NATURAL RESOURCES DEFENSE COUNCIL, CENTER FOR SCIENCE IN THE PUBLIC INTEREST, CENTER FOR ENVIRONMENTAL HEALTH, CENTER FOR FOOD SAFETY, CLEAN WATER ACTION, CONSUMER FEDERATION OF AMERICA, EARTHJUSTICE, ENVIRONMENTAL DEFENSE FUND, IMPROVING KIDS' ENVIRONMENT, LEARNING DISABILITIES ASSOCIATION OF AMERICA

March 18, 2016

Dr. Dennis Keefe
Director of the Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740

Re: Food additive petition regarding 30 ortho-phthalates submitted to FDA pursuant to 21 USC § 348.

Dear Dr. Keefe:

We submit this food additive petition to the Food and Drug Administration (FDA) requesting the agency:

1. Strike from its existing regulations its approvals of 30 ortho-phthalates as food additives in food contact articles; and
2. Prohibit the use of eight ortho-phthalates as food contact substances that the Consumer Products Safety Commission's (CPSC) Chronic Health Advisory Panel on Phthalates (CHAP) concluded are unsafe or the evidence indicates developmental health effects are likely. These phthalates are:
    a. Diisobutyl phthalate;
    b. Di-n-butyl phthalate;
    c. Butyl benzyl phthalate;
    d. Dicyclohexyl phthalate;
    e. Di-n-hexyl phthalate;
    f. Diisooctyl phthalate;
    g. Di(2-ethylhexyl) phthalate (DEHP);[1] and
    h. Diisononyl phthalate.

To determine whether a food additive is safe, Congress directed FDA to consider, among other requirements, "the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically-related substance or substances in such diet [.]" (21 U.S.C §348 (c)(5)(B)). In its recent decision regarding long-chain perfluorinated compounds

[1] Except for DEHP, the most common and most studied ortho-phthalate, we do not use acronyms for the various types to avoid confusion since many names are similar.

(PFCs),[2] the agency provided a roadmap to conduct such an assessment. We applied FDA's approach to the 30 ortho-phthalates approved by the agency as food additives, supplemented it with FDA's tolerance-setting requirements at 21 CFR 171.18, and concluded that:

1. **Ortho-phthalates are a class of chemically- and pharmacologically-related substances for purposes of determining safety pursuant to 21 U.S.C. 348 and 21 CFR Part 171.**
   A. Defining a class of chemically-related or pharmacologically-related substances is an essential first step to evaluating chemicals safety.
   B. Ortho-phthalates have a common functional group (i.e., diester of 1,2-dicarboxy-benzene).
   C. Ortho-phthalates share similar metabolic pathways.
   D. Eleven ortho-phthalates have reproductive, developmental and endocrine health effects. The remaining substances have either not been studied or the available data are inconclusive for these health effects.
   E. In the absence of adequate studies, all ortho-phthalates must be assumed to have reproductive, developmental and endocrine toxicity.
   F. Consistent with FDA's decision on PFCs and current regulations and statutes, ortho-phthalates must be considered a class of chemically- and pharmacologically-related substances.

2. **The Acceptable Daily Intake (ADI) for DEHP should be assigned to all ortho-phthalates.**
   A. The Acceptable Daily Intake (ADI) for ortho-phthalates should be determined consistent with 21 CFR 171.18.
   B. The cumulative effect of ortho-phthalates in the diet should be considered additive pursuant to 21 CFR 171.18.
   C. For reproductive, developmental, and endocrine health effects, DEHP is the most studied ortho-phthalate and has the lowest numerical Acceptable Daily Intake (ADI) based on male reproductive health effects.
   D. The most appropriate approach to developing an ADI for ortho-phthalates is to assign the ADI for DEHP to the class of ortho-phthalates identified here.

3. **The Estimated Daily Intake (EDI) for ortho-phthalates significantly exceeds the ADI and, therefore, the intentional use of ortho-phthalates as food contact substances are not safe as defined by FDA's regulations.**
   A. As a result of the extensive use of ortho-phthalates in raw material packaging, intermediate packaging, and food handling equipment, the estimated exposure from the use of an ortho-phthalate cannot be based on migration only from final packaging.
   B. Estimated exposure must also consider the possibility of other uses of ortho-phthalates determined to be Generally Recognized as Safe (GRAS) by industry without notice to FDA.
   C. Estimated exposure to ortho-phthalates must include all sources of exposure in the diet including drinking water, dietary supplements, contamination of the food supply, and, if any, natural sources.

[2] Indirect Food Additives, Paper and Paperboard Components, 81 *Fed. Reg.* 5 (Jan. 4, 2016) and regulatory docket at FDA-2015-F-0714.

D. For women and children, the cumulative exposure from current uses of ortho-phthalates in the existing diet exceeds the ADI.

For all these reasons, we conclude that there is no longer a reasonable certainty of no harm for the food contact use of these 30 ortho-phthalates. We explain our analysis in greater detail below.

Part I: Petitioners' Justification for its Conclusion

Section I-1: Ortho-phthalates are a class of chemically- and pharmacologically-related substances for purposes of determining safety under 21 U.S.C. 348 and 21 CFR Part 171.

In determining the safety of a food additive, 21 U.S.C. 348(c)(5)(B) directs FDA to consider, among other relevant factors, "the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet." Defining chemically-related or pharmacologically-related substances is an essential first step to evaluating safety.

Consistent with FDA's approach in its evaluation and approval of Food Additive Petition No. 4B4809 to remove the agency's approval of three perfluoroalkyl ethyl containing substances (PFCs),[3] we used the Organization for Economic Co-operation and Development (OECD) Guidance on Grouping of Chemicals[4] to identify whether the 30 ortho-phthalates included in this petition should be grouped together and considered as a class.

OECD list five rationales underpinning the class approach:
1. Common functional group(s) (e.g., aldehyde, epoxy, ester, specific metal ion);
2. A common mode or mechanism of action or adverse outcome pathway;
3. Common constituents or chemical classes, similar carbon range numbers. This is frequently the case with complex substances often known as "substances of unknown or variable composition, complex reaction products or biological material" (UVCB substances);
4. The likelihood of common precursors and/or breakdown products via physical or biological processes that result in structurally similar chemicals (e.g., the "metabolic pathway approach" of examining related chemicals such as acid/ester/salt); or
5. An incremental and constant change across the category (e.g., a chain-length category), often observed in physical chemical properties (e.g., boiling point range).

Chemicals that meet one or more of these rationale could be grouped within a class. Our analysis of the 30 ortho-phthalates included in this petition indicate that they meet two of the OECD rationales:

[3] Federal Register Notice Vol. 81, No. 1. January 4, 2016. Rules and Regulations. Page 5-8. To amend 21 CFR 176.170

[4] Guidance on Grouping of chemicals, second edition. Organization for Economic Co-operation and Development. April 14, 2014

1. **Common functional group(s)** (e.g., aldehyde, epoxy, ester, specific metal ion): The ortho-phthalates are diesters of 1,2-dicarboxy-benzene with two alkyl groups with a carbon chain of at least one carbon. (See Figure 1.)
2. **The likelihood of common precursors and/or breakdown products** via physical or biological processes that result in structurally similar chemicals (e.g., the "**metabolic pathway approach**" of examining related chemicals such as acid/ester/salt): As long ago as 1973, FDA scientists Shibko and Blumenthal[5] acknowledged that metabolism of these ortho-phthalates would give rise to similar breakdown products; in that case, the authors concluded they would be "phthalic acid and alcohols." Contemporary data from published studies demonstrate that ortho-phthalates share metabolic pathways but the products are different than those identified by Shibko and Blumenthal. The current knowledge of ortho-phthalates metabolism can be summarized as occurring in three steps:
   - Step 1: Diesters are cleaved into monoesters;
   - Step 2: Phase I oxidation of the alkyl side-chain of the monoester and modification with functional groups (e.g. hydroxyl, keto or carboxy group) or shortened by beta oxidation; and
   - Step 3: Hydrolytic monoesters and oxidized secondary metabolites can be conjugated with glucuronic acid. Steps two and three are common in ortho-phthalates with longer alkyl side-chain.[6,7]

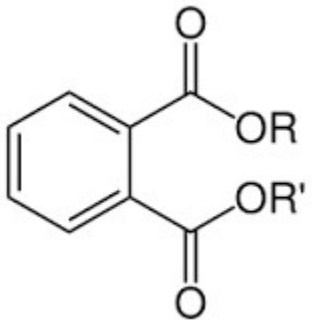

Figure 1: Ortho-phthalate functional group: diesters of 1,2-dicarboxy-benzene with two alkyl groups (R and R') with carbon chain of at least one carbon

Based on this evidence, we conclude that the 30 ortho-phthalates are a class of chemically-related substances. Our conclusion is in agreement with FDA's determination of PFCs as a class[8] stating:

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[5] Shibko and Blumenthal, Toxicology of Phthalic Acid Esters Used in Food Packaging Material, *Environmental Health Perspectives,* January 1973. Note: there is no disclaimer indicating that their views were not representative of the agency.

[6] Substance monograph: Phthalates—New and updated refrence values for monoesters and oxidized metabolites in urine for adults and children. Opinion of the Human Biomonitoring Commission of the German Federal Environment Agency. 2011. Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz 2011, 54 (6): 770-785

[7] Wittassek M, Koch HM, Angerer J, Bruning T. Assessing exposure to phthalates—The human biomonitoring approach. 2011. Mol. Nutr. Food Re. 55:71-31

[8] 81 FR 5. "Indirect Food Additives: Paper and Paperboard Components." Food and Drug Administration. Jan. 4, 2016 (*Amending* 21 CFR 176.170).

> Based on these two criteria, grouping the FCSs [food contact substances] herein, long-chain FTOHs [fluorotelomer alcohol], and long-chain PFCAs [perfluorocarboxylic acids] into a single chemical class can be justified based on: 1) the existence of at least one linear, perfluorinated carbon chain of ≥C8 in each of the compounds; and 2) data from published studies demonstrating metabolic conversion of FTOHs and PFCs similar in structure to the FCSs herein (perfluoroalkyl phosphate surfactants (PAPs)) to PFCAs in vitro and in animals.[9]

To our knowledge, FDA has not defined the term "pharmacologically-related" even though the term is explicit both in 21 U.S.C. 348 and 21 CFR Part 171. The Tolerances for Related Food Additives regulations at 21 CFR 170.18(a)[10] states that "[f]ood additives that cause **similar or related pharmacological effects will be regarded as a class**, and in the absence of evidence to the contrary, as having **additive toxic effects** and will be considered as related food additives."[11] [Emphasis added]

In its recent ruling on removing the agency's approvals of three PFCs,[12] FDA stated that, for the defined class, "**data for subsets of long-chain PFCs (demonstrating biopersistence and reproductive and developmental toxicity) are applicable to long-chain PFCs on a general basis** and that this data raises significant questions as to the safety of the authorized uses of the three FCSs subject to the petition (Ref. 4). We also concluded that there is a lack of data specific to the three subject FCSs subject to the petition to address these questions (Ref. 4)."[13] [Emphasis added] This statement by FDA indicates that all the chemically-related members of the class, even if safety data specific to some members of the class are lacking, are assumed to have similar toxicity effects—in other words, are pharmacologically-related.

As described above, the evidence of shared metabolic pathways for ortho-phthalates indicate that their toxicokinetic (i.e., how a substance gets into the body and what happens to it in the body) and toxicodynamic (i.e., chemicals' interactions with a biological target—e.g., receptors, proteins, DNA—and their biological effects) properties may be comparable, thus making the chemicals potentially available to reach most organs and systems when they reach the general circulation. When ortho-phthalates have been studied, similar or related pharmacological effects have been identified affecting children's health.[14] Reproductive, developmental and endocrine toxicity effects were among the health endpoints identified for multiple compounds and at low exposure. Furthermore, adverse effects on endpoints relevant to children's health have been

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[9] Memo from Toxicology Group 1, Division of Food Contact Notifications (DFCN) Penelope A. Rice, Ph.D., D.A.B.T. (HFS-275) to Regulatory Group 2 (DFNC) Paul Honigfort (HFS-275). July 27, 2015

[10] It was promulgated as 21 CFR 121.4 but re-designated to Section 170.18 in 1977.

[11] 21 CFR 170.18(a).

[12] 81 FR 5. "Indirect Food Additives: Paper and Paperboard Components." Food and Drug Administration. Jan. 4, 2016 (*Amending* 21 CFR 176.170).

[13] Id at page 7.

[14] CPSC, Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives Final Report (With Appendices), 2014 at http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf. See http://www.cpsc.gov/en/regulations-laws--standards/statutes/the-consumer-product-safety-improvement-act/phthalates/chronic-hazard-advisory-panel-chap-on-phthalates/ for details on the deliberative process the CHAP used to reach its conclusion.

shown for 13 ortho-phthalates. Table 1 lists the ortho-phthalates with health effects data. (See more detail analysis in Appendix III). And there appears to be no relationship between alkyl chain length and adverse effects, at least for those ortho-phthalates with available toxicity data. Therefore, based on similar toxicity effects, these 13 ortho-phthalates are pharmacologically-related food additives for purposes of 21 CFR 171.18.

The same regulation states that "in the absence of evidence to the contrary," toxic effects caused by pharmacologically-related chemicals should be considered "additive." Despite the sparsity of data regarding mixtures of ortho-phthalates, we found several publications reporting on additive effects of mixtures of four and five ortho-phthalates on developmental and reproductive endpoints.[15,16,17] The National Academy of Sciences report on phthalates also recommends that effects of ortho-phthalates should be considered additive.[18] Additional research shows that some phthalates could have additive effect with cholesterol-lowering medication on fetal testicular development[19] as well as synergistic effect in a mixture with other anti-androgen chemicals (e.g., fungicides that are present in food).[20] We have not been able to find evidence of ortho-phthalates not having additive effect on developmental or reproductive endpoints likely due to the limited publications that are mostly focused on male testicular development.

Additionally, 17 of the 30 (57%) ortho-phthalates do not appear to have been studied for reproductive, developmental or endocrine toxicity. This data gap is similar to that which existed in 1973, when FDA's scientists described the then-available data on the safety of the 24 ortho-phthalates allowed as food additives – then, a mere 8 of 24 (33%) had chronic studies.[21]

Based on FDA's decision related to PFCs in which the agency reasoned that in the presence of data gaps, the information that is available for one or more members of a chemical class applies to the class, and consistent with the OECD's guidelines that members of a chemical class are often related by effects on a given endpoint, we conclude that the 30 chemically-related ortho-phthalates included in this petition are also pharmacologically-related substances under 21 CFR 170.18.

The structural and pharmacological similarities among these chemicals make it imperative to remove the approval of all ortho-phthalates in the class to effectively reduce health risks.

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[15] Hannas BR et al. Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate and diisononyl phthalate. Toxicological Sciences 123:206-216

[16] Howdeshell KL et al. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-dawley rat in a cumulative, dose-additive manner. Toxicological Sciences 105:153-165. 2008

[17] Howdeshell KL et al. Dose addition models based on biologically relevant reductions in fetal testosterone accurately predict postnatal reproductive tract alterations by a phthalate mixture in rats. Toxicological Sciences 148:488-502. 2015

[18] Phthalates and cumulative risk assessment: The task ahead. Committee on the health risks of phthalates, National Research Council, National Academy of Sciences. 2008

[19] Beverly BEJ et al. Simvastatin and dipentyl phthalate lower ex vivo testicular testosterone production and exhibit additive effects on testicular testosterone and gene expression via distinct mechanistic pathways in the fetal rat. Toxicological Sciences 141:524-537. 2014

[20] Christiansen S et al. Synergistic disruption of external male sex organ development by a mixture of four antiandrogens. Environmental Health Perspectives 114:1839-1846. 2009

[21] Shibko and Blumenthal, 1973, page 134.

Removing the approval for one ortho-phthalate may result in its replacement with another one that is less studied and that may pose similar or greater risk. In the absence of adequate studies to the contrary, all ortho-phthalates must be assumed to have reproductive, developmental and endocrine health effects.

