different control values for testosterone production," the dose-response curves for DEHP and DINP were different, and that the number of animals per group was low (10 or more are preferred for each group).

In particular, the commenter noted that Sprague Dawley rats were either acquired from Charles River (DEHP) or Harlan (DINP) and control rats from each group had significantly different testosterone production (Charles River 5.36 ± 0.15 ng/testis, Harlan 7.00 ± 0.36 ng/testis).

The commenter also noted that because the dose-response curves for DEHP and DINP were "sufficiently different, global regression modeling may not be appropriate" (as done in Hannas et al. 2011). Additionally, using the ED_{50} "may not reflect the relative potency of DINP at low doses (e.g., ED_{01}, ED_{05})." The commenter requested that "CPSC reconsider using the Hannas et al. 2011 study as the basis for estimating relative potency."

Response 4.9: The CHAP established alternate approaches (such as Case 2) to POD selection that are useful in understanding the potential effects of POD and UF selection on risk. Staff notes the CHAP stated: "We considered these three cases to determine the sensitivity of the results to the assumptions for PEAAs and the total impact on the HI approach." (CHAP 2014, p. 4).

Staff concurs with the commenter that the study rats for DEHP and DINP were obtained from different suppliers (as noted by Hannas et al.) and that control testosterone production was different for each group of rats (also identified in the publication). However, staff notes that the authors of the publication normalized testosterone production for each group of rats to controls within the same group (DEHP controls were not pooled with DINP controls). Thus, the study adequately controlled for these differences.

Staff also concurs with the commenter's observation that each group had between 3 to 9 rats (identified in the study). Staff notes that using fewer than 10 animals per dose group is typical for biochemical assays (see e.g., Furr et al. 2014). The commenter did not provide a rationale for why additional animals per dose group were needed. Furthermore, staff does not consider that the number of rats per dose group substantially affected the overall shape of the dose response curve because there were a large number of doses used for estimating the ED_{50}s (5 for DINP, 7 for DEHP; including controls).

The commenter asserted that because the shapes of the dose-response curves for DEHP and DINP were sufficiently different, that global regression modeling may not be appropriate. However, staff notes that plots referred to by the commenter [Figure 5, *Dose-response curves for DEHP and DINP in SD rats* (*Hannas* et al., *2011*) in the comment CPSC-2014-0033-0111] did not normalize the data for the controls, and expressed the data as per testis, instead of percent of control. Thus, the plots for reductions in testosterone would appear to have differently shaped dose-response curves. Staff considers the curves plotted in Hannas et al. (2011; Figure 7) (log dose vs. percent of control) to be more appropriate for comparative purposes. Staff thinks these curves demonstrate that there is sufficient similarity in the shape of dose-response curves for DINP and DEHP and thus, that the potency difference between DEHP and DINP at the ED_{50} (2.3 times difference) is sufficiently representative of other doses (e.g., ED_{01}, ED_{05}).

Staff notes that a review paper by Benson (2009a) estimated that DINP is 2.6 times less potent than DEHP. This published *in vivo*-based potency estimate is below others cited for DINP by commenters (e.g., 10 – 20 times reduction in potency in Gray et al., 2000; 4 – 7 times reduction in potency in Clewell et al. (2013)).

As noted above in the introduction to comment response 4.3, there are a number of advantages to Case 2. Most importantly, the Hannas et al. study (2011) was ideally suited for a direct comparison of the relative potencies of different phthalates, because multiple phthalates were tested in the same laboratory using the same methods. In other words, the phthalates are all compared using the same criteria. Another advantage of Case 2 is that Hannas et al. tested phthalates at multiple doses, which improves the quality of dose response assessments and, therefore, improves the quality of comparisons among phthalates. Finally, Hannas et al. measured the effect of phthalates on the rate of testosterone synthesis, which is a critical, early step in the phthalate syndrome mechanism of action, and which leads to the development of other phthalate syndrome effects, such as reproductive tract malformations. Hannas et al. (2011) concluded, "The congruency between the potency of DINP for inhibiting T production and producing postnatal malformations in androgen-dependent tissues further supports the connection between these two toxicity endpoints." Thus, basing Case 2 on the rate of testosterone synthesis ensures that the PEAAs are appropriate to the mechanism of action.

Overall, staff considers that the Hannas et al. (2011) study was of high quality and was appropriate for the CHAP to use as an element for determining PODs for Case 2 in the CRA. As such, staff disagrees with the commenter's recommendation to eliminate Case 2 from HI calculations for DINP.

Comment 4.10: ED_{50} as a measure of relative potency. An industry commenter noted that the relative potencies of phthalates were inappropriately estimated by comparing ED_{50} doses required to reduce fetal testosterone production. The commenter asserted that applying the relative potency estimates derived from ED_{50}s to NOAELs was inappropriate because these

estimates might not accurately reflect the relative potencies at the dose at which there are no observed adverse effects.

Along similar lines, another industry commenter discussed the need for parallel dose-response curves when estimating relative potencies. The commenter explained: "relatively small discrepancies at one response level are likely to extrapolate to much larger discrepancies at responses distant from the point of the original calculation." The commenter also pointed to Figure 7 in Hannas et al. (2011) as evidence that the dose-response curve for DEHP was not parallel to that of DINP.

Response 4.10: Staff concurs that the potency estimate for DINP (2.3 times less potent than DEHP) was derived using ED_{50} values from the Hannas et al. (2011) publication. Staff notes that "high dose" effects, such as ED_{50}s or ED_{25}s traditionally have been used to estimate relative potency. For example, Allen et al. used ED_{25}s to minimize the effect of his dose-response model on relative potency, which may occur at lower doses (Allen et al. 1988). Similarly, Gold et al. used ED_{50}s because they are generally within the range of experimental values (Gold et al. 1991), whereas ED_{10}s are often at doses below the lowest dose tested. Staff considers both Allen et al., and Gold et al. to be expressing essentially the same reasoning. Furr et al. also used ED_{50}s to estimate the relative potencies of phthalates (Furr et al. 2014). Staff considers that the use of ED_{50}s for relative potency estimates is appropriate and in common practice.

Staff disagrees with the commenter's characterization of evidence regarding the overestimation of Case 2's DINP potency and hence, risk. In staff's view, Figure 7 in Hannas et al. (2011) appears to show a proportional dose response between DEHP and DINP, that is, similar shaped dose responses with different slopes. That is, the relative potencies of DEHP and DINP do not appear to vary significantly over the relevant range of the dose response. Therefore, because the CHAP used the long-accepted methodology of ED_{50}s for relative potency, and because the dose-response curves of DEHP and DINP appear to be proportional, staff concludes that the CHAP's use of ED_{50} did not overestimate the relative potency of DINP.

Comment 4.11: DINP POD. A commenter noted that the potency value for DINP in Case 2, 11.5 mg/kg/day, which was derived from a comparison to DEHP (DINP 2.3 times less potent than DEHP; Hannas et al., 2011) was inconsistent with *in vivo* data. The commenter indicated that the CHAP should have compared the theoretical POD with other studies, which would have shown the case 2 POD to be unsupported. The commenter also stated that the case 2 POD for DINP was more uncertain than in other cases, and should be disregarded for regulatory decision making. Furthermore, the commenter noted that the CHAP assumed that the relative potency between DINP and DEHP for the endpoint of testosterone production in male rat fetuses would apply to the other phthalate-related male reproductive adverse effects. The commenter concluded that this assumption was not validated by the CHAP, and if the CHAP validated the assumption against other studies, the CHAP would have determined that the Case 2 model was unsupported.

Finally, the commenter asserted that studies actually show that the no effect level for DINP for reduced testicular testosterone production is at least 100 mg/kg-day (Hannas et al., 2011; Clewell et al., 2012a). The commenter reasoned that because reduced testosterone production is an early biomarker of the potential for testicular tract malformations that would occur at higher doses, the CHAP's hypothetical no effect level derived for DINP of 11.5 mg/kg/day, which is lower than the 100 mg/kg-day level for the biomarker, is scientifically unsupported. The commenter

concluded that "This information clearly demonstrates the underlying assumptions and hypothesis for the model [Case 2] are incorrect."

Response 4.11: The commenters imply that Hannas et al. (2011) was not an *in vivo* study. Staff notes that Hannas et al. exposed live animals to phthalates. Measurements of the rate of testosterone synthesis were, by necessity, made in a biochemical assay using tissue obtained from the animals. Biochemical assays are frequently incorporated as a component of *in vivo* bioassays.

In Case 2, the CHAP's approach to using a study that included observation of effects from exposure both to DINP and DEHP allowed the CHAP to estimate the potency of DINP relative to DEHP, which is well-studied in experimental animals, and to use a DEHP POD to derive the DINP POD. Staff agrees that implicit in the relative potency approach is the assumption that the derived relative potency value can be applied to different phthalate syndrome-related health effects. To the extent that studies are available, staff agrees that a single value does not necessarily capture the potency relationship between DINP and DEHP. However, the available data do not fully characterize the toxicology of DINP. While the commenter indicated that the DINP POD should be no more than 100 mg/kg-day, this assertion is based on two studies that do not directly establish 100 mg/kg-day as the no effect level. Therefore, staff maintains that the CHAP's decision to use the alternate approaches in the three cases, including the relative potency approach in Case 2, is appropriate as a way to explore the effects of using different information streams in the risk assessment.

Comment 4.12: Relative potency based on *in vivo* studies. An industry commenter stated that the relative potency approach is not needed for DINP since sufficient quality *in vivo* studies with dose-response data exist. The commenter continued that relative potency approaches are only used where quality dose-response data do not exist. This view was substantially similar to that of other industry commenters. The commenters believed that enough *in vivo* data existed on DINP to obviate extrapolation from an *in vitro* potency estimate. The commenter asked that CPSC not consider Case 2 for this reason. The commenters also suggested that *in vivo* studies could be used for estimating relative potency and provided examples demonstrating a 10 – 100 times reduction in potency when DINP is compared to DEHP. One commenter noted that the CHAP failed to consider a "more reliable" *in vivo* potency estimate by Gray et al. (2000), which demonstrated that DINP is 10 – 20 times less active than DEHP. Another commenter estimated that the risk from DINP was overestimated by 4.3 to 8.6 times when considering the Gray study. Overall, the commenter thought that low potency estimates for DINP in case 2 artificially lowered the lower bound for MOE estimation and therefore Case 2 should be disregarded. Another commenter agreed and stated that the CHAP should have used a 50 mg/kg-day exposure level POD for DINP instead of 11.5 mg/kg-day, and using at that value, the lowest MOE for DINP for any population examined by the CHAP would be at least 2,800 (well above the 100 – 1,000 considered adequate).

Response 4.12: The commenters described the Hannas et al. study as an *in vitro* study. Staff notes that Hannas et al. exposed live animals to phthalates. Measurements of the rate of testosterone synthesis were, by necessity, made in a biochemical assay using tissue obtained from the animals. Biochemical assays are frequently incorporated as a component of *in vivo* bioassays. The term "*in vitro*" is usually used for studies performed entirely *in vitro*, such as using cultured tissue.

Staff also considers the estimation of relative potency in Hannas et al. (2011) to be valid and notes that substantially similar methods have been used in the estimation of relative potency in Furr et al. (2014).

Staff concludes that *in vivo* potency estimates can be informative, however. A review study by Benson (2009) estimated that DINP is 2.6 times less potent than DEHP when comparing primarily in vivo RfDs (small or absent male reproductive organs for DEHP versus retained areolas/nipples and reduced fetal testosterone for DINP). Benson's published relative potency estimate (DINP is 2.6 times less potent than DEHP) is more similar to the CHAP's estimate than other relative potency estimates cited for DINP by commenters (e.g., 10–20 times reduction in potency in Gray et al., 2000; 4 – 7 times reduction in potency in Clewell et al., 2013). Thus, staff concludes that a 2.3 times relative potency estimate is valid.

As such, staff disagrees that Case 2 should be disregarded. The consideration of all three cases is important in informing certain aspects of the potential risk. Staff notes that exposures to DINP in isolation now result in MOE estimates that are below the upper limit and nearing the lower limit considered adequate for protecting public health. See comment response 5.4. Section 5 provides a more detailed discussion of individual and cumulative risk assessments for DINP.

Comment 4.13: DEHP POD. A commenter questioned where in Case 2 the DEHP POD of 5 mg/kg-day (the base for estimating other doses) was established and suggested the POD was the same as in Case 3, which was based on a NOAEL for delayed preputial separation, increased reproductive tract abnormalities (e.g., malformations), and decreased sperm parameters.

A commenter also noted that the POD identified to be used for this case, 5 mg/kg-day, was 20 times lower than the POD for reductions in testosterone production (100 mg/kg-day) identified in the Hannas et al. (2011) study.

Response 4.13: Staff notes that the CHAP considered all the available published studies in identifying a consensus NOAEL for DEHP (CHAP 2014; Table A-3.) The CHAP (CHAP 2014, Appendix A, p. A-21) found that NOAELs clustered around 3–11 mg/kg-d, and concluded that "using a weight-of-evidence approach, the CHAP has conservatively set the NOAEL for DEHP at 5 mg/kg-d." Andrade et al. Andrade et al. (2006) identified a NOAEL of 5 mg/kg-day for DEHP based on delayed preputial separation, and Christiansen et al. (2010) identified a NOAEL of 3 mg/kg-day, based on decreased male AGD and increased nipple retention, as noted by the CHAP (Table A-3).

Normally, one expects the initiating event (testosterone reduction) to occur at lower doses and at earlier times than an ultimate effect such as reproductive malformations (https://www.epa.gov/sites/production/files/2013-12/documents/aop-wiki.pdf; https://aopwiki.org/aops/18). Staff understands that certain toxicology information from different studies appears to suggest that lower doses of DEHP and DINP induce reproductive abnormalities and higher doses affect hormonal initiating events (e.g., testosterone reduction) and thus give the appearance of biological inconsistencies which might result in an overestimate of risk.

Staff disagrees that selecting a lower NOAEL based on reproductive malformation instead of a higher NOAEL based on an initiating event is problematic. This is because there are differences between studies that can lead to the development of seemingly inconsistent results.

For example, studies using different animal species or strains (e.g. Harlan versus Sprague Dawley rats), different animals ages (with different windows of susceptibility), or different dosing strategies (e.g. wide-spread doses versus narrow doses, dosing duration and frequency) can appear inconsistent when reported together. The assessment of different, but similar endpoints when comparing across studies (e.g. serum testosterone versus testicular testosterone, versus testicular testosterone production) can also lead to apparently inconsistent results. Other reasons for why a toxicological initiating event has a higher NOAEL than a downstream pathology is that the dose response could be non-monotonic (essentially the toxic response is not directly correlated to a dose response in a linear fashion) or the downstream pathology is reliant on the modification of more than one toxicity pathway (multifactorial). All these factors can contribute to the differences described by the commenter.

Staff notes that this seeming inconsistency occurs frequently in hazard assessment and is primarily related to the amount of information available to the hazard assessor (toxicity database sufficiency). Some hazard assessors consider adding a database uncertainty factor when estimating exposure limits (e.g., RfDs, ADIs, TDIs) for chemicals with small toxicity databases (Dankovic et al., 2015).

Comment 4.14: Potency estimates for DBP and BBP. A commenter identified that Case 2 potency estimates were not derived for DBP and BBP in Hannas et al. (2011) and questioned how the CHAP assigned them equipotent status to DEHP. This commenter's observations were part of a longer discussion on how the shape of the dose-response curves affected potency derivations for DINP (via ED_{50}) and how there was a lack of a clear CHAP rationale for deriving potency estimates for DBP and BBP. Thus, the commenter concludes that the CHAP assessment approach lacks scientific rigor.

Response 4.14: Staff concurs with the commenter regarding potency estimates for DBP and BBP. The CHAP wrote that DIBP, DBP, BBP, and DEHP are "approximately equipotent in terms of testosterone modulated effects (Hannas et al. 2011) and that a NOAEL for DEHP was 5 mg/kg-day and "the other three phthalates were assumed to have equivalent values" (CHAP 2014, Appendix D, p. D-19).

Staff notes that the potencies of DBP and BBP were not directly estimated in Hannas et al. (2011). Hannas referenced a study (Howdeshell et al., unpublished), however, that conducted ED_{50} potency estimates for DBP. This study was conducted in a similar manner as in Hannas et al. (2011). The CHAP also noted that Gray et al. (2000) considered BBP to be of equivalent potency to DEHP (CHAP 2014, pp. A-12, A-22). A figure illustrating the "endocrine disrupting potency of the phthalates" was provided by the CHAP (CHAP report p. 16), demonstrating similar potency between BBP, DBP, DIBP, and DEHP (and DIHEXP and DCHP). Therefore, staff concurs with the CHAP's potency estimates for DBP and BBP.

Comments on Case 3

In Case 3, the CHAP derived PEAAs for each phthalate *de novo*, considering all the available published peer-reviewed studies for each phthalate (CHAP 2014, pp. 64, Appendix D, pp. D19-D20). When assessing studies for Case 3, the CHAP focused on "information concerning the effects of *in utero* exposure of phthalates in pregnant rats" (CHAP 2014, p. 23).

Comment 4.15: Case 3 risk characterization. One industry commenter supported the use of Case 3 in risk characterization, writing "Since risk characterization needs to be based on the

incidence of adverse effects and results from high quality studies, CHAP should have only relied on the study evaluations used as a basis for case three. Only the PODs derived for this case are sufficiently supported."

Response 4.15: Staff agrees with the commenter that Case 3 PODs are sufficiently supported to use in a CRA but disagrees that only Case 3 PEAAs should be used in the CRA. Cases 1 and 2 provided alternate approaches to POD selection that are useful in understanding the potential effects of POD and UF selection on risk.

Comment 4.16: Citation of DINP POD. A commenter indicated support for Case 3 in the CHAP's CRA, but asserted that the choice of a 50 mg/kg-day DINP POD for Case 3 was inadequately justified.

An industry commenter characterized the CHAP report information for Case 3 as "muddled" and stated the "basis for case 3 is unclear" because there was confusion regarding the source of the DINP NOAEL of 50 mg/kg-day for MNGs. The commenter related that the CHAP wrote that the NOAEL was based on nipple retention in Boberg et al. (2011). The CHAP's statement was incorrect, however, because the NOAEL for retained nipples in this study was 600 mg/kg-day and the study authors set a study NOAEL for antiandrogenicity at 300 mg/kg-day. The commenters added that consideration of other NOAELs might result in an overestimation of risk by a factor of 2 – 12. The commenter continued to explain that the CHAP also reported that this value was from Clewell et al. (2013b) and based on increased MNGs.

Response 4.16: Staff concurs that there were inconsistencies in the references for the DINP POD in the CHAP report. Staff notes that the NOAEL of 50 mg/kg-day referenced in the CHAP report for the Case 3 POD is from Clewell et al. (2013) and is based on the statistically significant induction of MNGs in the PND 2 testis at a LOAEL of 250 mg/kg-day. In Table 2.1 of the CHAP report, the reference for DINP should be Clewell et al., (2013), instead of Boberg et al., (2011). The CHAP's discussion of the derivation of the NOAEL for DINP can be found on pages 97–98 of the CHAP report. The sections that should have been updated to incorporate Clewell are Appendix A-23 and Table A-4. Staff refers the commenters to comment response 4.17 regarding discussions as to the relation of MNGs to phthalate syndrome.

Comment 4.17: DINP POD. A commenter questioned whether MNGs, the basis of Case 3, are relevant to antiandrogenicity or that MNGs are adverse. This commenter concluded that using 50 mg/kg-day as a POD for DINP was "indeed highly conservative." Overall, the commenter asserted that low POD for DINP in Case 3 artificially increased the risk from DINP. Another commenter asserted that MNGs are not regarded as phthalate–specific antiandrogenic effects. The commenter concluded that the transient reduction in AGD on PND 14 was a more appropriate endpoint (NOEL = 250 mg/kg-day). The commenter argues that a 250 – 300 mg/kg-day NOAEL is more clearly supported by the studies. Commenters noted that these discrepancies were also reported by two of the CHAP report peer reviewers.

Another commenter concluded that "the best available science – including a series of well-conducted animal studies – interpreted via sound toxicological and risk assessment practice supported a NOAEL for DINP of no less than 50 mg/kg-day", that no additional safety factors beyond the total of 100 needed to be used, and that the CHAP report should be corrected to use the 50 mg/kg-day POD.

Response 4.17: Staff agrees with the CHAP's conclusions regarding the DINP NOAEL for Case 3. The CHAP considered studies by Clewell et al. (2013a, 2013b), Hannas et al. (2011), and Boberg et al. (2011) as most relevant and highest quality for identifying a NOAEL for DINP (CHAP report, pp 97 – 98). The CHAP concluded that "the developmental NOAEL, based upon antiandrogenic endpoints (nipple retention, fetal testosterone production and MNGs), is between 50 and 300 mg/kg-day." The CHAP stated, "taking the conservative approach, the CHAP assigns the NOAEL for DINP at 50 mg/kg-day."

Staff agrees that the choice of a 50 mg/kg-day DINP POD was conservative. This conservatism was noted by the CHAP following a discussion of the most relevant studies (CHAP 2014, pp. 97–98). Staff also agrees with the CHAP's decision (and the commenter's comment) that the use of an UF of 100 is acceptable for phthalates in Case 3 (CHAP report Appendix D-20). Staff notes that it is common practice in risk assessment to select the most conservative health endpoint (from quality data sets) when performing a hazard assessment (Barnes and Dourson 1988; CPSC 1992; EPA 1991).

Staff does not agree that the use of other PODs for DINP (e.g., 300 or 600 mg/kg-day) for use in the CRA is warranted for Case 3. As noted above, selection of the most conservative health-based endpoint is done to ensure that the entire spectrum of health effects is considered when performing a risk assessment.

Staff also notes that the studies cited by the commenters with higher NOAELs (indicating lower risk) did not test doses as low as 50 mg/kg-day. For example, the lowest DINP dose tested by Hannas et al. (2011) was 500 mg/kg-day, and the lowest dose tested byBoberg et al. (2011) was 300 mg/kg-day. Thus, the studies cited by the commenters were not designed to identify a NOAEL as low as 50 mg/kg-day.

Although MNG formation is not directly linked to changes in testosterone production, and not necessarily a direct antiandrogenic effect of phthalate exposure, MNGs are a characteristic effect routinely observed in phthalate syndrome (NRC (2008), Howdeshell (2016), and Gaido (2007)). Therefore, the observation of MNGs formed after DINP exposure is consistent with the occurrence of MNGs associated with exposure to other active phthalates, such as DBP, and is a marker of phthalates' effects in the developing male reproductive system. Although MNGs might not be an adverse effect, finding MNGs following DINP exposure supports that DINP has a biological effect similar to the other active phthalates (comment response 1.20). Furthermore, it has been suggested that the presence of MNGs may be linked to reduced fertility or testicular germ cell cancer in humans (Ferrara et al. 2006).

Staff concludes that a number of quality studies demonstrates that a significant induction of MNGs occurs following dosing with DINP and other phthalates. Staff further concludes that the MNG NOAEL of 50 mg/kg-day is close to other potential phthalate syndrome endpoints (e.g., reduced testosterone) reported in other studies. Staff points out that the CHAP estimated from Hannas et al. (2011) that the NOAEL for fetal testosterone production is approximately 100 mg/kg-day. In addition, staff notes that the Boberg et al. (2011) study demonstrated a non-significant, DINP-induced dose-related decrease in testicular testosterone production and a 25 percent increase in MNGs at the lowest dose (300 mg/kg-day), suggesting that lower NOAELs for these effects may exist. Thus, staff concludes that the CHAP's assignment of the NOAEL for DINP at 50 mg/kg-day based on the observation of MNGs, is reasonable.

Section 4 Summary

The CHAP derived three sets of PEAA values (Cases) to explore the effect of different methodology (e.g., different uncertainty factors and PODs) on cumulative risk estimates to "determine the sensitivity of the results to the assumptions for PEAAs and the total impact on the HI approach." Staff concurs with the CHAP's use of three Cases. Furthermore, the risks resulting from the three Cases are remarkably similar. Staff concludes that each of the three Cases has certain advantages, as noted above, and that all three are appropriate for estimating human risk. Case 1 and Case 2 were developed by assessing each phthalate individually, using conventional risk assessment methods. Case 2 has the additional advantage that most of the phthalates were assayed in the same laboratory using the same methodology. Thus, Case 2 is ideal for comparing the potencies of individual phthalates. Using Case 3, the CHAP derived new PEAA values after considering all the available literature.

Staff concludes that the CHAP's approach of using three Cases is not only appropriate, but provides an additional degree of reliability to their CRA. Staff further concludes that all three Cases are useful for human health risk assessment.

5. Relative Contributions of Phthalates and Sources to Cumulative Risk

The CHAP estimated human exposure to phthalates using two independent and complementary methods: 1) Total phthalate exposure to actual individuals was calculated from HBM data (NHANES and SFF) (CHAP 2014, pp. 34 – 48). Although HBM provides good estimates of total exposure, it does not provide information on the sources of exposure. 2) Therefore, the CHAP also estimated human exposure for individual exposure scenarios, such as using specific products or contact with environmental media (CHAP 2014, pp. 49 – 60 and Appendix E1). The scenario-based exposure estimates can be developed using information about relevant sources of phthalate exposure (e.g., concentrations of phthalates in soil, dust, and in products); data on migration or leaching of phthalates from products; physiological information (e.g., body weight and skin surface area); and information about how the subpopulations use and interact with products, including frequency and duration of contact with products and environmental media.

The CHAP presented scenario-based exposure estimates[20] (method 2, described above) for infants, toddlers, children, and women of reproductive age/pregnant women. Scenarios included common activities such as (CHAP 2014, Table 2.10):

- playing with toys;
- interacting with child care articles;
- using household products such as paints, air fresheners or adhesives;
- sitting on furniture;
- using vinyl gloves;
- using personal care products (soaps, shampoos, lotions, deodorants, perfumes, hair spray, and nail polish);
- interacting with the environment (indoor and outdoor air, dust, and soil);
- eating;
- drinking; and
- taking medications.

The scenario-based approach was used to estimate the relative contribution (percent of total exposure) for each activity could then be determined (CHAP 2014, pp. 49 – 50; CHAP 2014, Appendix E1). Although children's toys and child care articles containing certain phthalates are currently prohibited, the CHAP estimated exposures that would hypothetically occur if phthalates were allowed in these products (CHAP 2014, pp. 49-50). This approach was able to provide exposure estimates for each of these activities as well as for the total exposure. This section includes comments on the relative contributions of specific phthalates — mainly DINP — and various sources of exposure to the cumulative risk. This section also includes comments on the four additional phthalates (DIBP, DPENP, DHEXP, and DCHP). Although the CHAP concluded that diet was the primary source of exposure to most phthalates (CHAP 2014, Table 2.0, Figure 2.1), the CHAP's analysis also showed that children's toys and child care articles could be a significant contributor to exposure in infants and toddlers (more than 10 percent of the total exposure) if phthalates were used in these products. The CHAP also showed that DINP

[20] Appendix E of the CHAP Report describes scenario-based estimates of phthalate exposure, which were performed by CPSC staff under the direction of the CHAP.

contributed between 1 and 15 percent of the cumulative risk in infants(CHAP 2014, Table 2.16; CPSC 2014b, Table 7). However, NHANES data indicate that DINP exposure to WORA has increased dramatically in recent data cycles, while DEHP exposure has decreased (CPSC 2015a; CPSC 2017a). As a result, while overall risk has decreased somewhat over time, DINP now contributes about as much as DEHP to the cumulative risk.

Overview of Public Comments on Relative Contributions to Cumulative Risk

Several commenters addressed the relative contributions of DINP in children's toys and child care articles to the cumulative risk: (a) some commenters claimed that DINP contributes little to cumulative risk, (b) commenters also claimed that exposure to DINP from children's toys and child care articles contributes little to cumulative risk, and (c) some commenters argued that DBP, BBP, and DEHP should not have been included in the CHAP's CRA.

Staff disagrees with the commenters' conclusions. Regarding (a) above, overall, CPSC staff concludes that the contribution of DINP to the cumulative risk is substantial and has increased since the CHAP completed its analysis. Analysis of recent NHANES data (TAB A) indicates that DINP exposure has increased 5-fold between 2005/2006 and 2013/2014 (CPSC 2017a). DINP now contributes roughly as much as DEHP to the cumulative risk. Regarding (b), staff notes that mouthing and dermal exposure[21] to children's toys and child care articles could contribute up to about 29 percent of total DINP exposure for infants if phthalates were allowed in these products (CPSC 2014b, Appendix E1, Table E1-S2). Regarding (c), staff agrees with the CHAP's inclusion of the DBP, BBP, and DEHP in the CRA, because exposures to DBP, BBP, and DEHP continue to occur from multiple sources (not just toys and child care articles) and, therefore, contributes to the cumulative risk.

DINP Contribution to Cumulative Risk

Comment 5.1: DINP contribution to risk. Many commenters objected to the Commission's proposal to permanently prohibit children's toys and child care articles containing more than 0.1 percent of DINP, claiming that DINP contributes little to the cumulative risk. Several commenters noted that the CHAP's CRA showed that the estimated risks associated with phthalate exposure were driven by DEHP and DBP, and that DINP contributed only a small portion of the combined risk (less than one percent). Other commenters supported the proposed rule's permanent prohibition of children's toys and child care articles containing more than 0.1 percent of DINP, pointing to the adverse health effects associated with DINP exposure and the recent data that show increasing use of DINP over time.

Response 5.1: Although staff agrees that DINP exposure currently constitutes only a portion of overall exposure and risk to phthalates, staff disagrees that the relative contribution of DINP to the overall risk is negligible. Staff agrees that DINP exposure has increased over time. Staff analysis of the latest NHANES data set (2013/2014) demonstrates that DINP contributes approximately 6 to 51 percent (medians) or 18 to 76 percent (95th percentiles) of the overall risk (HI), when considering WORA populations (CPSC 2017a) (TAB A). Analysis of the 2011/2012

[21] Staff interprets "mouthing" to include any contact of the toys or child care article with the mouth, lips, or tongue (Greene 2002; Kiss 2002). Dermal exposure occurs from contact with the skin, including handling toys (holding in the hand) or contact of child care articles with any skin surface (CHAP 2014, Appendix E-1).

data cycle demonstrates a similar pattern, with 5 to 47 percent (medians) or 4 to 43 percent (95th percentiles) of the overall risk to WORA being attributed to DINP (CPSC 2015a). Looking across the cycles suggests that the proportion that DINP contributes to the overall HI has increased in every data cycle since 2005/2006. The proportions have increased 6- to 13-fold (medians) or 6- to 25-fold (95^{th} percentiles) when considering data cycles from 2005/2006 to 2013/2014. The analysis shows that the relative contribution of DINP to the HI is highest when considering Case 2, followed by Case 3 and Case 1. DINP, therefore, is the major contributor to cumulative risk in WORA.

Furthermore, considering DINP in isolation, staff notes that the median and 95^{th} percentile hazard quotients for DINP have increased 4- to 5-fold over time (2005/2006 through 2013/2014).

Comment 5.2: Inclusion of DEHP, DBP, and BBP in CRA. Some commenters asserted that DEHP, DBP, and BBP exposures are associated with nearly all of the risk, but are not found in children's toys and child care articles. Because children's toys and child care articles containing these phthalates are already prohibited, the commenters conclude that, DEHP, DBP, and BBP cannot contribute to any cumulative phthalate risk from exposure to children's products. One commenter stated that if the CRA excludes the prohibited phthalates, the HI in a cumulative risk assessment is less than one; therefore, there is a reasonable certainty of no harm from the use of DINP in children's products. Furthermore, commenters indicated that the CHAP's use of exposure data that were collected before the prohibition involving DEHP, DBP, and BBP in children's toys and child care articles is not appropriate for deriving estimates of exposure, because the dominant risk driver in the older data (DEHP) is no longer in children's toys and child care articles. As a result, one commenter concluded that the CHAP's cumulative risk assessment does not provide a basis for regulatory action on individual children's products because DEHP, DBP, and BBP are permanently prohibited from children's toys and child care articles.

Response 5.2: The CHAP's charge was directed by statute. See Section 2. The CPSIA directed the CHAP to complete an examination of the full range of phthalates that are used in products for children, to consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates, and to consider the cumulative effect of total exposure to phthalates, both from children's products and from other sources. CPSIA § 108(b)(2). Therefore, the CHAP analysis included consideration of the cumulative effect of total exposure to the phthalates associated with male reproductive developmental effects (MRDE). Furthermore, the CHAP's analysis also included phthalate exposures from all sources pursuant to the statute, not only children's toys and child care articles.

Thus, the basis of the regulation is the cumulative risk assessment. The CHAP's analysis shows that a portion of the susceptible population experiences exposures that result in an HI greater than one, and that DINP contributes to exposure to the phthalates associated with MRDE, and therefore contributes to the risk of adverse health effects. Although children's toys and child care articles containing DEHP, BBP, and DBP are permanently prohibited, current HBM data show that significant exposures to DEHP, DBP, and BBP exist from the combination of all products and sources. Based on the CHAP's examination, as directed by the statute, the CHAP recommended that the interim prohibition on children's toys and child care articles containing DINP be made permanent. The results of staff's CRA using more recent NHANES HBM data show that phthalate exposures are still high enough that between two to nine WORA in a sample of 538 has an HI greater than one, depending on the PEAA Case. Male children for these women

would be at risk for MRDE. Declining exposures for certain phthalates over time has resulted in overall decreases in HIs. As described in section 5.4 of TAB A, the 2013/2014 NHANES data cannot be used to estimate how many WORA in the U.S. population have HIs greater than one.

In response to the commenters' assertion that most of the risk is due to exposure from DEHP, BBP, and DBP, the CHAP's and staff's analyses (CPSC, 2015; CPSC, 2017) show that DINP also contributes substantially to the cumulative risk. Specifically, considering 2013/2014 NHANES data, DINP contributes approximately 6 to 51 percent (medians) or 18 to 76 percent (95^{th} percentiles) of the overall risk (TAB A). Staff concludes that allowing DINP to be used in children's toys and child care articles would only increase the contribution of DINP to the cumulative risk. Although human exposures to some phthalates have declined in recent years, DINP exposure is increasing.

Comment 5.3: Dietary exposure. Many commenters noted that diet is the primary source of exposure for DINP and other phthalates in infants and children, and that children's toys and child care articles contribute very little to overall phthalate exposures, especially for women of reproductive age and fetuses. Commenters assert that DINP contributes so little to the combined risk from exposure to phthalates from all sources that a permanent prohibition of children's toys that can be placed in a child's mouth and child care articles containing DINP would have little effect on the overall risk and, thus, the prohibition is not supported. One of these commenters concludes that the only way to substantially reduce the risk would be to reduce exposure to the primary risk driver (DEHP).

Response 5.3: The CPSIA directed the CHAP to consider phthalate exposure from all sources. The CHAP used two different approaches to assess phthalate exposure (CHAP 2014, pp. 3-4). HBM provides an integrated measure of exposure to each phthalate, but does not provide information on the sources of exposure. Therefore, the CHAP also requested that CPSC staff provide a scenario-based exposure assessment from which the CHAP evaluated exposure from individual sources, such as toys, personal care products, and household products (CHAP 2014, pp. 49–50).

Based on the scenario-based exposure assessment, the CHAP and staff acknowledge that food, rather than children's toys or child care articles, provides the primary source of phthalate exposure to women and children. Figure 2.1 of the CHAP Report shows that, for most phthalates, ingestion of food and beverages was the main source of phthalate exposures to infants and to pregnant women. The other main contributors were soft plastic toys and teethers (via mouthing), and personal care products such as lotions, creams, oils, soaps, and shampoos via dermal contact.

However, given the results of the scenario-based exposure assessment, staff disagrees that the contribution from sources other than diet are negligible for DINP. The scenario-based exposure assessment included in the CHAP report shows that mouthing and dermal exposure to toys would contribute an average of 12.8 percent, 5.4 percent, and 1 percent of the overall DINP exposure to infants, toddlers, and children, respectively, if DINP were used in these products (CHAP 2014, Appendix E1, Tables E1-21, E1-22, and E1-23). Mouthing and handling soft plastic toys and teethers could contribute 12.8 percent (mean exposure) or 16.6 percent (95^{th} percentile exposures) of total DINP exposure in infants (CHAP 2014, Appendix E1, Table E1-21). Dermal contact with the evaluated toys and child care articles may contribute up to an additional 16.5 percent of exposures to infants (*Ibid.*, Appendix E-1, Table E1-21). Therefore,

although infants' DINP exposure was primarily from diet, up to 29 percent may be due to the presence of DINP in the evaluated toys and child care articles (*Ibid.*, Figure 2.1).

The European Commission (ECHA 2013, Table 4.89) also estimated infants' exposure to DINP from mouthing and handling toys. ECHA estimated that infants' DINP exposure from toys was on average, 29 µg/kg-day, which is greater than the scenario-based exposure estimate of 2.6 µg/kg-day included in the CHAP report (CHAP 2014, Appendix E1, Table E1-S2). The Australian Department of Health (NICNAS 2012, Table 5.2.5) estimated that infants' DINP exposure was on average 30 µg/kg-day for both toys and child care articles. This is greater than the scenario-based exposure estimate of 6 µg/kg-day for toys and child care articles combined (CHAP 2014, Appendix E1, Table E1-S2).

The CHAP and staff considered exposures from mouthing toys as a route of DINP exposure to infants and toddlers. In the scenario-based exposure assessment included in the CHAP report, diet accounted for approximately 60 – 80 percent of the exposures in these populations, while toys and child care articles accounted for about 19 to 29 percent of the total exposure. Staff notes that allowing DINP in children's toys and child care articles could increase exposure to DINP from these products, compared to exposures if DINP is not allowed in children's toys and child care articles. DINP exposure from children's toys and child care articles could account for up to about 29 percent of infants' total DINP exposure from all sources (CHAP 2014; Appendix E1, Table E1-21).

Comment 5.4: House dust and exposure estimation. One commenter made a variety of remarks on house dust. The commenter noted: house dust contributed to background exposure; DEHP was in 100 percent of dust samples; consumer products and building materials were the source of such dust; and EPA soil screening levels for DEHP were exceeded by the concentrations found.

Response 5.4: Staff notes that exposures from house dust have been considered in both the CHAP and staff analyses. Exposures from dust were estimated in the scenario-based exposure assessment included in the CHAP report (CHAP 2014, Tables E1-2, E1-6, E1-7, E1-19, E1-S1). The CHAP concluded that (CHAP 2014, Appendix E1, p. E1-35):

> For infants and toddlers, incidental ingestion of household dust contributed roughly 25 percent to the total BBP exposure and 15 percent to total DEHP exposure (Tables E1-S2, E1-S3). The sources of PEs in household dust are unknown but may include consumer products… For children, dust was a significant source of exposure to DEHP (18 percent).

House dust exposures were also indirectly considered by the CHAP and staff when estimating exposures for NHANES individuals. This is because urinary phthalate metabolite concentrations for each NHANES survey participant included exposures from all exposure routes. These estimates would have included exposures from house dust in the survey individual's residence, workplace, surrounding environment, and modes of transport.

Comment 5.5: DINP in isolation. In addition to asserting that phthalates other than DINP are responsible for nearly all the risks from phthalates and should not be included in an assessment of children's toys and child care articles, commenters discussed the risks associated with DINP by itself. Commenters asserted that the CHAP found no significant health risk from exposure to DINP by itself (considered in isolation), given the very large margin of exposure (MOE)

estimates for median exposures, as well as for the 95th percentile of exposure. Commenters concluded that because of the high MOEs for DINP from all sources, the margins of safety must be even larger for the children's products' contribution to DINP exposure, and thus, there is no basis for a permanent prohibition on children's toys that can be placed in a child's mouth and child care articles containing DINP. A commenter also stated that replacement of DEHP by DINP would not be expected to increase the risk because of DINP's lower potency. A commenter also asserted that even a doubling in DINP exposures would not increase the risk substantially and the prohibition of children's toys that can be placed in a child's mouth and child care articles containing DINP would therefore be unwarranted.

A commenter also provided MOE estimates for DINP using 2013/2014 NHANES exposure estimates for WORA using the case 3 PEAA and MCOP at the median (10000 – 11500) and 95th percentile (800 – 1100) and MCOP and MINP at the median (12000 – 13700) and 95th percentile (1000 – 1300). The commenter concluded that all estimates demonstrated that DINP did not pose a risk by itself.

Response 5.5: Staff notes that the CPSIA directed the CHAP to consider phthalate risk in isolation and in combination with other phthalates. As noted in comment response 10.1, and in Section 2, the weight of evidence, including cumulative risk, is the basis for CHAP's recommendations and the proposed rule. Staff's recommendation, to make permanent the interim prohibition of children's toys that can be placed in a child's mouth and child care articles containing DINP, was made considering the risk from DINP in combination with other phthalates.

Nonetheless, although the MOE evaluation was not the basis for the CHAP's recommendations, the CHAP considered the risk of MRDE from exposure to DINP in isolation by using the MOE methodology. Lower MOEs mean increased potential risk, and higher MOEs indicate a lower concern.

Staff agrees with the CHAP's analysis that the MOEs for DINP in isolation did not present a risk. However, staff notes that DINP exposure has been increasing since the CHAP completed its analysis. Furthermore, staff reiterates that the CHAP was directed to consider phthalate risks both in isolation and in combination with other phthalates. Ultimately, the CHAP and CPSC focused on cumulative effects of all phthalates.

Even if DINP were to replace DEHP or other phthalates in the CRA, it would be difficult to predict the effect on total exposure and risk. Replacing one phthalate with another would not necessarily result in the same exposures. However, staff is concerned that, because DINP exposures are increasing, DINP alone may dominate the cumulative risk in the future, and that DINP exposure in isolation may approach the level of concern, especially considering Case 2. CPSC staff analyzed more recent NHANES data (2013/2014) and estimated exposures and MOEs for individual phthalates like DINP.[22] The analysis demonstrates that the MOEs for WORA exposed to DINP range from 2300 to 150,000 (median) and 220 to 14,000 (95th percentile) for all three cases. These DINP MOEs are less than those estimated from 2005/2006

[22] Margins of Exposure (MOE) were estimated by staff using points of departure (PODs, in µg/kg-day) presented in the CHAP report (Table 2.15, p. 66) and daily intakes (DI, in µg/kg-day) as presented in CPSC, 2015 and 2017. The formula for estimating MOEs is the same as that used by the CHAP, i.e., MOE=POD/DI.

NHANES data, which range from 11,000 to 750,000 (median) and 1100 to 72,000 (95th percentiles). As mentioned above, lower MOEs are synonymous with increased potential risk.

Staff disagrees with the assertion that doubling the DINP exposure would not increase the risk substantially, and notes that currently, a certain proportion of WORA individuals have a DINP HQ greater than one and a certain proportion of WORA individuals have DINP HQs near one. Increasing exposure to DINP may increase the number of individuals with an HQ greater than one or may increase the HQs of individuals with an HQ greater than one. Furthermore, doubling DINP exposures would lower the MOE for DINP to 110 to 7000 (95th percentile). The CHAP noted that MOEs exceeding 100 to 1000 are typically "considered adequate for protecting public health" (CHAP 2014, p. 4).

Current analysis suggests, therefore, that DINP MOEs, in isolation, (e.g., the MOE is 220 for Case 2) are below the upper limit, and are nearing the lower limit considered adequate for protecting public health.

Comment 5.6 International risk assessments. Several commenters stated that a risk assessment of DINP had recently been conducted by Australia (NICNAS 2012), which commenters stated "upheld the safety of DINP for its intended uses."

In contrast, other commenters indicated that the European Union (EU), after re-evaluation in 2010 and 2013 (ECHA 2010; 2013), has maintained a restriction of DINP for toys and child care articles that can be placed in the mouth by children. One of these commenters pointed to conclusions of the ECHA 2013 evaluation, which stated that, "DINP has anti-androgenic properties and it could be appropriate to include this substance in a combined risk assessment of phthalates with anti-androgenic properties," and that risk from DINP "cannot be excluded if the existing restrictions were lifted." The commenter stated that this approach "is in agreement with the CHAP approach to cumulative risk assessment by grouping DEHP, DBP, DIBP, and DINP based on their antiandrogenic properties."

Response 5.6: Staff emphasizes that international regulatory requirements must be considered in the context of the applicable laws of each respective nation. Thus, consistent with the statutory framework of the CPSIA, the Commission considered cumulative risk for exposures to the phthalates associated with male reproductive developmental effects including DINP. Based on the results of the cumulative risk assessment, the Commission proposed to prohibit all children's toys (not just those that can be placed in the mouth) and child care articles containing DINP, consistent with the prohibition involving other phthalates associated with MRDE, to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals.

The different conclusions by CPSC and Australia about potential risks associated with DINP exposure result from the different evaluation approaches. The Australian evaluation (NICNAS 2012) affirmed that DINP has phthalate syndrome effects, but conducted risk analyses on DINP in isolation, and DINP combined with DEHP and DEP (a non-MRDE phthalate). In particular, the Australian evaluation used exposures calculated from activity scenario data to estimate MOEs and cumulative MOEs. The evaluation did not include CRA. Although MOEs were generated by the CHAP for DINP in isolation (using NHANES data), the Australian MOE approach is in contrast to the CHAP's CRA approach for multiple phthalates using NHANES HBM data as a primary exposure source.

Regarding the regulation of DINP in the EU, staff agrees that the CHAP's approach, the Commission's proposed rule, and staff's conclusions that the most recent HBM data are consistent with the ECHA (2013) conclusions about the potential for increased exposure to DINP and the appropriateness of a combined risk assessment based on antiandrogenic properties. Based on the CHAP's assessment, and staff's assessment of more recent NHANES data, staff reiterates its conclusion that DINP contributes to the risk for male reproductive developmental effects, and children's toys that can be placed in a child's mouth and child care articles containing DINP should be permanently prohibited.

A permanent prohibition of children's toys that can be placed in a child's mouth and child care articles containing DINP would prevent exposure of infants, toddlers, and children to DINP that results from oral, dermal or inhalation contact with these products. Staff considers that this prohibition is necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals. Without this prohibition, DINP exposures from sources other than children's toys and child care articles would add to the expected increase of DINP exposure from children's toys and child care articles. This would increase cumulative exposures, potentially placing an increased number of susceptible individuals at risk.

Regulation of Additional Phthalates

Comment 5.7: Regulating DIBP, DPENP, DHEXP, DCHP. One government commenter stated that DIBP, DPENP, DHEXP, and DCHP are not widely used in children's toys and child care articles and are not prohibited in the European Union. The commenter stated that the proposed rule "inevitably will extend inspection range, add cost to manufacturers and exporters and result in an unnecessary trade barrier."

Response 5.7: Staff agrees with the commenter's assertion that DIBP, DPENP, DHEXP, and DCHP may not be widely used in children's toys and child care articles and also that these phthalates are not involved in prohibitions in the EU.

The ability of these four phthalates to reduce fetal testosterone production (a component of phthalate syndrome) in two strains of Sprague-Dawley rats has been assessed by Furr et al. (2014). In this study three out of the four proposed phthalates (DPENP, DHEXP, and DCHP) had much greater potency than DEHP. The potency of the fourth (DIBP) was slightly less or similar to DEHP (Furr et al. 2014; Hannas et al. 2011). The additional phthalates also have lower molecular weights (they are smaller molecules), which tends to increase migration to the surfaces of toys and child care articles ((Dreyfus 2010; Dreyfus and Babich 2011), thereby increasing exposure. Staff concludes that allowing the use of DPENP, DIBP, DHEXP, or DCHP in children's toys or child care articles could increase the exposure, thus adding to the cumulative risks to sensitive populations.

Regarding the commenter's assertion that the prohibition of children's toys and child care articles containing the additional phthalates would add costs and result in a trade barrier, because, as summarized by the CHAP (CHAP 2014, pp. 111, 113, 116, 117), these phthalates are thought to be not widely used in children's toys and child care articles, the cost to manufacturers to reformulate the few products that might contain these phthalates should be small. Third party testing is already required for children's toys and child care articles containing prohibited phthalates and the incremental cost of adding the additional phthalates to the analysis is expected to be very small. The additional materials needed to evaluate the compliance of an additional

phthalate is estimated to be $0.35 per test or about 0.1 percent of a typical $300 phthalates test for a component part or material. The test equipment and sample preparation is the same. The data analysis procedure would need to be modified to include the new phthalates, but, because each phthalate can be isolated at unique elution times by gas chromatography, the identification and quantitation of these additional phthalates is not expected to pose additional burdens to qualified laboratories.

Comment 5.8: Interim prohibitions of children's toys that can be placed in a child's mouth and child care articles containing DNOP and DIDP, and monitoring of other phthalates (DMP, DEP, and DPHP). Commenters requested that the Commission revise the proposed rule to make the interim prohibitions involving DIDP and DNOP permanent. Commenters reiterated the CHAP's conclusions that DNOP is a potential developmental toxicant, causing supernumerary ribs, and a potential systemic toxicant, causing adverse effects on the liver, thyroid, immune system, and kidney, and that DIDP was a 'probable toxicant' based on reproductive and developmental effects, and adverse systemic effects on the liver and kidney. The commenter asserted: "(b)ecause several of these phthalates have another similar adverse health impact, it is conceivable that there could be a cumulative impact from exposures to a mixture of DINP, DNOP and DIDP, which would enhance the concern about harm."

Commenters asserted that without enough data to conduct a robust risk assessment, lifting the prohibition involving DNOP and DIDP will lead to elevated exposure to these two phthalates as others are included in prohibitions, posing an uncalculated risk to the population. Commenters suggested that the interim prohibitions should be made permanent to protect vulnerable populations, because these phthalates cannot otherwise meet the reasonable certainty of no harm safety standard.

Response 5.8: The CHAP concluded that DIDP and DNOP do not appear to possess antiandrogenic potential and therefore the CHAP did not include these two phthalates in the cumulative risk assessment. The CHAP, however, recognized that DIDP and DNOP are potential developmental toxicants and potential systemic toxicants, and performed individual phthalate risk assessments using NHANES biomonitoring data and the MOE approach. The CHAP's analysis showed high MOEs (greater than 1000 for all populations) that are sufficient to protect human health. Therefore, considering that exposure to DIDP and DNOP is low compared to the levels associated with adverse effects, the CHAP found no justification for continuing the interim prohibition of children's toys that can be placed in a child's mouth and child care articles containing DIDP (CHAP 2014, pp. 104-105)and DNOP (CHAP 2014, p. 95).

Staff notes that the CHAP's analysis showed that DNOP exposure levels are so low that one of the metabolites, MNOP, was not detectable in about 90 percent of humans (CHAP 2014, Table 2.6). Because the DNOP levels were not detected in 90 percent of people the MNOP urinary metabolite was not measured by NHANES after the 2009/2010 data cycle. Furthermore, the CHAP's analysis indicated that exposures would have to increase by a large measure before the acceptable levels of exposure would be exceeded for these two phthalates.

Staff does not consider that DNOP and DIDP present a risk to consumers at current exposure levels, and do not contribute to the cumulative risk of antiandrogenicity. By themselves, the MOEs for DNOP and DIDP are sufficiently high (i.e., greater than 1000) to protect human health. Therefore, staff concludes that there is no justification at this time for a continued prohibition on children's toys that can be placed in a child's mouth and child care articles

containing DIDP or DNOP, because a prohibition of these products is not necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety.

Comment 5.9: Prohibitions on children's toys that can be placed in a child's mouth and child care articles containing DNOP and DIDP. Some commenters stated that to meet the "reasonable certainty of no harm" standard, the Commission should make the interim prohibitions involving DNOP and DIDP permanent because the CHAP reported on developmental and systemic toxic effects caused by these chemicals in animal studies. The commenters noted that the CHAP report found exposure to these chemicals from toys and child care articles. The commenters were concerned that prohibiting other products with phthalates will lead to increased exposure to DNOP and DIDP raising questions about whether these chemicals can meet the "reasonable certainty of no harm" standard. They noted that children's products containing these two phthalates remain prohibited in the EU, other countries, and three states.

Response 5.9: As discussed in comment response 5.8, the CHAP concluded that DIDP and DNOP do not appear to possess antiandrogenic potential and therefore the CHAP did not include these two phthalates in the cumulative risk assessment. The CHAP examined DIDP and DNOP individually and found high MOEs (greater than 1000 for all populations) that are sufficient to protect human health. Therefore, staff concludes that there is no justification at this time for a continued prohibition involving DNOP or DIDP, because the prohibition is not necessary to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety.

Comment 5.10: Prohibition of children's toys and child care articles containing DIOP. Commenters suggest that the CPSC permanently prohibit children's toys and child care articles containing DIOP. Commenters cite DIOP's structure that suggests that DIOP is, as the CHAP Report states, "within the range of structure-activity characteristics associated with antiandrogenic activity." A commenter acknowledges a lack of exposure data for DIOP and that human exposure "appears to be negligible," but concludes that DIOP cannot be assumed to meet the CPSIA's statutory mandate "to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals," due to the lack of hazard and exposure data necessary to calculate risk to human health. One commenter urged the Commission to "ban the chemical until such time that the science affirmatively shows it to be safe."

Response 5.10: Staff acknowledges that in general, structural similarity to well-known chemicals can be considered in predicting potential activity of a less-studied chemical. However, prediction of potential adverse health effects cannot substitute for scientific observation of health effects associated with exposure to a chemical. Furthermore, the quality of a prediction depends on the prediction model, model validation steps, quality of input data, and the complexity of the biological activity (i.e., less complex activity is more likely to be associated with robust prediction, and more complex effects such as male developmental reproductive effects are likely to be associated with higher levels of uncertainty).

Although the CHAP recognized that the structure of DIOP suggests that it may be associated with antiandrogenic effects, no experimental data exist that would support a conclusion that DIOP causes MRDE. Furthermore, even if staff were to consider DIOP to cause MRDE, the lack of experimental data on adverse effects prevents any estimates of potency, which is necessary for

assessment of risk. Because we have neither potency nor exposure data on DIOP, its risk cannot be estimated. Thus, there is no basis for regulatory action on DIOP at this time.

Comment 5.11: Effective date. Two commenters stated that the Commission should allow sufficient time for manufacturers to respond to the rule by setting an effective date of at least one year from finalization of the rule. The commenters state this would be consistent with past CPSC practice and that industry should be given time prior to being held liable for any violations of the new, final rule. The commenters asserted their understanding that DIDP and DINP are difficult to differentiate through testing, and that if the prohibition on children's toys that can be placed in a child's mouth and child care articles containing DIDP was lifted while that for DINP was retained, laboratories would need additional time to address the technical testing difficulties.

Another commenter urged the Commission to shorten the proposed 180-day effective date in the final rule based on staff's analysis indicating the minimal impact of the new provisions of the rule to "ensure that there is no gap in the protections from DINP." The commenter urges the Commission to eliminate lag time in implementation of the permanent prohibition on children's toys or child care articles or make clear that the current interim prohibition will remain in place until the effective date of the final rule. The commenter asserted that the Commission should not allow a six-month gap during which toys currently prohibited could be legally sold. The commenters note that the Administrative Procedures Act allows the Commission to shorten the implementation period to less than 30 days "for good cause found and published with the rule." 5 USC § 553(d).