Table 1 List of ortho-phthalates with studies showing children's health effects (sorted by increasing length of longest chain)

FDA Name (CAS No.)	FDA approved food additives	FDA found chronic studies in 1973*	Literature search found evidence of children's health effects**
Dimethyl phthalate (131-11-3)	Pre-1973	Rat	Yes***
Diphenyl phthalate (84-62-8)	Pre-1973		No studies found
Methyl phthalyl ethyl glycolate (85-71-2)	Pre-1973	Rat	No studies found
Diethyl phthalate (84-66-2)	Pre-1973	Rat & dog	Yes
Diphenylguanidine phthalate (17573-13-6)	Between 1973 and 1985		No studies found
Ethyl phthalyl ethyl glycolate (84-72-0)	Pre-1973	Rat & dog	No studies found
Diallyl phthalate (131-17-9)	Between 1973 and 1985		Yes
Butyl benzyl phthalate (85-68-7)	Pre-1973		Yes
Diisobutyl phthalate (84-69-5)	Pre-1973		Yes
Di-n-butyl phthalate (84-74-2)	Pre-1973	Rat & dog	Yes
Butyl phthalyl butyl glycolate (85-70-1)	Pre-1973	Rat & dog	No studies found
Dicyclohexyl phthalate (84-61-7)	Pre-1973	Rat & dog	Yes
Di-n-hexyl phthalate (84-75-3)	Pre-1973		Yes
Di(butoxyethyl) phthalate (117-83-9)	Pre-1973		No studies found
Dimethylcyclohexyl phthalate (1322-94-7)	Pre-1973		No studies found
Diisooctyl phthalate (27554-26-3)	Pre-1973		Yes
Di(2-ethylhexyl) phthalate (117-81-7)	Pre-1973	Rat & dog	Yes
Di-n-octyl phthalate (117-84-0)	Pre-1973		Yes
n-butyl n-octyl phthalate (84-78-6)	Pre-1973		No studies found
Di(2-ethylhexyl) hexahydro-phthalate (no CAS no. found)	Pre-1973		No studies found
Diisononyl phthalate (28553-12-0)	Between 1973 and 1985		Yes

FDA Name (CAS No.)	FDA approved food additives	FDA found chronic studies in 1973*	Literature search found evidence of children's health effects**
n-butyl n-decyl phthalate (89-19-0)	Between 1973 and 1985		No studies found
n-amyl n-decyl phthalate (7493-81-4)	Pre-1973		No studies found
n-octyl n-decyl phthalate (119-07-3/ 1323-73-5)	Pre-1973		No studies found
Di-n-decyl phthalate (84-77-5)	Between 1973 and 1985		No studies found
Diisodecyl phthalate (26761-40-0)	Pre-1973		Yes
Dodecyl phthalate (21577-80-0)	Between 1973 and 1985		No studies found
Dihydroabietyl phthalate (26760-71-4)	Pre-1973		No studies found
Castor oil phthalate, hydrogenated (No CAS found)	Pre-1973		No studies found
Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol (68650-73-7)	Pre-1973		No studies found
Results for 30 FDA-approved food additives	**24 pre-1973 6 from 1973-85**	**6 rat and dog 2 rat**	**17 lack children's health studies**

* Did not report endpoints for the specific studies.
** Children's health effects include studies capable of measuring endpoints of reproductive, developmental or endocrine concern. See Appendix III for details.
*** The CHAP report stated that the evidence for DMP was inconclusive. Based the updated literature search, the petitioners concluded that there is evidence DMP is associated with children's health effects.

Section I-2: The Acceptable Daily Intake (ADI) for DEHP should be assigned to all ortho-phthalates.

A critical aspect of chemical safety assessment is the determination of an acceptable daily intake (ADI). The ADI is the amount of a substance that may be consumed daily over a lifetime without experiencing health risks. In 21 CFR 170.22, FDA states that "a food additive for use by man will not be granted a tolerance that will exceed 1/100th of the amount demonstrated to be without harm to experimental animals." This is generally the same process used to develop an ADI from animal toxicology data. Therefore, for the purpose of this petition, ADI and tolerance are considered synonyms.

The same regulation that requires that additives with similar or pharmacological effects be considered a class,[22] also establishes tolerance setting requirements. Regulations at 21 CFR 170.18(c) states that:

[22] 21 CFR 170.18(a).

> "[w]here food additives from two or more chemicals in the same class are present in or on a food, **the tolerance for the total of such additives shall be the same as that for the additive having the lowest numerical tolerance in this class**, unless there are available methods that permit quantitative determination of the amount of each food additive present or unless it is shown that a higher tolerance is reasonably required for the combined additives to accomplish the physical or technical effect for which such combined additives are intended and that the higher tolerance will be safe."[23] [Emphasis added]

As discussed in section I-3 below, food already contains many ortho-phthalates. Therefore, 21 CFR 171.18(a) requires that the tolerance for the total of the ortho-phthalates in food shall be the same as the individual ortho-phthalate with the lowest numerical tolerance. The regulation allows for an alternative method to calculate a higher tolerance if reasonably required for the combined additives to accomplish the physical or technical effect. With alternatives available to fulfill the purpose of ortho-phthalates (see Appendix I), a higher tolerance is not reasonably required. Even if reasonably required, we know of no scientifically defensible method to develop a higher tolerance given the data gaps.

In 1973, a year after the regulation was adopted, FDA scientists[24] proposed a practical approach for assessing the safety of several ortho-phthalates, many of which lacked safety data. They suggested that all ortho-phthalates be presumed to have the hazards of the most toxic one, which they indicated was DEHP. This approach was consistent with the regulatory language. Despite its regulations and the statement by the agency's scientists, we cannot find any instance in which the agency applied this approach to the seven new ortho-phthalates it approved after 1973 or in which FDA has used this approach to fill the data gaps for existing approvals of ortho-phthalates.

In an effort to apply the regulatory tolerance setting requirements, we searched for toxicity data that will allow us to calculate a no observed adverse effect level (NOAEL) and an acceptable daily intake (ADI) for ortho-phthalates. We found NOAELs for nine ortho-phthalates included in this petition in the CHAP report (CHAP uses the term point of departure as a synonym for NOAEL). CHAP used male developmental toxicity as the endpoint to identify the NOAEL. We summarize them in Table 2.[25]

To estimate the ADIs, we applied a total safety factor of 1000 to each NOAEL: 10 for inter-species variability x 10 for intra-species variability x 10 for severity of effects[26] on children and fetuses. See Table 2.

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[23] 21 CFR 170.18(c).

[24] Shibko and Blumenthal, Toxicology of Phthalic Acid Esters Used in Food Packaging Material, *Environmental Health Perspectives,* January 1973

[25] Adapted from CHAP report Table 5.1, page 80.

[26] In its January 2016 decision on PFCs, an FDA toxicologist used an additional 10X uncertainty factor in her calculation of the ADI based on prenatal exposure endpoint. It was justified due to the severity of finding (i.e., increased percentage litter loss). We believe that developmental, reproductive and endocrine toxicity effects observed after prenatal and postnatal exposure also represent severe findings due to their likely irreversibility.

Table 2: Acceptable daily intake estimates based on no observed adverse effect levels in toxicology studies and 1000 uncertainty factor.

Chemical	NOAEL ranges (mg/kg bw/day)[1]	Estimated ADI ranges (mg/kg bw/day)	Estimated ADI ranges (µg/kg bw/day)
Dibutyl phthalate (DBP)	5-50	0.005-0.050	5-50
Butylbenzyl phthalate (BBP)	5-66	0.005-0.066	5-66
Diethyhexyl phthalate (DEHP)	3-5	0.003-0.005	3-5
Diisononyl phthalate (DINP)	11.5-750	0.0115-0.750	11.5-750
Diisodecyl phthalate (DIDP)	≥600	≥0.600	≥600
Dimethyl phthalate (DMP)	≥750	≥0.750	≥750
Diethyl phthalate (DEP)	≥750	≥0.750	≥750
Diisobutyl phthalate (DIBP)	5-125	0.005-0.125	5-125
Di-n-hexyl phthalate (DHEXP)	≤250	≤0.250	≤250
Dicyclohexyl phthalate (DCHP)	16	0.016	16

[1] Adapted from CHAP report Table 5.1, page 80.

Based on our estimated ADIs and following the tolerance setting requirements "for the total of such additives" (21 CFR 170.18(c)), we concluded that the tolerance for the total ortho-phthalates in this petition should be 3 µg/kg bw/day which is the same as for DEHP, the additive with the lowest available numerical tolerance in the class as required by the regulation. It is important to clarify that the estimated ADI does not apply to each individual chemical, but rather to the 30 ortho-phthalates in the class. 21 CFR 170.18 clearly states that "[w]here food additives from two or more chemicals in the same class are present in or on a food, the tolerance for the total of such additives shall be the same as that for the additive having the lowest numerical tolerance in this class."

Unless the evidence shows another ortho-phthalate has a lower numerical tolerance in the class for any endpoint, then the value for DEHP should be used to set the tolerance for total ortho-phthalates in the diet.

FDA took a similar approach in its determination of an ADI for long-chain PFCs.[27] The agency selected the no observed effect level (NOEL) for pre- and postnatal development endpoint (i.e. percent litter loss) available for perfluorooctanoic acid (PFOA), a member of the class as defined by FDA, and applied a safety factor of 1000.[28] Then, it compared the calculated ADI to the

[27] Memo from Toxicology Group 1, Division of Food Contact Notifications (DFCN) Penelope A. Rice, Ph.D., D.A.B.T. (HFS-275) to Regulatory Group 2 (DFNC) Paul Honigfort (HFS-275). July 27, 2015

[28] [U]sing the Abbott et al. study NOEL of 0.3 mg/kg for the severe finding of increased percent litter loss, and applying a safety factor of 1000. Total safety factor = 10 for intra-species variability x 10 for inter-species variability x 10 for severity of effect. Memo from Toxicology Group 1, Division of Food Contact Notifications (DFCN)

estimated daily intake (EDI) calculated for PFOA, concluding that the EDI was greater than the ADI and that this raises safety concerns. Due to a lack of data specific to most members of the class, FDA applied the evidence of harm from a subset of chemicals to all the chemicals in the class.

As CHAP and others have noted, some product manufacturers will substitute one chemical in the class of ortho-phthalates with another as they are chemically similar. Estimating the tolerance for the entire class is a critical step in the determining the cumulative effect of these chemically- and pharmacologically-related substances pursuant to 21 U.S.C. 348(c)(5)(B).

In summary, based on our estimate, the ADI for the total ortho-phthalates in the class is 3 μg/kg bw/day.

Section I-3: The Estimated Daily Exposure (EDI) for ortho-phthalates significantly exceeds the ADI and, therefore, the intentional use of ortho-phthalates as food contact substances are not safe as defined by FDA's regulations.

The presence of more than one ortho-phthalate in the diet has been well documented.[29,30,31] FDA's guidance[32] recommends that the estimated exposure to a food additive includes all dietary sources of exposure. This includes drinking water, dietary supplements and naturally occurring substances.

For food contact substances such as ortho-phthalates, FDA reports a cumulative estimated daily intake (CEDI) which is based on the EDI for all approved uses. We found CEDIs for 9 of the 30 ortho-phthalates[33] it has approved. See Table 3.

We do not know why FDA has not provided estimates for the other 21 ortho-phthalates it has expressly approved in its rules. One possible reason is that the agency approved them without data from food migration tests even though migration data in the various food types contacting the food contact substance is needed to estimate the EDI.[34] Alternatively, FDA may have assumed migration into food would not occur from the approved uses.[35] Current evidence indicates that, at least for some ortho-phthalates the assumption "under normal conditions of use would not reasonably be expected to migrate into food" that was cited in the 1973 review turned out to be a flawed assumption because the chemicals are commonly found in the diet, as described below and in additional detail in Appendix II.[36]

Penelope A. Rice, Ph.D., D.A.B.T. (HFS-275) to Regulatory Group 2 (DFNC) Paul Honigfort (HFS-275). July 27, 2015

[29] Arnold Schecter et al. Environ Health Perspectives 121:473–479 (2013)

[30] Teresa Cirillo et al. Exposure to di-3-ethylhexyl phthalate, di-n-butyl phthalate and bisphenol A through infant formulae. J. Agricultural and Food Chemistry 63:3303-3310. 2015

[31] Serrano et al. Phthalates and diet: a review of the food monitoring and epidemiology data. Environmental Health 13:43, 2014

[32] Guidance for industry: estimating dietary intake of substances in food.

[33] CEDI Database. http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/CEDI/default.htm

[34] Guidance for Industry: Preparation of premarket submissions for food contact substances: Chemistry recommendations. 2007

[35] Shibko and Blumenthal, 1973

[36] Arnold Schecter et al. Environ Health Perspect 121:473–479 (2013).

We also question the validity of the reported CEDI because, if migration experiments were conducted in the original food additive petitions decades ago, they are unlikely to have adhered to FDA's current Chemistry Guidance.[37] We based this analysis upon FDA's recent chemistry assessment included in its decision of the safety of three long-chain PFCs that were the subject of FAP 4B4809.[38]

CPSC's CHAP provided current exposure estimates[39] for eight of the 12 ortho-phthalates it evaluated that were FDA-approved food additives based on biomonitoring data. Only diisononyl phthalate exposure data were reported by both FDA CEDI database and CHAP. CHAP found that the estimated average dietary exposure to diisononyl phthalate for women was more than 13 times greater than FDA's average cumulative estimated daily intake. See Table 3. These two values cannot be compared since FDA's CEDI estimates only includes migration from final packaging and do not include the migration estimates from various intermediate packaging and food manufacturing and handling process. In contrast, the CHAP dietary estimate includes all uses of diisononyl phthalate in contact with food as it is measured in urine.

In contrast to FDA's approach, the CHAP estimates were calculated using actual measures based on biomonitoring—which reflects contribution from various foods in the diet—and food consumption data.

Table 3 Exposure summary for 30 ortho-phthalate approved by FDA as food additives (sorted by increasing length of longest chain)

FDA Name (CAS No.)	CEDI[a] Adult Mean (µg/kg bw/day)	CHAP 2014[e] Women Mean (µg/kg bw/day)	CHAP 2014[e] Women 95% (µg/kg bw/day)	Schecter 2013[b] Mean adult daily intake (µg/kg bw/day)	Schecter 2013[b] Mean infant daily intake (µg/kg bw/day)
Dimethyl phthalate[c] (131-11-3)	0.5	Unknown	Unknown	0.004	0.006
Diphenyl phthalate (84-62-8)	None available	NA	NA	NA	NA
Methyl phthalyl ethyl glycolate[c] (85-71-2)	0.35	NA	NA	NA	NA
Diethyl phthalate (84-66-2)	None available	0.093	0.36	0.033	0.020
Diphenylguanidine phthalate[d] (17573-13-6)	None available	NA	NA	NA	NA
Ethyl phthalyl ethyl glycolate (84-72-0)	None available	NA	NA	NA	NA

[37] Guidance for Industry: Preparation of premarket submissions for food contact substances: Chemistry recommendations.
[38] Memorandum from Jessica Cooper, Division of Food Contact Notifications, Chemistry Review Team II to Paul Honigfort, Division of Food Contact Notifications, Regulatory Team II. July 23, 2015
[39] Table E1-S1: Estimated phthalate ester exposure (ug/kg/day) by individual exposure scenario for women. Appendix E1-49

Diallyl phthalate[d] (131-17-9)	None available	NA	NA	NA	NA
Butyl benzyl phthalate (85-68-7)	None available	0.16	0.25	0.085	0.188
Diisobutyl phthalate (84-69-5)	None available	0.13	0.46	0.020	0.043
Di-n-butyl phthalate (84-74-2)	None available	0.078	0.23	0.184	0.064
Butyl phthalyl butyl glycolate (85-70-1)	0.35	NA	NA	NA	NA
Dicyclohexyl phthalate (84-61-7)	None available	Unknown	Unknown	0.008	0.010
Di-n-hexyl phthalate (84-75-3)	None available	Unknown	Unknown	0.006	0.006
Di(butoxyethyl) phthalate[c] (117-83-9)	0.35	NA	NA	NA	NA
Dimethylcyclohexyl phthalate (1322-94-7)	None available	NA	NA	NA	NA
Diisooctyl phthalate (27554-26-3)	None available	Unknown	Unknown	NA	NA
Di(2-ethylhexyl) phthalate (DEHP) (117-81-7)	None available	1.4	4.9	0.673	4.203
Di-n-octyl phthalate[c] (117-84-0)	None available	0.13	0.36	0.021	0.140
n-butyl n-octyl phthalate[c] (84-78-6)	0.35	NA	NA	NA	NA
Di(2-ethylhexyl) hexahydro-phthalate (no CAS no. found)[c]	None available	NA	NA	NA	NA
Diisononyl phthalate[d] (28553-12-0)	0.35	4.8	15		
n-butyl n-decyl phthalate[d] (89-19-0)	0.35	NA	NA	NA	NA
n-amyl n-decyl phthalate[d] (7493-81-4)	None available	NA	NA	NA	NA
n-octyl n-decyl phthalate[c] (119-07-3 / 1323-73-5)	None available	NA	NA	NA	NA
Di-n-decyl phthalate[d] (84-77-5)	0.05	NA	NA	NA	NA
Diisodecyl phthalate (26761-40-0)	None available	3.2	9.3		
Dodecyl phthalate[d] (21577-80-0)	None available	NA	NA	NA	NA
Dihydoabietyl phthalate (26760-71-4)	0.35	NA	NA	NA	NA
Castor oil phthalate, hydrogenated (No CAS found)	None available	NA	NA	NA	NA
Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol (68650-73-7)	None available	NA	NA	NA	NA
Results for 30 FDA-approved food additives	**9 of 30 have estimates**	**8 of 30 have biomonitoring estimates**	**8 of 30 have biomonitoring estimates**	**9 of 30 detected in foods sold in supermarkets**	**9 of 30 detected in foods sold in supermarkets**

[a] CEDI: Cumulative estimated daily intake. Available at http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/CEDI/default.htm. Accessed on 7/17/2015
[b] Arnold Schecter *et al*. Environ Health Perspect 121:473–479 (2013). Table 2, page 475
[c] Food additives FDA scientists said in 1973 were not reasonably expected to migrate into food.
[d] Food additive approved between 1973 and 1985
[e] Based on CHAP Table E1-S1 Appendix E1-49
NA: not applicable
Bw: body weight
Shaded rows indicate estimated exposures greater than estimated 3 µg/kg-d tolerance for the class.