One commenter asked for clarification on Section 5(c) of Public Law 112-28. The commenter stated that the section could be interpreted to provide for a retroactive application (back to 2011) of any final phthalates rule.

Response 5.11: Regarding the commenters' request for an extended effective date, based on their understanding that DINP and DIDP may be difficult to differentiate through testing, staff acknowledges that, relative to other gas chromatography mass spectrometry tests, differentiating DINP and DIDP can be slightly more difficult than differentiating other phthalates from each other. However, the expectation is that all phthalate testing data should be reviewed by an experienced human operator, and that this operator is capable of making the determination without much additional effort. Laboratories can differentiate DINP and DIDP using currently available equipment and methods. Furthermore, manufacturer's always have the option of maintaining current formulations while they address any perceived challenges differentiating DINP and DIDP. Staff concludes that there is no need to change the proposed effective date, based on any concern about the ability to test and differentiate DINP and DIDP.

Staff notes that some DIDP technical mixtures may contain DINP. If these technical mixtures are used in children's toys or child care articles, the toys or articles are subject to the content limit prohibitions in the draft final rule. If the proposed rule is finalized, manufacturers of products subject to the prohibitions on children's toys and child care articles containing DINP should ensure that their use of DIDP technical mixtures do not result in noncompliant products based on inadvertent DINP content.

Staff recommends that the final rule take effect 180 days after publication in the *Federal Register*. Staff concludes that because very few products should need to be reformulated, this period should be sufficient time for manufacturers to ensure that their products do not contain the regulated phthalates. Because staff anticipates that those few products requiring reformulation

will require modifications in design, supply chain, testing procedures, documentation, and other factors, staff declines the suggestion by some commenters to eliminate or shorten the implementation period. The interim prohibitions will remain in effect until that final rule takes effect.

The final rule is prospective in nature, and would apply to products manufactured or imported after the effective date. As mentioned, however, the interim prohibition remains in place until the final rule takes effect.

Section 5 Summary

Overall, CPSC staff concludes that the contribution of DINP to the cumulative risk is substantial. If DINP were allowed in children's toys and child care articles it could contribute 15 percent of the cumulative risk in infants (CPSC 2014b). Analysis of recent NHANES data indicates that, in WORA, DINP contributes at least as much as DEHP to the cumulative risk (CPSC 2017a). Although diet is the primary source of exposure to many phthalates, staff notes that mouthing and contact with children's toys and child care articles could contribute up to an about 29 percent of total exposure for infants if phthalates were allowed in these products. Finally, staff agrees with the CHAP's including regulated phthalates (DBP, BBP, and DEHP) in the CRA, because exposure occurs from multiple sources and, therefore, contributes to the cumulative risk.

6. Scope of Prohibition Involving DINP and Four Additional Phthalates

The Commission proposed making permanent the interim prohibition involving DINP. In doing so, the Commission also proposed changing the scope of products covered from children's toys that can be placed in a child's mouth and child care articles containing DINP to all children's toys and child care articles containing DINP, which is the same scope of products in the permanent prohibition. In addition, the Commission did not propose prohibiting any phthalate-containing children's products other than toys and child care articles.

Overview of Public Comments on the Scope of Prohibitions Involving Phthalates

Several commenters objected to the proposal to expand the scope of the prohibition involving DINP from "toys that can be placed in a child's mouth" to "children's toys," arguing that mouthing toys is the primary source of risk from toys and, therefore, that no oral exposure can occur from toys too large (greater 5 cm in all dimensions). b) Some commenters cited a report by the European Chemicals Agency (ECHA) as support for not expanding the prohibition. This report recommended retaining the prohibition involving DINP, which, in Europe, applies to toys that can be placed in a child's mouth (ECHA 2013). In contrast, other commenters supported the expanded scope.

Researchers studying children's mouthing activity consider "mouthing" to include any contact of the toys or child care article with the mouth, lips, or tongue (EPA 2011; Greene 2002; Groot et al. 1998; Juberg et al. 2001; Kiss 2002). In addition, handling toys and then putting fingers and hands in the mouth can also lead to oral exposure. Because the CHAP used mouthing data from Greene (2002), their estimates of oral exposure from mouthing toys (CHAP 2014, Appendix E-1) includes any behavior in which the toy contacts the mouth. The ECHA report cited by commenters (ECHA 2013) also used mouthing data from Greene (2002). Thus, both the CHAP's and ECHA's assessments of DINP exposure include all children's toys (comment response 6.1, 6.2). The ECHA report concluded that the prohibition on toys and child care articles containing DINP that can be placed in a child's mouth should not be lifted, but the report did not state any conclusions about whether to expand the prohibition's scope to all children's toys. There was no indication that the issue of expanding the scope to all toys was even considered by ECHA (comment response 6.4).

Staff concludes that expanding the scope of the proposed permanent prohibition involving DINP to include all children's toys would prevent additional mouthing and dermal exposures from handling toys not included in the interim prohibition.

A few commenters expressed disappointment that the Commission did not expand the scope of the phthalate regulations to encompass all children's products. Staff does not have sufficient information to adequately assess the quantitative exposure and risk from phthalates in children's products other than children's toys and child care articles. The CHAP was not able to assess exposure and risk from the broader range of children's products, largely due to the lack of information (CHAP 2014, Appendix E-1, p. E1-47) (comment response 6.6).

Comment 6.1: Expanded scope of prohibition involving DINP to all children's toys. Several industry commenters, in addition to their objection to the proposed rule's continued prohibition of children's toys that can be placed in a child's mouth and child care articles containing DINP

(see comments on the prohibition involving DINP in Section 5), objected to the expansion of the scope of the prohibition involving DINP from children's toys that can be placed in a child's mouth and child care articles to all children's toys and child care articles. Commenters asserted that the Commission has little justification to prohibit children's toys that can be placed in a child's mouth and child care articles containing DINP, and even less basis to expand the scope of the prohibition from "mouthable toys" to all children's toys. One commenter explained that because mouthing is responsible for most risk, expanding the prohibition to all toys would have little effect on the risk. Another commenter asserted that the CHAP's cumulative risk assessment is not relevant to individual children's products because the assessment included DEHP, DBP, and BBP, which are already permanently regulated in children's toys.

Response 6.1: As noted in Section 5, the Commission's proposed rule concerning the permanent prohibition of all children's toys and child care articles containing more than 0.1 percent of DINP is based on the CHAP's CRA. As instructed by the statute, the CHAP's CRA considered the cumulative effect of exposure to all phthalates, including DEHP, DBP, DIBP, BBP, and DINP, from all sources, including children's products. Staff's analysis of the most recent two-year data collection cycle (NHANES 2013/2014) shows that there were from two to nine individuals with a HI greater than one in a sample of 538, depending on the PEAA Case. Although DEHP, DBP, and BBP are permanently regulated in children's toys and child care articles, current HBM data show that significant exposures to these phthalates continue to exist from the combination of all products and sources. Based on analysis of newer HBM data, staff concludes that allowing DINP to be used in children's toys and child care articles would only increase the contribution of DINP to the cumulative risk. While human exposures to some phthalates have declined in recent years, DINP exposure is increasing.

Under provisions of section 108 of the CPSIA, the interim prohibition involving DINP applies to "any children's toy that can be placed in a child's mouth" or "child care article." Further, the law provides that if a toy or part of a toy in one dimension is smaller than 5 centimeters, it can be placed in the mouth. Thus, the interim prohibition does not include toys that can only be brought to the mouth, but cannot be placed in mouth due to the toy's dimensions.

Generally, exposure to chemicals from children's toys occurs through oral (both direct and indirect) and dermal exposure. Direct oral exposure occurs from a toy placed in the mouth, from a child's behaviors that include sucking and chewing. Direct oral exposure also occurs through contact that does not involve the toy being placed in the mouth, from behaviors such as licking, and any other contact with the toy with the lips and tongue. Such behaviors, and potential exposures to chemicals from the toys, can occur even if the toy does not meet the statutory definition of having at least one dimension smaller than 5 centimeters.

Indirect oral exposure can also occur through handling of toys, in which some of the chemical that collects on a child's hands during their contact with toys is transferred to the mouth during normal hand-to-mouth contacts (e.g., thumb-sucking, eating after or during play without handwashing, other absentminded or intentional touching of lips or mouth). Handling of toys can also cause exposure through absorption into the body of the chemical through the skin (dermal exposure).

In the NPR, the Commission noted that oral exposure is the primary exposure pathway to phthalates and proposed expanding the scope of the prohibition to all children's toys for DINP, as described in the NPR (79 FR 78335), and further detailed in the staff briefing package. Studies

show that mouthing in young children primarily involves fingers, pacifiers, teethers, and toys, and that mouthing of other articles is less frequent (EPA 2011; Greene 2002; Groot et al. 1998; Juberg et al. 2001; Kiss 2002). Thus, toys are among the children's products most often involved in mouthing. Regarding the statute's reference to toys that can be placed in a child's mouth, as described above, staff notes that a toy that can be placed in the mouth is not synonymous with a 'mouthable' toy.[23] Thus, staff considers that mouthable toys are not limited to those toys that can be placed in the mouth, and that common mouthing behaviors that consist of a child's contact with the toy with lips and tongue are considered to be potential pathways for exposure if the chemical substance is present on the surface of the toy.

As noted in staff's briefing package, the CHAP estimated potential phthalate exposures from children's toys and child care articles (CHAP 2014, pp. 49-60 and Appendix E1). Staff notes that the CHAP's phthalate exposure estimates for mouthing included both mouthing involving the toy being placed in the mouth and mouthing of toys either that were not placed in the mouth or that were too big to be placed in the mouth. Although the available assessments do not provide phthalate exposure estimates separately for mouthing of toys that are larger than 5 cm in every dimension and mouthing of toys that are smaller than 5 cm in any dimension, staff concludes that exposures from both groups of toys contribute to the cumulative risk.

Furthermore, the staff briefing package states that exposure occurs from handling toys, as well as from mouthing, and that the additional exposure from handling toys would add to the cumulative risk (CPSC 2014b, p. 30). The European Chemicals Agency (ECHA) came to a similar conclusion when it estimated that exposures from handling toys contribute to total DINP exposure (ECHA 2013, Table 4.90). In the ECHA analysis, the assessment of exposure from handling toys considered only the dermal exposure, and did not specifically evaluate indirect oral exposure from children handling toys and normal hand-to-mouth behavior. Finally, while staff does not have exposure estimates for indirect oral exposure from handling toys and normal hand-to-mouth behavior, staff concludes that exposures from handling toys will further contribute to the cumulative risk.

As previously noted by staff, HBM data shows DINP exposure is increasing. Staff further notes that oral exposure to toys is the primary phthalate exposure pathway, and that oral exposure includes not just placing items in the mouth, but also includes behaviors such as licking, and any other contact with the toy and tongue. Staff concludes that expanding the prohibition involving DINP from toys that can be placed in a child's mouth to all children's toys would decrease exposure of infants, toddlers, children, and pregnant women to DINP that results from oral, dermal or inhalation contact with these products. Staff considers that expanding the prohibition involving DINP to all children's toys is necessary meet the statutory mandate to protect the health of children.

Comment 6.2: CRA support for prohibition involving DINP and expansion of scope. Several commenters indicated that the CRA clearly supported the proposed prohibition involving DINP and the proposed expansion of scope from toys that can be placed in the mouth to all

[23] In fact, the mouthing studies such as Greene (2002), cited above and in the staff briefing memorandum, and others (see EPA 2011, ECHA 2013) consider mouthing to include a number of behaviors such as contact with an object with the lips or tongue, in addition to actions such as biting, chewing and sucking, which involve placing an object in the mouth.

children's toys. Commenters cited evidence that DINP is associated with MRDE, the CHAP's CRA that shows the contribution of DINP to phthalates risk, and human biomonitoring data that show that exposures to DINP are increasing, which would increase the contribution of DINP to the overall risk.

Response 6.2: Staff agrees with the commenters that scientific evidence demonstrates that DINP can induce MRDE and that as discussed in comment response 6.1, additional exposures from DINP from children's toys that are not placed in the mouth add to the overall cumulative risk.

Comment 6.3: Basis for prohibition involving DINP. A commenter suggested that the Commission's expansion of the prohibition involving DINP to all children's toys and child care articles was not based on a statutorily required risk-based analysis, and instead was based on the consideration that additional testing costs would be marginal.

Response 6.3: Regarding testing and other costs, while the Commission certified under the RFA that the proposed rule is not expected to have a significant economic impact on a substantial number of small entities, this conclusion is not the basis for the expansion in scope to all children's toys for DINP.

Regarding DINP, as stated in comment response 6.1, the expansion in the scope of the prohibition involving DINP is based on consideration of exposure that occurs through oral exposure through direct mouthing (whether or not the toy can be placed in the mouth), dermal exposure from handling, and indirect oral exposure through handling and subsequent hand-to-mouth contact, and the contribution of these pathways of exposure to the cumulative risk.

Staff based the justification for expanding the scope of the prohibition involving DINP on potential health risks, not economic factors.

Comment 6.4: CPSC cited an outdated EU analysis regarding DINP. One commenter stated that CPSC's explanation for the expansion of DINP prohibitions to all children's toys incorrectly implied that the basis for the EU's phthalates regulation was not up to date. Additionally, the commenter asserted that CPSC was not accurate regarding what EC 2005 says regarding the basis for the narrower scope of the restriction on DINP. The commenter further noted that EC 2005 concluded that it is appropriate to have a less restrictive regulation involving DINP, because the data for DINP indicate a much lower concern for risk (no reproductive toxicity and uncertainties on exposure) compared to DEHP and other low molecular weight phthalates.

Response 6.4: Staff notes that the phthalate restrictions were unchanged in the 2006 regulation (EC 2006, pp. 40-41). EC 2006 consolidates numerous chemical regulations, including the phthalate restrictions, under the general heading of Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, and other regulations. Staff did not intend to imply that the European regulations are outdated.

Staff cited the original EC regulation (EC 2005), because it discussed uncertainty in the scientific information for DINP, DIDP, and DNOP, which was not retained in EC 2006. Paragraph 11 of EC 2005 states, "Scientific information regarding di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP) and di-*n*-octyl phthalate (DNOP) is either lacking or conflictual, but it cannot be excluded that they pose a potential risk if used in toys and childcare articles…" In paragraph 12, EC 2005 went on to say, "However, the restrictions for DINP, DIDP, and DNOP should be less severe than the ones proposed for DEHP, DBP, and BBP for reasons of proportionality." Staff interpreted this to mean that the less stringent prohibitions involving DINP, DIDP, and

DNOP were due to uncertainty in the scientific information for these three phthalates. The Commission concluded in the NPR, based on staff input, that, in light of new data on phthalates and the CHAP report, the prohibition involving DINP was justified, whereas the prohibitions involving DIDP and DNOP were not needed.

Comment 6.5: Re-evaluation of EU risk assessment of DINP. One commenter asserted that CPSC disregarded the European Chemicals Agency (ECHA) re-evaluation of the health risks of DINP (ECHA 2013), which was completed in 2013 and adopted by the EU Commission in 2014, which determined that the EU retain the existing restriction (EC 2006) on children's toys that can be placed in the mouth and child care articles for DINP. In addition, the EU submitted a related comment noting that ECHA conducted an extensive review in 2010 on DINP, DIDP and DNOP (ECHA 2010), and concluded that exposure other than mouthing did not present further risk.

Response 6.5: Staff has since reviewed the 2013 ECHA report, which recommended that the existing prohibition involving DINP be retained, but the prohibition involving DIDP could be lifted.[24] Specifically, ECHA (2013, p. 7) stated, "ECHA concluded that a risk from the mouthing of toys and childcare articles with DINP and DIDP cannot be excluded if the existing restriction were lifted. No other risks were identified." Staff notes a few key points regarding the 2013 ECHA report.

First and foremost, staff notes, that the 2013 ECHA report did not specifically address the distinction between children's toys and toys that can be placed in a child's mouth.

Second, staff also notes that the 2013 ECHA report used different health end points (liver toxicity) as the focus, rather than the MRDE focus used by the CHAP and CPSC. Finally, staff notes that the 2013 ECHA report did not consider cumulative health risks from multiple phthalates. For the most part, the ECHA assessment considered the health risks from DINP and DIDP in isolation. ECHA did consider the combined risks of liver toxicity from DINP and DIDP. In contrast, the CHAP's CRA was based on MRDE and did not include DIDP, because DIDP does not cause MRDE.

In the 2010 report, ECHA considered a possible expansion of prohibitions involving DINP beyond children's toys and child care articles to all children's products, but concluded that there was insufficient information to justify an expansion at that time (pp. 18–21). This recommendation aligns with those made by staff in the NPR. However, the EU did not expand prohibitions beyond all children's toys and child care articles that could be placed in the mouth, contrasting with CPSC's NPR. Staff concurs with the assessment made by the EU in their comment that the difference in conclusion is due to the different approaches- namely that the ECHA did not consider cumulative risk, and considered a liver toxicity endpoint versus MRDE. The ECHA report concluded that the prohibition on toys and child care articles containing DINP that can be placed in a child's mouth should not be lifted, but the report did not state any conclusions about whether to expand the prohibition's scope to all children's toys. There was no indication that the issue of expanding the scope to all toys was even considered by ECHA.

Finally, staff emphasizes that international regulatory requirements must be considered in the context of the applicable laws of each respective nation. Thus, consistent with the statutory framework of the CPSIA, when issuing the NPR, the Commission considered the cumulative risk

[24] The EC did not act on the recommendation to lift the prohibition on DIDP.

for exposures to the phthalates associated with male reproductive developmental effects, including DINP. Based on the results of the cumulative risk assessment, the Commission concluded in the NPR that the expansion of the permanent prohibition involving DINP to all children's toys and child care articles is necessary to protect the health of children. For the reasons described here, staff still concurs with that conclusion.

Comment 6.6: Expanding the scope of prohibitions involving phthalates to all children's products. One commenter expressed disappointment that CPSC is not expanding the scope of the provisions involving phthalates to include other children's items such as raincoats, footwear, backpacks, school supplies, and clothes. The commenter questioned the CPSC's justification for not expanding the scope to all children's products based on limited available information. The commenter asserts that a lack of data does not mean CPSC should assume there is no problem. The commenter notes that CDC researchers found measurable levels of many phthalates metabolites in the general population, and that some phthalates affect the reproductive system of animals.

Another commenter claimed that the Commission's reasoning for extending the prohibition concerning DINP to all toys, but not to prohibit other children's products with phthalates beyond toys is inconsistent. The commenter wrote that CPSC chose not to expand the prohibitions involving phthalates to all children's products because, quoting the staff briefing memorandum, "staff believes that increased exposure to phthalates from most children's products would be negligible." The commenter interprets that staff's rationale for the negligible exposure is that those products are not frequently mouthed. The commenter claims that this rationale supports not expanding the scope of the prohibition involving DINP beyond toys that can be placed in the mouth.

Response 6.6: In the NPR, the Commission explained that it did not propose to expand the scope of the prohibitions to include all children's products primarily because of a lack of information to assess the impact on children's health.

Staff has not found new information that would change the basis underlying the Commission's decision not to expand the scope of the rule to all children's products and the rationale that there is not enough information to adequately assess the health impact of children's products other than children's toys and child care articles. Staff notes that the lack of information includes specific marketing information (what type, how many, and what fraction of the population uses children's products within CPSC's jurisdiction), as well as relevant peer-reviewed publications specifically demonstrating phthalate residue concentrations in and exposure types, durations, and frequencies from children's products within CPSC's jurisdiction. In contrast to children's products in general, a wealth of use information exists for children's toys and child care articles (EPA 2008; EPA 2011). Numerous scientific publications also demonstrate phthalate residues in and exposures from phthalates in children's toys and child care articles (Barušić et al. 2015; CHAP 2014; CPSC 2002; Ting et al. 2009; Xie et al. 2016).

Staff concurs with the commenter and notes that there is limited evidence, popular press articles, and international publications (e.g., Tønning et al. 2010a; Tønning et al. 2010b; Tønning et al. 2009; Tønning et al. 2010c) which suggest that a few children's products may have phthalate residues. Staff does not consider these sources of information to be of sufficient relevance, quality, or quantity, to support expanding the scope of prohibitions involving phthalates to all children's products.

Staff also notes that the theoretical exposure from children's products is comparatively less than that from children's toys and childcare articles. In the NPR, the Commission noted that oral exposure is the primary exposure pathway to phthalates and that dermal exposure contributes only secondarily to exposure. This has also been demonstrated by others (Ashworth and Cressey 2014). Studies also show that mouthing of toys, teethers, pacifiers and fingers occurs more frequently and is of longer duration than the mouthing of other articles (e.g., other children's products) by young children (EPA 2011; Greene 2002; Groot et al. 1998; Juberg et al. 2001; Kiss 2002). In addition, children's products that might contact the skin (e.g. textiles) are thought to contain lower concentrations of phthalates (Laursen et al. 2003; TERA 2016) and so will result in lower exposures. Those children's products that might contain phthalates, such as backpacks (Xie et al. 2016) are typically not in contact with the skin, and thus also have lower exposure. In addition, toys are more likely than other children's products to be made of materials that could be plasticized with phthalates (Dreyfus 2010; Laursen et al. 2003; Tønning et al. 2009; Wormuth et al. 2006).

Staff recognizes the continued lack of reliable and nationally relevant information about children's products and the presence of phthalates in and exposure to phthalates from children's products in general compared to children's toys and child care articles (CPSC 2014a). Staff notes that there is less theoretical exposure from children's products compared to toys based on children's mouthing behavior. For these reasons, staff disagrees with the commenter's assertion that the Commission's rationale for the proposed rule (expanding the scope of the prohibition to all children's toys and child care articles containing DINP and not expanding the scope to all children's products containing phthalates) is inconsistent.

Section 6 Summary

Staff concludes that expanding the scope of the proposed permanent prohibitions involving DINP to include all children's toys would prevent exposure to a potentially significant source of phthalates, toys not included in the interim prohibition. Staff notes that toys are one of the most frequently mouthed items, and that children can have oral contact with toys that are too large to be placed inside the mouth (Greene 2002).

Staff further concludes that information on phthalate exposure from children's products beyond toys and child care articles is quite limited, and exposure is difficult to assess (CHAP 2014, Appendix E-1, p. E-47) although the potential exposure to DINP from other children's products is expected to be less than that from toys. Thus, staff is not recommending an expansion of the scope of the prohibition to children's products containing DINP or any other phthalate.

7. Epidemiology

Epidemiology Studies

Epidemiology is the study of the distribution and determinants of health-related states and events in specified human populations, and the application of this study to the control of diseases and other health problems. Often, the goal of epidemiological studies is to identify associations, including causal relationships between an exposure and a health outcome.

The CHAP identified and reviewed a number of published epidemiological studies related to the potential association of exposure to phthalates with human health, focusing on the association of maternal phthalate exposure with male reproductive tract developmental endpoints and neurodevelopmental outcomes. The CHAP provided an overall conclusion about the evidence provided by the reviewed studies, noting some inconsistencies among studies, and included comments on some of limitations of individual studies, such as study size, and timing of sample collection.

Staff notes that adverse effects associated with rat phthalate syndrome or human testicular dysgenesis syndrome (e.g., hypospadias, cryptorchidism, testicular cancer, impaired fertility) are observed with regularity in the U.S. population. Collectively, these effects in humans are referred to as testicular dysgenesis syndrome (TDS) (Skakkebaek et al. 2001).

The mean incidence rate in the United States for hypospadias is around 6.47 per 1000 live births (Mai et al. 2015; for all male populations combined from 2008-2012), which equates to approximately 13,000 new hypospadias per year.

Cryptorchidism is also observed in the U.S. population and is the most common reproductive disorder reported for newborns. Cryptorchidism occurs in up to 4.6 percent of male live births (greater than 2.5 kg; up to 45.3 percent in newborns less than 2.5 kg) (Kolon et al. 2014). This equates to approximately 95,000 newborns per year. It is estimated that young men with cryptorchidism have a 4-fold increased risk for testicular germ cell cancer (Banks et al. 2012).

Testicular cancer occurs in about 9,000 people per year in the United States. (Siegel et al. 2017). Approximately 400 of these people will die each year from complications related to testicular cancer. The number of cases of testicular cancer has increased over fifteen percent the past 15 years, when considering statistics reported by the American Cancer Society (Greenlee et al. 2001; Siegel et al. 2017). A similar trend has been reported world-wide (Huyghe et al. 2003).

Impaired male fertility has been reported in approximately 9.4 or 11.5 percent of males age 15–44 or 25–44 (Chandra et al. 2013; from 2006-2010 data) and 7 percent of males overall (Krausz 2011; Lotti and Maggi 2015).

The causative factors for these TDS (phthalate syndrome-like) adverse effects in humans are unknown (as reviewed in Kolon et al. 2014). Phthalates have been proposed as possible contributors to TDS (Scott et al. 2007; Skakkebaek et al. 2001).

Overview of Public Comments on Epidemiology

Some commenters claimed that the epidemiological literature on phthalates does not support the CHAP's recommendations due to uncertainties and inconsistencies in the data. Some commenters asserted that the epidemiology studies have not established a cause and effect

relationship between phthalate exposure and MRDE effects in humans. Commenters concluded, therefore, there is no evidence to support the CHAP's recommendations and the Commission's proposed regulations.

Staff agrees with the CHAP's conclusion that there is a growing body of studies showing an association of phthalate exposure with MRDE effects in infant and adult males (CHAP 2014, p. 27). Staff agrees that existing phthalate epidemiological studies have not established a cause and effect relationship. However, the CHAP's CRA is primarily based on animal data. Therefore, epidemiological studies establishing a causal relationship between exposure and effect are not required to conclude that a substance or mixture is "probably toxic to humans" (CPSC 1992; EPA 1991; IARC 2002; NTP 2016) or to support a regulation (CPSC 1992). 16 C.F.R. § 1500.3 (c)(2)(ii). Epidemiological data are rarely able to establish cause and effect for any exposure. Based on the CPSC's chronic hazard guidelines (CPSC 1992), staff considers that there is sufficient evidence in animal studies to conclude that certain phthalates are probably toxic to humans. Epidemiological data provide supporting evidence for the animal data and also support the conclusion that the results of animal studies are relevant to humans.

Comment 7.1: Role of epidemiology studies and CHAP recommendations. Some industry commenters suggested that human epidemiological evidence for phthalate-induced effects was equivocal or inconsistent with results published in animal studies, and did not support the CHAP's conclusions and recommendations. One NGO commenter wrote that some epidemiology studies may have demonstrated an association between male reproduction (e.g., sperm concentration) and phthalates, but not consistently, and that these results are sometimes different than those observed in experimental animals. Some commenters also noted that there is no evidence that highly phthalate-exposed individuals had a greater incidence of adverse reproductive effects. One commenter asserted that the CHAP provided no evidence documenting a reduction in developmental outcomes after a reduction in phthalate exposures.

Response 7.1: The CHAP's CRA and recommendations to the Commission are primarily based on animal studies. The CHAP also reviewed the available epidemiological (CHAP 2014, pp. 27-33 and Appendix C) evidence and concluded: "There is a rapidly growing body of epidemiological studies on the association of exposure to phthalates with human health." Overall, staff concludes:

- Staff agrees with the CHAP's conclusion that, "There is a rapidly growing body of epidemiological studies on the association of exposure to phthalates with human health." (CHAP 2014, p.2);
- The CHAP's conclusion is consistent with a recent NAS (2017) report that also concluded that there is a "moderate level of evidence" from epidemiological studies that DEHP and DBP induce MRDE in humans (based on changes in AGD). The NAS report conclusions provide additional confidence that phthalates cause MRDE in humans;
- Epidemiological studies establishing a causal relationship between exposure and effect are not required to conclude that a substance or mixture is "probably toxic to humans" (CPSC 1992; EPA 1991; IARC 2002; NTP 2016); and
- Based on the CPSC's chronic hazard guidelines (CPSC 1992), staff considers that there is sufficient evidence in animal studies to conclude that certain phthalates are probably toxic to humans. Epidemiological data provide supporting evidence for the animal data and also support the conclusion that the animal data are relevant to humans.