In Section 2, we estimated the tolerance for the class of ortho-phthalates as 3 µg/kg/day, pursuant to 21 CFR 170.18. Table 3 shows that women's average dietary exposures for diisononly phthalate and diisodecyl phthalate are 4.8 and 3.2 µg/kg bw/day, respectively, and thus are greater than the tolerance. And women in the 95th percentile exposure for DEHP are also higher than tolerance. Additionally, Schecter *et al.*, showed that mean infant intake of DEHP (calculated based on selected baby food bought in supermarkets in the US) was also greater than the tolerance for the class.

An EDI greater than the tolerance is indicative of safety concerns. More importantly, the estimates on Table 3 are for single chemicals and for a subset of chemicals in the class. However, the law mandates (at 21 USC § 348(c)(5)(A)) that a petition consider "the probable consumption of the additive and of any substance formed in or on food because of the use of the additive." Unfortunately, based on the sparsity of available information, the petitioners are unable to make a cumulative exposure estimate that extends to the 30 ortho-phthalates in the class. We anticipate that neither FDA nor industry has information on probable exposure of all ortho-phthalates, particularly as some uses may have been approved in secret industry decisions as to GRAS status. Without these data, it is unwarranted—even impossible—to conclude that the allowed uses meet the legal safety standard requiring a reasonable certainty of no harm. Even without such information, the data clearly show that women and children are already exposed to levels of ortho-phthalates above the estimated tolerance and that any additional exposure from intentional use of ortho-phthalates as a food contact substance is unsafe.

In addition, the law requires (at 21 USC § 348(c)(5)(B)) that FDA consider "the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet." Therefore, the agency must consider ALL sources of ortho-phthalates in the diet, whether from final product packaging, raw material packaging, food handling equipment or contamination and from natural and artificial sources. As a result of the extensive approved uses of ortho-phthalates, the estimated exposure from all uses cannot be based on migration from final packaging alone contrary to FDA's practice.[40] As mentioned above, the estimates for exposure must also consider the possibility of other uses of ortho-phthalates determined to be GRAS without notice to FDA.

[40] Guidance for industry: Preparation of premarket submissions for food contact substances: Chemistry recommendations

A 2013 study[41] by University of Washington researchers made clear the significance of sources of exposure to ortho-phthalates that are outside the context of final packaging for food. Members of a diet-intervention group designed to eliminate all likely sources of ortho-phthalates (and bisphenol A) nonetheless had extremely high levels of DEHP metabolites in their urine. The tested levels of metabolites in people's urine were 25 times greater than those before the study. Investigators subsequently found that the main source of DEHP was most likely a single spice, with some additional exposures from milk and other dairy-based foods.

Another indication that ortho-phthalates are being "transferred" by current food manufacturing practices from farm to fork derives from a 2013 study identifying eight ortho-phthalates that were used at all steps in the process of collecting, processing and selling milk products.[42] These data provide strong evidence that ortho-phthalates migrate from food handling, manufacturing or processing equipment. Yet, an ambiguous "good manufacturing practice" requirement is the sole limit currently on the amount of ortho-phthalates that may leach into food—providing, as a practical matter, no standard at all.

To be clear, there is nothing in the law or the rules indicating that the sources of the ortho-phthalates in the diet must be identified. While it is unnecessary, if FDA does determine that there is some portion of the ortho-phthalates in the diet from contamination[43,44] unrelated to their uses as a food additive, the agency should use its authority at 21 CFR Part 109 to set standards for ortho-phthalates as unavoidable contamination.

Available exposure data for a subset of ortho-phthalates within the class clearly indicate that current exposures on the part of women and children to these substances is too high and poses a serious safety concern. Moreover, the remaining 21 members of the class lack exposure information. For the class as a whole, then, there is no longer a reasonable certainty of no harm. FDA is obligated by 21 USC §348 to withdraw approvals for the 30 chemicals in the class.

Part II Other Related Issues

Section II-1: FDA's working groups on ortho-phthalate safety

On September 23, 2014, FDA's Associate Commissioner for Legislation reported to then-Representative Henry Waxman that the Center for Food Safety and Applied Nutrition (CFSAN) had formed an internal Phthalate Task Group in 2008 to conduct a post-market evaluation of approved, regulated ortho-phthalate food additives "to further address the potential risks raised in

[41] Sheela Sathyanarayana, Garry Alcedo, Brian E. Saelens, Chuan Zhou, Russell L. Dills, Jianbo Yu and Bruce Lanphear. (2013) Unexpected results in a randomized dietary trial to reduce phthalate and bisphenol A exposures. Journal of Exposure Science and Environmental Epidemiology 23:378-84.
[42] Fierens T, Van Holderbeke M, Willems H, De Henauw S, Sioen I. Transfer of eight phthalates through the milk chain – A case study. Environment International 51:1-7
[43] Nelson MA, Ondov JM, VanDerveer MC, Buchholz BA. Contemporary fraction of bis(2-ethylhexyl) phthalate in stilton cheese by accelerator mass spectrometry. 2013. Proceedings of the 21st International Radiocarbon Conference edited by A J T Jull & C Hatté. RADIOCARBON, Vol 55, Nr 2–3, 2013, p 686–697
[44] Tian C, Ni J, Chang F et al. Bio-source of di-n-butyl phthalate production by filamentous fungi. 2016. Scientific Reports 6,19791; doi: 10.1038/srep19791

the contemporary literature and to ensure that the authorized uses continued to meet the "reasonable certainty of no harm" safety standard for food additives".[45]

While we recognize the resource constraints that the agency faces, eight years have passed since the working group was formed, and we are not aware that FDA has publicly released any results of its reviews or made any final decisions regarding whether approved uses of ortho-phthalates are safe.

Based on the publicly available information, the extent of FDA's ortho-phthalates assessment has been limited to two ortho-phthalates, DEHP and dibutyl phthalate, for the following uses:

1) DEHP in polyvinyl chloride (PVC) medical devices, where it warned against DEHP's use based on evidence of adverse effects in laboratory animals, stating that "of greatest concern are effects on the development of the male reproductive system and production of normal sperm in young animals." FDA concluded that "the male fetus, male neonate, and peripubertal male would appear to be high-risk groups."[46]
2) DEHP in bottled water, where it set strict contamination limits[47] consistent with the drinking water standards set by the U.S. Environmental Protection Agency.
3) DEHP and dibutyl phthalate in drug and biologic products, including prescription and non-prescription products. Guidance for industry strongly recommends limiting the use of DEHP and dibutyl phthalate as excipients, stating that "concerns have been expressed because of their reproductive and developmental toxicity."[48] The guidance also states that FDA "generally does not consider DBP [dibutyl phthalate] or DEHP safe or suitable as an inactive ingredient in OTC [over the counter] monograph products."

Section II-2: Disproportionate impact on children's health

As stated earlier, children and developing fetuses are likely to be the most vulnerable and most adversely impacted by exposure to ortho-phthalates. FDA has an obligation under Executive Order 13045 regarding protection of children from environmental health risks and safety risk[49] to ensure that its policies, programs, activities and standards specifically address these risks. The order expressly applies to food and drink.

Should FDA choose to set tolerances other than zero for the ortho-phthalates included in this petition, we believe the agency should apply the same criteria used in its 2016 decision on long-chain PFCs in which it added an additional 10-fold safety factor—to the default 100-fold recommended at 21 CFR § 170.22—due to the severity of effect to developing fetuses and children. Such evidence warrants additional factors under 21 CFR 170.22, as "evidence…which justifies use of a different safety factor."

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[45] Kraus, Letter to the Honorable Henry A. Waxman, 2014.
[46] FDA, Public Health Notification: PVC Devices Containing the Plasticizer DEHP, 2002. See http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062182.htm.
[47] 21 CFR 165.110, as amended by 76 FR 64810, Oct. 19, 2011.
[48] Guidance for Industry: Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products. 2012. Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration. See http://www.fda.gov/downloads/Drugs/Guidance%20ComplianceRegulatoryInformation/Guidances/UCM294086.pdf
[49] See http://yosemite.epa.gov/ochp/ochpweb.nsf/content/whatwe_executiv.htm.

Conclusion

As a result of our analysis, we conclude that there is no longer a reasonable certainty of no harm for the food contact use of the 30 ortho-phthalates that are the subject of this petition for the following reasons:

- Absence of data specific to 57% of ortho-phthalates in the class to address reproductive, developmental and endocrine toxicity;
- Absence of adequate migration data to determine dietary exposure to the great majority of chemicals in the class from their food-contact use;
- Lack of a basis for deriving the cumulative exposure from all sources including approved uses, natural occurrence and contamination;
- Insufficient data to account for consumer's systematic exposure resulting from chronic low dose dietary exposure to this class of chemicals;
- Available data indicating current exposures are above the estimated tolerance for the class.

If FDA accepts this petition, it will allow the agency to review the safety of ortho-phthalates, other than those requested to be banned, using contemporary knowledge and modern scientific evidence, and, subsequently, based on adequate data, either:

1) approve uses through food additive petitions submitted pursuant to 21 CFR § 171.130, or
2) find no objection to Food Contact Substance Notifications (FCN) submitted pursuant to 21 CFR § 170.100.

Through the revocation and subsequent submission and review approaches requested in this petition, the agency can ensure that any newly approved uses meet the legal standard by demonstrating a reasonable certainty of no harm. These demonstrated gaps in hazard and exposure data would need to be addressed prior to the renewed use of these chemicals in food.

This petition does not include polyethylene terephthalate because of the significantly different chemical structure of its monomer: the ester groups are on opposite ends (*para*) of the benzene ring.

Please note that this is NOT a citizens' petition.

We have enclosed three copies per 21 CFR § 171.1.

If you have questions or comments, please contact Tom Neltner at tneltner@edf.org or 202-572-3263. Copy Erik D. Olson at eolson@nrdc.org, Laura MacCleery at lmaccleery@cspinet.org and Dr. Maricel Maffini at drmvma@gmail.com on all responses.

Sincerely,

Erik Olson
Natural Resources Defense Council

Laura MacCleery
Lisa Lefferts
Center for Science in the Public Interest

Caroline Cox
Center for Environmental Health

Cristina Stella
Center for Food Safety

Lynn Thorpe
Clean Water Action

Tom Gremillion
Consumer Federation of America

Peter Lehner
Eve Gartner
Earthjustice

Tom Neltner
Environmental Defense Fund

Joan Ketterman
Improving Kids' Environment

Maureen Swanson
Learning Disabilities Association of America

Maricel Maffini
Independent Consultant

Index to Appendices:

Appendix I
Responses to elements required by 21 CFR § 171.1

Per 21 CFR § 171.1, we provide responses to the requested elements of a food additive petition with one element per page.

Name and Pertinent Information Concerning Food Additive

The identity of the food additive is as follows:

1.	Name:	Ortho-phthalates described in Table I-1 below in selected sections of 21 CFR Parts 175, 176, 177, 178, and 181
2.	Chemical formula:	Not applicable. Multiple chemicals
3.	Formula weight:	Not applicable. Multiple chemicals
4.	Chemical Abstract Service No.:	Not applicable. Multiple chemicals
5.	INS No.:	Not applicable. Multiple chemicals
6.	UNI No.:	Not applicable. Multiple chemicals

Table I-1 Summary of regulations affected by this petition for each ortho-phthalate.

FDA Name	CAS No.	21 CFR 175	21 CFR 176	21 CFR 177	21 CFR 178	21 CFR 181
Dimethyl phthalate / dimethyl orthophthalate	131-11-3	175.105		177.1010 177.1590 177.2420		
Diphenyl phthalate	84-62-8	175.105			178.3740	
Methyl phthalyl ethyl glycolate / 1,2-Benzenedicarboxylicacid, 1-(2-ethoxy-2-oxoethyl) 2-methyl ester	85-71-2	175.105				
Diethyl phthalate	84-66-2	175.105 175.300 175.320			178.3910	181.27
Diphenylguanidine phthalate	17573-13-6			177.2600		
Ethyl phthalyl ethyl glycolate / Ethyl carbethoxymethyl phthalate	84-72-0	175.105 175.300 175.320				181.27
Diallyl phthalate	131-17-9	175.105	176.170 176.180			
Diisobutyl phthalate	84-69-5	175.105		177.1200		
Butyl benzyl phthalate	85-68-7	175.105	176.170 176.180	177.2420	178.3740	
Di-n-butyl phthalate	84-74-2	175.105 175.300	176.170 176.180* 176.300	177.1200 177.2420 177.2600		
Butyl phthalyl butyl glycolate / Butyl carbobutoxymethyl phthalate	85-70-1	175.105 175.300 175.320				181.27
Dicyclohexyl phthalate	84-61-7	175.105	176.170	177.1200	178.3740	
Dihexyl phthalate / Di-n-hexyl phthalate	84-75-3	175.105			178.3740	

FDA Name	CAS No.	21 CFR 175	21 CFR 176	21 CFR 177	21 CFR 178	21 CFR 181
Di(butoxyethyl) phthalate / Bis(2-n-butoxyethyl) phthalate	117-83-9	175.105				
Dimethylcyclohexyl phthalate	1322-94-7			177.1200		
Diisooctyl phthalate	27554-26-3	175.105 175.300				181.27
Di(2-ethylhexyl) phthalate	117-81-7	175.105 175.300 175.380* 175.390*	176.170* 176.180* 176.210	177.1010 177.1200 177.1210* 177.1400*	178.3910	181.27
Dioctyl phthalate / Di-n-octyl phthalate	117-84-0	175.105		177.1460 177.2600		
Butyloctyl phthalate / n-butyl n-octyl pthalate	84-78-6	175.105				
Di(2-ethylhexyl) hexahydrophthalate		175.105				
Diisononyl phthalate / Bis(7-methyloctyl) phthalate	28553-12-0				178.3740	
Amyl decyl phthalate / n-amyl n-decyl phthalate.	7493-81-4			177.2600		
Butyl decyl phthalate / n-butyl n-decyl pthalate	89-19-0	175.105				
Decyl octyl phthalate / Octyldecyl phthalate / n-octyl n-decyl phthalate	119-07-3	175.105		177.2600		
Didecyl phthalate / Di-n-decyl phthalate	84-77-5		176.300	177.2600		
Diisodecyl phthalate / Bis(8-methylnonyl) phthalate	26761-40-0	175.105 175.300		177.1210 177.2600	178.3910	
Dodecyl phthalate	21577-80-0		176.300			
Dihydoabietyl phthalate	26760-71-4	175.105				
Castor oil phthalate, hydrogenated	FDA # 977037-59-4			177.1200		
Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol	68650-73-7			177.1200		
* These sections do not specifically mention the ortho-phthalates. However, they do reference a provision of another section that does mention ortho-phthalates, indirectly incorporating them into the allowed uses. Therefore, they are affected by this petition. We do not include them in Appendix IV since we are not requesting that FDA alter the words in those sections.						

Directions, Recommendations, and Suggestions Regarding Proposed Use
We are asking FDA to revoke the approvals for ortho-phthalates as described in the section above.

Data establishing that food additive will have intended physical or other technical effect.
We are asking FDA to revoke the approvals for ortho-phthalates as described in the section above. As a result, there is no intended physical or technical effect.

Description of practicable methods to determine the amount of the food additive in the food
We are asking FDA to revoke the approvals for ortho-phthalates. As a result, there should be no amount of the food additive in the food.

Full reports of investigations made with respect to the safety of the food additive
See Appendices II and III.

Proposed tolerances for the food additive
We are asking FDA to revoke the approvals for ortho-phthalates as described in the section above and prohibit the use of the following:

- Diisobutyl phthalate (DIBP).
- Di-n-butyl phthalate (DBP).
- Butyl benzyl phthalate (BBP).
- Dicyclohexyl phthalate (DCHP).
- Di-n-hexyl phthalate (DHEXP).
- Diisooctyl phthalate (DIOP).
- Di(2-ethylhexyl) phthalate (DEHP).
- Diisononyl phthalate (DINP).

Appendix II describes current estimated exposures for these chemicals.

Full information on each proposed change to the original regulation
See Appendix IV for the specific changes requested to selected sections of 21 CFR Parts 175, 176, 177, 178, and 181. Text in strikethrough font is to be deleted.

Environmental review component
This food additive petition is categorically excluded from the need to prepare an Environmental Assessment under 21 CFR § 25.32(m) as an "action to prohibit or otherwise restrict or reduce the use of a substance in food, food packaging, or cosmetics." It complies with the categorical exclusion criteria pursuant to 40 CFR § 1508.4. We have identified no extraordinary circumstances as defined at 21 CFR § 25.21 for the action requested in this petition which would require the submission of an Environmental Assessment.

Where food manufacturers need substitutes, the food additives approved by FDA in its regulations and the food contact substances cleared by FDA through the Food Contact Substance Notification (FCNs) program provide hundreds of alternatives. While most of those hundreds of alternative food additives were approved by FDA before the National Environmental Policy Act was adopted and have not been reassessed by the agency for their current risk, we did not identify a potential for serious harm to the environment or protected species from the marginal increase in production or use of these alternatives.