The CHAP considered the available human and animal data for each of the evaluated phthalates in summaries (CHAP 2014, pp. 82-121) and in detail (CHAP 2014, Appendices A-C), and used these data to develop its CRA and support its conclusions. Staff notes that the CHAP's findings are based in large part on the animal data with additional support from epidemiological studies. Based on the CPSC's chronic hazard guidelines (CPSC 1992), staff considers that there is sufficient evidence in animal studies to conclude that certain phthalates are probably toxic to humans. Epidemiological data provide supporting evidence for the animal data and also support the conclusion that the animal data are relevant to humans. Epidemiological studies establishing a causal relationship between exposure and effect are not required to conclude that a substance or mixture is "probably toxic to humans" (CPSC 1992) or to support a regulation. Other federal and international agencies (e.g., EPA 1991; IARC 2002; NTP 2016) employ comparable approaches as the CPSC chronic hazard guidelines to evaluating the weight of the evidence from animal and epidemiological studies.

Staff acknowledges that there are a few inconsistencies in the findings from epidemiological studies. Staff notes that, generally, inconsistencies among epidemiological studies are common due to differences in study methods, characteristics of the study population, study size, and the statistical power of the study to detect associations. However, staff's review of the epidemiology studies concurs with the CHAP's assessment that, with few exceptions, the studies are generally consistent with one another and with the results of animal studies (CHAP, 2014, pp. 27–33).

The CHAP found that a growing number of epidemiological studies have reported associations of phthalate exposure with adverse health effects in humans (CHAP, 2014, pp. 27–33). Many of these effects are consistent with MRDE observed in animal studies.

Regarding one commenter's assertion that the CHAP provided no evidence documenting a reduction in developmental outcomes after reducing phthalate exposures, staff is not aware of any studies designed specifically to look at populations with changing phthalate exposures over time, nor were any such studies cited by the commenter.

A growing body of epidemiological studies reports associations between phthalate exposure and human health effects that are consistent with effects seen in animals. The epidemiological data, in combination with animal studies, provide additional support to conclude that the phthalates considered in the CHAP's CRA are "probably toxic to humans." Finally, staff notes that establishing cause and effect in epidemiological studies is not required by federal and international agencies to conclude that a substance is likely to cause similar effects in humans.

Comment 7.2: CHAP's interpretation of certain epidemiological studies. One industry commenter stated that "[t]he 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," and specifically referenced Suzuki et al. (2012).

Another commenter argued that studies cited in the CHAP report as providing supporting evidence for association of phthalate exposure with of pubertal development effects or gynecomastia (Colon et al. 2000; Durmaz et al. 2010; Lomenick et al. 2009; Rais-Bahrami et al. 2004) do not support the key findings discussed by the CHAP (e.g., Swan and Suzuki) because of methodological limitations or a lack of effects.

Response 7.2: The commenter specifically asserted that the CHAP misrepresented the study by Suzuki et al. (Suzuki et al. 2012). The CHAP's discussion of studies on gestational phthalate

exposure and male reproductive tract developmental effects (CHAP 2014, pp. 28-29) included a statement that two studies reported an effect with higher maternal urinary concentrations of DEHP metabolites. One of these studies (Swan 2008; Swan et al. 2005) reported effects associated with multiple metabolites of DEHP. Another study, Suzuki et al. (2012) reported a significant effect only for the DEHP metabolite MEHP, although the sum of DEHP metabolites also showed a suggestive (non-statistically significant) association.[25] Staff disagrees that the CHAP's summary statement of the two studies is a misrepresentation of the findings, because one study reported significant associations with multiple DEHP metabolites, and the second study reported significant or suggestive associations with multiple DEHP phthalates.

The commenter also claimed that the CHAP did not mention that the Suzuki et al. (2012) study did not find associations between certain phthalate metabolites and the developmental outcome, except in tables and an appendix. However, staff notes that the CHAP cited the lack of association between the specific metabolites and the assessed outcome throughout the text of the report in the recommendation section for each phthalate (see subsections for each phthalate in section 5 of the CHAP Report), in Appendix C, where this study and similar studies were discussed, and in the tables that present the three studies that addressed gestational exposure to phthalates and reproductive tract development outcomes.

Regarding the comment about certain studies cited by the CHAP that do not support the key findings, the commenter may have misunderstood the CHAP's use of epidemiology information provided in Appendix C of the CHAP Report. Appendix C presents a summary and discussion of available epidemiological studies on phthalates. However, the studies cited by the commenter were not used by the CHAP in developing its CRA, because the studies were not directly related to MRDE. The CHAP did not claim that the four studies mentioned by the commenter demonstrated an association between phthalates and pubertal development or gynecomastia, although the CHAP discussed limitations of the four studies that could affect the ability to identify the occurrence of health effects. The CHAP did not cite these endpoints or any of the four studies in the conclusions and recommendations of the CHAP Report.

Staff does not agree with the commenters' claims that the CHAP did not adequately characterize the studies or their findings. Therefore, staff concludes that the CHAP's review of epidemiological data was thorough and objective.

Comment 7.3: Anogenital distance. Several industry comments discussed the association between phthalate exposure and reduced AGD. One commenter acknowledged that associations have been demonstrated between particular phthalate monoesters and reduced AGD, but indicated that these effects occurred sporadically and inconsistently, even when performed by the same laboratory. Some industry commenters claimed that the CHAP did not critically assess the association between phthalate exposure and reduced AGD in young boys (Swan 2008; Swan et al. 2005). The commenters noted inconsistencies in results among the published studies.

One commenter claimed that "AGD and AGI are not linked with any adverse clinical health outcome and thus lack of clinical relevance has been considered by others to be a weakness with these outcomes (McEwen and Renner 2006; Weiss 2006)," and requested this be addressed in

[25] That is, there was a positive effect, but it was not statistically significant.

the report.[26] In contrast, other commenters indicated that other studies have contrasting claims, noting that "these markers are linked with diminished reproductive health in males." (Eisenberg et al. 2011; 2012a; 2012b; Mendiola et al. 2011).

Response 7.3: The CHAP considered and discussed the inconsistent epidemiological data. The CHAP noted the need to carefully evaluate both negative findings and positive findings, indicating that studies must be examined for adequacy of experimental design, sample size, and the presence of confounders that may have masked a possible effect or contributed to reported effects (CHAP 2014, p. 21). Ultimately, the CHAP integrated the available epidemiological evidence with the evidence from animal studies to support the use of human AGD as a relevant measure to assess the antiandrogenic mode of action of phthalates during fetal development.

Staff notes that, generally, inconsistencies among epidemiological studies are common due to differences in study methods, characteristics of the study population, study size, and the statistical power of the study to detect associations. However, staff concludes that, with few exceptions, the epidemiology studies are generally consistent with one another and with the results of animal studies. The CHAP found that a growing number of epidemiological studies have reported associations of phthalate exposure with adverse health effects, such as reduction in AGD (CHAP, 2014, pp. 27–33).

Staff disagrees with the commenter's assertion that AGD and AGI are not linked to adverse clinical outcomes. Reduced AGD is one of many effects associated with phthalate syndrome. As discussed in Section 1, studies (e.g., Boberg et al. 2011; Clewell et al. 2013b) demonstrate that phthalates cause permanent effects on male reproductive development. Jain and Singal (2013) reported that infants with undescended testis (cryptorchidism - an adverse clinical outcome) had a significantly shorter AGD and AGI when compared to infants with descended testis. Thankamony et al. (2014) reported the results of a comparative study involving AGD (and penile length) in infants that were normal and those with hypospadias or cryptorchidism. They determined that AGD was statistically reduced in boys with hypospadias or cryptorchidism when compared to boys without these pathologies. They concluded "The findings support the use of AGD as a quantitative biomarker to examine the prenatal effects of exposure to endocrine disruptors on the development of the male reproductive tract."

Comment 7.4: DEHP exposure from medical procedures. An NGO commenter stated that if there is "no firm evidence that any effects have occurred or are likely to occur in adults and infants most heavily exposed to DEHP as a result of intensive medical procedures," then it would be highly unlikely that less potent phthalates would induce an adverse reproductive effect in the human population. The commenter indicated that phthalate exposures are much higher (thousands of times) for this sub-population undergoing medical procedures compared to other populations.

Response 7.4: As discussed above in the introduction for this section, staff notes that adverse effects associated with rat phthalate syndrome or human testicular dysgenesis syndrome (e.g. hypospadias, cryptorchidism, testicular cancer, impaired fertility) (Scott et al. 2007; Skakkebaek et al. 2001) are observed with regularity in the U.S. population. The causative factors, including

[26] The anogenital index (AGI) is an index used to measure the AGD. AGI is computed as the AGD divided by weight, or AGI = AGD/weight (mm/kg).

the possible role of phthalate exposure, for these phthalate syndrome-like adverse effects in humans are not well characterized.

Staff notes that few studies have specifically investigated possible health outcomes from phthalate exposures from medical equipment. The commenter cited two studies, one of which the CHAP also discussed (Rais-Bahrami et al. 2004). While this study did not find phthalate-related health effects, the CHAP concluded that the very small sample size limits its usefulness. Staff considers additional confounders to be problematic in this study, such as a lack of extracorporeal membrane oxygenation exposure data, a maximum subject age of 16 years old, exposure to the parent phthalate DEHP versus the metabolite MEHP (which the author also noted), and questionable endpoints (e.g. serum testosterone and phallic length). The CHAP concluded that larger studies on medically-exposed infants would be informative and should be conducted. A 2015 review by the EU also concluded that more research is needed in this area (EU 2016).

Staff concludes that because of the uncertainties in the existing data, no conclusions can be drawn from high exposures to DEHP in medical procedures.

Comment 7.5: Human epidemiology data and DINP antiandrogenicity. One industry commenter makes several arguments that the available epidemiology data do not support the assertion that DINP is associated with reproductive effects in humans. The commenter stated that an epidemiology consultant reviewed four epidemiology studies (Joensen et al. 2012; Jurewicz et al. 2013; Main et al. 2006; Mieritz et al. 2012) that evaluated DINP's association with adverse human reproductive effects and found that MINP was positively correlated with FSH in one study (Joensen et al. 2012), but not with the sum of DINP metabolites in that study, nor with MINP in a second study (Main et al. 2006). The commenter noted that other effects such as sperm motility were equivocal in one study (Jurewicz et al. 2013), but not another (Mieritz et al. 2012) and there were no other correlations.

The same commenter also stated that equivocal results were seen in a recent study that reported slight reductions in AGD associated with DINP metabolites in mother's urine (Bornehag et al. 2015), but not with DEHP metabolites even though "DEHP is much more potent than DINP in animal studies." The commenter concluded that "the overwhelming weight of the studies provides no basis to attribute the correlations reported for other phthalates to DINP," and "epidemiological studies on DINP indicate that it is not associated with antiandrogenic effects in humans." The commenter referenced a new prospective cohort study (Swan et al. 2005) and noted that no correlations were seen with DINP metabolites and AGD in the offspring. The commenter further noted that the epidemiology studies should not be used to conclude causation, there were many inconsistencies in results between studies, random chance may have contributed to inconsistent study results, and some of the study results are implausible (e.g., reproductive effects correlated to DEP exposure instead of DEHP).

The commenter discounts the positive finding for DINP in Bornehag et al. (2015), a study on prenatal exposure and MRDE, because that study also did not find an effect related to DEHP, which would be expected to have a larger effect than DINP because of its relative potency. The commenter also discounts the epidemiological studies because of results for DEP and DEHP that conflict with the animal data.

Another industry commenter noted that statistical chance may have been responsible for some of the epidemiology studies' positive association. This commenter cited an epidemiology study (Axelsson et al. 2015), which showed 5 percent positive findings, as an example of the possible

effect of chance. The commenter also noted inconsistent effects in studies, unexpected associations (DEHP exposures have dropped and this is not reflected in effect data), and negative associations (DINP is not associated with reproductive issues). The commenter concluded that the epidemiology data did not disprove that humans are less sensitive than rodents and that the weight of the current information did not support that humans developed reproductive or developmental issues following exposure to phthalates.

Response 7.5: Of the four studies mentioned by the commenter (Joensen et al. 2012; Jurewicz et al. 2013; Main et al. 2006; Mieritz et al. 2012), two were of adults (Joensen et al. 2012; Jurewicz et al. 2013) and one was of boys aged 6–19 years (Mieritz et al. 2012). The CHAP concluded that studies in adult men were less relevant to the CHAP's work, because exposures measured during adulthood cannot be used to infer childhood or early life exposure (Joensen et al. 2012; Jurewicz et al. 2013). Staff agrees that studies in adults or older boys are likely not relevant to possible development reproductive effects from gestational exposure, and thus, staff believes that the consideration of these studies is not informative.

The two studies mentioned as having conflicting results for association with effects on FSH were conducted in very different populations. The first study compared FSH levels to urinary phthalate metabolite levels in adult men (Joensen et al. 2012). The second study compared FSH levels in baby boys with measurement of phthalates in their mothers' breast milk (Main et al. 2006).

Observational epidemiology studies control for the possibility of random chance, bias, or confounding in their study design and analysis (Jepsen et al., 2004). Staff notes that the primary epidemiology studies mentioned by commenters (Suzuki et al. 2012; Swan 2008; Swan et al. 2005) (e.g., Swan 2008; Swan et al. 2005; Suzuki et al. 2012; Huang et al. 2009, (Adibi et al. 2015) have discussion regarding the minimization of these effects. Commentary is dependent on the study and differs in scope and complexity. Some notable ways that authors have endeavored to identify and control potential chance, bias, or confounding include:

1) conducting pilot studies to examine variable associations before conducting the primary study;
2) addressing confounding factors (e.g., ethnicity, smoking status, time of day, season, gestational age of urine sample, neonatal age, interindividual differences in xenobiotic metabolism, study centers, and many others);
3) making health measurements (e.g., AGD) consistent by using trained staff and SOPs; and
4) using appropriate statistical methods to assess relationships between the variables and account for variation or covariation.

Staff concludes that simple calculation of the percent of positive findings (e.g., 5 percent as referred to by the commenter) in a study does not take into account strategies used by the author to control for potential chance, bias, and confounding. Although the commenter presented a theoretical concern, the commenter did not show that the concern applied to any of the key epidemiological studies. In studies where these issues are controlled and statistical methods are appropriate, staff considers the reported epidemiology results to be valid.

Staff concludes that most of the studies cited by the commenters are not relevant to the current rulemaking on children's toys and child care articles, because they involved adults or older children. The results from Bornehag et al., while relevant, are inconclusive. Staff notes that there

are many potential reasons for inconsistent results in epidemiological studies of phthalates. Humans are simultaneously exposed to multiple phthalates, which makes it difficult to distinguish the effects of different phthalates. Staff concludes that the overall weight of the evidence demonstrates an association between prenatal phthalate exposure and MRDE effects in infants.

Comment 7.6: Phthalates alter semen quality. One NGO commenter referenced a new study by the University of Pittsburgh that the commenter asserts reinforces studies done by Harvard researchers showing that phthalates may alter human sperm DNA and semen quality.

Response 7.6: This study (Adibi et al. 2015), while focused on adult exposures to phthalates, supports the CHAP conclusions and recommendations. The CHAP considered both gestational and adult exposure studies in its evaluation, but focused on the studies of effects of gestational exposures and MRDE, because the fetus is considered the most sensitive population, and meets the statutory requirements in the CPSIA to consider the level at which there is a "reasonable certainty of no harm to children, pregnant women, or other susceptible individuals ..."

Comment 7.7: Diethyl Phthalate (DEP). Two industry commenters provided an example of inconsistency between epidemiological and animal studies. The commenters noted that MEP (a metabolite of DEP) was associated with reduced AGD in two studies (Swan 2008; Swan et al. 2005), but not in two other studies (Huang et al. 2009; Suzuki et al. 2012). One commenter also stated that the association between MEP exposure and reduced AGD in Swan's epidemiological studies was of little toxicological significance, because DEP does not cause rat phthalate syndrome. Thus, the commenters concluded that the weight of evidence does not support a causal relationship between phthalate exposure and reduced AGD in human offspring.

Response 7.7: The positive association between decreased AGD and DEP metabolite concentration was reported by Swan et al. (2005) and later updated in Swan (2008). Swan et al. (2005) recognized this association for DEP and noted that:

> there are three other human studies suggesting reproductive toxicity (Colón et al. 2000; Duty et al. 2003b; Main KM, unpublished data[27]). It is, therefore, uncertain whether the absence of data in rodents showing reproductive toxicity is the result of failure to detect it, unmeasured confounding in human studies, or interspecies differences in response to these compounds.

Staff agrees with Swan's (2005) characterization of potential reasons for the correlation of MEP to decreased AGD. The CHAP considered both positive and negative studies in arriving at its recommendations. Staff considers that the CHAP's weight-of-evidence approach appropriately accounted for inconsistency among and within studies.

Comment 7.8: Studies not cited in the CHAP report. One industry commenter included a list of epidemiology studies and review articles that were not cited in the CHAP report, claiming that the CHAP ignored 32 relevant publications on phthalates. The commenter concluded that the CHAP ignored relevant literature in its report.

[27] Now published. See Main et al. 2006.

Response 7.8: Staff disagrees that the CHAP ignored relevant literature in its report. The CHAP cited approximately 250 articles using a systematic approach as discussed in comment response 7.1 to select the most relevant and informative articles.

Staff notes that more than 5,500 articles on phthalates were published between the time when the phthalate syndrome was first described in 1980 and the CHAP's final literature update at the end of 2012 (NLM 2017). Thus, the commenter referred to less than one percent of the phthalates literature available to the CHAP. It would have been practically impossible for the CHAP to cite every article in its report.

The commenter identified five of the 32 articles as epidemiology studies:

- Calafat et al. (2004) measured exposure, but not health effects;
- Chevrier et al. (2012) is a brief communication that describes an occupational exposure study of pregnant women. The study had a significant limitation in that phthalate metabolites were measured in the morning, prior to work, not after work. Therefore, the metabolite measurements would not accurately reflect the women's worktime exposure;
- Mieritz et al. (2012) was a study of gynecomastia (breast development in males), which is not associated with phthalate syndrome or testicular dysgenesis syndrome. Therefore, it is not directly relevant to the CHAP's CRA;
- Lin et al. (2011) is a study of estrogenic effects, which are not relevant to the CHAP's CRA; and
- Fredericksen et al. (2012) studied the onset of puberty in girls, which is not relevant to the CHAP's CRA.

Staff concludes that the five epidemiology articles identified by the commenter are not relevant to the CHAP's CRA for the reasons noted above.

The commenter also enumerated 27 review articles that the CHAP did not include in its report. Review articles discuss experimental or epidemiological research studies published by other authors, but they generally do not provide new experimental or epidemiological data. Review articles are considered secondary sources. In contrast, original research articles, which provide new data, are considered primary sources. In its review, the CHAP properly focused on primary sources. The CHAP considered review articles, in part, as a means of ensuring that its literature search included all the relevant studies (CHAP 2014, p. 12). In addition, the CHAP cited reviews by authoritative bodies, such as the National Toxicology Program, National Academy of Sciences, and the International Association for Research on Cancer.

Of the 27 review articles identified by the commenter, several were on broad topics, such as endocrine disruption, environmental chemicals, or plastics and, therefore, had minimal relevance to the CHAP's CRA (Bellinger 2013; Polanska et al. 2012; Talsness et al. 2009; Wigle et al. 2008; Yiee and Baskin 2010). Some review articles were narrowly focused, such as an incident involving adulterated food (Polanska et al. 2012); included a small number of studies (Grady and Sathyanarayana 2012; Lottrup et al. 2006; Main 2008); or were informational articles written for specific audiences, such as nurses (Jaeger et al. 2005; Pak et al. 2011; Talsness et al. 2009) or clinicians (Chou and Wright 2006).

Some of the reviews did not include health effects relevant to the CHAP's CRA, such as effects in females or effects not associated with MRDE (Chakraborty et al. 2012; Hatch et al. 2010; Yen et al. 2011). Some reviews were relevant, but relatively old (Fisher 2004; Latini et al. 2004; Shea 2003). Four articles were published following the CHAP's final literature update (Bellinger 2013; Braun et al. 2013; Gallinger and Nguyen 2013; Kay et al. 2013), including one co-authored by a CHAP member (Braun et al. 2013).

Of the seven remaining review articles, they were current and relevant when the CHAP was formed in 2010 (Johnson et al. 2012; Jurewicz and Hanke 2011; Kamrin 2009; Lyche et al. 2009; Martino-Andrade and Chahoud 2010; Matsumoto et al. 2008; Sathyanarayana 2008). While these are excellent reviews, they did not provide any new experimental or epidemiological data.

Staff concludes that the CHAP properly focused its attention on primary literature sources. Staff further concludes that the CHAP properly exercised its own professional judgment in reviewing original research themselves, rather than relying on the interpretations of other authors in reviewing the relevant scientific studies.

Finally, staff continues to monitor new experimental and epidemiological studies reporting associations between phthalate exposure and human health effects following publication of the CHAP report. Staff concludes that the new epidemiology and animal toxicity studies published following the CHAP's final literature review generally support the CHAP's conclusions and recommendations.

Section 7 Summary

Overall, staff agrees with the CHAP's conclusion that there is a growing body of studies showing an association of phthalate exposure with MRDE effects in infant and adult males. However, epidemiological studies establishing a causal relationship between exposure and effect are not required to conclude that a substance or mixture is "probably toxic to humans" (CPSC 1992; EPA 1991; IARC 2002; NTP 2016) or to support a regulation. Such studies are rarely available for any chemical. Based on the CPSC's chronic hazard guidelines (CPSC 1992), staff considers that there is sufficient evidence in animal studies to conclude that certain phthalates are probably toxic to humans. Epidemiological data provide supporting evidence for the animal data and also support the conclusion that the animal data are relevant to humans.

8. IQA, Peer Review and Legal

Overview of Public Comments on Legal Issues and Peer Review

Section 108 of the CPSIA establishes the legal framework for the CHAP's work and the CPSC's rulemaking. The CHAP and CPSC followed all applicable legal requirements. Several comments raised legal issues, focusing primarily on the Information Quality Act (IQA), peer review, and statutory requirements of the CPSIA and APA.

IQA/peer review. Some commenters asserted that the CHAP report and CPSC's rulemaking did not comply with the IQA and the information quality guidelines issued by the Office of Management and Budget (OMB) and CPSC, as well as OMB's peer review bulletin which was issued under the IQA. Some commenters asserted that the CHAP report is a highly influential document and is therefore subject to a more stringent peer review process.

According to OMB, a scientific assessment is "highly influential" if it could have an impact of more than $500 million in any year or it is novel, controversial, or precedent-setting or has significant interagency interest." Even if considered a highly influential scientific document disseminated by CPSC, the CHAP report met all aspects of the OMB's and CPSC's information quality guidelines and OMB's peer review bulletin. We note also that these are all guidance documents that provide agencies with flexibility in determining how to best meet them. The CHAP's process was transparent and objective: the CHAP held seven public meetings and eight public teleconferences, heard testimony from stakeholders, and sought input from scientific experts. The CHAP report clearly explained the CHAP's methods and how the CHAP reached its conclusions. In addition, the report was subjected to an independent peer review. Both the CHAP members and peer reviewers were nominated by the National Academy of Sciences and subject to specific conflict of interest requirements (comment response 8.1-8.8).

CPSIA and APA requirements. Some commenters asserted that the CHAP and CPSC failed to comply with the CPSIA's requirements for the CHAP and for the phthalates rulemaking. For example, some commenters asserted that the CHAP had not reviewed all relevant data and that the CPSIA did not require a cumulative risk assessment. Commenters opined on the role of the CHAP report in the rulemaking. Commenters also expressed opinions about the meaning of the term "reasonable certainty of no harm" and the relevance of the CPSA and the FHSA.

The CHAP and CPSC followed all requirements stated in the CPSIA (comment response 8.17-8.26). The CHAP considered all relevant data available at the time of its analysis, and CPSC staff subsequently reviewed (and requested comment on) more recent relevant data. Although the CPSIA did not require the CHAP to conduct a cumulative risk assessment, it did require the CHAP to "consider the cumulative effect of total exposure to phthalates" and to consider health effects of phthalates "in isolation and in combination with other phthalates." The CHAP reasonably determined that a cumulative risk assessment was the most appropriate method to fulfill this direction. We believe that the CPSIA does not require the Commission to rigidly adhere to the CHAP's recommendations. Rather, the CHAP report is advisory, and the Commission must use its judgment to decide on appropriate regulatory action in accordance with the specific criteria stated in section 108(b)(3)(A) and (B) of the CPSIA, and after considering public comments. This rulemaking follows that approach. Regarding the meaning of "reasonable certainty of no harm," section 108 of the CPSIA established this as the standard the Commission should use for the phthalates rulemaking; other statutory metrics (e.*g.*, unreasonable risk under

the CPSA or banned hazardous substance under the FHSA) do not apply. We believe that "reasonable certainty of no harm" requires a highly protective standard, but does not require 100 percent certainty of no harm. In accordance with the direction that the CPSC's rulemaking be conducted pursuant to section 553 of the APA, the Commission issued a proposed rule requesting public comments, and staff has considered issues raised by those comments (comment responses 8.9-8.16).

Comment 8.1: IQA general: Several commenters asserted that the CHAP report and the phthalate rulemaking must comply with the Office of Management and Budget's (OMB's) Guidelines issued under the Information Quality Act (IQA). For example, a comment from a group of consumer product manufacturers, suppliers, retailers, and trade associations stated: "The lack of transparency throughout the development of the CHAP report and its reliance on old data demonstrates a failure to comply with OMB's and the Commission's own guidelines for ensuring the quality, objectivity, utility and integrity of disseminated information." These commenters noted that CPSC's information quality guidelines state that "the Commission will apply 'risk assessment practices … that are widely accepted among domestic and international public health agencies.'" One commenter asked that its comments serve as a request for correction under the IQA. The commenters stated that the OMB's IQA Guidelines require agencies' disseminations meet a basic standard of quality in terms of objectivity, utility and integrity.

Response 8.1: The Information Quality Act, P.L. No. 106-554, required OMB to draft guidelines "that provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information … disseminated by Federal agencies in fulfillment of the purposes and provisions" of the Paperwork Reduction Act. In addition, the IQA required each agency to issue its own guidelines. On February 22, 2002, OMB issued its final guidelines, "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integration of Information Disseminated by Federal Agencies" ("OMB Guidelines"). 67 FR 8452. OMB noted that the OMB Guidelines are designed:

- not to be "'one-size-fits-all' government-wide guidelines";
- "so that agencies will meet basic information quality standards";
- "so that agencies can apply them in a common-sense workable manner"; and
- for agencies to "apply these standards flexibly."

OMB's Guidelines direct agencies to develop information management processes for reviewing and substantiating the quality of information before its dissemination. Under OMB's Guidelines, "quality" includes "objectivity," "utility," and "integrity." Agencies also must issue their own guidelines and must establish administrative mechanisms to allow persons to seek correction of information that does not meet OMB's or the agency's guidelines. As directed, the CPSC issued Information Quality Guidelines (CPSC Guidelines) in October 2002.[28] CPSC's Guidelines substantially follow OMB's Guidelines, relating them to the specific work of the CPSC and the types of information CPSC disseminates. CPSC's Guidelines set forth procedures to request correction of disseminated information that does not adhere to OMB's or CPSC's Guidelines.