If the manufacturer determined that these additives were also insufficient and no additives were "generally recognized as safe" without FDA review, the manufacturers would submit a food additive petition for agency review. In this review, the agency would consider compliance with the National Environmental Policy Act.

Determining whether a specific additive is an acceptable substitute involves a detailed analysis of each use. However, we identified the following alternatives.

- *Sec. 175.105 Adhesives:* FDA has approved more than 1200 chemicals other than the 22 ortho-phthalates it has approved for use in adhesives.
- *Sec. 175.300 Resinous and polymeric coatings:* FDA has approved more than 600 chemicals other than the seven ortho-phthalates it has approved for use in resinous and polymeric coatings.
- *Sec. 175.320 Resinous and polymeric coatings for polyolefin films:* FDA has approved more than 215 chemicals other than the three ortho-phthalates it has approved for use in resinous and polymeric coatings for polyolefin films.
- *Sec. 176.170 Components of paper and paperboard in contact with aqueous and fatty foods:* FDA has approved more than 500 chemicals other than the three ortho-phthalates it has approved for use as components of paper and paperboard in contact with aqueous and fatty foods.
- *Sec. 176.180 Components of paper and paperboard in contact with dry food:* FDA has approved more than 500 chemicals other than the two ortho-phthalates it has approved for use as components of paper and paperboard in contact with dry food.
- *Sec. 176.210 Defoaming agents used in the manufacture of paper and paperboard*: FDA has approved more than 250 chemicals other than the one ortho-phthalates it has approved for use as defoaming agency in adhesives.
- *Sec. 176.300 Slimicides:* FDA has approved more than 50 chemicals other than the three ortho-phthalates it has approved for use in slimicides.
- *Sec. 177.1010 Acrylic and modified acrylic plastics, semirigid and rigid:* FDA has approved more than 100 chemicals other than the two ortho-phthalates it has approved for use in semirigid and rigid acrylic and modified acrylic plastics.
- *Sec. 177.1200 Cellophane:* FDA has approved more than 200 chemicals other than the seven ortho-phthalates it has approved for use in cellophane.
- *Sec. 177.1210 Closures with sealing gaskets for food containers:* FDA has approved more than 60 chemicals other than the one ortho-phthalates it has approved for use in sealing gaskets for food containers.
- *Sec. 177.1460 Melamine-formaldehyde resins in molded articles:* FDA has approved more than four chemicals other than the one ortho-phthalates it has approved for use in melamine-formaldehyde resins in molded articles.
- *Sec. 177.1590 Polyester elastomers:* FDA has approved more than eight chemicals other than the one ortho-phthalates it has approved for use in polyester elastomers.
- *Sec. 177.2420 Polyester resins, cross-linked:* FDA has approved more than 70 chemicals other than the three ortho-phthalates it has approved for use in cross-linked polyester resins.

- *Sec. 177.2600 Rubber articles intended for repeated use:* FDA has approved more than 200 chemicals other than the seven ortho-phthalates it has approved for use in repeated-use rubber articles.
- *Sec. 178.3740 Plasticizers in polymeric substances:* FDA has approved more than ten chemicals other than the five ortho-phthalates it has approved for use as plasticizers in polymeric substances.
- *Sec. 178.3910 Surface lubricants used in the manufacture of metallic articles:* FDA has approved more than 40 chemicals other than the three ortho-phthalates it has approved for use as surface lubricants in the manufacture of metallic articles.
- *Sec. 181.27 Plasticizers:* FDA has approved eight chemicals other than five ortho-phthalates it has approved for use as prior-sanctioned plasticizers.

Appendix II
Estimated daily intakes for ortho-phthalates

As shown below, there are many sources of exposures to ortho-phthalates. However, exposure information is unknown in most cases.

Table II-1 Exposure summary for 30 ortho-phthalate approved by FDA as food additives (sorted by increasing length of longest chain)

FDA Name (CAS No.)	CEDI[a] Adult Mean (µg/kg bw /day)	CHAP 2014[e] Women Mean (µg/kg bw /day)	CHAP 2014[e] Women 95% (µg/kg bw/day)	Schecter 2013[b] Mean adult daily intake (µg/kg bw /day)	Schecter 2013[b] Mean infant daily intake (µg/kg bw /day)
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Ethyl phthalyl ethyl glycolate (84-72-0)	None available	NA	NA	NA	NA
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Diisobutyl phthalate (84-69-5)	None available	0.13	0.46	0.020	0.043
Di-n-butyl phthalate (84-74-2)	None available	0.078	0.23	0.184	0.064
Butyl phthalyl butyl glycolate (85-70-1)	0.35	NA	NA	NA	NA
Dicyclohexyl phthalate (84-61-7)	None available	Unknown	Unknown	0.008	0.010
Di-n-hexyl phthalate (84-75-3)	None available	Unknown	Unknown	0.006	0.006
Di(butoxyethyl) phthalate[c] (117-83-9)	0.35	NA	NA	NA	NA
Dimethylcyclohexyl phthalate (1322-94-7)	None available	NA	NA	NA	NA
Diisooctyl phthalate (27554-26-3)	None available	Unknown	Unknown	NA	NA
Di(2-ethylhexyl) phthalate (DEHP) (117-81-7)	None available	1.4	4.9	0.673	4.203

Di-n-octyl phthalate[c] (117-84-0)	None available	0.13	0.36	0.021	0.140
n-butyl n-octyl phthalate[c] (84-78-6)	0.35	NA	NA	NA	NA
Di(2-ethylhexyl) hexahydro-phthalate (no CAS no. found)[c]	None available	NA	NA	NA	NA
Diisononyl phthalate[d] (28553-12-0)	0.35	4.8	15	NA	NA
n-butyl n-decyl phthalate[d] (89-19-0)	0.35	NA	NA	NA	NA
n-amyl n-decyl phthalate[d] (7493-81-4)	None available	NA	NA	NA	NA
n-octyl n-decyl phthalate[c] (119-07-3 / 1323-73-5)	None available	NA	NA	NA	NA
Di-n-decyl phthalate[d] (84-77-5)	0.05	NA	NA	NA	NA
Diisodecyl phthalate (26761-40-0)	None available	3.2	9.3	NA	NA
Dodecyl phthalate[d] (21577-80-0)	None available	NA	NA	NA	NA
Dihydoabietyl phthalate (26760-71-4)	0.35	NA	NA	NA	NA
Castor oil phthalate, hydrogenated (No CAS found)	None available	NA	NA	NA	NA
Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol (68650-73-7)	None available	NA	NA	NA	NA
Results for 30 FDA-approved food additives	**9 of 30 have estimates**	**8 of 30 have biomonitoring estimates**	**8 of 30 have biomonitoring estimates**	**9 of 30 detected in foods sold in supermarkets**	**9 of 30 detected in foods sold in supermarkets**

[a] CEDI: Cumulative estimated daily intake. Available at http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/CEDI/default.htm. Accessed on 7/17/2015
[b] Arnold Schecter *et al.* Environ Health Perspect 121:473–479 (2013). Table 2, page 475
[c] Food additives FDA scientists said in 1973 were not reasonably expected to migrate into food.
[d] Food additive approved between 1973 and 1985
[e] Based on CHAP Table E1-S1 Appendix E1-49
NA: not applicable
Bw: body weight
Shaded rows indicate estimated exposures greater than estimated 3 μg/kg/day tolerance for the class.

The CHAP estimated the dietary intake of eight ortho-phthalates for four subpopulations—women, infants, toddlers and children—using food residue data from a total diet study published in 2011.[50] We incorporate the CHAP report by reference. Its assessment is summarized on Table II-2.

[50] CHAP report, Appendix E1-12, page 388.

CHAP experts stated that "[e]xposures were calculated with equations specific to the exposure route and the physicochemical processes by which exposure may occur. Exposure from direct ingestion was estimated by:

$$EO.1=C\times M\times N\times B\times F/W$$[51]

Where: EO.1, estimated oral exposure by ingestion, µg/kg-d; C, concentration in product or environmental medium, µg/g; M, mass ingested per event, g; N, frequency of exposure, events per day, d-1; B, fraction absorbed by the gastrointestinal tract, unitless; F, fraction of population exposed by this scenario, unitless; W, body weight, kg."

Table II-2: CHAP estimated phthalate dietary intake of eight ortho-phthalates by population

Phthalate[5]	CHAP Estimated dietary intake (µg/kg bw/day)[1]							
	Women		Infants		Toddlers		Children	
	Average[3]	95th %ile[4]	Mean	95th %ile	Mean	95th %ile	Mean	95th %ile
DEHP	1.4	4.9	5	18	7.6	26[2]	4.2	15
DEP	0.093	0.36	0.3	1.2	0.67	2.7	0.34	1.4
DIDP	3.2	9.3	9.3	25	16	45	9	26
DNOP	0.13	0.36	0.38	0.98	0.6	1.6	0.35	0.92
DINP	4.8	15	14	36	24	69	14	40
DBP	0.078	0.23	0.20	0.53	0.36	0.98	0.21	0.58
BBP	0.16	0.25	0.55	0.67	0.64	1.1	0.39	0.64
DIBP	0.13	0.46	0.35	1.2	0.73	2.7	0.41	1.5
DMP	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
DPENP	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
DHEXP	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
DCHP	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
DIOP	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
DPHP	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown

[1] The total exposure was calculated using the Bradley, 2011 food residue data; the food categorization scheme was based on EPA National Center for Environmental Assessment (NCEA), 2007. CHAP Supplemental Data Tables E1-S1 to E1-S4 (page 425-433)
[2] Above the EPA's reference dose of 20 µg/kg-d. (http://www.epa.gov/iris/subst/0014.htm).
[3] Average exposure is the population average.
[4] 95th percentile is the average user
[5] DEHP: di(2-ethylhexyl) phthalate
DEP: diethyl phthalate
DIDP: diisodecyl phthalate
DNOP: di-n-octyl phthalate
DINP: diisononyl phthalate
DBP: dibutyl phthalate
BBP: butylbenzyl phthalate
DIBP: diisobutyl phthalate
DMP: dimethyl phthalate
DPENP: di-n-pentyl phthalate. Not an approved food additive.
DHEXP: di-n-hexyl phthalate
DCHP: dicyclohexyl phthalate
DIOP: diisooctyl phthalate
DPHP: di(2-propylheptyl) phthalate. Not an approved food additive.

[51] CHAP report, Appendix E1-4, page 380

Several publications have reported on the widespread presence of multiple ortho-phthalates in the multiple foods. For instance, the CHAP report noted the presence of eight ortho-phthalates in six food commodities. Table II-3 is a reprint of the CHAP findings.

Table II-3: Distribution of eight ortho-phthalates esters in food commodities based on 261 retail food items.

Table E1-16 Mean and 95th percentile concentrations of selected phthalate esters in food commodities (µg/g).[a]

Food Commodity		DEP	DBP	DIBP	BBP	DNOP	DEHP	DINP	DIDP
Grain	*Mean*	5.1	12.3	25.2	9.0	12	78	639	393
	0.95	11.4	35.4	91.6	25.7	35	234	2984	1198
Dairy	*Mean*	21.1	6.8	18.2	7.1	12	173	508	326
	0.95	89.2	17.2	69.9	16.4	26	554	1394	943
Fish	*Mean*	13.6	12.8	10.0	14.7	17	98	819	377
	0.95	40.2	51.5	40.7	46.6	45	286	2174	1281
Meat	*Mean*	5.1	6.8	5.5	12.2	11	54	298	236
	0.95	16.1	28.3	14.2	35.0	38	191	927	986
Fat	*Mean*	7.2	20.8	17.3	108.8	47	689	1481	1055
	0.95	29.2	54.2	46.5	93.2	133	2784	2851	2397
Eggs	*Mean*	4.7	5.2	5.7	9.4	20	24	385	259
	0.95	8.2	8.8	10.9	19.8	71	39	742	407

[a] Mean and 95th percentile concentrations were estimated from data in Bradley (2011) as described in Carlson and Patton (2012). Nondetects were treated as one-half the detection limit.

In 2013, researchers have demonstrated the presence of ortho-phthalates in foods commonly found in grocery stores. Schecter *et al.* measured nine ortho-phthalates in 72 individual food samples purchased in Albany, NY. The ortho-phthalates were DEHP, diethyl phthalate (DEP), di-n-octyl phthalate (DNOP), dibutyl phthalate (DBP), butylbenzyl phthalate (BBP), dimethyl phthalate (DMP), diisobutyl phthalate (DIBP), dicyclohexyl phthalate (DCHP) and di-n-hexyl phthalate (DHEXP, noted in the publication as DnHP). At least one phthalate was measured in all food samples representing 13 food categories, from beverages and dairy to condiments, meat, vegetables and infant food and. Figure II-1 is a reprint of the detection frequencies of ortho-phthalates esters by food group published in Environmental Health Perspectives on April 2013.[52]

[52] Schecter A, Lorber M, Guo Y et al. Phthalate Concentrations and Dietary Exposure from Food Purchased in New York State. 2013. Environ Health Perspect 121:473–479 (2013). http://dx.doi.org/10.1289/ehp.1206367

Figure II-1. Detection frequencies [n(%)] of phthatlates esters by food group from Albany, New York. Reprinted from Schecter *et al.* (EHP 121:473, 2013, page 475)

Table 2. Detection frequencies [*n* (%)] of phthalate esters by food group from Albany, New York.

Food	No. of samples	DMP	DEP	DiBP	DBP	DnHP	BBzP	DCHP	DEHP	DnOP
Beverages	8	2 (25)	0	3 (38)	0	0	0	0	1 (13)	0
Milk	2	0	1 (50)	1 (50)	1 (50)	0	1 (50)	0	2 (100)	1 (50)
Other dairy	9	4 (44)	6 (67)	7 (78)	5 (56)	3 (33)	6 (67)	1 (11)	9 (100)	1 (11)
Fish	5	2 (40)	3 (60)	2 (40)	2 (40)	1 (20)	2 (40)	0	4 (80)	0
Fruits/vegetables	5	0	1 (20)	4 (80)	0	0	2 (40)	0	2 (40)	0
Grain	7	5 (71)	7 (100)	6 (86)	6 (86)	3 (43)	7 (100)	0	7 (100)	0
Beef	2	1 (50)	2 (100)	0	0	1 (50)	1 (50)	0	0	1 (50)
Pork	4	2 (50)	4 (100)	1 (25)	0	0	1 (25)	0	3 (75)	1 (25)
Poultry	6	3 (50)	5 (83)	0	0	1 (17)	2 (33)	0	5 (83)	0
Meat and meat products	13	7 (54)	12 (92)	1 (8)	0	2 (15)	4 (31)	0	9 (69)	2 (15)
Vegetable oils	3	1 (33)	0	2 (67)	1 (33)	1 (33)	3 (100)	1 (33)	2 (67)	1 (33)
Condiments	6	3 (50)	3 (50)	5 (83)	3 (50)	0	4 (67)	1 (17)	5 (83)	1 (17)
Infant food	7	0	4 (57)	5 (71)	2 (29)	0	6 (86)	1 (14)	7 (100)	2 (29)
Total	65[a]	24 (37)	37 (57)	36 (55)	20 (31)	10 (15)	35 (54)	4 (6)	48 (74)	8 (12)

LODs (wet weight): DBP = 1.4, DEHP = 3.7, DnOP = 1.0, all others = 0.2 ng/g.
[a]Total number of individual samples, does not include samples in more than one group.

Children are one of the most susceptible populations to exposure to ortho-phthalates. Schecter *et al.* found that seven out of nine ortho-phthalates were present in infant food DEHP was present in all samples tested; di-n-hexyl phthalate (DnHP or DHEXP) and dimethyl phthalate (DMP) were not detectable. The authors' estimated intake was 4.2 µg/kg bw/day for DEHP.

A 2015 study[53] showed that most infant formula samples have measurable levels of DEHP (86% of liquid and 96% powder milks) and dibutyl phthalate (82% of liquid and 96% of powder milks). Using weight growth and dietary exposure parameters recommended by the World Health Organization and Food and Agriculture Organization, the researchers estimated that the highest intake of DEHP and dibutyl phthalate occurs at 30 days of age and could reach up to 55 µg/kg bw/day for DEHP and 18 µg/kg bw/day for dibutyl phthalate in the worst case scenario.

Breast milk has also been shown to contain ortho-phthalates; a recent study found that based on estimated daily intake of mono and diesters of six ortho-phthalates, up to 8% of breast-fed newborn infants was exposed to more than 30 µg DEHP/kg bw/day, a dose considered anti-androgenic; and exposure of 6% of the newborns exceeded the 10 µg/kg bw/day tolerable daily intake for di-n-butyl phthalate.[54] A study from Taiwan showed that the DEHP daily intake of adolescent boys exceeded the reference dose of 20 µg/kg bw/day by 3.4% and the tolerable daily intake of 50 µg/kg/day by 0.4%. [55,56] A recent using biomonitoring data showed children (mean age 7 years) were exposed to up to 15 µg DBP and 17 µg DIBP/kg bw/day exceeding the tolerable daily intake of 10 µg/kg bw/day. The cumulative risk assessment calculated as hazard

[53] Cirillo T, Latini G, Castaldi MA et al. Exposure to Di-2-Ethylhexyl Phthalate, Di-N-Butyl Phthalate and Bisphenol A through Infant Formulas. 2015. Journal of Agriculture and Food Chemistry 63:3303-3310
[54] Kim S, Lee J, Park J et al. Concentrations of phthalate metabolites in breast milk in Korea: Estimating exposure to phthalates and potential risks among breast-fed infants. 2015. Sci Total Environ. 508:13-19
[55] Hou JW, Lin CL, Tsai YA et al. The effects of phthalate and nonylphenol exposure on body size and secondary sexual characteristics during puberty. 2015. Int J Hyg Environ Health 218:603-615
[56] This finding is not surprising considering that adolescent boys are considered the group that consumes the most food among those 2 years of age and older.

index was also above 1 in 13.3% of children mean age 7 years and 4% of children mean age 11 years. [57]

A 2014 comprehensive review[58] of food monitoring data showed that infants on a typical diet were exposed to 42.1 µg of DEHP/kg bw/day, this is more than double the EPA reference dose of 20 µg/kd bw/day. Adolescents in a diet high in dairy and meat also exceeded EPA's reference dose. The authors reported that DEHP was typically found in high concentrations in some meats, fats and dairy products. More importantly, **all these studies show children's exposures well above our estimated tolerance of 3 µg/kg bw/day for the class which is of high safety concern.**

Even though FDA applied limitations to using DEHP and diisooctyl phthalate only on foods with high water content because "the available toxicology would not support unlimited migration into fatty foods",[59] the agency has not set a numerical limit for the amount of ortho-phthalates as a class or individual ortho-phthalates that is acceptable in the diet and still meets the reasonable certainty of no harm safety standard. The only limitation was the ortho-phthalates "be used in accordance with good manufacturing practice for food packaging materials."

DEHP is measured in many fatty foods as demonstrated by the above referenced data. It is clear that the limitation imposed by FDA in the late 1950s (i.e. to be used in high water content food) has failed. From the approved uses, it is unclear whether that limitation was meant to be for final packaging only or if it also applies to all materials in contact with food through manufacturing, processing, handling and holding.

The data we present in this petition demonstrate what in 1973 FDA's scientists stated as a strong possibility, namely "large number of [ortho-]phthalates and their regulated uses could result in many phthalate esters migrating to foods."

[57] Hartman C, Uhl M, Weiss S et al. Human biomonitoring of phthalate exposure in Austrian children and adults and cumulative risk assessment. 2015 Int J Hygiene Env Health 218:489-499
[58] Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. 2014. Environmental Health 13:43
[59] Shibko SI and Blumenthal H. Toxicology of phthalic acid esters used in food-packaging material. 1973. *Environmental Health Perspectives* January issue, 131-137

Appendix III
Toxicity literature review for ortho-phthalates

This appendix contains 5 parts:
Part 1: Description of literature search
Part 2: Animal toxicity studies findings
Part 3: Review of Consumer Product Safety Commission Chronic Hazard Advisory Panel on Phthalates and Phthalates Alternatives 2014 Report
Part 4: Human studies findings
Part 5: List of references and additional relevant publications

Part 1: Description of literature search

The Consumer Protection Safety Commission Chronic Health Advisory Panel 2014 report and all the references within are incorporated by reference.

The petitioners identified the publicly available animal and human literature relevant to the ortho-phthalates listed in Table III-1 whose approval at 175.105, 173.300, 175.380, 175.390, 176.170, 176.180, 176.210, 177.1010, 177.1200, 177.1210, 177.1400, 178.3910, 181.27, 178.3740, 176.300, 177.2420, 177.2600, 177.1460, 177.1590, 175.320 petitioners seek to have the Food and Drug Administration revoke. Although the focus was on ortho-phthalates not evaluated by the CHAP, the review also included an update on the 12 ortho-phthalates that are approved food additives reviewed by CHAP.

Key terms considered in the literature review
We used the following chemical-related search terms to ensure our review was broad: full chemical name as listed in the CFR sections; CAS Register Numbers; common abbreviation. See table below.

FDA Name	Common Abbreviation	CAS RN
Dimethyl phthalate	DMP	131-11-3
Diphenyl phthalate		84-62-8
Methyl phthalyl ethyl glycolate		85-71-2
Diethyl phthalate	DEP	84-66-2
Diphenylguanidine phthalate		17573-13-6
Ethyl phthalyl ethyl glycolate		84-72-0
Diallyl phthalate	DAP	131-17-9
Butyl benzyl phthalate	BBP	85-68-7
Diisobutyl phthalate	DIBP	84-69-5
Di-n-butyl phthalate	DBP	84-74-2
Butyl phthalyl butyl glycolate		85-70-1
Dicyclohexyl phthalate	DCHP	84-61-7
Di-n-hexyl phthalate	DHEXP	84-75-3
Di(butoxyethyl) phthalate		117-83-9
Dimethylcyclohexyl phthalate		1322-94-7
Diisooctyl phthalate	DIOP	27554-26-3

FDA Name	Common Abbreviation	CAS RN
Di(2-ethylhexyl) phthalate	DEHP	117-81-7
Di-n-octyl phthalate	DNOP	117-84-0
n-butyl n-octyl phthalate		84-78-6
Di(2-ethylhexyl) hexahydro-phthalate		No CAS no. found
Diisononyl phthalate	DINP	28553-12-0
n-butyl n-decyl phthalate	BDP	89-19-0
n-amyl n-decyl phthalate		7493-81-4
n-octyl n-decyl phthalate	ODP	119-07-3/1323-73-5
Di-n-decyl phthalate		84-77-5
Diisodecyl phthalate	DIDP	26761-40-0
Dodecyl phthalate		21577-80-0
Dihydroabietyl phthalate		26760-71-4
Castor oil phthalate, hydrogenated		No CAS no. found
Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol		68650-73-7

In addition to the chemicals' names, we used the following keywords: anti-androgen, reproductive, developmental, prenatal, postnatal, rat, mouse, estrogen, androgen, testosterone, thyroid, testes, uterus, ovary, ovaries, endocrine, mammary, fetal growth, brain, behavior, IQ, fertility, bone, and osteogenesis. Our objective was to identify relevant animal and human studies.

An example of literature search in PubMed would be: (diethylhexyl phthalate OR DEHP OR 117-81-7) AND (anti-androgen OR reproductive OR developmental OR prenatal OR postnatal OR rat OR mouse OR estrogen OR androgen OR testosterone OR thyroid OR testes OR uterus, OR ovary OR ovaries OR endocrine OR mammary OR fetal growth OR brain OR behavior OR IQ OR fertility OR bone OR osteogenesis)

Sources of information included in the review

Public literature databases that were searched for this review included: PubMed, Google Scholar, ToxNet, ChemIDplus advanced, the U.S. EPA's website, the Agency for Toxic Substances and Disease Registry (ATSDR)'s website, and IPCS Inchem.

Searches for ortho-phthalates not reviewed by the CHAP had no date restriction. We limited the dates of the literature searches for the 12 ortho-phthalates that are approved food additives and were reviewed by the CHAP from January 1, 2014 to March 1, 2016.

Part 2: Animal toxicology studies findings

A) CHAP report, 2014

Incorporated by reference. See Table III-4 for summary of findings.

B) Shibko and Blumenthal, 1973

In addition to the CHAP report, an important source of information was a 1973 review titled "Toxicology of phthalic acid esters used in food-packaging material" by FDA's scientists S.I. Shibko and H. Blumenthal and published in Environmental Health Perspective (EHP). The authors reviewed the information available to the agency for the 23 ortho-phthalates approved for use in contact with food as of 1973. They reported some toxicology data for 16 of the 24. We reprint below Table 5 (Lethal dose (LD) 50 data) and Table 6 (no-effect levels) of the EHP review.

Table III-1: Reprint from Shibko and Blumenthal's 1973 EHP review (page 133)

Table 5. Acute oral LD_{50} values for phthalate esters in the rat.

Phthalate ester	LD_{50}, g/kg body wt
Di-2-ethylhexyl phthalate	31
Diethyl phthalate	9.5 – 31
Butylphthalyl butyl glycolate	7
Butyl benzyl phthalate	18
Dicyclohexyl phthalate	>40
Di-*n*-hexyl phthalate	29.6
Diphenyl phthalate	8
Dibutyl phthalate	8 – 16
Diisobutyl phthalate	15
Diisodecyl phthalate	64
Dimethyl phthalate	6.9

Table III-2: Reprint from Shibko and Blumenthal's 1973 EHP review (page 134)

Table 6. Available data on no-effect levels of phthalates for rats and dogs (oral administration)

Phthalate	No-effect level, mg/kg of body weight/day[a]				
	Subacute		Chronic		
	Rat	Dog	Rat	Dog	Reference[b]
Dimethyl phthalate	—	—	1000(104)	—	*(3)*
Diethyl phthalate	2500(6)	1250	1250(104)	625(52)	FDA
Dibutyl phthalate	50(16)	—	125(52)	18(52)	*(4)*, *(5)*, FDA[a]
Dialkyl 79 phthalate	60(13)	—	—	—	*(6)*
Di-*n*-hexyl phthalate	50(13)	125(13)	—	—	FDA
Diisobutyl phthalate	50(16)	25–500(18)	—	—	FDA
Diisooctyl phthalate	100(4)	100(14)	—	—	FDA
Diisodecyl phthalate	150(13)	75(13)	—	—	FDA
Diphenyl phthalate	1000(13)	500(13)	—	—	FDA, *(7)*
Dicyclohexyl phthalate	—	—	27(104)	14(52)	*(5)*, FDA
Methylphthalyl ethyl glycolate	240(4)	—	750(104)	—	FDA
Ethylphthalyl ethyl glycolate	500(17	—	250(104)	250(52)	*(8)*, *(8)*, *(8)*
Butylphthalyl butyl glycolate	—	—	450(104)	140(104)	FDA
Di-2-ethylhexyl phthalate	200(13)	500(13)	65(104)	60(52)	(9), *(10)*, *(11)*, *(11)*
Dibutoxyethyl phthalate	500(4)	—	—	—	*(12)*
Butyl benzyl phthalate	500(13)	250(13)	—	—	*(7)*

[a] Figures in parentheses represent duration of study in weeks.

[b] Reference numbers are listed for the data appearing from left to right in the table; FDA denotes data were obtained from FDA files.

A summary of the Shibko and Blumenthal data is in Table III-4.

C) Literature search in the public domain, no date limitation

We were unable to find any toxicology or exposure data for 8 ortho-phthalates neither reviewed by CHAP nor listed in FDA's 1973 review. We did find very limited data for 10 ortho-phthalates listed in FDA's review but not reviewed by CHAP. Table III-3 summarizes the findings for the 18 ortho-phthalates.

Table III-3: Summary of toxicology findings in publicly available databases for ortho-phthalates NOT evaluated by the CHAP.

	Chemical name (CAS No.)	Findings
1	Diphenyl phthalate (84-62-8)	• LD50, oral, rat: 8g/kg. • No-effect level, rat, subacute: 1000 mg/kg; dog, subacute: 500 mg/kg. Shibko and Blumenthal, EHP 1973.
2	Methyl phthalyl ethyl glycolate (85-71-2)	• No-effect level, rat, subacute: 240 mg/kg; rat, chronic: 750 mg/kg. Shibko and Blumenthal, EHP 1973.
3	Diphenylguanidine phthalate (17573-13-6)	No toxicity or exposure data found
4	Ethyl phthalyl ethyl glycolate (84-72-0)	• LD50, oral, mouse 5660uL/kg. Journal of Biomedical Materials Research. Vol. 8, Pg. 11, 1974.

	Chemical name (CAS No.)	Findings
		• No-effect level, rat, subacute: 500 mg/kg; rat, chronic: 250 mg/kg; dog, chronic: 250 mg/kg. Shibko and Blumenthal, EHP 1973.
5	Diallyl phthalate (131-17-9)	• Rats exposed in utero; evaluation at gestational day 20. Significantly reduced fetal body weight; significant increase in incidence of fetuses with skeletal variations; also retarded ossification of certain bones. Saillenfait *et al.* 2008[1] • Significant increase in micronuclei frequency and levels of fragmented apoptotic cells in mussels. Barsiene *et al.* 2006[2] • Among several dialkyl phthalates, ortho isomer of diallyl phthalate was most potent to bind to estrogen receptor in vitro. Nakai *et al.* 1999[3] • LD50, oral, rat: 656mg/kg. National Toxicology Program Technical Report Series. Vol. NTP-TR-284, Pg. 1985 • LD50, oral, rabbit: 1700mg/kg. "Industrial Hygiene and Toxicology," 2nd ed., Patty, F.A., ed., New York, John Wiley & Sons, Inc., 1958-63Vol. 2, Pg. 1904, 1963.
6	Butyl phthalyl butyl glycolate (85-70-1)	• LD50,oral, rat: 7g/kg • No-effect level, rat, chronic: 450 mg/kg; dog, chronic: 140 mg/kg. Shibko and Blumenthal, EHP 1973.
7	Di(butoxyethyl) phthalate (117-83-9)	• LD50, oral, rat: 8380mg/kg. Journal of Industrial Hygiene and Toxicology. Vol. 30, Pg. 63, 1948. • No-effect level, rat, subacute: 500 mg/kg. Shibko and Blumenthal, EHP 1973.
8	Dimethylcyclohexyl phthalate (1322-94-7)	No toxicity or exposure data found
9	n-butyl n-octyl phthalate (84-78-6)	• No toxicity or exposure data found. • It is mentioned in a report by Litton Bionetics Inc titled Acute Toxicity of 14 ortho-phthalates to rainbow trout under flow-through conditions; not publicly available.
10	Di(2-ethylhexyl) hexahydro-phthalate (no CAS no. found)	• No toxicity or exposure data found.
11	n-butyl n-decyl phthalate (89-19-0)	• LD50, oral, rat: 20.8mL/kg. American Industrial Hygiene Association Journal. Vol. 30, Pg. 470, 1969.
12	n-amyl n-decyl phthalate (7493-81-4)	No toxicity or exposure data found.
13	n-octyl n-decyl phthalate (119-07-3 / 1323-73-5)	• LD50, oral, rat: 45200uL/kg (45.2mL/kg). American Industrial Hygiene Association Journal. Vol. 30, Pg. 470, 1969. • Equivocal results in mouse lymphoma assay in the presence and absence of rat liver S-9. Barber *et al.* J Appl Toxicol (2000) 20:69-80
14	Di-n-decyl phthalate (84-77-5)	• LD50, oral, rat: >64mL/kg. American Industrial Hygiene Association Journal. Vol. 23, Pg. 95, 1962.
15	Dodecyl phthalate (21577-80-0)	No toxicity or exposure data found
16	Dihydroabietyl phthalate (26760-71-4)	No toxicity or exposure data found
17	Castor oil phthalate, hydrogenated (No CAS found)	No toxicity or exposure data found
18	Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol (68650-73-7)	No toxicity or exposure data found
Shade rows: Petitioners were unable to find toxicology or exposure data for these chemicals.		

	Chemical name (CAS No.)	Findings
[1] Saillenfait AM, Gallissot F, Sabate JP. Evaluation of the developmental toxicity of diallyl phthalate administered orally to rats. Food and Chemical Toxicology 46:2150-2156. 2008 [2] Barsiene J, Syvokiene J, Bjornstad A. Induction of micronuclei and other nuclear abnormalities in mussels exposed to bisphenol A, diallyl phthalate and tetrabromodiphenyl ether-47. Aquatic Toxicology 78 Suppl 1:S105-108. 2006 [3] Nakai M, Tabira Y, Asai D *et al.* Binding characteristics of dialkyl phthalates for the estrogen receptor. Biochem Biophys Res Commun. 254:311-314. 1999		

We were unable to find any toxicology or exposure data for 8 ortho-phthalates neither reviewed by CHAP nor listed in FDA's 1973 review. We did find outdated and very limited data for 10 ortho-phthalates listed in FDA's review but not reviewed by CHAP. Table III-4 summarizes the findings for the 18 ortho-phthalates.

Table III-4 is a summary of toxicology findings for 30 ortho-phthalates listed in Table 1, page 7 of this petition as of 2014.