[28] CPSC Information Quality Guidelines. Available at: https://www.cpsc.gov/en/Research--Statistics/Information-Quality-Guidelines/.

Under CPSC's Guidelines, if a person questions the quality of information disseminated in an NPR, CPSC will use the existing process of responding to comments on the NPR to address the request for correction and will describe its responding actions in the notice for the final rule. CPSC is following that process here. Discussion of specific issues is provided in the following responses.

Comment 8.2: Applicability of IQA guidelines. Commenters asserted that the CHAP report is subject to the IQA requirements. They stated that, although the CHAP report was prepared by a third party, the Commission has adopted the recommendations in a way that reasonably suggests the agency agrees with the information, and that the language of the CPSIA which requires that the Commission's determination regarding the interim prohibition be "based on" the CHAP report supports this conclusion. The commenters also asserted that the CHAP report is "influential" under the IQA Guidelines because it meets the OMB standard for influential because it has "a clear and substantial impact on important public policies or private sector decisions."

Response 8.2: OMB's Guidelines apply to federal agencies that are subject to the Paperwork Reduction Act, 42 U.S.C. chapter 35. 67 FR 8453. This includes the CPSC. As noted previously, the CPSC has also issued its own guidelines relating OMB's guidelines to CPSC's work. Both OMB's and CPSC's Guidelines apply to information that the agency "disseminates." OMB's Guidelines define the term "dissemination" to mean "agency initiated or sponsored distribution of information to the public," with several exclusions. OMB's discussion of this term states: "if an agency, as an institution, disseminates information prepared by an outside party in a manner that reasonably suggests that the agency agrees with the information, this appearance of having the information represent agency views makes agency dissemination of the information subject to the guidelines." 67 FR 8454. As the commenters note, the CHAP report was not prepared by CPSC but by a third party. If CPSC took no further action with regard to the CHAP report, one might conclude that the CHAP report was not disseminated by CPSC. However, in the NPR, CPSC based its recommendations on the CHAP report as required by section 108 of the CPSIA. Thus, we agree that OMB's and CPSC's Guidelines apply to the CHAP report.

OMB's Guidelines define "influential" as:

> "Influential", when used in the phrase "influential scientific, financial, or statistical information", means that the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions. Each agency is authorized to define "influential" in ways appropriate for it given the nature and multiplicity of issues for which the agency is responsible.

67 FR 8460. CPSC's Guidelines state that most of the information disseminated by CPSC does not meet the standard of influential as defined by the OMB Guidelines. The definition of "influential" places significant emphasis on the agency's discretion to determine what information is influential. Although most of the information CPSC disseminates is not likely to be considered "influential," the CHAP report differs from other CPSC information in several respects. For example, the CHAP report was directed by statute, concerns chemicals used in a range of products, provides an assessment of cumulative effect of total exposure to phthalates, and provides the basis for mandated rulemaking. We cannot say with certainty that the CHAP report "will have or does have a clear and substantial impact on important public policies or

important private sector decisions." However, we can understand that some may consider that to be the case. In any event, if the CHAP report is considered "influential," it met the OMB Guidelines' provisions for such documents. The OMB Guidelines state: "If an agency is responsible for disseminating influential scientific, financial, or statistical information, agency guidelines shall include a high degree of transparency about data and methods to facilitate the reproducibility of such information by qualified third parties." 67 FR 8460. As discussed in the CHAP report (pages 12–13), the CHAP clearly explained its data and methods, and the CHAP's analysis was in fact reproduced with later data by third parties.

Comment 8.3: Objectivity of CHAP report. Commenters argued that the CHAP Report (and by extension, the rulemaking) does not meet the IQA Guidelines' standard of "objectivity," which state that the information must be "accurate, reliable, and unbiased," and "must be generated using sound statistical and research methods." In addition, the commenters argue that because the CHAP Report is influential information regarding risks to health, safety or the environment, it "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 . . . .' " The IQA Guidelines state that if information has been subjected to independent peer review, the information is presumed to be of acceptable objectivity. A commenter argued that this presumption does not apply to the CHAP report, because the peer review was "conducted secretly." Specifically, the commenter states that the commenter only recently learned the identity of peer reviewers and that the charge to the peer reviewers, the draft report they reviewed, and that the peer reviewers' comments were not released.

Response 8.3: As the commenters noted, the OMB Guidelines state: "'Objectivity' includes whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner." 67 FR 8459. According to the OMB Guidelines, this involves presenting the information within a proper context and identifying the sources of the information. *Id*. The OMB Guidelines further state: "In addition, 'objectivity involves a focus on ensuring accurate, reliable, and unbiased information." In a scientific context, this means "using sound statistical and research methods." *Id*.

The CHAP report met the "objectivity" standard enunciated in the OMB Guidelines. The fact that the commenters might have conducted the analysis differently does not mean that the CHAP's analysis was not "objective." The CHAP report clearly set forth its data sources and noted that it assessed studies using the criteria of reliability, relevance, and adequacy established by the Organisation for Economic Cooperation and Development. CHAP report at pp. 13–14). The CHAP held open meetings during the process of developing its analysis, inviting experts to present their latest research findings and taking submissions of a large volume of written material. The CHAP members were selected in accordance with section 28 of the CPSA through a process to ensure their independence from bias (e.g., nominated by National Academy of Sciences; free from compensation by or substantial financial interest in a manufacturer, distributor or retailer of a consumer product; not employed by the federal government, with certain scientific/research related exceptions). The CHAP explained its choices, such as the decision to focus on the effects on male reproductive development and noted that this approach was consistent with a National Research Council (NRC) report (NRC 2008, p.3). Similarly, the CHAP explained its decision to conduct a cumulative risk assessment and explained the

methodology the CHAP used which also was consistent with one of the methods discussed in the NRC report (NRC 2008).

For an analysis of risks to human health, safety and the environment that an agency disseminates, OMB's Guidelines direct agencies to "adapt or adopt" the information quality principles of the SDWA. 67 FR 8460. The SDWA directs agencies to use: "(i) the best available, peer reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data)." *Id.* at 8457. We note that the SDWA direction is very similar to the charge to the CHAP in section 108 which states, among other things, that the CHAP is to "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." CPSIA, § 108(b)(2)((B)(v). As explained in the responses to comments 1.2, 1.7, 3.11, and 10.2, the CHAP report met this direction.

Finally, as the commenters mentioned, the OMB Guidelines state that if information was "subjected to formal, independent, external peer review, the information may generally be presumed to be of acceptable objectivity." 67 FR 8459. The CHAP report underwent "formal, independent, external peer review" by a panel of experts selected in same manner as the CHAP members. As discussed further in response to comment 8.7, the peer review satisfied OMB's Peer Review Bulletin. Thus, the presumption of acceptable objectivity should apply to the CHAP report.

Comment 8.4: IQA deficiencies. A commenter asserted that the CHAP report had numerous methodological flaws that violated the IQA. The commenter argued that the CHAP Report's IQA deficiencies would invalidate the phthalate rulemaking unless they are corrected because the proposed rule was premised almost entirely on the CHAP Report and the Commission's determination regarding the interim prohibition involving DINP must be "based on" the CHAP Report. The commenter further asserted that OMB's IQA Guidelines are "binding" on agencies (citing *Prime Time Int'l Co. v. Vilsack*, 599 F.3d 678, 685 (D.C. Cir. 2010)). Another commenter stated that issuing the phthalates rule as proposed would provide "an inviting case for potential IQA enforcement" under the approach proposed in the article, *Revitalizing the Information Quality Act as a Procedural Cure for Unsound Regulatory Science: a Greenhouse Gas Rulemaking Case Study*, written by Lawrence A. Kogan. According to the commenter, that article suggests bringing an action under the APA to address IQA violations.

Response 8.4: Elsewhere in this document, staff responds to the specific methodological "flaws" the commenter identifies. Regarding the broader legal point, we note that OMB's Guidelines are not legally enforceable requirements. As guidelines, they are essentially interpretive rules, which, by their nature, do not establish binding requirements. *See, e.g., U.S. Iowa League of Cities v. EPA*, 711 F.3d 844, 873 (8th Cir., 2013) ("interpretive rules do not have the force of law"). Notably, the IQA directed OMB to "issue guidelines . . . that provide policy and procedural guidance to Federal agencies." The IQA did not direct that OMB, or any agency, to undertake substantive legislative rulemaking. Consolidated Appropriations Act of 2001, Pub. L. No. 106-554, § 515 (codified at 44 U.S.C. § 3516 Note). OMB's Guidelines repeatedly stress their flexibility, noting that they are not intended to be "prescriptive, 'one-size-fits-all'" and that OMB intends for agencies to "apply them in a common-sense and workable manner." 67 FR at 8452 and 8453. The only binding requirement set forth in the IQA was the mandate that OMB

issue guidelines and that each agency subject to the PRA also issue guidelines tailored to the agency. In fact, courts that have examined the IQA have found that the IQA (and thus, necessarily, OMB's guidelines) "creates no legal rights in any third parties." *Salt Inst. v. Leavitt*, 440 F.3d 156, 159 (4th Cir. 2006). *See also Mississippi Comm. on Environmental Quality v. EPA*, 790 F.3d 138 (D.C. Cir. 2015) (dismissing argument that IQA created a legal requirement for EPA to use "best available science and supporting studies"). We take no position on the general theory of bringing a legal action under the APA to address IQA violations. As explained throughout this document, the CHAP report and CPSC's rulemaking meet the provisions of the IQA and the APA.

Comment 8.5: Utility. Commenters noted that under the IQA, "utility" refers to the usefulness of information to its intended users. The commenters asserted that the CHAP's reliance on older NHANES data and inclusion of prohibitions involving phthalates made the assessment "not useful for rulemaking decisions" about likely levels of exposure; "[o]nly information based on the most recent data has utility for assessing risk and making risk-management decisions."

Response 8.5: The CHAP used 2005/2006 NHANES data on pregnant women to assess phthalate exposure as part of the CRA, to satisfy the CPSIA's charge to "examine the likely levels of children's, pregnant women's, and others' exposure to phthalates . . .." CPSIA §108 (b)(2)(B)(iii). This data set was the most recent data on pregnant women available at the time the CHAP completed its analysis in July 2012 (CHAP 2014, p. 31), and that dataset was the last to include a larger sample of pregnant women. The CPSC staff subsequently analyzed NHANES WORA data from 2007/2008 through 2013/2014 (see comment response 3.2) using the CHAP's analytical methodology. Thus, staff has updated the CHAP's information to provide the most recent (and useful) data to develop recommendations for the final rule.

Peer Review Comments

Comment 8.6: CHAP report as "highly influential." Commenters asserted that the CHAP report qualifies as a "highly influential" scientific assessment under the OMB's peer review bulletin, which includes in that category an assessment that "is novel, controversial, or precedent-setting or has significant interagency interest." Commenters argue that the CHAP report qualifies as "highly influential" because the rulemaking that is based on the CHAP report could broadly impact federal risk assessment policy and because of the CHAP's "novel" cumulative risk assessment. The commenters stated that therefore, the CHAP report should be subject to a peer review that comports with the highest standards for transparency, openness, and objectivity as outlined in the OMB's peer review bulletin.

Response 8.6: The OMB *Final Information Quality Bulletin for Peer Review* (70 Fed. Reg. 2664 (Jan. 14, 2005)) defines "highly influential scientific assessments" as a scientific assessment that:

(1) could have a potential impact of more than $500 million in any year; or
(2) is novel, controversial, or precedent-setting or has significant interagency interest.

The draft final rule extends the prohibition of toys that can be placed in a child's mouth to all children's toys (and child care articles) containing more than 0.1 percent of DINP, and prohibits children's toys and child care articles containing four additional phthalates. Because the number of products affected by the expanded scope of products involving DINP is limited, and the four additional phthalates are not currently used in large numbers of children's toys and child care articles, it is unlikely that the rule could have an annual impact of more than $500 million.

However, the CHAP report might be considered novel, controversial, precedent-setting, or having significant interagency interest. Thus, the CHAP report could qualify as a highly influential scientific assessment under the OMB peer review bulletin.

Comment 8.7: OMB peer review bulletin's requirements for "highly influential" assessments. Commenters asserted that the CHAP failed to adhere to OMB bulletin for the peer review of a highly influential scientific assessment and that this set an extremely concerning precedent for a federal chemical assessment, especially one that could impact federal risk assessment policy broadly in the areas of cumulative risk assessment and endocrine policy. Some commenters asserted that the peer review was "secret." One of these commenters stated that the commenter had only recently learned the identity of the peer reviewers, and that neither the CHAP nor CPSC had released the charge to the peer reviewers, the draft report that was reviewed, or the peer reviewers' report. And, the commenters asserted, they did not know what, if any, changes the CHAP had made in response to the peer review.

In contrast, other commenters supported the peer review process used for the CHAP report, stating that the peer review was part of an open and transparent process. One commenter noted that four independent scientists peer-reviewed the draft CHAP report and that the CHAP had solicited public and industry comments and held 13 public meetings (six by teleconference), which were webcast and were well attended by industry. Another commenter asserted that the CHAP process itself constituted an in-depth and thorough peer review by the best available scientists of the best available science on the exposure to and health hazard from 14 phthalates and 6 phthalates alternatives. The commenter noted that despite the fact that this process was a peer review in and of itself, and the fact that Congress did not require any further review of the CHAP report, the CHAP members themselves requested an additional peer review through the standard and accepted practice used by scientific journals, the designation of anonymous experts to review and comment on the CHAP report. The commenter stated that the CPSC went to the extraordinary length of publishing those comments and the CHAP report before and after the expert review so the public would have ample opportunity to see the concerns raised and how they were addressed. Finally, the commenter noted that the peer reviewers were overwhelmingly supportive of the CHAP report and validated the integrity and scientific soundness of the process.

Response 8.7: The CHAP report was the work product of an independent scientific panel that was established pursuant to section 108 of the CPSIA. That section makes no mention of peer review. However, the CHAP requested confidential peer review of the draft CHAP report. CPSC contracted with Toxicology Excellence for Risk Assessment (TERA), a non-profit organization that specializes in peer review of scientific reports, to manage the peer review process. To protect the independence of the CHAP, the CPSC staff chose to hold the peer reviewers to the same criteria as the CHAP members. Peer reviewers were nominated by the National Academy of Sciences and were not employed by manufacturers of the products under consideration or by the federal government, except the National Institutes of Health, National Toxicology Program, or the National Center for Toxicological Research. As explained below, we believe that the peer review process used to review the draft CHAP report comports with the requirements of the OMB peer review bulletin.

In general, the Bulletin requires, "to the extent permitted by law," that agencies conduct peer review on all influential scientific information the agency intends to disseminate. The Bulletin defines "influential scientific information" as "scientific information the agency reasonably can

determine will have or does have a clear and substantial impact on important public policies or private sector decisions." *Id*. at 2675. We believe that the CHAP report would be considered "influential" under this definition. According to the Bulletin, "dissemination" means "agency initiated or sponsored distribution of information to the public." *Id*. at 2674. The preamble notes that the Bulletin "does not directly cover information supplied by third parties (e.g., studies by private consultants, companies and private, non-profit organizations, or research institutions such as universities). However, if an agency plans to disseminate information supplied by a third party (e.g., using this information as the basis for an agency's factual determination that a particular behavior causes a disease), the requirements of the Bulletin apply, if the dissemination is 'influential.'" In the case of the CHAP report, although the report was written by a third party, we believe that by relying on the CHAP report in support of the NPR, the Commission disseminated the CHAP report.

Although the Bulletin uses the term "requirements," the document emphasizes the intent to allow agencies flexibility in determining appropriate methods of peer review. For example, the preamble notes:

> We recognize that different types of peer review are appropriate for different types of information. *Under this Bulletin, agencies are granted broad discretion to weigh the benefits and costs of using a particular peer review mechanism for a specific information product. The selection of an appropriate peer review mechanism for scientific information is left to the agency's discretion.*

70 Fed. Reg. at 2665. (emphasis added).

The Bulletin specifies requirements regarding the selection of reviewers, the choice of the peer review mechanism, and transparency of the review. Additional requirements apply for peer review of "highly influential scientific assessments," that is, assessments that:

- could have a potential impact of more than $500 million in any year, or
- is novel, controversial, or precedent-setting, or has significant interagency interest.

Id. at 2675. For highly influential scientific assessments, the peer review must meet additional requirements concerning:

- Selection of reviewers: The Bulletin emphasizes consideration of reviewers' expertise and balance; avoidance of conflicts of interest; and independence from the sponsoring agency.
- Information access: The agency must provide reviewers with sufficient information to understand and analyze the draft assessment.
- Transparency: The peer review report must include:
    - the written charge to the peer reviewers;
    - the peer reviewers' names;
    - the peer reviewers' report(s); and
    - the agency's response to the peer reviewers report(s).

- Opportunity for public comment: The Bulletin provides: "*Whenever feasible and appropriate*, the agency shall make the draft scientific assessment available to the public for comment at the same time it is submitted for peer review (or during the peer review process) and sponsor a public meeting where oral presentations on scientific issues can be

made to the peer reviewers by interested members of the public." (emphasis added). 70 Fed. Reg. 2675 – 76.

Regarding the highly influential scientific assessments criteria, the CHAP report may meet the criteria to qualify for the additional peer review requirements under the OMB peer review bulletin. Some might consider it "novel, controversial, or precedent-setting," and it could be of "significant interagency interest" because, as the CHAP report indicates, many of the products that contain phthalates (e.g., food and cosmetics) fall under other agencies' jurisdiction.

The peer review process used for the draft CHAP report complied with the additional requirements for highly influential scientific assessments described above. For example, as noted by some commenters, the peer review of the draft report was conducted by four independent scientists, using the same criteria (by nomination of the National Academy of Sciences) that was required for selecting the CHAP members. Additionally, the peer reviewers were not employed by manufacturers of the products under consideration or by the federal government, except the National Institutes of Health, the National Toxicology Program, or the National Center for Toxicological Research.

Additionally, the CPSC made public the identity of the peer reviewers, the charge to the peer reviewers, the draft report that was reviewed, and the peer reviewers' report. All of this information was made available on the CPSC website at the same time the final CHAP report was released to the public and is available on the CPSC website in accordance with the additional requirements for a highly influential scientific assessment.[29] As commenters noted, the CPSC went to the extraordinary length of publishing the peer review comments and the CHAP before and after the expert review so the public would have ample opportunity to see the concerns raised and how they were addressed.

Finally, regarding public comment as discussed in the response to comment response 8.8, the peer review process used by CPSC regarding public comment complied with the OMB peer review bulletin.

Comment 8.8: Peer review and public comment. Many commenters asserted that as a "highly influential" assessment, the CHAP report should have been subject to an open public comment period as set forth in the OMB peer review bulletin. Commenters asserted that the OMB peer review bulletin establishes strict minimum requirements for the peer review of highly influential scientific assessments, including a requirement that an agency "make the draft scientific assessment available to the public for comment at the same time it is submitted for peer review . . . and sponsor a public meeting where oral presentations on scientific issues can be made to the peer reviewers by interested members of the public." Commenters argue that if the process in the OMB peer review bulletin had been followed, there would have been an opportunity to comment on flaws in the CHAP's analysis, including the timeliness and relevance of the data. The commenters contend that the CHAP report would have benefited from the knowledge and expertise in the scientific community from this type of review process and might have avoided the lack of confidence the CHAP's final report has engendered.

[29] See https://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/The-Consumer-Product-Safety-Improvement-Act/Phthalates/Chronic-Hazard-Advisory-Panel-CHAP-on-Phthalates/.

One of the commenters sponsored an independent peer review of the final CHAP report. The commenter contended that serious scientific questions identified by these independent subject matter experts call into question the validity, reliability and transparency of the CHAP report and underscore the inappropriateness of using the analysis in the CHAP report as the basis for rulemaking under the CPSIA.

Response 8.8: The OMB bulletin states that "The selection of an appropriate peer review mechanism for scientific information is left to the agency's discretion." *Id*. at 2665. The OMB peer review bulletin advises that "[a]gencies are directed to choose a peer review mechanism that is adequate, giving due consideration to the novelty and complexity of the science to be reviewed, the relevance of the information to decision making, the extent of prior peer reviews, and the expected benefits and costs of additional review." *Id.* at 2668. We also note that CPSC staff consulted with OMB staff before finalizing the peer review plan for the CHAP report as recommended by the OMB peer review bulletin.

Several commenters asserted that the bulletin required public peer review because the OMB peer review bulletin states:

> Whenever feasible and appropriate, the agency shall make the draft scientific assessment available to the public for comment at the same time it is submitted for peer review (or during the peer review process) and sponsor a public meeting where oral presentations on scientific issues can be made to the peer reviewers by interested members of the public.

Id. at 2676. Notably, this "requirement" begins with the phrase "whenever feasible and appropriate," allowing the agency to determine if it is not feasible or appropriate to have a public peer review. Additionally, although the Bulletin uses mandatory language ("the agency shall"), the Bulletin is a guidance document and is not legally enforceable. Section XII "Judicial Review" of the Bulletin states:

> This Bulletin is intended to improve the internal management of the executive branch, and is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity, against the United States, its agencies or other entities, its officers or employees, or any other person.

Id. at 2677. *See Family Farm Alliance v. Salazar*, 749 F. Supp. 2d 1083 (E.D. Cal. 2010) (finding that claim that U.S. Fish and Wildlife Service had not conducted appropriate peer review was not judicially reviewable). As noted by commenters, the draft CHAP report was not provided to the public for comment at the time that the CHAP submitted the report for peer review. However, contrary to the assertions of commenters, the agency was not required by the OMB bulletin to make the draft scientific assessment available to the public for comment at the same time it is submitted for peer review, or to sponsor a public meeting where oral presentations on scientific issues could be made to the peer reviewers by interested members of the public.

In addition, we note that, although the draft CHAP report was not made available to the public at the same time the report was submitted for peer review, the CHAP report was developed through a very open public process: the CHAP's meetings were open to the public and the CHAP

solicited and considered opinions and documents submitted from the public and experts. That information is all available on the CPSC website.[30]

As noted above, the OMB bulletin allows CPSC significant flexibility regarding whether to solicit public comment on a draft report explicitly limiting such comment to circumstances when this approach is "feasible and appropriate." *Id.* at 2676. The preamble to the Bulletin confirms this flexibility, stating: "In some cases, an assessment may be so sensitive that it is critical that the agency's assessment achieve a high level of quality before it is publicized. In those situations, a rigorous yet confidential peer review may be appropriate, prior to public release of the assessment." *Id*. at 2672.

As permitted by the OMB bulletin, staff and the CHAP decided that public comment on the draft CHAP report in this case was not feasible and appropriate. Staff and the CHAP members desired that the report should achieve a high level of quality before it was released to the public. There were also concerns that a public comment process would compromise the integrity of the CHAP review process by subjecting the CHAP to nonscientific pressure and scrutiny that would be appropriate for a rulemaking but not appropriate for peer review. We conclude, as discussed in the response to comment response 8.7, that the draft CHAP report was subjected to "a rigorous yet confidential peer review . . . prior to public release of the assessment" and CPSC appropriately exercised its discretion when it did not require a public peer review process under the OMB bulletin.

The Administrative Procedure Act (APA) and Other Procedural Requirements

Comment 8.9: Openness of process. Several commenters stated generally that the process for the CHAP report and CPSC's rulemaking has not been open and transparent. In contrast, other commenters asserted that the CHAP process was a sound and fair process, was highly public, and considered public comments and written submissions (including from industry representatives who charge that the process was not open). These commenters noted that all meetings of the CHAP were open to the public and that industry representatives had numerous opportunities to raise their concerns to CPSC including at meetings with CPSC staff and with Commissioners.

Response 8.9: The CHAP's process for developing its report and the CPSC's rulemaking process have been open and transparent in accordance with all requirements. As detailed in comment response 10.3, the CHAP held public meetings and teleconferences, and the CHAP-related materials were posted on CPSC's website. CPSC staff met with various stakeholders; summaries of these meeting were also posted on CPSC's webpage. Commissioners have also met with stakeholders.

When CPSC published the NPR on December 30, 2014 it provided a 75-day comment period (until March 15, 2015) 79 FR 78324 (Dec. 30, 2014). After receiving requests for additional time to comment, the Commission extended the comment period until April 15. 80 FR 14879. In addition, staff conducted two analyses of more recent NHANES biomonitoring data sets (work many stakeholders suggested staff should do), and posted reports of staff's analyses on the CPSC website. The Commission published two notices of availability soliciting comments from the

[30] See http://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/The-Consumer-Product-Safety-Improvement-Act/Phthalates/Chronic-Hazard-Advisory-Panel-CHAP-on-Phthalates/.

public regarding staff analyses of more recent NHANES biomonitoring data sets. 80 FR 35938 (June 23, 2015) and 82 FR 11348 (February 22, 2017).

Comment 8.10: Memorandum on transparency and open government. One commenter stated that the phthalates rulemaking "has not complied with the spirit of" the guidance in President Obama Administration's *Memorandum on Transparency and Open Government*[31] which states that supporting materials in a rulemaking should be posted as part of the electronic docket during the notice and comment period. The commenter states that no supporting documents are in the rulemaking docket and that "[a]t a minimum, CPSC should include the draft and final CHAP Reports, the peer review comments on the CHAP Report, the staff briefing package, and any critical review of the CHAP report by the CPSC staff in the rulemaking docket."

Response 8.10: In accordance with section 108 of the CPSIA, the CHAP was established as an independent scientific body that conducted its analysis and prepared its report before the Commission initiated any rulemaking. Thus, there was no rulemaking docket during the course of the CHAP's work, and these materials were not posted on regulations.gov. In the interest of transparency, however, rather than wait until a rulemaking had begun, CPSC established a page on its own website because there was not yet an entry on the regulations.gov website. After the publication of the NPR, all comments to the NPR and supplemental materials have been posted in the docket on regulations.gov. Although the CHAP report is not posted on regulations.gov, the NPR (which is posted there) provides a link to the CPSC public web page[32] that contains not only the CHAP report, but also all the CHAP-related materials that preceded the NPR, including the draft CHAP report sent for peer review and the peer reviewer comments on the draft report. 79 FR 78326. In addition, the NPR provides a link to staff's NPR briefing package.[33] *Id*.

Comment 8.11: Executive Order 13563. One commenter asserted that CPSC's rulemaking must (and fails to) comply with Executive Order (E.O.) 13563, *Improving Regulation and Regulatory Review*,[34] which, according to the commenter, requires that "an agency can propose or adopt a regulation 'only upon a reasoned determination that its benefits justify its costs'" and that "'each agency shall ensure the objectivity of any scientific and technological information and processes used to support the agency's regulatory actions.'"

Response 8.11: As an independent agency, CPSC is not required to comply with E.O. 13563. Section 7(a) of E.O. 13563 states that, for purposes of the E.O., the term "agency" has the same meaning as set forth in section 3(b) of E.O. 12866. That definition of "agency" excludes "independent regulatory agencies."

Although CPSC is not subject to E.O. 13563, the phthalates rulemaking is fully consistent with the general principles the E.O. enunciates. As discussed in response to comment 8.17, the

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[31] Available at: https://www.archives.gov/files/cui/documents/2009-WH-memo-on-transparency-and-open-government.pdf.
[32] Chronic Hazard Advisory Panel (CHAP) on Phthalates. Available at: https://www.cpsc.gov/chap.
[33] Staff briefing package on Proposed Rule: "Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates." Available at: https://www.cpsc.gov/chap. https://www.cpsc.gov/Global/Newsroom/FOIA/CommissionBriefingPackages/2015/ProposedRule-Phthalates-112514.pdf.
[34] Available at: https://obamawhitehouse.archives.gov/the-press-office/2011/01/18/executive-order-13563-improving-regulation-and-regulatory-review.

rulemaking relies upon objective scientific and technological information. Regarding benefit-cost analysis, section 108 of the CPSIA set forth specific determinations for the Commission to make in the phthalates rulemaking. Nowhere does the statute direct CPSC to determine that the benefits of the rule justify its costs. Instead, the statute directs CPSC to "ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." The Commission has followed the statutory direction and made the requisite determinations.

Comment 8.12: CPSC obligation under the APA. In comments on the CPSC staff's analysis of NHANES data collected after the CHAP completed its analyses, a commenter asserted that under the APA, "the Commission has an obligation to disregard the CHAP's report to the extent it is incorrect, unreasonable, inconsistent with existing CPSC policy, practice, regulations or governing statutes, or is based on data that is outdated or of poor quality." The commenter set out the minimum requirements of informal rulemaking: adequate notice, sufficient opportunity for public to comment, and a final rule that is not arbitrary and capricious (including multiple considerations).

Response 8.12: The CPSIA requires the Commission to "base" its determination on the CHAP report, but also requires notice and comment rulemaking. We agree that under section 553 of the APA, the Commission must evaluate the CHAP report along with comments submitted in response to the proposed rule and engage in reasoned decision making to issue a final rule. This is the approach the agency has taken. The Commission provided adequate notice in the NPR (describing the CHAP report, providing staff's evaluation of the CHAP report and explanation of, and reasons for, the proposed rule) and provided sufficient opportunity for the public to comment (even extending the comment period and obtaining comment on two staff reanalysis documents).

Comment 8.13: The APA and need for current data. Commenters asserted that because the NPR "rests on outdated data" for the cumulative risk assessment, CPSC should withdraw the NPR, conduct a reanalysis with current exposure data, and repropose the rule with a new comment period. The commenter stated that CPSC's reliance on "decade-old data" in the NPR is not reasonable and therefore violates the APA which requires that agency's decision bear a reasonable connection to the facts on the record. Commenters requested that the Commission rerun the CHAP's analysis with more recent data and allow the public to comment on the reanalysis.

Response 8.13: The agency followed the direction of section 108 of the CPSIA. Under that provision, the Commission's determination regarding the interim prohibition is to be "based on" the CHAP report and the Commission is to evaluate the CHAP's findings and recommendation and determine whether to prohibit other children's products containing other phthalates. Section 108 of the CPSIA also directs the Commission to conduct its rulemaking using the notice and comment procedures of the APA. Accordingly, the Commission issued a proposed rule that was based on staff's assessment of the CHAP's work. In addition, staff conducted two analyses of more recent NHANES biomonitoring data sets (work many stakeholders suggested staff should do), posted reports of staff analyses on the CPSC website, and the Commission requested public comment on each analysis. 80 FR 35938 (June 23, 2015) and 82 FR 11348 (February 22, 2017). Thus, the NPR and requests for comments on staff's reports comply with the notice and comment requirement of the APA. Staff has considered its analyses, comments received on CPSC's analyses, and all the comments on the proposed rule.

Comment 8.14: Rulemaking is "precautionary" and departs from past CPSC rulemaking. A commenter criticized the phthalates rulemaking as a "departure from typical analytical and methodological regulations promulgated by the CPSC." The commenter stated that, unlike previous regulations, CPSC is not basing the rule on sound science, but is adopting the CHAP's decisions which "are informed significantly by the precautionary principle" (which, according to the commenter, treats chemicals as "guilty until proven innocent," and which is adhered to by the European Union, but up until now has not been used in U.S. rulemaking). Similar comments were made by others.

In contrast, other commenters supported a precautionary approach. One such commenter noted that, given the sensitivity of very young children to endocrine disrupting compounds and developmental toxicants, the uncertainties support "a precautionary approach to phthalate exposure; erring on the side of protection rather than reintroducing hazardous chemicals into the marketplace."

Response 8.14: Section 108 of the CPSIA establishes the criteria for the Commission's rulemaking. Regarding the phthalates that are subject to the interim prohibition, the Commission must determine whether to continue those prohibitions "in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." For other phthalates and other children's products, the Commission must determine whether additional prohibitions are "necessary to protect the health of children." These provisions differ from the rulemaking criteria in sections 7 and 9 of the CPSA and in sections 2 and 3 of the FHSA. Thus, the phthalates rulemaking is a departure from previous CPSC rules because Congress used different language, and we are following the specific direction in section 108.

Comment 8.15: Appearance of prejudgment on the part of the CHAP and CPSC – particularly regarding DINP. One commenter asserted that the CHAP report and the NPR give the appearance that the CHAP and CPSC had made a prejudgment to continue the prohibition involving DINP. The commenter claimed that the following points support this conclusion:

1) CHAP failed to correct errors pointed out by peer reviewers;
2) CHAP (and NPR) did not consider relative risks of alternatives to DINP;
3) A CHAP member made derisive remarks about (and ad hominem attack on) author of paper questioning dose addition and added to the "appearance that the CHAP did not wish to consider any information that would challenge the conclusion it had already arrived at";
4) CHAP failed to use most recent exposure data;
5) CPSC failed to reanalyze the cumulative risk before issuing NPR;
6) In the NPR, CPSC referenced studies CPSC stated demonstrate antiandrogenic effects, but some show DINP not to be antiandrogenic; and
7) CPSC refused to have CPSC's scientists meet with industry scientists before and after CHAP issued its report.

Some other commenters asserted that the CHAP's recommendations and the CPSC's rulemaking seemed pre-determined. In contrast, other commenters found that the process was sound and fair. One stated: "We commend the CHAP and CPSC for conducting the process of the scientific

review and subsequent issuing of the proposed rule in an open and transparent manner." Another stated: "we appreciate the verified independence and expertise of the CHAP members, the scientific rigor of their analyses, the peer-review of CHAP work, and the transparency of CHAP meetings and the final report. Their scientific expertise and lack of financial ties to the phthalate industry support our confidence in their findings."

Response 8.15: Staff disagrees with the commenter's assertion that the CHAP or CPSC predetermined the outcome of this process. Based on CPSC staff's technical review of the CHAP report, staff agrees with the CHAP's findings and recommendations. Staff concludes that the CHAP carefully considered all available relevant information, including data and analysis presented to the CHAP during the public meetings or in writing. In making its recommendation to the Commission on the draft final rule, staff has considered the CHAP report, CPSC staff's analyses of more recent NHANES exposure data, and all comments submitted in response to the NPR and staff's analyses. Regarding the commenter's specific assertions:

1) The CHAP responded to the points made by the peer reviewers and included these responses along with the CHAP report transmitted to the Commission.[35]
2) The CHAP considered the potential health risks from phthalate alternatives in CHAP report (CHAP 2014) on pages 22–23; page 51; pages 121–142; Table 2.1; Table 2.12; Appendix A, pages A-39–A-45; Appendix B, pages B-18–B-22; and all of Appendix E-2. In all, the CHAP devoted 54 pages of their report to evaluating the risks from phthalate alternatives.

   The staff's briefing package discussed phthalate alternatives throughout, including on pages 1, 18, 23–24, 26–27, and 39; and Table 2.
3) The author to whom the commenter refers presented his findings to the CHAP in July 2010, submitted written comments, and some CHAP members saw the author's work presented at a Society of Toxicology meeting in 2011 (Sargent et al. 2011). The CHAP did not find the author's theory supported by empirical data. Staff agrees with the CHAP's conclusions on dose addition, as discussed in the responses to comments 1.25, 2.5, 2.7, and 2.8.
4) As discussed in Section 3 of this TAB B, the CHAP used 2005/2006 exposure data, the last sample with a sufficient number of pregnant women. CPSC staff has subsequently analyzed later NHANES data.
5) Staff has analyzed new NHANES data (CPSC 2015a; 2017a) and provided its analyses for public comment.
6) As discussed in comment response 1.3, staff concludes that DINP is antiandrogenic.
7) Staff met with industry scientists 10 times, beginning on June 22, 2009[36] and as recently as March 21, 2017. The CHAP heard presentations from industry scientists on multiple occasions. The CHAP and staff received over 60 communications from industry representatives.

[35] https://www.cpsc.gov/s3fs-public/CHAP.PDF.
[36] Meetings with industry and communications to the CHAP and staff may be found at https://www.cpsc.gov/chap.

Comment 8.16: Compliance with APA. A commenter asserted that continuing the interim prohibition involving DINP is arbitrary and capricious (in violation of the APA) because:

1) there is a reasonable certainty of no harm without such a prohibition (due to permanent prohibition involving DEHP);
2) DINP contributes only a small fraction to overall risk;
3) the endpoint of antiandrogenicity is likely inappropriate;
4) it is questionable that DINP should be included in a cumulative risk assessment;
5) it is questionable that a cumulative risk assessment provides a reasonable basis for a regulatory decision;
6) DEHP levels have dropped so that the HI is now well below 1; and
7) even using the 2005/2006 NHANES data, the contribution of DINP to the overall HI is minimal and the major source of exposures is diet; children's products account for only a small fraction of overall HI.

In contrast, another commenter stated that the CHAP's recommendation and the Commission's proposal to permanently prohibit children's toys and child care articles containing more than 0.1 percent of DINP are justified. The commenter stated that data indicating that DINP is a potential health risk have gotten stronger since release of the CHAP report.

Response 8.16: In general, the APA requires that agencies' rulemaking be based on reasoned decision-making. Staff's briefing package explains the reasons for its recommendations, based on the CHAP report, staff's analysis of more recent NHANES data, and the public's comments concerning the rulemaking and the CHAP report. The specific issues the commenter raised about regulation of DINP and the apparent reductions over time in exposure to DEHP are addressed in detail in Sections 1, 2, and 5 of this TAB B.

CPSIA's Requirements for the CHAP

Comment 8.17: Review of all relevant data. Several commenters noted that the CPSIA directed the CHAP to "review all relevant data, including the most recent, best available … scientific studies … that employ objective data collection practices." A commenter asserted that the CHAP's "selective use and systematic mischaracterization of the data" did not meet this requirement. Commenters argued that the CHAP's reliance on the 2005/2006 NHANES data set rather than later data sets that were available to the CHAP before the CHAP's stopping point (2007/2008, 2009/2010 and 2011/2012 data sets) violated the CPSIA's direction to review "all relevant data" and to include "the most recent" studies. They asserted that this is particularly important because, due to the drop in DEHP exposures, there has been a significant decline in total risk. Other commenters stated that the CHAP's analysis "represents the cutting edge and most current and best available science," a significant improvement over methodologies currently used for government review of chemical risk that considered one chemical at a time.

Response 8.17: The CHAP used 2005/2006 NHANES data on pregnant women to assess phthalate exposure as part of the CRA, to satisfy the CPSIA's charge to "examine the likely levels of children's, pregnant women's, and others' exposure to phthalates . . .." CPSIA §108 (b)(2)(B)(iii). This data set was the most recent data on pregnant women available at the time the CHAP completed its analysis in July 2012 (CHAP 2014, p. 35), and was the last dataset to

include a larger sample of pregnant women. The CPSC staff subsequently analyzed NHANES WORA data from 2007/2008 through 2013/2014 (see comment response 3.2) using the CHAP's analytical methodology.

The CHAP considered new scientific information published up to the end of 2012 and used standard and acceptable methods for study review, conducting an unbiased literature search and publication identification and in-depth review and reporting of the most important publications. Specifically, the CHAP included many elements of systematic review methods in its work. The CHAP used a defined literature search strategy and limited the search to studies published through 2012. The CHAP considered the quality, relevance, and weight of evidence (WOE) of individual studies. The CHAP described criteria for evaluating published studies (CHAP 2014, pp. 19–23) and ensured that all studies and data were publicly available. The CHAP also described the criteria used to formulate its recommendations on individual phthalates and phthalate alternatives (CHAP 2014, p. 79). The CHAP criteria included review of animal and human data, weight of evidence, study replication, human exposure, hazard, and risk (CHAP 2014, pp. 82–142). Staff concludes that the CHAP conducted a thorough review of a large body of literature on a complex environmental health question using appropriate methods.

All current scientific publications and NHANES data sets have been analyzed by the CHAP and CPSC staff in preparation of the draft *Federal Register* notice for the final rule and the use of these data, therefore, fulfils CPSIA's directive to review "all relevant data" and to include "the most recent" studies (see Section 3 and comment response 10.1 for more information).

Comment 8.18: Foreseeable use and likely exposure. Several commenters noted that 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." The commenters asserted that this means the CHAP must base its assessment of risks from cumulative exposure on exposure levels that are likely and based on reasonable estimates. Commenters argued that ignoring the more recent data that shows a significant drop in DEHP exposure does not give a "likely" estimate of current exposure. Additionally, the commenters asserted that including permanent prohibitions involving phthalates in the analysis is not realistic and does not predict "likely" exposures.

Other Commenters noted that the CHAP's inclusion of DINP in its cumulative risk assessment was consistent with the CPSIA's direction to the CHAP to consider "foreseeable use" of phthalates. The commenters stated that DINP is antiandrogenic and DINP exposure was the highest in infants, toddlers, and children among the nine phthalates measured.

Response 8.18: As explained above, the 2005/2006 NHANES dataset that the CHAP used was the most recent data on pregnant women available at the time the CHAP completed its analysis in July 2012 (CHAP 2014, p. 31) and included a larger sample of pregnant women.

The CPSC staff has since analyzed more-recent NHANES data from 2007/2008, 2009/2010, 2011/2012, and 2013/2014 (CPSC 2015a; CPSC 2017a) using the same methodology used by the CHAP (TAB A). As explained in comment response 3.1 and 3.2, staff's recommendations for the final rule consider the most recent NHANES data.

As noted in comment response 2.9, the CHAP's CRA estimated phthalate exposure from all phthalates and all sources, not only children's toys and child care articles. Because the CPSIA prohibition covers only children's toys and child care articles, exposures to DEHP, DBP, and

BBP still occur from other sources. Staff concludes that the CHAP and subsequent staff analyses provide a robust assessment of the "likely levels" of pregnant women's current exposures to phthalates.

Staff agrees that because DINP is antiandrogenic, it was appropriate to include DINP in the CRA of all phthalates shown to contribute to male reproductive developmental effects; its use is increasing as reflected in the NHANES biomonitoring data. A more detailed discussion of these issues is in Section 2 of this TAB.

Comment 8.19: CPSIA direction to CHAP to conduct a Cumulative Risk Assessment. One commenter stated that the CPSIA direction to the CHAP to "consider the cumulative effect of total exposure to phthalates" did not mean that the CHAP had to conduct a cumulative risk assessment. The commenter argued that the CHAP could have considered cumulative effects in a more general (qualitative) way and that the cumulative effects of exposure were just one of multiple factors the CPSIA directed the CHAP to consider.

In contrast, other commenters asserted that a cumulative risk assessment was well within the CPSIA's direction to the CHAP; noting that the CPSIA provided a clear mandate to "review the toxicity of phthalates cumulatively" and consider "the exposure to all sources of these chemicals." One comment from a group of commenters stated that the cumulative risk analysis was specifically required by Congress.

Response 8.19: Several provisions in the direction to the CHAP in section 108(b)(2) require the CHAP to consider cumulative effects of phthalates. Specifically, the statute directs the 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";
- "consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates"; and
- "consider the cumulative effects of total exposure to phthalates, both from children's products and from other sources, such as personal care products."

Thus, the CPSIA required the CHAP to use some method to evaluate the health effects of multiple phthalates from multiple products. The statute did not specify that the only way to do this was through a cumulative risk assessment. However, nothing in the statute prohibited the CHAP from conducting a cumulative risk assessment. As explained in the CHAP report, and in the NPR, based on the CHAP's knowledge and expertise, the CHAP decided that a cumulative risk assessment was the most appropriate method to fulfill the direction given to the CHAP. Furthermore, the CHAP used a CRA approach consistent with those recommended by a National Academy of Sciences committee that was convened specifically to consider methods for assessing the cumulative risks from phthalates (NRC 2008). Thus, the CHAP used its judgment and provided an explanation for the choice.

CPSIA's Requirements for the Rulemaking

Comment 8.20: Commission's role regarding CHAP report. Comments questioned the Commission's reliance on the CHAP report in the NPR. One commenter stated: "the CPSC has essentially codified the CHAP report," giving the CHAP "de-facto rulemaking authority." Another commenter stated that the CPSIA's direction to the Commission to base its rulemaking

determination on the CHAP report "does not relieve the Commission of its obligation to critically review the CHAP report and its underlying premises and analyses." A subsequent comment from the same commenter reiterated that the CPSIA phrase "based on" does not require CPSC to "rigidly adhere to the CHAP's recommendations, but rather the Commission must examine the report critically, along with other relevant information and make a "reasoned, independent decision" in accordance with the APA. The commenter stated that reading the CPSIA to mandate that the Commission issue a rule that follows the CHAP's recommendations would raise serious Constitutional questions by vesting government powers in a private entity and would also conflict with section 108 of the CPSIA and sections 28 and 31 of the CPSA (e.g., the word "advisory") which make the CHAP's advisory role clear. Another commenter stated that CPSC acted appropriately on the CHAP report, noting that "CPSC made its own decision, issued its own proposed rule, and solicited public comment from industry and others on its proposed rule."

Response 8.20: Section 108(b)(3) of the CPSIA requires that the Commission's rule concerning the interim prohibition be "based on" the CHAP report and that the Commission evaluate the findings and recommendations of the CHAP to determine whether to prohibit any other children's products containing any other phthalates. We agree that the statutory language does not require rigid adherence to the CHAP report and that the Commission cannot simply "rubber-stamp" the CHAP's recommendations. Rather, the CHAP report is advisory and the Commission must use its judgment to decide on appropriate regulatory action in accordance with the specific criteria stated in section 108(b)(3)(A) and (B) and must consider public comments it received . This is exactly the process the Commission followed. The NPR summarized the CHAP report, including the CHAP's recommendations. 79 FR 78326-78330. The NPR then presented CPSC staff's evaluation of the CHAP report and the Commission's assessment of the CHAP's recommendations. *Id*. 78330–78338. Additionally, CPSC staff conducted a reanalysis of the CHAP's evaluation of certain exposure data, and staff reviewed and considered the comments submitted in response to the NPR to develop staff's recommendation to the Commission. All of this information provides the basis for the Commission's decision on the final rule.

Comment 8.21: Basing the rule on a Cumulative Risk Assessment. One commenter asserted that the CPSIA did not mandate that the CPSC base its rulemaking determination on a cumulative risk assessment. The commenter stated: "To the extent the Commission bases its determination on a cumulative risk assessment, the issue is whether the results of that risk assessment indicate that it is necessary to continue the prohibition involving DINP, DIDP and/or DnOP "in order to ensure a reasonable certainty of no harm." Another commenter asserted that the CPSIA gave CPSC authority "to ban phthalates that may only have a cumulative contribution to negative health outcomes like hormone production." Another commenter asserted that the CPSIA's direction to the Commission to "evaluate the findings and recommendations" of the CHAP and declare children's products containing phthalates to be banned "as the Commission determines to be necessary to protect the health of children" gives the Commission authority to rely on the CHAP's cumulative risk assessment.

Response 8.21: We agree that Congress did not direct the Commission to base its rulemaking on a cumulative risk assessment. As noted, Congress directed the CHAP to consider the cumulative effect of phthalates. Congress stated the criteria for the Commission's rulemaking in section 108(b)(3) of the CPSIA. With regard to substances subject to the interim prohibition, the Commission must determine whether to continue the prohibition "to ensure a reasonable

certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." The CPSIA requires the Commission to base this determination on the CHAP report. With regard to children's products containing any phthalates, the Commission must determine whether those prohibitions are "necessary to protect the health of children." The CPSIA requires the Commission to evaluate the CHAP's findings when considering this determination. The statute neither requires nor prohibits the Commission from making these determinations based on a cumulative risk assessment. However, given that the statute directed the CHAP to consider the cumulative effect of phthalates, and that the statute stated that the rule must be "based on" the CHAP report (at least concerning the interim prohibition, it is reasonable for the Commission's rule to rely on the cumulative risk assessment performed by the CHAP.

Reasonable Certainty of No Harm

Comment 8.22: Meaning of "reasonable certainty of no harm" in relation to CPSA. Several commenters addressed the meaning of the phrase "reasonable certainty of no harm." One commenter stated that, although the phrase "reasonable certainty of no harm" in CPSIA section 108(b)(3)(A) does not appear in other statutes that CPSC administers, the standard must be interpreted in the context of CPSC's other laws and case law. In this view, the phrase essentially means "reasonably necessary to prevent or reduce an unreasonable risk of injury." The commenter asserted that "unreasonable risk" as interpreted by case law is the appropriate standard to apply to CPSIA section 108(b)(3)(A) and that there must be substantial evidence to support the Commission's determination.

Response 8.22: For the Commission to issue a consumer product safety rule under sections 7, 8 and 9 of the CPSA, the Commission must determine that the product presents an unreasonable risk of injury and that a rule is necessary to reduce or prevent the unreasonable risk. As noted in the previous responses, section 108(b)(3) establishes the criteria that the Commission is to use to determine appropriate phthalate regulations. The term "unreasonable risk" does not appear anywhere in section 108. Section 108(b)(f) states that the permanent and interim prohibitions, and any rule that the Commission issues under section 3(b)(3), "shall be considered a consumer product safety standard." However, section 108(f) concerns the effect on state laws, not the findings or process the Commission is to use to issue a consumer product safety standard under section 108(b)(3). Nothing in the legislative history of section 108 indicates that Congress intended the Commission to make "unreasonable risk" determinations or that case law related to the Commission's rules issued under sections 7, 8 and 9 of the CPSA would apply to the phthalate rulemaking.

Comment 8.23: 'Reasonable certainty" is not 100 percent. A commenter asserted that the phrase "reasonable certainty" indicates that Congress did not intend for CPSC to determine that there is 100 percent certainty of no harm. The commenter stated that CPSC has applied the standard to DINP to essentially require absolute certainty even though the risk is "vanishingly small" and "highly speculative."

In contrast, a commenter emphasized that the CPSIA calls for ensuring a "'reasonable certainty of *no* harm' (emphasis added)." The commenter stated that due to the increase in exposures to DINP as demonstrated by NHANES data, the statutory standard supports the need to maintain the prohibition involving DINP in child care products and toys.

Response 8.23: For the Commission's determination regarding the interim prohibition involving DINP, section 108 requires the Commission to determine whether action is needed "to ensure a reasonable certainty of no harm . . . with an adequate margin of safety." This language calls for a highly protective standard, but staff agrees with the commenter that "a reasonable certainty of no harm" is not "100% certainty of no harm."

Comment 8.24: Meeting a "reasonable certainty of no harm" standard. Commenters asserted that the CPSIA's standard of "reasonable certainty of no harm" is met without continuing the prohibition involving DINP. Commenters reasoned that, because the CPSIA permanently prohibited children's toys and child care articles containing more than 0.1 percent of DEHP, DBP, and BBP, those phthalates cannot contribute to any cumulative risk from these products in the future. Without those phthalates, the HI clearly is less than one, and thus a reasonable certainty of no harm from use of DINP in these products.

Other commenters asserted that it "turns logic upside-down" to suggest that "as DEHP is replaced by less toxic phthalates, there is a reasonable certainty of no harm from increasing exposures to the remaining phthalates." These commenters reasoned that the contribution of replacement phthalates to the cumulative risk is unknown at this point, but we do know they present hazards beyond antiandrogenic effects (such as liver toxicity, thyroid effects, and cancer).

Response 8.24: Staff explains in Section 5 of the comment/response document that the CHAP determined that DINP contributes to the cumulative risk. The CHAP considered phthalate exposure from all sources, and for all phthalates individually and in combination. Because DEHP, BBP, and DBP continue to exist in the environment and contribute to the cumulative risk, their HQs are included in the calculation that shows that a portion of the population continues to have an HI greater than one, and therefore is at risk for MRDE. Thus, as described in Section VII, a prohibition involving DINP is necessary for a reasonable certainty of no harm to pregnant women or other susceptible individuals with an adequate margin of safety.

Comment 8.25: FDA and "reasonable certainty." A commenter noted that although CPSC has not previously used the "reasonable certainty of no harm" standard, the FDA uses that standard when examining food additives. The commenter states that when FDA evaluates NHANES data under this standard FDA assesses exposure at the 90th percentile in examination of food additives to protect "high exposure" consumers over their lifetime. The commenter concludes that given staff findings on the CPSC 2015 analysis, the continued interim prohibition involving DINP may not be warranted.

Response 8.25: In addition to the CPSIA, we are aware of two statutory schemes that use a "reasonable certainty of no harm" standard. The Food Quality Protection Act of 2006 (FQPA) amended the Food, Drug, and Cosmetic Act (FDCA) to regulate pesticide residues in the food supply. The FQPA requires EPA to establish tolerance levels (or exemptions) for the maximum permissible level of pesticide residue on food products. To do this, EPA must determine that the tolerance level is "safe." The FQPA defines the word "safe" in this context to mean "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." 21 U.S.C. § 346a(b)(2)(ii). Congress directed EPA to consider appropriate safety factors. For each pesticide tolerance, EPA must "ensure that there is a reasonable certainty

that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue." *Id.* § 346a(b)(2)(ii)(I).

Similarly, the FDCA's requirements concerning food additives require the FDA to assess the safety of food additives. 21 U.S.C. § 348. The FDA reviews petitions requesting approval of new food additives to determine whether the proposed use of the additive is safe. Relevant FDA regulations state:

> Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:
>
> (1) The probable consumption of the substance and of any substance formed in or on food because of its use.
>
> (2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.
>
> (3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

21 C.F.R. § 170.3. The regulatory schemes established under the FQPA and FDCA have language that is similar to section 108. However, the products regulated and the specific requirements under those statutes differ significantly from the phthalates provision in section 108. Thus, applying FDA's 90th percentile analysis does not necessarily make sense for CPSC's analysis of phthalates. In a very general sense, CPSC's phthalates rulemaking has similarities with these two statutory provisions; CPSC has evaluated the phthalates based on expert scientific opinion (the CHAP), takes into account the cumulative effect of phthalates, and provides for appropriate safety factors.

Comment 8.26: Permanent prohibition of children's toys and child care articles containing DIOP. Commenters stated that to meet the "reasonable certainty of no harm" standard, the Commission should permanently prohibit children's toys and child care articles containing DIOP because, although the CHAP noted a lack of exposure data regarding DIOP, the commenters believe that the structure activity relationships suggest toxicity. The commenters stated that "DIOP cannot be assumed to meet the safety standard due to the lack of hazard and exposure data necessary to calculate risk to human health." A group of commenters asserted that under the CPSIA, CPSC must evaluate the CHAP's findings regarding DIOP and prohibit the chemical's use in toys and child care articles "as the Commission determines necessary to protect the health of children." These commenters stated that rejecting the CHAP's recommendation for a ban is inconsistent with this Congressional mandate. They urged the Commission to prohibit children's toys and child care articles containing DIOP "until such time that the science affirmatively shows it to be safe" and "reject the 'no data = no problem' premise."

Response 8.26: Under section 108(b)(3)(B), to prohibit any children's products containing DIOP, the Commission must determine that the prohibition is "necessary to protect the health of children." The Commission must have information to support such a determination. Thus, under

section 108(b)(3), a lack of data cannot form the basis for regulating. The CHAP noted the need for more information, but did not conclude that current information supported a prohibition. As noted in the NPR, section 108(b)(3) did not give the Commission authority to issue a temporary prohibition, and without sufficient information to determine that prohibiting certain products containing DIOP is necessary to protect the health of children, the Commission could not issue a permanent prohibition.