Table III-4 Summary of animal studies for 30 ortho-phthalates (sorted by increasing length of longest chain)

FDA Name (CAS No.)	Reproductive	Endocrine	Developmental	Acute (LD50)[1]	Subacute[2]	Chronic[3]
Dimethyl phthalate (131-11-3)	CHAP[4]: No reproductive guidelines studies have been published.	CHAP: None reported	CHAP: No detected	FDA 1973[5]: rat	NA[6]	FDA 1973: rat
Diphenyl phthalate (84-62-8)	NA	NA	NA	In rat [a]	NA	NA
Methyl phthalyl ethyl glycolate (85-71-2)	NA	NA	NA	NA	FDA 1973: rat	FDA 1973: rat
Diethyl phthalate (84-66-2)	CHAP: Decreased: sperm concentration (F1); gestation length (F1); uterus weight (F2) Increased: prostate weight (F1); sperm without tail (F1); age of vaginal opening (F1)	CHAP: Decreased: serum testosterone, serum DHT; testicular testosterone	CHAP: Increased: incidence of skeletal defects (rudimentary ribs)	FDA 1973: in rat	FDA 1973: rat and dog	FDA 1973: rat and dog
Diphenylguanidine phthalate (17573-13-6)	NA	NA	NA	NA	NA	NA
Ethyl phthalyl ethyl glycolate (84-72-0)	NA	NA	NA	Mouse [b]	FDA 1973: in rat	FDA 1973: in rat and dog
Diallyl phthalate (131-17-9)	NA	Nakai *et al.* 1999[7]. Ortho isomer of diallyl phthalate was most potent to bind to estrogen receptor in vitro among several dialkyl phthalates.	Saillenfait *et al.* 2008[8]. Gestational day 20 fetuses had significantly reduced fetal body weight; significant increase in incidence of skeletal variations; also retarded ossification of certain bones.	Rat [c] Rabbit [d]	NA	NA
Butyl benzyl phthalate (85-68-7)	CHAP: Decreased: ovarian and uterine weights (F0), mating and fertility (F1 males and females); male	CHAP: Decreased: serum testosterone	CHAP: Decreased: testis weights, male anogenital distance, serum testosterone	FDA 1973: rat	FDA 1973: rat and dog	NA

FDA Name (CAS No.)	Reproductive	Endocrine	Developmental	Acute (LD50)[1]	Subacute[2]	Chronic[3]
	reproductive organs weight; sperm number and motility Increased: reproductive tract malformations; histopathological changes in testis and epididymis (F1)		Increased: nipple retention, anogenital distance in females, incidence of hypospadias, undescended testes, frequency and incidence of fused ribs, anophtalmia, cleft palate, exencephaly, spina bifida, acephalostomia, onphalocele Delayed: preputial separation, puberty in F1 males and females, fetal testicular caudal migration.			
Diisobutyl phthalate (84-69-5)	CHAP: Decreased: testis weight. Increased: spermatogenic cell death, cytoskeletal disorganization in Sertoli cells	CHAP: Decreased: testicular testosterone production	CHAP: Decreased: anogenital distance; expression of steroidogenesis genes. Increased: nipple retention, incidence undescended testes and hypospadias.	FDA 1973: rat	FDA 1973: rat and dog	NA
Di-n-butyl phthalate (84-74-2)	CHAP: Decreased: male fertility; number pregnant rats Increased: testicular toxicity	CHAP: Decreased testicular testosterone, serum progesterone	CHAP: Reduced: spermatocyte and epididymis development; anogenital distance; testosterone Increased: cryptorchidism, hypospadias	FDA 1973: rat	FDA 1973: rat and dog	NA
Butyl phthalyl butyl glycolate (85-70-1)	NA	NA	NA	FDA 1973: rat	NA	FDA 1973: rat and dog
Dicyclohexyl phthalate	CHAP: Atrophy of seminiferous tubules.	CHAP: None reported	CHAP: Decreased: anogenital distance.	FDA 1973: rat	NA	FDA 1973: rat and dog

FDA Name (CAS No.)	Reproductive	Endocrine	Developmental	Acute (LD50)[1]	Subacute[2]	Chronic[3]
(84-61-7)	Decreased: spermatic head count (F1). Increased: estrous cycle length (F0)		Increased: preputial separation time; nipple retention; hypospadias.			
Di-n-hexyl phthalate (84-75-3)	CHAP: Testicular and seminiferous tubule atrophy. Decreased: testis, epididymal and seminal vesicle weights; uterine weight; number of litters per pair, number of live pups/litter and proportion of pups born alive; epididymal sperm concentration and motility.	CHAP 2014: None reported	CHAP: Decreased: anogenital distance. Increased: incidence undescended testes; hypospadias; underdeveloped testes; seminiferous tubules degeneration.	FDA 1973: rat	FDA 1973: rat and dog	NA
Di(butoxyethyl) phthalate (117-83-9)	NA	NA	NA	Rat [e]	FDA 1973: rat	NA
Dimethylcyclohexyl phthalate (1322-94-7)	NA	NA	NA	NA	NA	NA
Diisooctyl phthalate (27554-26-3)	CHAP: No published single or multigenerational reproductive studies.	CHAP: None reported	CHAP: Intraperitoneal route of administration showed high incidence of soft tissue abnormalities.	NA	FDA 1973: rat and dog	NA
Di(2-ethylhexyl) phthalate (117-81-7)	CHAP: Adversely affects male reproductive tract development and reproductive toxicity in adults.	CHAP: Interferes with the normal function of male hormone; associated with 'phthalate syndrome': malformation of male reproductive tract including external genitalia, nipple	CHAP: Causes male reproductive organs malformations (or absence), intrauterine death. Decreased: anogenital distance in males.	FDA 1973: rat	FDA 1973: rat and dog	FDA 1973: rat and dog

FDA Name (CAS No.)	Reproductive	Endocrine	Developmental	Acute (LD50)[1]	Subacute[2]	Chronic[3]
		retention, reduced anogenital distance.	Increased: nipple retention; testis weight. Delayed: vaginal opening and first estrous; preputial separation; intrauterine development.			
Di-n-octyl phthalate (117-84-0)	CHAP: No detected	CHAP: Decreased T4 and T3	CHAP: Increased incidence of supernumerary ribs	NA	CHAP: Hepatomegaly, hepatic fat accumulation, changed liver texture and appearance.	CHAP: Increased liver and kidney weight in F0 and F1; kidney toxicity altered histopathology; altered liver enzyme. Reduced thyroid follicle size and colloid density.
n-butyl n-octyl phthalate (84-78-6)	NA	NA	NA	NA	NA	NA
Di(2-ethylhexyl) hexahydro-phthalate (no CAS no. found)	NA	NA	NA	NA	NA	NA
Diisononyl phthalate (28553-12-0)	CHAP: No detected	CHAP: Decreased: testicular testosterone, fetal testicular testosterone production.	CHAP: Decreased: anogenital distance, sperm motility. Increased: nipple retention, other malformation of androgen-dependent organs and testes, incidence of multinucleated gonocytes.	NA	NA	CHAP: Kidney toxicity; renal tubular cell carcinomas. Liver toxicity; hepatocellular adenomas.

FDA Name (CAS No.)	Reproductive	Endocrine	Developmental	Acute (LD50)[1]	Subacute[2]	Chronic[3]
			Adverse effect on skeletal and kidney development and pup growth.			Mononuclear cell leukemia.
n-butyl n-decyl phthalate (89-19-0)	NA	NA	NA	Rat [f]	NA	NA
n-amyl n-decyl phthalate (7493-81-4)	NA	NA	NA	NA	NA	NA
n-octyl n-decyl phthalate (119-07-3 / 1323-73-5)	NA	NA	NA	Rat [g]	NA	NA
Di-n-decyl phthalate (84-77-5)	NA	NA	NA	Rat [h]	NA	NA
Diisodecyl phthalate (26761-40-0)	CHAP: Decreased: prostate and seminal vesicle weight; ovarian weight (F0); number normal sperm (F0). Increased: testis weight; testis, epididymis and seminal vesicle weight (F1); length estrous cycle (F0).	CHAP: None reported	CHAP: Decreased: F1 and F2 pup survival; body weight gain. Increased: rudimentary cervical/or accessory 14th ribs; supernumerary (7th) cervical rib; rudimentary lumbar (14th) ribs; liver weight in F1; liver hypertrophy and eosinophilia in F1 and F2; time of preputial separation in F2.	FDA 1973: rat	CHAP: Increased: liver and kidney weights. Change in serum triglycerides and cholesterol. FDA 1973: rat and dog	CHAP: Increased: liver and kidney weights. Liver histological changes.
Dodecyl phthalate (21577-80-0)	NA	NA	NA	NA	NA	NA
Dihydroabietyl phthalate (26760-71-4)	NA	NA	NA	NA	NA	NA

FDA Name (CAS No.)	Reproductive	Endocrine	Developmental	Acute (LD50)[1]	Subacute[2]	Chronic[3]
Castor oil phthalate, hydrogenated (No CAS found)	NA	NA	NA	NA	NA	NA
Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol (68650-73-7)	NA	NA	NA	NA	NA	NA
Results for 30 FDA-approved food additives	**NA for 18 or 30**	**NA for 18 or 30**	**NA for 18 or 30**	**NA for 13 or 30**	**NA for 18 or 30**	**NA for 20 or 30**

[1] LD50: lethal dose 50
[2] Subacute: study duration <90 days
[3] Chronic: study duration was 90 days or longer
[4] CHAP: Chronic Health Advisory Panel report published in 2014
[5] FDA 1973: Shibko and Blumenthal, Toxicology of Phthalic Acid Esters Used in Food Packaging Material, *Environmental Health Perspectives,* January 1973. No target organs were described; some information was provided on species, study duration, LD50 and no-effect level.
[6] NA: not available. Unable to find data in the public literature.
[7] Nakai M, Tabira Y, Asai D *et al.* Binding characteristics of dialkyl phthalates for the estrogen receptor. Biochem Biophys Res Commun. 254:311-314. 1999
[8] Saillenfait AM, Gallissot F, Sabate JP. Evaluation of the developmental toxicity of diallyl phthalate administered orally to rats. Food and Chemical Toxicology 46:2150-2156. 2008

References cited on Table III-4:

[a] American Industrial Hygiene Association Journal. Vol. 23, Pg. 95, 1962.
[b] Journal of Biomedical Materials Research. Vol. 8, Pg. 11, 1974.
[c] National Toxicology Program Technical Report Series. Vol. NTP-TR-284, Pg. 1985
[d] "Industrial Hygiene and Toxicology," 2nd ed., Patty, F.A., ed., New York, John Wiley & Sons, Inc., 1958-63Vol. 2, Pg. 1904, 1963.
[e] Journal of Industrial Hygiene and Toxicology. Vol. 30, Pg. 63, 1948
[f] American Industrial Hygiene Association Journal. Vol. 30, Pg. 470, 1969.
[g] American Industrial Hygiene Association Journal. Vol. 30, Pg. 470, 1969.
[h] American Industrial Hygiene Association Journal. Vol. 23, Pg. 95, 1962.

Our broad and thorough review of the literature indicates that for a handful of ortho-phthalates, there is a substantial amount of evidence indicating they are potentially hazardous chemicals, especially for pregnant women and children. For the majority of ortho-phthalates included in this petition, however, toxicology data gaps persist and there is insufficient scientific information to support their safety.

In a letter to former Representative Henry Waxman, Mr. Kraus, Associate Commissioner for Legislation at FDA stated that the last premarket review of ortho-phthalate safety the agency conducted was in 1985. He also wrote "[i]n 2008, FDA's Office of Food Additive Safety (OFAS) within the Center for Food Safety and Applied Nutrition (CFSAN) established a Phthalate Task Group (PTG) to conduct a post-market evaluation of approved, regulated phthalate food additives to further address the potential risks raised in the contemporary literature and to ensure that the authorized uses continued to meet the "reasonable certainty of no harm" safety standard for food additives." To our knowledge, FDA has not made public the results and conclusions of the post-market evaluation by the Phthalates Task Group.

It has been seven years since the PTG was formed and FDA has not taken "appropriate regulatory action to remove these materials from the market place" as Mr. Kraus said would occur should "our review indicates that existing data no longer support the continued safe use of these materials in food contact applications."[60] It is the petitioners' opinion supported by our toxicology literature review that the existing data—and lack thereof-- no longer support the safe use of the 30 ortho-phthalates included in this petition.

This lack of agency's action could be due to a couple of reasons:

1- FDA has not completed its review either for lack of resources, scientific data, or both;
2- FDA concluded the approved uses of ortho-phthalates meet the safety standard of reasonable certainty of no harm. We believe this would be an improbable conclusion considering that
   - eight ortho-phthalates (approved as food additives) fully evaluated by the CHAP for uses in toys and child care products were recommended for banning. If the CHAP experts concluded that their uses in toys are unsafe after a thorough risk assessment--including cumulative risk assessment for five ortho-phthalates with anti-androgenic effects--it would be hard to explain their use in food is safe since the safety standard for uses in toys and child care products is "reasonable certainty of no harm"[61], the same as for additives in food;
   - two ortho-phthalates, dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP), should be avoided in FDA's Center for Drug Evaluation and Research (CDER)-regulated products,[62] due to concerns about having "reproductive and developmental toxicity." FDA "has determined that there is evidence that exposure to DBP and DEHP from pharmaceuticals presents a potential risk of developmental and

[60] Thomas A. Kraus, Associate Commissioner for Legislation. U.S. Food and Drug Administration. Letter to Mr. Waxman. September 23, 2014.
[61] Consumer Product Safety Improvement Act of 2008. Section 108.
[62] Guidance for Industry Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products. 2012. Center for Drug Evaluation and Research (CDER), US Food and Drug Administration.

reproductive toxicity" and it is very clear that FDA "generally does not consider DBP or DEHP safe or suitable as an inactive ingredient in OTC monograph products;"
- toxicology data is very limited, outdated, or non-existent for those ortho-phthalates not reviewed by the CHAP; and
- it is unlikely FDA was able to conducted a cumulative effect assessment of all approved ortho-phthalates according to 21CFR §170.3(i) to fully assess their safe use.

Part 3: Review of Consumer Product Safety Commission Chronic Hazard Advisory Panel (CHAP) on Phthalates and Phthalates Alternatives 2014 Report

The CHAP report and all the references within were incorporated by reference. Section 108(b)(2) of the Consumer Product Safety Improvement Act of 2008 (CPSIA) requires 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. (Emphasis added)

We believe FDA should take CHAP's conclusion into consideration due to the many similarities —from the safety standard to considering cumulative effects—between the Food Additive Amendment of 1958 and the CPSIA of 2008 mandate to the CHAP,

The CHAP assessed the risks of 14 ortho-phthalates, 12 of which are approved food additives. In general, the risk of individual compounds was considered for all 14 ortho-phthalates, while cumulative risks were considered for anti-androgenic ortho-phthalates only; these were di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), butylbenzyl phthalate (BBP), diisononyl

phthalate (DINP) and diisobutyl phthalate (DIBP). The CHAP concluded that dose addition was adequate for mixtures of ortho-phthalates to provide the foundation of a cumulative risk assessment. This approach is similar to that in 21CFR §170.18(a): "**food additives that cause similar or related pharmacological effects will be regarded as a class, and in the absence of evidence to the contrary, as having additive toxic effects and will be considered as related food additives**."

Unlike FDA that limits exposure to the diet, the CHAP conducted aggregate exposures including diet, household products, toys and children products and personal care products. The experts reported that overall, food, beverages and drugs via direct ingestion "constituted the highest [ortho-]phthalates exposure to all subpopulations."[63]

After a thorough, public and transparent process, the CHAP published its recommendations that we reproduce below:

> *Permanently Banned Ortho-phthalates*. The CHAP recommends no further action by CPSC on dibutyl phthalate (DBP), butylbenzyl phthalate (BBP), or di(2-ethylhexyl) phthalate (DEHP) at this time because they are already permanently banned in children's toys and child care articles at levels greater than 0.1%. However, the CHAP recommends that **U.S. agencies responsible for dealing with DBP, BBP, and DEHP exposures from food and other products conduct the necessary risk assessments with a view to supporting risk management steps**. (Emphasis added)
>
> *Interim Banned Ortho-phthalates*. The CHAP recommends that the interim ban on the use of diisononyl phthalate (DINP) in children's toys and child care articles at levels greater than 0.1% be made permanent. This recommendation is made because DINP does induce Antiandrogenic effects in animals, although with lesser potency than other active ortho-phthalates, and therefore can contribute to the cumulative risk from other antiandrogenic ortho-phthalates. Moreover, the CHAP recommends that **U.S. agencies responsible for dealing with DINP exposures from food[64] and other products conduct the necessary risk assessments with a view to supporting risk management steps.** (Emphasis added)
>
> On the other hand, di-n-octyl phthalate (DNOP) and diisodecyl phthalate (DIDP) do not appear to possess antiandrogenic potential; nonetheless, the CHAP is aware that both are potential developmental toxicants (causing supernumerary ribs in laboratory animals) and potential systemic toxicants (causing adverse effects on the liver and kidney in laboratory animals). However, because the MOEs in humans are likely to be very high for these compounds individually, the CHAP does not find compelling data to justify maintaining the current interim bans on the use of DNOP or DIDP in children's toys and child care articles. Therefore, the CHAP recommends that the current bans on DNOP and DIDP be lifted but that **U.S. agencies responsible for dealing with DNOP and DIDP exposures from food and child care products conduct the necessary risk assessments with a view to supporting risk management steps**. (Emphasis added)

[63] Executive Summary, CHAP report, page 3

[64] DINP had the maximum potential for exposure to children and exposures were primarily from food. CHAP report page 7

Ortho-phthalates Not Banned. The CHAP recommends no action on dimethyl phthalate (DMP) or diethyl phthalate (DEP). However, the CHAP recommends that **U.S. agencies responsible for dealing with DEP exposures from food, pharmaceuticals, and personal care products conduct the necessary risk assessments with a view to supporting risk management steps**. (Emphasis added)

CPSC has recently detected di(2-propylheptyl) phthalate (DPHP) in some children's toys. Given the general lack of publically available information on DPHP, the CHAP is unable to recommend any action regarding the potential use of DPHP in children's toys or child care articles at this time. However, the CHAP **encourages the appropriate U.S. agencies to obtain the necessary toxicological and exposure data to assess any potential risk from DPHP**. (Emphasis added)

Based on the limited available data, CHAP found that current exposures to diisobutyl phthalate (DIBP), di-n-pentyl phthalate (DPENP), di-n-hexyl phthalate (DHEXP), and dicyclohexyl phthalate (DCHP) individually do not indicate a high level of concern. Although DIBP is not widely used in toys or child care articles, CPSC has recently detected DIBP in some children's toys. Furthermore, the toxicological profiles of DIBP, DPENP, DHEXP, and DCHP are very similar to other antiandrogenic ortho-phthalates, including DBP and DEHP. Therefore, exposure to DIBP, DPENP, DHEXP, or DCHP contributes to the cumulative risk from other antiandrogenic ortho-phthalates. The CHAP recommends that DIBP, DPENP, DHEXP, and DCHP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1%.