Federal Hazardous Substances Act

Comment 8.27: FHSA criteria. A commenter asserted that the CHAP's analysis does not meet the requirements of the CPSIA because the CHAP report did not present its analysis in terms of the criteria stated in the Federal Hazardous Substances Act (FHSA). The commenter reasoned that the CHAP should have applied the FHSA criteria because section 108(b)(2)(C) of the CPSIA states that the CHAP is to make recommendations to the Commission regarding phthalates and phthalate alternatives that "should be declared banned hazardous substances." The term "banned hazardous substance" is defined in the FHSA. The commenter believes that because the CPSIA used a term from the FHSA, Congress intended for the CHAP to conduct its analysis by applying FHSA criteria.

Response 8.27: The commenter bases its argument that the CHAP should have followed FHSA criteria only on the presence in CPSIA section 108 of a phrase that appears in the FHSA. Neither section 108 nor the legislative history of that provision makes any mention of the FHSA. Rather, section 108(b)(2)(B) provides detailed direction to the CHAP about the criteria that the CHAP is to consider in its examination. Moreover, section 108(f) clearly states that the statutory prohibitions and the Commission's future phthalates rule "shall be considered consumer product safety standards under the Consumer Product Safety Act." It is not logical that Congress would expect the CHAP to apply FHSA criteria (without mentioning that statute) to provide a report to the Commission for a rule that is to be treated as a rule under the CPSA. In fact, section 108 established a unique procedure for phthalates, making it clear that Congress did not intend for the Commission to undertake rulemaking under the FHSA. The CHAP and the Commission followed the specific process and criteria set forth in section 108.

Comment 8.28: Role of CRA in rulemaking for an individual chemical under the FHSA. A commenter asserted that the CPSIA did not authorize the CHAP to make a recommendation regarding a prohibition involving DINP itself, based on a cumulative risk assessment because such an assessment would not be permitted under the FHSA. The commenter reasoned that under the FHSA's definition of "hazardous substance" the CHAP would have to find "that a mixture of phthalates is a 'hazardous substance' and that children's products containing that mixture should be declared 'banned hazardous substances.'" However, according to the commenter, the CHAP improperly recommended a prohibition of the individual chemical DINP (as opposed to a mixture) on the basis that it contributes to an overall cumulative risk. Another commenter disagreed with this reasoning and pointed out that under the FHSA a "hazardous substance" could be "*any substance* or mixture of substances" that meets certain criteria (emphasis added).

Response 8.28: As stated in the previous response, section 108 sets out the criteria for the CHAP's report and the Commission's phthalates rulemaking. Whether or not a prohibition involving DINP would be permitted under the FHSA's definition of "hazardous substance" is irrelevant. Section 108 directed the CHAP to examine all the factors and considerations stated in section 108(b)(2)(B) and develop a report that would include recommendations to the

Commission about any phthalates or phthalate alternatives not involved in the permanent prohibition stated in section 108 (a) that should also be prohibited. Although section 108(b)(2)(C) used a phrase found in the FHSA ("banned hazardous substance"), that phrase does not establish criteria for the CHAP's inquiry; those criteria are stated in section 108(b)(2)(B). Similarly, Congress set out the criteria for the Commission's rulemaking in section 108(b)(3). For the phthalates involved with the interim prohibition, the Commission must consider whether to continue the prohibition "in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety." For children's products containing any other phthalates, the Commission must determine whether any additional prohibitions are "necessary to protect the health of children." To comply with this specific statutory direction, the Commission must apply these criteria rather than any findings or criteria stated in the FHSA or CPSA.

Comment 8.29: "Hazardous substance" under the FHSA. A commenter asserted that the CHAP's risk assessment improperly included consideration of exposures to substances that are excluded from the FHSA's definition of "hazardous substance," such as foods and drugs. 15 U.S.C. § 1261(f)(2). The commenter stated: "it is improper to use exposures to phthalates in foods and drugs (as is necessarily the case by using biomonitoring data) to determine whether a mixture of phthalates meets the definition of 'hazardous substance' and whether children's products containing that mixture meet the definition of 'banned hazardous substance.'"

Response 8.29: As noted previously, there is no indication in the statutory text or the legislative history that Congress intended the CHAP to be governed by the FHSA. The direction to the CHAP explicitly requires the CHAP to consider phthalates that are in products outside of the CPSC's jurisdiction. The CHAP "shall … consider the cumulative effect of total exposure to phthalates, both from children's products and from other sources, *such as personal care products*." Section 108(b)(2)(B)(iv) (emphasis added). Many personal care products are considered cosmetics and are under the jurisdiction of the FDA. Apparently, Congress intended for the CHAP's examination to be broader than just products under CPSC's authority. Although the Commission cannot regulate products outside of its jurisdiction, Congress could (and did) direct the CHAP to take a broader look.

Expansion of Prohibition Involving DINP to All Children's Toys

Comment 8.30: Legal authority. Commenters asserted that the CPSIA did not authorize the Commission to expand the interim prohibition (which covered children's toys that can be placed in a child's mouth and child care articles) to all children's toys. The commenters stated that because section 108(b)(3)(A) directs the Commission to determine whether to "continue in effect the prohibition under paragraph (1) [the interim ban]," the Commission has authority only to continue the prohibition that was originally enacted by Congress.

Response 8.30: The direction to the Commission for rulemaking under section 108(b)(3)(A) concerns continuation of the interim prohibition stated in section 108(b)(1). However, Congress also directed the Commission to evaluate the CHAP report and determine whether "any children's product containing any phthalates" should be prohibited as "necessary to protect the health of children." Section 108 (b)(3)(B). Thus, the Commission has the authority to expand the interim prohibition to all children's toys (not just those that can be placed in the mouth) if the Commission determines that the expansion is necessary to protect health of children.

Comment 8.31: Section 8 of the CPSA. Commenters asserted that, for the Commission to expand the prohibitions covered by the interim prohibition, the Commission would need to take action under section 8 of the CPSA. As one of these commenters noted, CPSIA section 108(b)(3)(B) directs the Commission to evaluate that CHAP's report and "declare any children's product containing any phthalates to be a banned hazardous product under section 8 of the Consumer Product Safety Act …, as the Commission determines necessary to protect the health of children." The commenter asserted that this language does not authorize the expansion of the interim prohibition because:

- the language refers to "children's products" rather than the discrete categories of "children's toy that can be placed in a child's mouth or child care article" which are subject to the instruction in section 108(b)(3)(A); and
- the language only permits a prohibition when "necessary" to protect children's health, but the primary mode of exposure to phthalates is oral, so expansion is not necessary.

The commenters also stated that it is not clear that the CHAP intended this expansion and the CHAP did not provide any rationale for expanding the scope.

Response 8.31: Section 108's use of the term "banned hazardous product" and reference to section 8 of the CPSA does not require the Commission to follow the CPSA's rulemaking process and findings set out in section 8 of the CPSA. Rather, the Commission must apply the specific criteria established in section 108(b)(3). As noted previously, to expand the interim prohibition to include all children's toys (not just those that can be mouthed), the Commission must determine that the expansion is "necessary to protect the health of children." Staff addresses this issue in Section 6 of the comment/response document.

Other Legal Issues

Comment 8.32: Limited testing costs as justification for prohibiting children's toys and child care articles containing the additional phthalates. One commenter asserted that "the Commission proposes to begin banning several additional phthalates, and its primary justification for doing so, despite limited scientific support, is that the testing costs for additional phthalate bans are minimal once some phthalate testing is already mandatory." The commenter stated that this rationale is not risk-based and understates the costs of testing and compliance, which is particularly important when Congress has directed CPSC to reduce the costs of testing.

Response 8.32: As the Commission explained in the NPR, the basis for proposing to prohibit children's toys and child care articles containing phthalates that are not covered by the permanent or interim prohibition is that they (DIDP, DPENP, DHEXP, and DCHP) are antiandrogenic phthalates that adversely affect male reproductive development. 79 FR 78330. The NPR discussed the likelihood that a prohibition of children's toys and child care articles containing these phthalates would have a minimal impact on testing costs as part of the Commission's consideration of the impact the proposed rule could have on small businesses. *Id.* 78339 – 78341. Under the Regulatory Flexibility Act, the Commission must assess the potential impact the proposed rule would have on small businesses that would be subject to the rule. However, the minimal impact on testing costs was not the reason the Commission proposed extending the prohibitions to children's toys and child care articles containing DIBP, DPENP, DHEXP, and DCHP. Aside from the general statement that CPSC understated the costs of testing

and compliance, the commenter did not provide any information about the costs that manufacturers would incur for testing to and compliance with the proposed rule. Staff responds to other comments concerning testing costs in section 9 of the comment/response document.

Comment 8.33: Sources of exposure and the limited impact of CPSC's rulemaking. Some commenters asserted that CPSC's rule is not justified because many of the sources of exposure discussed by the CHAP are outside of CPSC's jurisdiction. One of these commenters stated that in the CPSIA, the purpose for the CHAP and the charge to the CHAP specified phthalates in products for children (specifically, children's toys and child care articles). The commenter stated that the CHAP report in fact demonstrates that sources not within the CPSC's jurisdiction are the primary source of exposure to DINP.

In contrast, a commenter noted that the fact that children's toys account for a small part of exposures does not mean CPSC's action is insignificant, but rather, governments routinely act on small increments of a problem (as endorsed by the Supreme Court in *Massachusetts v. EPA*). The commenter called on other agencies that regulate products that contribute to exposure (such as FDA) to take action and for CPSC to work with such agencies.

A commenter stated that the CHAP exceeded its charge to examine phthalates that are used in products for children by making recommendations to agencies other than the CPSC regarding phthalate regulation.

Response 8.33: Clearly, the CPSC only has authority to regulate items within its jurisdiction. Both the CPSIA and the agency's rulemaking recognize that limitation. CPSC's rule covers certain children's products that are entirely within the CPSC's jurisdiction. However, Congress directed the CHAP to examine the health effects of products outside of CPSC's jurisdiction as well, requiring the CHAP to "consider the cumulative effect of total exposure to phthalates, both from children's products and from other sources, such as personal care products." § 108(b)(2)(B)(iv).

As the other commenter noted, there is no requirement that agencies must remedy 100 percent of a problem when they seek to regulate. In addition, as the Supreme Court also recognized in *Massachusetts v. EPA*, an agency need not refrain from acting just because another agency may also have a role to play. *Massachusetts v. EPA* (regarding EPA's and DOT's obligations concerning greenhouse gases, the Court stated: "there is no reason to think the two agencies cannot both administer their obligations and yet avoid inconsistency").

Regarding the commenter's assertion that the CHAP exceeded its charge by making recommendations to other agencies, those recommendations were not used by staff or the Commission as support for this rulemaking.

Comment 8.34: Preemption. One commenter asked that the Commission clearly state the preemptive effect that CPSC's rule would have on state and local legislation regarding phthalates and phthalate alternatives "for which the CHAP and the Commission have found no evidence of risk" and that CPSC has chosen not to regulate. The commenter mentioned as an example a California proposal under Proposition 65 that would require every consumer product sold containing phthalates to provide a warning that the product "can expose you to phthalates known to the State of California to cause cancer and birth defects or other reproductive harm."

Response 8.34: As explained in the NPR, section 108(f) states that any rule the Commission issues under section 108 shall be considered a consumer product safety standard issued under the

Consumer Product Safety Act (CPSA). As a consumer product safety standard, the phthalate rule is subject to the preemption provisions in section 26 of the CPSA. Section 26(a) of the CPSA states that, when a consumer product safety standard is in effect, no state or political subdivision of a state has authority to establish or continue a safety standard or regulation that "prescribes requirements as to the performance, composition, contents, design, finish, construction, packaging, or labeling of the product" designed to deal with the same risk of injury associated with the product, unless the requirements are identical to federal standard. 15 U.S.C. § 2075(a). Thus, when the phthalate rule is in effect, no state or political subdivision of a state may establish or continue in effect such requirements dealing with the same risk of injury unless the state requirement is identical to the CPSC's rule. With regard to phthalate alternatives, section 108(f) of the CPSIA states: "Nothing in this section or the Consumer Product Safety Act shall be construed to preempt or otherwise affect any state requirement with respect to any phthalate alternative not specifically regulated in a consumer product safety standard under the Consumer Product Safety Act."

Determining the extent of preemption requires knowing the details of both the Federal and state (or local) requirements. Thus, we cannot respond to hypothetical questions. However, Congress has apparently resolved the preemption question regarding warning requirements such as Proposition 65. The CPSIA amended the CPSA to state: "Nothing in this Act or the Federal Hazardous Substances Act shall be construed to preempt or otherwise affect any warning requirement relating to consumer products or substance that is established pursuant to State law that was in effect on August 31, 2003." 15 U.S.C. § 2051 note re preemption; Pub. Law 110-314, Sec. 231 (Aug. 14, 2008). Proposition 65 was enacted in 1986.

9. Economic and Compliance Issues

Overview of Public Comments on Economic and Compliance Issues

Two commenters agreed with staff's conclusion that the proposed regulations would have a small impact on testing costs. However, some commenters disagreed, saying that the proposed regulations could be detrimental to small manufacturers. Staff maintains that any increase in testing costs would be small, and that there will be no significant impact on small entities.

One commenter asked whether the CPSC guidance on component part testing (16 C.F.R. part 1199)[37] would apply to DIBP, DPENP, DHEXP, and DCHP. Staff notes that the principles in the guidance on component part testing should apply to all prohibitions involving phthalates.

Comment 9.1: Testing costs. Two commenters from trade associations asserted that the rule will not have a large impact on testing costs. Several industry commenters questioned the potential impact of the rule on small entities as addressed in the RFA, stating that any increase in third party testing costs could be detrimental to small toy companies. Commenters asserted that the impacted industries almost without exception have already stopped using phthalate esters as plasticizers, thus creating test burden for which there is no benefit. Commenters were also concerned about the costs to transition the marketplace to other non-prohibited chemicals (finding replacement phthalates and revising product formulations).

[37] Available at: http://www.ecfr.gov/cgi-bin/text-idx?SID=a0c4999f6a33294f4921e81a0f48180c&node=pt16.2.1199&rgn=div5.

A commenter expressed concerns about possible barriers to international trade, noting that the NPR differs significantly from other countries' approaches and regulations, and prohibits products containing phthalates that are not restricted in the European Union. Other commenters stated that CPSC's proposal is consistent with the EU. These commenters focused particularly on DINP.

A laboratory commenter addressed the issue of testing for DIDP and DINP and urged the Commission to "clarify how testing is to be performed for products containing technical mixtures of DINP and DIDP as part of the New Rule or associated test methods still to be developed." The commenter pointed out that some technical mixtures called "DIDP" may be compounds that can contain small amount of DINP (up to six percent in one case). The commenter noted that the technical mixtures have different Chemical Abstracts Service (CAS) Registry Numbers than materials containing only DIDP. The commenter added that when DINP is detected in a sample, additional analytical steps are needed (at additional cost) to determine if the DINP is present as a 'pure' chemical or if the DINP is part of a technical mixture. The commenter concludes by stating:

> We urge the commission to take the opportunity in its consideration of the proposed rule and the associated test method to specify that the limit is intended to apply to all DINP present in a plastic sample, whether present as a standalone substance or as part of a mixture regardless of the origin.

One commenter suggests that the Commission should not "miss this opportunity" to reduce third party testing costs by limiting the prohibition involving phthalates to only those areas necessary to protect the health of children. Another commenter urged the Commission to issue determinations for additional materials that are known not to contain the regulated phthalates to decrease testing burden.

Response 9.1: As stated in the NPR and certified by the Commission, the expected additional burden associated with the proposed rule is small, with no significant impact on a substantial number of small entities. Staff agrees with the trade association commenters that there would be no large impact on testing costs. Staff has received no other information about cost impacts that would affect staff's assessment.

Regarding expressed concerns about barriers to international trade, as a party to the World Trade Organization (WTO) Agreement on Technical Barriers to Trade (TBT), staff examined relevant international standards for testing phthalates in children's toys and child care articles and the prohibitions for children's toys and child care articles containing specified phthalates established by other countries. The only international standard on phthalates is International Organization for Standardization (ISO) 8124-6:2014. This ISO standard specifies a method for testing toys and children's products to determine if they contain phthalates; it does not establish any content limit.

CPSC is promulgating this rule in response to specific statutory requirements. For DINP, there is no comparable regulation in another country that addressed the use of DINP in all children's toys for children 12 years of age and younger and child care articles for children under three years of age, which are the age limits defined by the CPSIA. The draft final rule's requirements would apply equally to all certifiers of children's products, both domestic manufacturers and importers. Thus, the draft final rule does not favor domestic manufacturers over importers and is not a barrier to international trade.

Regarding the concern about the need to determine the origin of any DINP found in a children's toy or child care article, staff emphasizes that the prohibition involving DINP applies regardless of the origin of the DINP or the phthalate formulation used. Therefore, children's toys and child care articles containing DINP in concentrations greater than 0.1 percent are prohibited even if DINP in was not added intentionally, such as could be the case with the use of some technical mixtures labeled "DIDP." It will not be necessary for laboratories to undertake any additional effort to determine the source of DINP found in a children's toy or child care article. There will be no additional analytical steps needed if the prohibition involving DIDP is removed.

Regarding the commenter's request for the Commission to issue determinations for materials that are known not to contain the regulated phthalates, this request is beyond the scope of this rulemaking. However, staff notes that on August 30, 2017, the Commission published in the Federal Register (82 FR 41163) the final rule determining that that seven specific plastics (polypropylene, polyethylene, general purpose polystyrene, medium-impact polystyrene, high-impact polystyrene, super high-impact polystyrene, and acrylonitrile butadiene styrene) do not contain any phthalates listed in section 108 of the CPSIA in concentrations above 0.1 percent. The effect of this rule is that third party testing of the specified plastics with specified additives is not required to demonstrate compliance with the phthalates prohibitions on children's toys and child care articles, which may result in lower testing costs for some children's toys and child care article manufacturers. The rule is effective on September 29, 2017.

Comment 9.2: Applicability of CPSC's *Statement of Policy: Testing of Component Parts with Respect to Section 108 of the CPSIA*, to DIBP, DPENP, DHEXP, and DCHP. An international government commenter suggested that CPSC provide further clarification as to whether the four additional plasticizers (DIBP, DPENP, DHEXP, and DCHP) are covered by the CPSC document *Statement of Policy: Testing of Component Parts with Respect to Section 108 of the CPSIA*[38] and the final guidance on inaccessible component parts in children's toys and child care articles containing phthalates.

Response 9.2: The Statement of Policy covers all the current prohibitions involving phthalates. The principles in the Statement of Policy should apply to any new prohibitions involving phthalates in children's toys and child care articles.

Comment 9.3: Small businesses not associated with children's toys or child care articles. CPSC received two comments from two manufacturers of flexible vinyl materials that have been using DINP for a number of years in a variety of applications, including commercial roofing, military tents, geomembranes, juvenile bedding, protective garments, medical devices, outdoor marking products, military and commercial tent materials, and book binders. The commenters stated that the proposed regulation on DINP would impact some of their product lines today.

Response 9.3: The rule has a narrow scope. The draft final rule makes permanent the interim prohibition on children's toys and child care articles containing more than 0.1 percent of DINP. The commenter did not provide sufficient information to determine if their "juvenile bedding" is a child care article under section 108 of the CPSIA, and thus is subject to the prohibitions involving DINP in the draft final rule. Therefore, it is uncertain if there is an impact on one of their product lines by making the interim prohibition involving DINP permanent. None of the

[38] Available at: https://www.cpsc.gov/s3fs-public/pdfs/blk_media_componenttestingpolicy.pdf.

other specific product lines mentioned by the commenters would be considered children's toys or child care articles, and therefore, would not be affected by the proposed prohibitions.

Comment 9.4: Costs and benefits of the proposal. One NGO commenter stated "that the proposed CPSC rule comes close to acknowledging the scientific weakness of the case to extend the ban on DINP to non-mouthable products, by arguing that the effect of the ban would be minimal." The commenter added that the CPSC's argument proposing that the prohibition's effect would be minimal was based on CPSC's conclusion that few products would need to be reformulated to comply with the broader scope; and the prohibition was not expected to have a significant impact on the cost of third party testing for phthalates. The commenter stated that it was troubling that:

> CPSC doesn't bother to consider any effect on consumers or the potential that in the future, smaller manufacturers would be burdened by this regulation, which offers no demonstrated public health benefits in exchange for even "minimal" costs.

The commenter adds that "the CPSC fails to take into account the potential for future uses of DINP in non-mouthable children's products." The commenter states: "the notion that the effect on manufacturers is supposedly minimal is a weak basis for keeping a safe and useful chemical out of the hands (but not mouths) of consumers, even children."

Response 9.4: The proposed rule was based on the requirements in section 108 of the CPSIA that the Commission determine, based on the CHAP report, whether to continue the prohibitions involving DINP, DIDP, or DNOP to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety. Section 108 also requires the Commission to evaluate the findings and recommendations of the CHAP, and declare any children's product containing any phthalates to be a banned hazardous product as the Commission determines necessary to protect the health of children. These provisions differ from the rulemaking criteria in the CPSA and in the FHSA, which require the Commission to find that there is a reasonable relationship between the costs and benefits of a rule. CPSC did not prepare a regulatory analysis, which would have examined the benefits and costs of the proposed rule. Thus the phthalates rulemaking is a departure from previous CPSC rulemakings under CPSA and FHSA because section 108 of the CPSIA does not require a cost-benefit analysis.

CPSC did conduct an analysis of the impact of the proposed rule on small entities in accordance with the Regulatory Flexibility Act. This analysis found, as indicated by the commenter, that because child care articles and many children's toys containing DINP were already prohibited, the proposed rule would have minimal impact on small businesses. However, as discussed above, this finding was not the justification for the proposed rule.

CPSC staff is not sure what the commenter meant by the statement that it did not consider the "potential that in the future, smaller manufacturers would be burdened by this regulation" and neither did the commenter provide any information that would allow staff to assess whether its analysis sufficiently took into account the potential future burdens. Because the commenter did not provide any more information about what the potential future burdens on small manufacturers would be, staff cannot address this comment further.

10.Other Issues

Overview of Public Comments on Other Issues

The CHAP was systematic when reviewing literature used in the CHAP report and used a weight of evidence approach when crafting recommendations for phthalates and phthalate alternatives. The CHAP was transparent in the process used, and in analysis and reporting when drafting the CHAP report.

a. Systematic Review

"Systematic review" is the use of methods to increase objectivity and transparency when collecting and analyzing scientific data (Rooney et al. 2014). The use of systematic review is well-established for analyzing clinical studies and making recommendations concerning human health, where such analyses generally involve limited numbers and types of studies. However, systematic review is only recently being adopted for use in assessing environmental health questions (EPA 2015a; NTP 2015). As discussed by the CHAP, environmental health includes many different scientific fields and types of data, such as animal toxicology, human epidemiology, and exposure and risk estimation. Because the included fields are disparate and broad, applying systematic review procedures to environmental health poses unique challenges.

Some industry commenters stated that the CHAP report was not a "systematic review." As explained by the CHAP, "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" (CHAP 2014, p. 12). Nonetheless, the CHAP included elements of systematic review in its work, such as a defined literature search strategy, describing criteria for evaluating studies, and describing criteria for formulating its recommendations. Staff notes that, when the CHAP convened in 2010, federal agencies such as the Environmental Protection Agency (EPA) and National Toxicology Program (NTP) had not yet adopted systematic review methods, and tools such as specialized software for characterizing publications were also not available. Systematic review is only recently being adopted by federal agencies for use in assessing environmental health (EPA 2015a; NTP 2015).

b. Weight of Evidence

A weight of evidence (WOE) approach considers multiple types of positive and negative evidence to reach conclusions. The evidence considered is usually interpreted and weighted (relative values or weights) by criteria relevant to the issue being investigated.

Industry commenters also claimed that the CHAP did not consider the weight of the evidence (WOE) in its report. Staff notes that the CHAP specifically included WOE in the criteria for making recommendations (CHAP 2014, p. 79). The CHAP also included a section on WOE in its recommendations for each phthalate and phthalate alternative (CHAP 2014, pp. 82-142).

c. Transparency

A number of commenters raised concerns regarding transparency of the CHAP process. Some commenters claimed that the CHAP process was secret and performed behind closed doors, while others commended the transparency of the process. Other commenters stated that the technical studies and data that CPSC used to make decisions should be made public.

CPSC staff disagrees with claims that the CHAP process was secret or lacking transparency. The CHAP held seven public meetings and six public teleconferences. The CHAP heard testimony from stakeholders in public, and received written comments throughout the CHAP process. All written submissions, oral presentations, and data submitted to the CHAP are available on the CPSC web site (www.cpsc.gov/chap). The CHAP did not use information that was not available to the public.

d. Phthalate Alternatives

Some commenters stated if prohibitions involve certain phthalates, then manufacturers will be forced to use alternative plasticizer chemicals whose safety or toxicity are not known, thus potentially putting people at greater risk. Staff agrees that for some phthalate alternatives, the available data on either toxicity or exposure were limited (CHAP 2014, pp. 121-142). For one alternative (DINX), toxicity data exist, but they were not available to the CHAP.[39] Staff notes that CPSC lacks the authority to require manufacturers to perform toxicity or exposure tests, or to provide existing data. Staff plans to work with other federal agencies, including the National Toxicology Program (NTP) and EPA to obtain additional data on phthalate alternatives.

Systematic Review

As mentioned above, systematic review is a term used to describe a process to identify, select, and critically evaluate data from studies that focus on a specific scientific question (National Toxicology Program).

As discussed by the CHAP, environmental health includes many different scientific fields and types of data, such as animal toxicology, human epidemiology, and exposure and risk estimation. Because the included fields are disparate and broad, applying systematic review procedures to environmental health poses unique challenges and requires more resources to complete than standard literature and data reviews.

Weight-of-evidence review is generally included as part of the systematic review process. The use of systematic review is well-established for analyzing clinical studies and making health care recommendations, where such analyses generally involve limited numbers and types of studies. However, systematic review is only recently being adopted for use in assessing environmental health questions (EPA 2015a; NTP 2015).

For their review, the CHAP did not conduct a systematic review, but defined a literature review process and discussed the results of their review and the criteria for formulating their recommendations. In this way the CHAP methodically reviewed the information needed for the CHAP report.

Weight of Evidence

A weight of evidence (WOE) approach considers multiple types of positive and negative evidence to reach conclusions. The evidence considered is usually interpreted and weighted (relative values or weights) by criteria relevant to the issue being investigated.

[39] Presentation of Dr. Rainer Otter, BASF, to the CHAP. July 2010.

The CHAP used a WOE approach when determining if phthalates or phthalate alternatives induced MRDE. A WOE approach was also more broadly used by the CHAP when integrating all the information used to make recommendations.

Comment 10.1: Nature of CHAP review approach. One commenter supported the CHAP's analysis and stated that the CHAP report "represents the cutting edge and most current and best available science." This commenter indicated that the CHAP report represents a significant improvement over the methods that are currently used for government review of chemical risk that consider one chemical at a time.

Industry commenters stated that the CHAP report is neither a systematic review nor a WOE review. Several commenters stated that a WOE approach should be applied. The commenters noted that, based on established best practices of systematic evidence-based reviews, the CHAP should have employed a consistent WOE framework, based on specific hypothesized mechanisms of action to permit data from laboratory experiments, epidemiological investigations, and mechanistic research to be integrated in a manner that provided a robust understanding of the potential hazards and risks that exposures to a substance could pose to humans. Two industry commenters stated that the CHAP should have demonstrated how the CHAP graded, rated, and interpreted the epidemiology studies. Commenters indicated that the framework should have specified a clear and systematic approach for addressing the uncertainties of the data equally. Specifically:

- discussions on each phthalate focused on study LOAELs and NOAELs and not the WOE; the CHAP did not consider the data collectively and integrate the evidence to reach conclusions related to the question at hand;
- integration of the data should have considered issues beyond the dose at which an effect was observed (e.g., potential for an effect threshold, clear definition of mechanism of action, differences in metabolism, differences in dose-response for the various effects); instead the CHAP selected the lowest doses associated with an effect, but did not consider the severity of the effect and whether or not these effects were even adverse;
- the CHAP focused solely on study design and did not include consideration of model relevance, database consistency and strength, and strength of the evidence. This is particularly evident when assessing and integrating the findings from epidemiological studies. The CHAP acknowledged the weakness of the epidemiological database in at least two instances, yet the CHAP concluded that based on the human data on gestational exposure and reduced AGD, exposure to DEP, DBP and DEHP metabolites should be reduced, ignoring the weaknesses they had previously identified;
- sensitivity, though mentioned, was seemingly not analyzed as a basis for weighting of various approaches and/or identification of critical data gaps; and
- WOE analysis including consideration of broader biological knowledge as a basis for more robust discussion of potential species differences for bounding of the PODs was not evident and WOE considerations across the available database (beyond those that are study specific) were also not specified.

Response 10.1: The CHAP used the WOE approach in two different manners. First, the CHAP wrote a "Weight of Evidence" section for each recommendation for each phthalate and phthalate alternative. In these sections, the WOE discussion was divided into experimental design issues (discussion of the relevant studies) and replication issues (whether a sufficient number of studies

have demonstrated the adverse effect) related to hazard studies. The section integrated the weight of hazard evidence to conclude whether the phthalate or phthalate alternative induced MRDE.

The CHAP also used WOE more broadly when developing overall recommendations for each phthalate or phthalate alternative. In particular, the CHAP considered factors such as those below in this WOE approach (CHAP report p. 79):

- For publications and studies reviewed:
  - Was the experimental design of the study appropriate for the purpose of the study?
  - Did the study have adequate power?
  - Were confounders adequately controlled?
  - Were findings replicated in other studies or other laboratories/populations?
- Related to phthalate hazards:
  - What is the nature of the adverse effects reported in animal and human studies of toxicity?
  - Did the findings include evidence of the phthalate syndrome or other evidence of reproductive or developmental toxicity?
  - What are the hazards identified in animal studies?
  - What are the dose-response data? What are the NOAELs?
  - What is the relevance to humans of findings in animal studies?
- Related to phthalate exposure:
  - What are the exposures of concern—sources and levels?
- Related to risk:
  - What is the relationship between levels of human exposure and POD (NOAEL)?
  - What are the results of the HI calculations?
  - What is the likely risk to humans?

Staff concludes that the CHAP used the WOE approach appropriately in both manners. Staff notes that the CHAP WOE approach used literature or data retrieved and reviewed by the CHAP and that this process was repeatable and transparent.

The CHAP stated, however, that "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" (CHAP report, p. 12). This does not mean that the CHAP review was unsystematic and biased. It means that the CHAP did not design a written approach beforehand and then follow that approach for grading and interpreting publications and results. Many fields of information (e.g. toxicology, epidemiology, exposure, risk assessment) would have required prohibitive amounts of resources for a systematic review. When the CHAP convened in 2010, federal agencies such as EPA and NTP had not yet adopted systematic review methods, and tools such as specialized software for characterizing publications were also not available. Furthermore, as noted above, systematic

review is only recently being adopted by federal agencies for use in assessing environmental health (EPA 2015a; NTP 2015).

The CHAP used standard and acceptable methods for study review, conducting an unbiased literature search and publication identification and in-depth review and reporting of the most important publications. Specifically, the CHAP included many elements of systematic review methods in its work. The CHAP used a defined literature search strategy and limited the search to studies published through 2012. The CHAP considered the quality, relevance, and WOE of individual studies. The CHAP described criteria for evaluating published studies (CHAP 2014, pp. 19–23) and ensured that all studies and data were publicly available. The CHAP also described the criteria used to formulate its recommendations on individual phthalates and phthalate alternatives (CHAP 2014, p. 79). The CHAP criteria included review of animal and human data, WOE, study replication, human exposure, hazard, and risk (CHAP 2014, pp. 82–142).

Staff concludes that the CHAP conducted a thorough review of a large body of literature on a complex environmental health question using appropriate methods. Although the CHAP, which began in 2010, did not have all of the systematic review methods that are available today, the CHAP incorporated many of the elements that are now included in systematic review methods in their work, as described above. Staff also notes that other federal agencies, including EPA and NIEHS, are still in the process of implementing systematic review methods.

Staff concludes that the CHAP report adequately described its methods and criteria. The CHAP's methods for evaluating evidence of toxicity from animal and epidemiological studies were generally consistent with the methods used by CPSC and other federal agencies (CPSC 1992; EPA 2012b; WHO 2000).

Comment 10.2: Data Concerns - CHAP failed to consider best available science and did not add safety factors. Commenters argued that the CHAP violated the directions provided by the CPSIA because the commenter interpreted the phrase:

> 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

as meaning that the CHAP should first describe the best available scientific evidence and then add safety factors to account for uncertainty in the data.

One of these commenters argues that the "best available science" includes an industry analysis of more recent NHANES data which purports to show that the cumulative Hazard Index is below one. Furthermore, the commenter asserts that "there is no uncertainty regarding the decreasing levels of DEHP exposure shown in the NHANES data, despite the CHAP's and staff's apparent efforts to create it."

Response 10.2: Staff disagrees with the commenter that the CHAP did not use the best available science. The CHAP based its calculations on the 2005/2006 dataset (these data were revised in 2012). The CHAP also reviewed the 2007/2008 NHANES summary data. In addition to the NHANES data, the CHAP also relied upon data from the Study for Future Families (SFF) for data on infants.

There have been 5 NHANES data sets between 2005 and 2014. As described on the CDC website,[40] the NHANES data sets are revised, on occasion, due to errors in chemical analyses or errors in the statistical weighting of the NHANES population. Below, we discuss these NHANES datasets.

NHANES 2005/2006 Dataset. The CHAP based its calculations of the hazard index for pregnant women on exposure data in the latest NHANES data that were available at the time of the CHAP's analyses, which is the 2005/2006 data, as revised in February 2012. As explained in the CHAP report (CHAP 2014, p 35):

> This cycle of NHANES was the most recent version in which phthalate data were available at the time of our analyses. Previous cycles were not combined with the 2005/2006 data due to study design changes associated with fasting requirements.

The 2005/2006 data were revised by NHANES in February 2012 (CDC 2012a, b). The CHAP revised its analyses to include the revised data (i.e., from the 2012 revision) before completing the draft CHAP report. The 2005/2006 NHANES data set included data on larger numbers of pregnant women than the subsequent NHANES data sets.

NHANES 2007/2008 Dataset. As reflected in multiple locations in the CHAP report, the CHAP also reviewed the 2007/2008 NHANES summary data. The CHAP considered and discussed 2007/2008 NHANES summary data for the general population when comparing to the 2005/2006 data set and in relation to concentrations of individual phthalates (CHAP 2014, pp. 39, 42, 74, 75, 87, 98, 111). The 2007/2008 NHANES data first became available in October 2010, but were revised in September 2011 and January 2012.

NHANES 2009/2010 Dataset. NHANES data for 2009/2010 became available in September 2012. These data became available after the analysis was completed. Thus, the CHAP did not review the 2009/2010 dataset.

NHANES 2011/2012 Dataset. The 2011/2012 NHANES data were available in July 2014, then withdrawn August 2014. The revised 2011/2012 NHANES data were available in October 2014.

NHANES 2013/2014 Dataset. The 2013/2014 NHANES data were available in late December 2016.

SFF Data. NHANES does not include data on children younger than age 6 years old. Therefore, the CHAP used additional data from the Study for Future Families (SFF) to obtain data on infants. This study covers the time period 1999−2005. The SFF is a study of infant-mother pairs. Mothers were tested both during and after pregnancy. To staff's knowledge, there is no plan to update this study. Even if the hazard index for pregnant women was recalculated based on new NHANES exposure data, the risk estimates for infants and their mothers would remain the same because the SFF data is separate from the NHANES data. Using the SFF data, the CHAP estimated that up to five percent of pregnant women and infants had a hazard index greater than one.

Staff does not agree that the CHAP did not adequately describe or conduct its analysis. In fact, the CHAP presented in detail both the relevant toxicological literature used in the analysis and the basis for the application of safety factors (also called uncertainty factors). The commenter

[40] National Health and Nutrition Examination Survey. Available at: https://www.cdc.gov/nchs/nhanes/.

may have misunderstood the use of 'uncertainty' in the context of the CHAP report. An uncertainty factor (UF) is a number that is used to account for uncertainties in applying available data. Because humans and animals (used in studies) may have differing sensitivities to the exposure of a chemical, a UF is applied to account for the uncertainty in relative sensitivity (an interspecies UF). Among humans, different factors (e.g., age, sex, health status, genetics) may vary individual sensitivity to chemical exposure (intraspecies UF). Additional UFs may be applied to account for limitations in the available data. The CHAP generally applied interspecies and intraspecies UFs, and applied additional factors in specific cases for other data limitations. UFs are used to derive acceptable dose or exposure levels, such as an acceptable daily intake or potency estimate for antiandrogenicity, not to dispute whether DEHP exposure has decreased since the 2005/2006 NHANES study. UFs are discussed in more detail in Section 4.

Regarding the commenter's description of "best available science," staff's analyses included a consideration of all submitted comments, including the industry analysis of the newer NHANES data. See Section 3 for staff's response to comments relating to HBM and the analysis of newer NHANES data sets.

Comment 10.3: Access to all of the data that the CHAP and CPSC staff used. One NGO commenter suggested that the CPSC should ensure that an open and transparent process is accessible for review and comment of all the data the panel of scientists and the CPSC staff used.

A number of commenters raised concerns regarding transparency in the CHAP and CPSC process. Many of these comments were general in nature, requesting that CPSC and the CHAP be more transparent in their consideration of certain types of information. Others asserted that the CHAP process was secret and performed behind closed doors. Other commenters questioned the transparency of particular aspects of the CHAP report such as the methods used to review the scientific health evidence and assess cumulative risk. Still others commented that the technical studies and data that CPSC used to make decisions should be made public to promote transparency.

In contrast, other commenters commended the transparency of the CHAP process, CHAP meetings, CHAP Report peer review and evaluation, and the CPSC staff biomonitoring analysis (2015).

Response 10.3: CPSC staff disagrees with commenters' characterization of the CHAP process or the CPSC rulemaking process as secret or lacking transparency. The CHAP's approach to responding to their charge was discussed in public during the seven public meetings and six public teleconference calls. During these public meetings, the CHAP discussed the methods the CHAP would use to conduct the cumulative risk assessment. The CHAP's methods for estimating cumulative risk were also described in detail in the CHAP report (p. 61–65; Appendix D). Alternatives to their approach were also described (CHAP report p. 62). Furthermore, the datasets and other scientific reports used by the CHAP to conduct the assessment were documented (cited) in the CHAP report. All of the data submitted to the CHAP, CPSC contractor reports, and peer-reviewed staff reports used by the CHAP were posted on the CPSC public website.[41] The CHAP elected not to use industry studies on DINX and DPHP because the

[41] Chronic Hazard Advisory Panel (CHAP) on Phthalates. Available at: https://www.cpsc.gov/chap.

manufacturer would not make the toxicology studies available to the public.[42,43] All subject matter expert comments from the peer review of the CHAP draft report[44] were considered by the CHAP. Changes to the CHAP report resulting from these comments were outlined in the CHAP report (p. 1–3). NHANES data are available from the Centers for Disease Control and Prevention.[45]

Staff concludes that because all of the information that the CHAP used for its report is publicly available, the process was open and transparent.

Comment 10.4: Consider prohibitions involving other phthalates. Some commenters asserted that "The CHAP's lack of recommendations for additional regulatory action on phthalates like DIOP, DMP, DEP, DPHP or many of the alternatives evaluated is not an endorsement of their safety" because of the lack of sufficient hazard and exposure data on these chemicals. The commenters addressed phthalates that are not currently involved in prohibitions in children's toys and child care articles and that were not recommended for specific regulatory action by the CHAP and CPSC, including DMP, DEP, and DPHP. The commenters suggest that the CPSC continue to review and monitor DMP and DPHP, and urge other relevant federal agencies to do the same. Commenters noted that the CHAP identified an incomplete dataset for DMP, and that evidence exists for liver toxicity and other systemic effects of DMP. Commenters also noted that DPHP production has increased in recent years, which suggests that human exposures are also likely to continue to increase as DPHP replaces other phthalates as a plasticizer.

Commenters urged CPSC to recommend that the appropriate agencies take action to reduce exposure to DEP due to evidence in humans of reproductive and developmental toxicity including antiandrogenic effects, and evidence of human exposure.

Response 10.4: CPSC staff participates in several interagency collaborations to discuss issues of mutual interest, including phthalates. Staff agrees that follow-up activities are needed to obtain additional toxicology and exposure data on certain phthalates and phthalate alternatives. Staff has proposed a future CPSC project to obtain additional toxicity and exposure data on selected phthalates and phthalate alternatives, which would address the "lack of sufficient hazard and exposure data" mentioned by the commenters. This project is on hold pending the availability of funding.

Staff notes that the CHAP concluded that there is no evidence showing that DMP and DPHP cause MRDE, although DMP may cause other adverse health effects. More complete data for DEP suggest potential reproductive or non-reproductive developmental effects in humans, although such effects have not been confirmed in experimental animal studies.

Data on exposure are also limited for DMP and DPHP, especially for children's toys and child acre articles. As the CHAP noted, exposure to DEP, largely from sources other than children's toys and child care articles, has been better characterized.

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[42] Log of Meeting. Chronic Hazard Advisory Panel (CHAP) on Phthalates and Phthalate Substitutes. July 26–28, 2010. Available at: https://www.cpsc.gov/PageFiles/126329/chap072010.pdf.

[43] Comments on Hexamoll® DINCH and DPHP. Dr. Rainer Otter, BASF. Presented to the CHAP, July 26, 2010. Presented to the CHAP, July 26, 2010. Available at: http://www.cpsc.gov/PageFiles/126341/otter.pdf.

[44] Peer Review of the CHAP Draft Report on Phthalates and Phthalate Substances. Available at: http://www.cpsc.gov/PageFiles/169893/Peer-Review-Report-Comments.pdf.

[45] National Health and Nutrition Examination Survey. Available at: https://www.cdc.gov/nchs/nhanes/.

Thus, staff agrees with the CHAP that health effects and exposure data on these phthalates are inadequate to support regulatory action by CPSC.

Comment 10.5: Risks from phthalate alternatives. Numerous commenters expressed concern that if prohibitions involve specific phthalates (that have lots of toxicology and exposure data), then manufacturers will be forced to use alternative plasticizer chemicals for which the safety or toxicity are not known, thus potentially putting people at greater risk.

Some commenters expressed concern that less is known about the health effects of the alternatives than the effects of the phthalates included in the prohibitions. Three commenters recommended that before making the proposed prohibition effective, the safety of the replacement/alternative plasticizers should be thoroughly tested. The commenters suggested that the alternative plasticizers may not be as safe as DINP.

One industry commenter stated that the direction in the CPSIA to the CHAP was to consider all phthalates and phthalate alternatives, and to make recommendations regarding both phthalates and phthalate alternatives. The commenter stated that limited data exists on the phthalate alternatives. The commenter asserted that DINP should not be permanently banned because the CHAP Report and the proposed rule did not consider the relative risks of phthalate alternatives, whose risks are less studied, for DINP, which the commenter claims is well-studied and has negligible risks.

Another commenter noted that the CHAP report and staff report (2017) failed to assess the risk to DINX, a phthalate alternative, because of the lack of MRDE toxicity data and that its large presence in toys and childcare articles (33 percent of the samples) meant that its exposure and risk was underestimated.

Response 10.5: Staff disagrees with the commenter's assertion that the CHAP and staff did not consider the potential health risks from phthalate alternatives. The CHAP (CHAP 2014) considered phthalate alternatives on pages 22–23; page 51; pages 121–142; Table 2.1; Table 2.12; Appendix A, pages A-39—A-45; Appendix B, pages B-18—B-22; and all of Appendix E-2. In all, the CHAP devoted 54 pages of their report to evaluating the risks from phthalate alternatives. Staff's briefing package for the NPR (CPSC 2014b) discussed phthalate alternatives throughout, including on pages 1, 18, 23–24, 26–27, and 39; and Table 2.

The CPSC staff shares the commenters' concerns about the shift of chemical use from phthalates with known toxicity to phthalate alternatives with less toxicity for exposure information. The CHAP identified several data gaps for phthalate alternatives (CHAP 2014, pp. 121-142). For some alternatives, data on either toxicity or exposure were limited. For DINX, toxicity data exist, but they were not available to the CHAP.[46] In the absence of toxicity data on DINX, its risk cannot be estimated. Thus, there is no basis for regulatory action on DINX at this time.

Staff agrees with the CHAP's recommendation that appropriate federal agencies should perform additional research and risk assessment activities on phthalates and phthalate alternatives to fill in data gaps. Staff has proposed a project to undertake additional work on phthalate alternatives and emerging phthalates to address data gaps and conduct additional risk assessments, as recommended by the CHAP, pending Commission approval. Staff plans to work with other federal agencies, including the National Toxicology Program (NTP) and EPA to obtain

[46] Presentation of Dr. Rainer Otter, BASF, to the CHAP. July 2010.

additional data on phthalate alternatives. As noted previously, funds are not yet available for this effort, but have been requested. Additionally, CPSC does not have the authority to require manufacturers to perform toxicity or exposure tests, or to provide existing data. Rather, manufacturers are responsible for ensuring that their children's products do not present a hazard under the Federal Hazardous Substances Act, and should choose alternative plasticizers with this requirement in mind. Staff notes that manufacturers are not limited to using phthalate alternatives. They have the option of using plastics such as polypropylene and polyethylene that do not require plasticizers to make them flexible.

Some commenters proposed that permanent prohibitions should not include DINP until phthalate alternatives are thoroughly studied. Staff notes that DINP has already been covered by the interim prohibition for the past 8 years, since February 2009. In 2014, the Commission proposed a permanent prohibition involving DINP due to the risk of adverse effects on male reproductive development (MRDE), as assessed by the CHAP. The Commission's proposal to permanently prohibit children's toys and child care articles containing more than 0.1 percent of DINP was made based on the known health risks of DINP, not on the potential risks from phthalate alternatives.

To summarize, the CHAP reviewed all the available information on six phthalate alternatives. The CHAP did not recommend prohibiting the use of any children's toys or child care articles containing phthalate alternatives because the CHAP identified a number of data gaps. Thus, the CHAP recommended that the appropriate federal agencies perform additional research and risk assessment activities on phthalate alternatives to fill in the data gaps. Staff plans to work with other federal agencies to pursue the CHAP's recommendation for additional work. Finally, staff notes that manufacturers have the option of using plastics that do not require plasticizers to make them flexible. Manufacturers are responsible for ensuring that their children's products do not present a hazard under the Federal Hazardous Substances Act, and should choose alternative plasticizers with this requirement in mind.

Comment 10.6: Interagency coordination with EPA TSCA phthalate reviews. One commenter requested that CPSC join EPA in reviewing and regulating phthalates under TSCA (Frank R Lautenberg Chemical Safety for the 21st Century Act) because EPA can regulate chemicals in consumer products ("articles"). The commenter was concerned that the CPSC final rule might not reflect the same consensus achieved by EPA under TSCA. The commenter acknowledges the congressional mandate to promulgate a rule based on the CHAP findings within a short time frame, but urges CPSC to be an integral part of the EPA chemical review process, so that the final rule reflect the scientific data.

Response 10.6: As acknowledged by the commenter, CPSC has been mandated by the CPSIA to promulgate a phthalates final rule that has considered the CHAP report and any additional information. CPSC staff participates in several interagency collaborations to discuss issues of mutual interest, including phthalates and TSCA. The CHAP included multiple speakers from EPA presenting on various aspects of toxicity, exposure, and risk during the CHAP process. CPSC staff has also attended EPA presentations and workgroup meetings regarding phthalates that induce MRDE. Staff also notes several differences between the CPSIA and TSCA statutory mandates, including chemicals of interest and product scope.

Overall, staff has coordinated with EPA about phthalates and will continue to do so, but notes that CPSC has been specifically mandated by Congress to address the risk of phthalates in products under CPSC's jurisdiction.

Comment 10.7: Delay of phthalate rule publication. A commenter asserted that industry was delaying the CPSC promulgation of the phthalates rule.

Response 10.7: Staff notes that information and public comments involved in the phthalate regulation are extremely complex and that a considerable amount of time has been required to summarize and respond to that information.

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TAB C: Draft Final Rule Prohibiting Children's Toys and Child Care Articles Containing Specified Phthalates; Impact on Small Business

TAB C

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MD 20814

Memorandum

Date: May 12, 2017

TO : Kent R. Carlson, Ph.D.,
Project Manager, Phthalates Team
Directorate for Health Sciences

THROUGH: Gregory B. Rodgers, Ph.D.
Associate Executive Director
Directorate for Economic Analysis

FROM : Robert Franklin
Senior Staff Coordinator
Directorate for Economic Analysis

SUBJECT : Draft Final Rule Prohibiting Children's Toys and Child Care Articles Containing Specified Phthalates; Impact on Small Business

The draft final rule prohibiting children's toys and child care articles containing specified phthalates is unchanged from the proposed rule, which was published in the *Federal Register* on December 30, 2014. The draft final rule would make the interim prohibition[1] involving diisononyl phthalate (DINP) permanent. Although the interim prohibitions only applied to children's toys and child care articles that could be placed in a child's mouth, the draft final rule, like the proposed rule, would prohibit all children's toys containing more than 0.1 percent of this phthalate. It would also prohibit children's toys and child care articles containing more than 0.1 percent of diisobutyl phthalate (DIBP), di-n-pentyl phthalate (DPENP), di-n-hexyl phthalate (DHEXP), and dicyclohexyl phthalate (DCHP). Like the proposed rule, the draft final rule would lift the interim prohibitions on children's toys that can be placed in a child's mouth and child care articles containing di-n-octyl phthalate (DNOP) and diisodecyl phthalate (DIDP).

The Commission certified that the proposed rule would not have a significant impact on a substantial number of small entities. Because the provisions of the draft final rule are the same as those of the proposed rule, the same analysis on which the Commission based its certification of the proposed rule is applicable to the draft final rule. The Commission's certification of the proposed rule was based on the following rationale:

[1] For this rulemaking, "prohibition" means prohibiting children's toys or child care articles with specified phthalate concentrations above 0.1 percent in any accessible component part of the children's toy or child care article.

Effect on manufacturers:

1. Children's toys that can be placed in a child's mouth and child care articles containing more than 0.1 percent of DINP have been prohibited since 2009. Thus, no manufacturer would have to reformulate any products in these categories.
2. Only children's toys that cannot be placed in a child's mouth (no dimension of the toy is less than 5 cm.) containing more than 0.1 percent of DINP would have to be reformulated. Thus, only a small subset of children's toys that cannot be placed in a child's mouth would be affected by the draft final rule.
3. The CHAP found that DIBP, DPENP, DHEXP, and DCHP are not widely used in children's toys and child care articles. Therefore, relatively few manufacturers would have to reformulate products to eliminate these phthalates due to the draft final rule.

Third party certification costs:

The draft final rule would have a small marginal impact on the cost of third party testing for the following reasons:

1. All children's toys and childcare articles are already subject to third party testing for di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and benzyl butyl phthalate (BBP).
2. Currently, children's toys that can be placed in a child's mouth and child care articles must also be tested for the presence of DINP.
3. Laboratory equipment and methods are already in place for testing the prohibited phthalates, therefore the additional cost of testing for DIBP, DPENP, DHEXP, and DCHP would be very low;
4. Identification and quantification protocols for prohibited phthalates would need minimal modification to include DIBP, DPENP, DHEXP, and DCHP because each of these phthalates can be isolated at unique elution times by gas chromatography. It should not be difficult, therefore, for qualified conformity assessment bodies to identify and quantify these phthalates. Thus, the additional cost of analysis of DIBP, DPENP, DHEXP, and DCHP would be very low; and
5. The additional cost of laboratory materials would be very low. Chemical standards for testing would be required for DIBP, DPENP, DHEXP, and DCHP. Conversely, the standards for DNOP and DIDP would no longer be required. Therefore, the number of chemical standards needed would increase by two. The need for the two additional standards is expected to increase the cost of third party testing for phthalates by less than 35 cents per test. This added cost is relatively small compared to current cost of phthalate testing, which is approximately $300 per product or component part.

Since the NPR was published, CPSC staff has not discovered new information that would cause a revision to the above analysis. Several public comments addressed the potential impacts of the proposed rule on firms, but none provided qualitative or quantitative evidence that the proposed rule would have a significant impact on a substantial number of small entities. These comments are summarized below and addressed in more detail in TAB B of the draft final rule Briefing Package.

Overall testing costs:

A few commenters raised the issue of testing costs, but provided no information that the cost per test of the proposed rule would be significantly greater than the current cost of testing. The commenters were unclear whether they were addressing the cost of statutorily required phthalates testing, or the marginal increase in the testing costs associated with the proposed rule.

Analytical issue:

A few commenters expressed the concern that the need to distinguish whether DINP was present because a DINP commercial product was used or because DINP was simply present in a DIDP commercial mixture could increase the testing costs. The commenters stated that this was not an issue now because both DINP and DIDP were prohibited. However, the proposed rule prohibits children's toys and child care articles containing more than 0.1 percent of DINP regardless of the source of the DINP. Therefore, if a laboratory detects DINP in concentrations exceeding 0.1 percent, the product would not be in compliance irrespective of the source of DINP. This is also the procedure for addressing the current prohibition involving DINP; therefore, there would be no increase in testing costs. See comment response 9.1 in TAB B for more information.

Staff notes that if DINP is present in some DIDP commercial mixtures, manufacturers may not be able to use certain DIDP commercial mixtures in children's toys and child care articles even though the prohibition on children's toys that can be placed in a child's mouth and child care articles containing DIDP itself has been lifted.

Numbers of products requiring testing:

Some commenters objected to the proposed change in the scope of the prohibition involving DINP from children's toys that can be placed in the child's mouth to all children's toys, but no commenters provided evidence that expanding the scope of the prohibition would result in substantially higher testing costs. Staff notes that testing is already required for all children's toys containing DEHP, BBP, and DBP, and the number of products requiring testing would be unchanged. Furthermore, as discussed above, the incremental increase in testing costs is expected to be small. Therefore, CPSC staff has no basis for changing its conclusion that the expansion of the scope of the prohibition involving DINP would impact few companies.

Conclusion:

In conclusion, the impact of the draft final rule is limited. The draft final rule, like the proposed rule, would maintain a prohibition on children's toys that can be placed in the child's mouth and child care articles containing more than 0.1 percent of DINP, expand the prohibition to all children's toys containing more than 0.1 percent of DINP, and prohibit children's toys and child care articles containing more than 0.1 percent of DIBP, DPENP, DHEXP, and DCHP. Few manufacturers will need to reformulate their products to comply with the draft final rule. The impact on the cost of third party testing for phthalates also would be minimal. CPSC staff concludes that no information was received in response to the proposed rule, nor has CPSC staff developed any other information that changes the staff's analysis on which the Commission's certification of the proposed rule is based. Based on the same analysis, the Commission could certify that the draft final rule would not have a significant impact on a substantial number of small entities.