Toxicity data are limited for diisooctyl phthalate (DIOP), but structure-activity relationships suggest that antiandrogenic effects are possible. The CHAP recommends that DIOP be subject to an interim ban from use in children's toys and child care articles at levels greater than 0.1% until sufficient toxicity and exposure data are available to assess the potential risks.

Phthalate Alternatives. Although data on most phthalate alternatives are limited, there is no evidence that any of the alternatives considered by the CHAP presents a hazard to infants or toddlers from mouthing toys or child care articles. Therefore, the CHAP recommends no action at this time. However, the CHAP recommends that **the appropriate U.S. agencies obtain the necessary exposure and hazard data to estimate total exposure to the phthalate alternatives and assess the potential health risks.** (Emphasis added) Specifically, the CHAP recommends:

- 2,2,4-trimethyl-1,3 pentanediol diisobutyrate (TPIB). The CHAP recommends that the **appropriate U.S. agencies obtain the necessary exposure and hazard data to estimate total exposure to TPIB and assess the potential health risks**.
- Di(2-ethylhexyl) adipate (DEHA). Data on exposure from toys and child care articles are not available. The CHAP recommends that the **appropriate U.S. agencies obtain the necessary data to estimate DEHA exposure from diet and children's articles, and assess the potential health risks.**

- Di(2-ethylhexyl) terephthalate (DEHT). Information on total exposure to DEHT is not available. The CHAP recommends that the **appropriate U.S. agencies obtain the necessary exposure data to estimate total exposure to DEHT and assess the potential health risks**.
- Acetyl tributyl citrate (ATBC). Data on ATBC are somewhat limited. The CHAP recommends that the appropriate **U.S. agencies obtain the necessary exposure and hazard data to estimate total exposure to ATBC and assess the potential health risks**.
- Diisononyl hexahydrophthalate (1,2-cyclohexanedicarboxylic acid, diisononyl ester) (DINX). Given the lack of publically available information on DINX, the CHAP strongly encourages the **appropriate U.S. agencies to obtain the necessary toxicological and exposure data to assess any potential risk from DINX**.
- Tris(2-ethylhexyl) trimellitate (TOTM). The CHAP strongly recommends that appropriate exposure information be obtained before TOTM is used in toys and child care products.

Part 4: Human studies findings

As mentioned in Part 1, we performed a literature search for human studies related to:

A- *Ortho-phthalates not reviewed by CHAP:* we were unable to find any human studies for these 18 ortho-phthalates. As mentioned earlier, this search was not restricted to a specific time frame.

B- Ortho-phthalates reviewed by CHAP: we found information on nine ortho-phthalates published between January 1, 2014 and March 1, 2016. Although the CHAP report was published in 2014, we expanded the search to include all of 2014 to compensate for delays between the end of CHAP's work and the publication of its final report. A summary of our findings are in Table III-5; superscripts indicate the source of data and the full citations are included in Part 5-2 below.

To summarize the findings we discriminated the data based on the time of exposure, i.e. prenatal or postnatal. We defined prenatal as those studies evaluating associations between maternal urinary concentrations of ortho-phthalate metabolites with endpoints measured in their children at different ages after birth. Postnatal were studies evaluating associations between urinary concentrations of ortho-phthalate metabolites and endpoints measured in the same individual regardless of age. Endpoints were related to developmental (in the broad sense of the term, as in health effects observed in children months or years after being exposed in utero to ortho-phthalates), reproductive and endocrine toxicity.

Table III-5 Summary of human studies for ortho-phthalates (sorted by increasing length of longest chain)

FDA Name (CAS No.)	Prenatal[1]	Postnatal[2]
Dimethyl phthalate (131-11-3)	A few epidemiologic studies measured urinary concentrations of the DMP metabolite monomethyl phthalate (MMP). In those that did, there were no associations of maternal urinary MMP concentrations with measures of male reproductive tract development (specifically, shortened AGD). No human studies reported associations of MMP with neurodevelopment. Three publications measured MMP but reported associations of neurodevelopmental tests with a summary measure of low molecular weight phthalates (including MEP, MMP, MBP, and MIBP).[a] Umbilical cord and placenta samples. Correlated with altered expression of placental proteins responsible for fetal growth and development. [b]	Urinary concentration of mono-methyl phthalate was inversely associated with pubarche in boys. [c]
Diphenyl phthalate (84-62-8)	None found	None found
Methyl phthalyl ethyl glycolate (85-71-2)	None found	None found
Diethyl phthalate (84-66-2)	Several epidemiologic studies measured urinary concentrations of the DEP metabolite MEP. Of those that did, some reported associations of maternal urinary MEP concentrations with measures of male reproductive tract development (specifically, shortened AGD), whereas other studies did not. Several studies reported associations of poorer scores on neurodevelopment tests with MEP or with a summary measure of low molecular weight phthalates that was largely explained by MEP concentrations. [a] In female infants, it was positively associated with altered expression of placental proteins responsible for fetal growth and development. [b] Maternal urinary metabolite was associated with lower BMI in girls but not boys. [d]	Statistically significant inverse association between progesterone and DEP metabolite MEP in pregnant women. [p] Men's urinary concentration of MEP was associated with longer time to pregnancy, approximately 20% reduction in fecundity [q] Urinary metabolites were positively correlated with abdominal obesity in adolescents.[c]

FDA Name (CAS No.)	Prenatal[1]	Postnatal[2]
	Maternal urinary metabolite was not associated with anogenital distance or penile width.[e] Maternal urinary metabolite was associated with lower insulin secretion among pubertal boys and higher leptin among pubertal girls. [j]	
Diphenylguanidine phthalate (17573-13-6)	None found	None found
Ethyl phthalyl ethyl glycolate (84-72-0)	None found	None found
Diallyl phthalate (131-17-9)	None found	None found
Butyl benzyl phthalate (85-68-7)	Several epidemiologic studies measured urinary concentrations of the BBP metabolite MBZP. In those that did, there were no associations of maternal urinary MBZP concentrations with measures of male reproductive tract development (specifically, shortened AGD). A few studies reported associations of MBZP with poorer scores on neurodevelopment tests, whereas others did not. [a] In boys, higher MBzP concentrations in maternal urine were associated with higher scores of oppositional behavior and conduct problems; whereas they were associated with reduced anxiety scores in girls. [t] Positive association between prenatal urinary concentrations of BBP metabolite MBzP and SHBG levels [s] Prenatal metabolite of BBP was significantly associated with asthma-like symptoms and diagnosis of current asthma. [v] Maternal urinary metabolite was not associated with anogenital distance or penile width.[e] High maternal urinary metabolite increased the risk of food allergy in children during the first 2 years of life (OR 4.17). [g] Maternal urinary metabolite concentration was significantly associated with reduced	Boys psychomotor development index was positively related to BBP metabolite MBzP; there was no significant effect among girls [r] Significant association between BBP exposure during pregnancy and preterm birth [s] Significant inverse association between urinary BBP metabolites and serum testosterone in girls and young women [u] Men's urinary concentration of MBP was associated with longer time to pregnancy, approximately 20% reduction in fecundity [q] Inverse association between urinary metabolite concentration and sperm motility. [f] Peripubertal urinary metabolite was associated with lower IGF-1 among pubertal boys. [j] Semen metabolite concentration was associated with decreased sperm curvilinear and straight-line velocity and increased percentage of abnormal heads and tails. [m]

FDA Name (CAS No.)	Prenatal[1]	Postnatal[2]
	serum thyroid stimulating hormone in cord blood. [i]	
Diisobutyl phthalate (84-69-5)	Several epidemiologic studies measured urinary concentrations of MIBP. Of those that did, there were associations of maternal urinary MIBP concentrations with measures of male reproductive tract development (specifically, shortened AGD). Several studies reported associations of MBP with poorer scores on neurodevelopment tests, whereas another did not. [a] In boys, concentrations of MIBP in maternal urine were associated with higher scores for inattention, rule-breaking behavior, aggression and conduct problems. [t] Child full scale IQ was inversely associated with prenatal urinary metabolite concentration of DIBP. Among children with mothers with the highest versus lowest quartile DIBP metabolite concentration, IQ was 6.7 points lower, respectively. [w] Maternal urinary metabolite was not associated with anogenital distance or penile width.[e]	Significant association between DIBP exposure during pregnancy and preterm birth [s] Urinary metabolite was positively correlated with abdominal obesity in adolescents.[c]
Di-n-butyl phthalate (84-74-2)	Several epidemiologic studies measured urinary concentrations of DBP metabolite MBP. Of those that did, there were associations of maternal urinary MBP concentrations with measures of male reproductive tract development (specifically, shortened AGD); however other studies did not find such association. Several studies reported associations of MBP with poorer scores on neurodevelopment tests; while others did not. [a] Child full scale IQ was inversely associated with prenatal urinary metabolite concentration of DBP. Among children with mothers with the highest versus lowest quartile DBP metabolite concentration, IQ was 6.7 points lower, respectively. [w]	Urinary concentration of DBP metabolites were marginally associated with increased odds of co-occurring attention deficit disorder and learning disability in children [x] Significant association between DBP exposure during pregnancy and preterm birth [s] Significant inverse association between urinary DBP metabolites and serum testosterone in men between 40-60 years of age. [u] Body mass index and waist circumference were positively associated with urinary DBP metabolite in adult females. [y] Men's urinary concentration of MBP was associated with longer time to pregnancy, approximately 20% reduction in fecundity [q]

FDA Name (CAS No.)	Prenatal[1]	Postnatal[2]
	Positive association between prenatal urinary concentrations of DBP metabolite MBP and SHBG levels, reduced odds of adrenarche and increased odds of puberty [s] Prenatal metabolite of DBP was significantly associated with asthma-like symptoms and diagnosis of current asthma. [v] Maternal urinary metabolite was not associated with anogenital distance or penile width.[e] Maternal urinary metabolite was significantly associated with externalizing problem scores, delinquent and aggressive behavior at age 8 years. [l]	Urinary metabolite was positively correlated with abdominal obesity in adolescents.[c] Peripubertal urinary metabolite was associated with lower IGF-1 among pubertal boys. [j] Urinary metabolite concentration was positively associated with below-reference sperm concentration and total sperm count. [k] Semen metabolite concentration was associated with decreased semen volume. [m]
Butyl phthalyl butyl glycolate (85-70-1)	None found	None found
Dicyclohexyl phthalate (84-61-7)	No published human studies. [a]	None found
Di-n-hexyl phthalate (84-75-3)	No published human studies. [a]	None found
Di(butoxyethyl) phthalate (117-83-9)	None found	None found
Dimethylcyclohexyl phthalate (1322-94-7)	None found	None found
Diisooctyl phthalate (27554-26-3)	No epidemiologic studies measured metabolites of DIOP in relation to male reproductive health or neurodevelopmental endpoints. [a]	None found
Di(2-ethylhexyl) phthalate (DEHP) (117-81-7)	Several epidemiologic studies measured urinary concentrations of metabolites of DEHP, including MEHP, MEHHP, MEOHP, and mono (2-ethyl-5-carboxypentyl) phthalate (MECPP). Of those that did, there were associations of maternal urinary Mono (2-ethylhexly) phthalate (MEHP), MEHHP, and MEOHP concentrations with measures of male reproductive tract development (specifically, shortened AGD). One study did not find association between MEHP and AGD. Several studies reported associations of MEHP with poorer scores on	Increasing urinary concentrations of DEHP metabolites increased the odds of attention deficit disorder in children [x] In girls, there was a negative association between mental development index and DEHP urinary metabolites, whereas there was no significant effect among boys. [r] Significant association between DEHP exposure during pregnancy and preterm birth [s] Significant inverse association between urinary DEHP metabolites and serum testosterone in males of most ages. [u]

FDA Name (CAS No.)	Prenatal[1]	Postnatal[2]
	neurodevelopment tests, whereas others did not. [a] In boys, the sum of DEHP metabolites in maternal urine was associated with higher scores for somatic problems [t] Prenatal urinary concentrations of DEHP metabolites showed positive association with SHBG levels, reduced odds of adrenarche and increased odds of puberty [s] First trimester maternal urinary concentrations of DEHP metabolites were significantly and inversely associated with two anogenital distance measurements (anoscrotal distance and anopenile distance). [bb] Umbilical cord and placenta samples. Correlated with altered expression of placental proteins responsible for fetal growth and development. And negatively correlated with birth weight and gestational age in male infants [b] Maternal urinary metabolite was associated with lower BMI in girls but not boys. [d] Maternal urinary metabolite was not associated with anogenital distance or penile width.[e] Maternal urinary metabolite was significantly associated with shorter ano-scrotal distance in male infants. [h] Maternal urinary metabolite was associated with higher IGF-1 among pubertal girls. [j] Maternal urinary metabolites were significantly associated with externalizing problem scores, delinquent and aggressive behavior at age 8 years. [l]	Inverse correlation between urinary DEHP metabolites and neutral alpha-glucosidase, a marker of epididymal function in adult men. [z] Body mass index was positively associated with urinary DEHP metabolite in adult females. [y] Statistically significant inverse association between free T4 and DEHP metabolites in pregnant women. [p] Women with high levels of urinary DEHP metabolites had mean ages of menopause 1.9 to 3.8 years earlier than women with lower levels. [aa] Urinary metabolites were positively correlated with abdominal obesity in adolescents.[c] Peripubertal urinary metabolite was associated with lower IGF-1 among pubertal boys and higher IGF-1, insulin secretion and insulin resistance in girls. [j] Urinary metabolites concentration was positively associated with below-reference sperm concentration and total sperm count. [k] Semen metabolites concentrations were associated with decreased semen volume, sperm curvilinear and straight-line velocity. [m] Higher urinary metabolites levels were significantly associated with decrease in antral follicle count among women seeking infertility care. [n] Urinary metabolite was associated with higher age-, sex- and height-standardized blood pressure in children. [o]
Di-n-octyl phthalate (117-84-0)	No published human studies [a] Positive association between prenatal urinary concentrations of DNOP metabolite MCPP and SHBG levels [s]	Boys psychomotor development index was positively related to DNOP metabolite MCPP; there was no significant effect among girls [r]

FDA Name (CAS No.)	Prenatal[1]	Postnatal[2]
		Significant association between DNOP exposure during pregnancy and preterm birth [s] Significant inverse association between urinary DNOP metabolites and serum testosterone in girls and young women [u] Statistically significant inverse association between free T3 and DNOP metabolite MCPP in pregnant women. [p]
n-butyl n-octyl phthalate (84-78-6)	None found	None found
Di(2-ethylhexyl) hexahydro-phthalate (no CAS no. found)	None found	None found
Diisononyl phthalate (28553-12-0)	No epidemiologic studies measured metabolites of DINP in relation to male reproductive health or neurodevelopment endpoints. [a] Maternal urinary metabolite was not associated with anogenital distance or penile width.[e] Maternal urinary metabolite was significantly associated with shorter ano-scrotal distance in male infants. [h]	Higher urinary concentrations of monocarboxyoctyl phthalate (MCOP), a metabolite of di-isononyl phthalate (DiNP) were associated with shorter luteal phase in women attempting pregnancy. [cc] Significant inverse association between urinary DINP metabolites and serum testosterone in girls and young women [g] Inverse correlation between urinary DINP metabolites and serum testosterone in adult men. [z] Statistically significant inverse association between free T3 and DINP metabolite MCOP in pregnant women. [p] Urinary metabolite was associated with higher age-, sex- and height-standardized blood pressure in children. [o]
n-butyl n-decyl phthalate (89-19-0)	None found	None found
n-amyl n-decyl phthalate (7493-81-4)	None found	None found
n-octyl n-decyl phthalate (119-07-3 / 1323-73-5)	None found	None found
Di-n-decyl phthalate (84-77-5)	None found	None found
Diisodecyl phthalate (26761-40-0)	No published human studies [a]	Significant inverse association between urinary DIDP metabolites and serum testosterone in girls and young women [u]

FDA Name (CAS No.)	Prenatal[1]	Postnatal[2]
		Urinary metabolite was associated with higher age-, sex- and height-standardized blood pressure in children. [o]
Dodecyl phthalate (21577-80-0)	None found	None found
Dihydroabietyl phthalate (26760-71-4)	None found	None found
Castor oil phthalate, hydrogenated (No CAS found)	None found	None found
Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol (68650-73-7)	None found	None found
Results for 30 FDA-approved food additives	**8 of 30 have prenatal human data**	**9 of 30 have postnatal human data**

[1]Prenatal: studies evaluating associations between maternal urinary concentrations of ortho-phthalate metabolites during pregnancy with endpoints measured in children born to those mothers; measurements were performed months or years after birth.
[2]Postnatal: studies evaluating associations between urinary concentrations of ortho-phthalate metabolites and endpoints measured in the same individual.

Part 5: List of references and additional relevant studies

1- References to animal studies cited on Table III-4

a) American Industrial Hygiene Association Journal. Vol. 23, Pg. 95, 1962.

b) Journal of Biomedical Materials Research. Vol. 8, Pg. 11, 1974.

c) National Toxicology Program Technical Report Series. Vol. NTP-TR-284, Pg. 1985

d) "Industrial Hygiene and Toxicology," 2nd ed., Patty, F.A., ed., New York, John Wiley & Sons, Inc., 1958-63Vol. 2, Pg. 1904, 1963.

e) Journal of Industrial Hygiene and Toxicology. Vol. 30, Pg. 63, 1948

f) American Industrial Hygiene Association Journal. Vol. 30, Pg. 470, 1969.

g) American Industrial Hygiene Association Journal. Vol. 30, Pg. 470, 1969.

h) American Industrial Hygiene Association Journal. Vol. 23, Pg. 95, 1962.

2- References to human studies cited on Table III-5

a) Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives. July 2014.

b) Neonatal phthalate ester exposure induced placental MTs, FATP1 and HFABP mRNA expression in two districts of southeast China. Li B, Xu X, Zhu Y *et al.* 2016 Sci Rep. 6:21004

c) The effects of phthalate and nonylphenol exposure on body size and secondary sexual characteristics during puberty. Hou JW, Lin CL, Tsai YA *et al.* 2015. Int J Hyg Environ Health 128:603-15.

d) Prenatal phthalate exposures and body mass index among 4 to 7 year old children: A pooled analysis. Buckley JP, Engel SM, Braun JM *et al.* 2016. Epidemiology (Jan 6, ahead of print)

e) Prenatal exposure to phthalates and anogenital distance in male infants from a low-exposed Danish cohort (2010-2012). Jensen TK, Frederiksen H, Kyhl HB *et al.* 2015. Environ Health Perspect. (Dec 15 published ahead of print)

f) Phthalate exposure and semen quality in fertile US men. Thurston SW, Mendiola J, Bellamy AR *et al.* 2015. Andrology (Nov 24 published ahead of print)

g) The effect of prenatal exposure to phthalates on food allergy and early eczema in inner-city children. Stelmach I, Mjak P, Jerzynska J *et al.* 2015. Allergy Asthma Prox. 36:72-78

h) Prenatal phthalate exposures and anogenital distance in Swedish boys. Bornehag CG, Carlstedt F, Jonsson BA *et al.* 2015. Environ Health Perspect. 123:101-107

i) Relationship of urinary phthalate metabolite with serum thyroid hormones in pregnant women and their newborns: a prospective birth cohort in Taiwan. Kuo FC, Su SW, Wu CF *et al.* 2015. PLoS One 10(6):e0123884.

j) Relating phthalate and BPA exposure to metabolism in peripubescence: The role of exposure timing, sex, and puberty. Watkins DJ, Peterson KE, Ferguson KK *et al.* 2016. J Clin Endocrinol Metab 101:79-88

k) Phthalate exposure and human semen quality: Results from an infertility clinic in China. Wang YX, You L, Zeng Q *et al.* 2015. Environ Res 142:1-9

l) Prenatal exposure to phthalate esters and behavioral syndromes in children at 8 years of age: Taiwan Maternal and Infant Cohort Study. Lien YJ, Ku HY, Su PH *et al.* 2015. Environ Health Perspect 123:95-100

m) Semen phthalates metabolites, semen quality parameters and serum reproductive hormones: A cross-sectional study in China. Wang YX, Zeng Q, Sun Y *et al.* 2016. Environ Pollut. 211:173-182

n) Urinary phthalate metabolites and ovarian reserve among women seeking infertility care. Messerlian C, Souter I, Gaskins AJ *et al.* 2016. Hum Reprod 31:75-83

o) Association of exposure to di-2-ethylhexylphthalate replacements with increased blood pressure in children and adolescents. Trasande L, Attina TM. 2015. Hypertension 66:301-308

p) Urinary phthalate metabolites in relation to maternal serum thyroid and sex hormone levels during pregnancy: a longitudinal analysis. Johns LE, Ferguson KK, Soldin OP, *et al.* 2015. Reproductive Biology and Endocrinology 13:4 doi: 10.1186/1477-7827-13-4

q) Urinary bisphenol A, phthalates, and couple fecundity: the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. Germaine M. Buck Louis, Rajeshwari Sundaram, Anne M. Sweeney *et al.* 2014. Fertility and Sterility 101:1359-1366.

r) Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. Martha M. Téllez-Rojo, Alejandra Cantoral, David E. Cantonwine *et al.* 2013. Science of the Total Environment 386-390. doi:10.1016/j.scitotenv.2013.05.021

s) Environmental phthalate exposure and preterm birth. Ferguson KK, McElrath TF, Meeker JD. 2014. JAMA Pediatrics 168:61-67.

t) Prenatal Phthalate Exposures and Neurobehavioral Development Scores in Boys and Girls at 6–10 Years of Age. Roni W. Kobrosly, Sarah Evans, Amir Miodovnik *et al.* 2014. Environmental Health Perspectives 122:521-528.

u) Urinary Phthalate Metabolites Are Associated With Decreased Serum Testosterone in Men, Women, and Children From NHANES 2011–2012. John D. Meeker and Kelly K. Ferguson. 2014. Journal of Clinical Endocrinology and Metabolism 99:4346-4352.

v) Asthma in Inner-City Children at 5–11 Years of Age and Prenatal Exposure to Phthalates: The Columbia Center for Children's Environmental Health Cohort. Robin M. Whyatt, Matthew S. Perzanowski, Allan C. Just *et al.* 2014. Environmental Health Perspectives 122:1141-1146.

w) Persistent associations between maternal prenatal exposure to phthalates on child IQ at age 7 years. Pam Factor-Litvak, Beverly Insel, Antonia M. Calafat *et al.* 2014. PLOS One 1-15. DOI:10.1371/journal.pone.0114003

x) Association between phthalates and attention deficit disorder and learning disability in U.S. children, 6–15 years. Vidita Chopra, Kim Harley, Maureen Lahiff *et al.*. 2014. Environmental Research 128:64-69.

y) Associations of urinary phthalates with body mass index, waist circumference and serum lipids among females: National Health and Nutrition Examination Survey 1999–2004. L Yaghjyan, S Sites, Y Ruan *et al.* 2015. International Journal of Obesity 39, 994–1000.

z) Phthalates, perfluoroalkyl acids, metals and organochlorines and reproductive function: a multipollutant assessment in Greenlandic, Polish and Ukrainian men. Virissa Lenters, Lützen Portengen, Lidwien A M Smit *et al.* 2015. Occupational and Environmental Medicine 72:385–393.

aa) Persistent Organic Pollutants and Early Menopause in U.S. Women. Natalia M. Grindler, Jenifer E. Allsworth, George A. Macones *et al.* PLoS ONE 10(1): e0116057. doi:10.1371/journal.pone.0116057

bb) First trimester phthalate exposure and anogenital distance in newborns. Swan SH, Sathyanarayana S, Barrett ES *et al.* 2015. Human Reproduction 30(4):963-72.

cc) Urinary Concentrations of Phthalate Metabolites and Bisphenol A and Associations with Follicular-Phase Length, Luteal-Phase Length, Fecundability, and Early Pregnancy Loss. Anne Marie Jukic, Antonia M. Calafat, D. Robert McConnaughey *et al.* 2015. Environmental Health Perspectives. Advanced publication July 10, 2015. http://dx.doi.org/10.1289/ehp.1408164

3- Additional relevant publications

a) Temporal Trends in Phthalate Exposures: Findings from the National Health and Nutrition Examination Survey, 2001–2010. Ami R. Zota, Antonia M. Calafat, and Tracey J. Woodruff. 2014. Environmental Health Perspectives 122:235-241

The authors examined temporal trends in urinary concentrations of phthalate metabolites in the U.S. population. They combined data on metabolites of 10 ortho-phthalates: DMP, DEP, DPB, DIBP, BBP, DCHP, DEHP, DNOP, DINP and DIDP for more than 11,000 participants from five NHANES cycles.

Their results demonstrate that the US population exposure to ortho-phthalates has changed in the last 10 years, while exposures to DBP, BBP and DEHP have declined, exposures to DINP and DIBP have increased. They concluded that "the significant data gaps" made it difficult to explain the trends but "may at least in part reflect" stricter regulation imposed in certain consumer products.

b) Phthalates and diet: a review of the food monitoring and epidemiology data. Samantha E Serrano, Joseph Braun, Leonardo Trasande, Russell Dills and Sheela Sathyanarayana. 2014. Environmental Health 13:43

The authors sought to identify primary foods associated with increased exposure through a review of the food monitoring survey and epidemiological data aiming at identifying primary foods/diets associated with phthalate biomarker levels. They analyzed urinary metabolites for 9 phthalates (DMP, DEP, DIBP, DBP, DNOP, DINP, DIDP, BBP and DEHP).

Foods with consistent reports of high phthalate concentrations included meats, specifically poultry; oils and fats; dairy, cream in particular. Foods with consistent low concentrations included dairy (yogurt, milk); eggs; grain (pasta, noodles and rice); fruits and vegetables and beverages and water. Foods with varied concentrations included seafood; bread and cereal; and spices.

The authors' exposure estimate based on a typical diet resulted in infants being exposed to more than double the amount of DEHP the US Environmental Protection Agency (EPA) consider safe (EPA reference dose: 20 µg/kg/d); adolescents with a diet high in dairy and meat also exceeded EPA's RfD.

Appendix IV
Proposed Changes to FDA Approvals

Table IV-1 Summary of regulations requested to be changed by this petition for each ortho-phthalate.

FDA Name	CAS No.	21 CFR 175	21 CFR 176	21 CFR 177	21 CFR 178	21 CFR 181
Dimethyl phthalate / dimethyl orthophthalate	131-11-3	175.105		177.1010 177.1590 177.2420		
Diphenyl phthalate	84-62-8	175.105			178.3740	
Methyl phthalyl ethyl glycolate / 1,2-Benzenedicarboxylicacid, 1-(2-ethoxy-2-oxoethyl) 2-methyl ester	85-71-2	175.105				
Diethyl phthalate	84-66-2	175.105 175.300 175.320			178.3910	181.27
Diphenylguanidine phthalate	17573-13-6			177.2600		
Ethyl phthalyl ethyl glycolate / Ethyl carbethoxymethyl phthalate	84-72-0	175.105 175.300 175.320				181.27
Diallyl phthalate	131-17-9	175.105	176.170 176.180			
Diisobutyl phthalate	84-69-5	175.105		177.1200		
Butyl benzyl phthalate	85-68-7	175.105	176.170 176.180	177.2420	178.3740	
Di-n-butyl phthalate	84-74-2	175.105 175.300	176.170 176.300	177.1200 177.2420 177.2600		
Butyl phthalyl butyl glycolate / Butyl carbobutoxymethyl phthalate	85-70-1	175.105 175.300 175.320				181.27
Dicyclohexyl phthalate	84-61-7	175.105	176.170	177.1200	178.3740	
Dihexyl phthalate / Di-n-hexyl phthalate	84-75-3	175.105			178.3740	
Di(butoxyethyl) phthalate / Bis(2-n-butoxyethyl) phthalate	117-83-9	175.105				
Dimethylcyclohexyl phthalate	1322-94-7			177.1200		
Diisooctyl phthalate	27554-26-3	175.105 175.300				181.27
Di(2-ethylhexyl) phthalate	117-81-7	175.105 175.300	176.210	177.1010 177.1200	178.3910	181.27
Dioctyl phthalate / Di-n-octyl phthalate	117-84-0	175.105		177.1460 177.2600		
Butyloctyl phthalate / n-butyl n-octyl pthalate	84-78-6	175.105				
Di(2-ethylhexyl) hexahydrophthalate		175.105				
Diisononyl phthalate / Bis(7-methyloctyl) phthalate	28553-12-0				178.3740	
Amyl decyl phthalate / n-amyl n-decyl phthalate.	7493-81-4			177.2600		

FDA Name	CAS No.	21 CFR 175	21 CFR 176	21 CFR 177	21 CFR 178	21 CFR 181
Butyl decyl phthalate / n-butyl n-decyl pthalate	89-19-0	175.105				
Decyl octyl phthalate / Octyldecyl phthalate / n-octyl n-decyl phthalate	119-07-3	175.105		177.2600		
Didecyl phthalate / Di-n-decyl phthalate	84-77-5		176.300	177.2600		
Diisodecyl phthalate / Bis(8-methylnonyl) phthalate	26761-40-0	175.105 175.300		177.1210 177.2600	178.3910	
Dodecyl phthalate	21577-80-0		176.300			
Dihydoabietyl phthalate	26760-71-4	175.105				
Castor oil phthalate, hydrogenated	FDA # 977037-59-4			177.1200		
Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol	68650-73-7			177.1200		
Note: There are sections that do not specifically mention the ortho-phthalates but reference a provision of one of the sections listed above. They are affected, but not altered, by this petition. We include them in Table I-1 in Appendix I but not here since we are not requesting that FDA alter the words in those sections.						

21 CFR 175 INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS

EXISTING Sec. 175.105 Adhesives.

(a) Adhesives may be safely used as components of articles intended for use in packaging, transporting, or holding food in accordance with the following prescribed conditions:
  (1) The adhesive is prepared from one or more of the optional substances named in paragraph (c) of this section, subject to any prescribed limitations.
  (2) The adhesive is either separated from the food by a functional barrier or used subject to the following additional limitations:
    (i) *In dry foods.* The quantity of adhesive that contacts packaged dry food shall not exceed the limits of good manufacturing practice.
    (ii) *In fatty and aqueous foods.*
      (*a*) The quantity of adhesive that contacts packaged fatty and aqueous foods shall not exceed the trace amount at seams and at the edge exposure between packaging laminates that may occur within the limits of good manufacturing practice.
      (*b*) Under normal conditions of use the packaging seams or laminates will remain firmly bonded without visible separation.

(b) To assure safe usage of adhesives, the label of the finished adhesive container shall bear the statement "food-packaging adhesive".

(c) Subject to any limitation prescribed in this section and in any other regulation promulgated under section 409 of the Act which prescribes safe conditions of use for substances that may be employed as constituents of adhesives, the optional substances used in the formulation of adhesives may include the following:
  (1) Substances generally recognized as safe for use in food or food packaging.
  (2) Substances permitted for use in adhesives by prior sanction or approval and employed under the specific conditions of use prescribed by such sanction or approval.
  (3) Flavoring substances permitted for use in food by regulations in this part, provided that such flavoring substances are volatilized from the adhesives during the packaging fabrication process.
  (4) Color additives approved for use in food.

(5) Substances permitted for use in adhesives by other regulations in this subchapter and substances named in this subparagraph: *Provided, however,* That any substance named in this paragraph and covered by a specific regulation in this subchapter, must meet any specifications in such regulation.
~~Butyl benzyl phthalate~~
~~Butyldecyl phthalate~~
~~Butyloctyl phthalate~~
~~Butyl phthalate butyl glycolate~~
~~Di(butoxyethyl) phthalate~~
~~Dibutyl phthalate~~
~~Dicyclohexyl phthalate~~
~~Di(2-ethylhexyl)hexahydrophthalate~~
~~Di(2-ethylhexyl)phthalate~~
~~Diethyl phthalate~~
~~Dihexyl phthalate~~
~~Dihydroabietylphthalate~~
~~Diisobutyl phthalate~~
~~Diisodecyl phthalate~~
~~Diisooctyl phthalate~~
~~Dimethyl phthalate~~
~~Dioctylphthalate~~
~~Diphenyl phthalate~~
~~Ethyl phthalyl ethyl glycolate~~
~~Methyl phthalyl ethyl glycolate~~
~~Octyldecyl phthalate~~
Polymers: Homopolymers and copolymers of the following monomers:
~~Diallyl phthalate~~

EXISTING Sec. 175.300 Resinous and polymeric coatings.
Resinous and polymeric coatings may be safely used as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, in accordance with the following prescribed conditions:
(a) The coating is applied as a continuous film or enamel over a metal substrate, or the coating is intended for repeated food-contact use and is applied to any suitable substrate as a continuous film or enamel that serves as a functional barrier between the food and the substrate. The coating is characterized by one or more of the following descriptions:
(1) Coatings cured by oxidation.
(2) Coatings cured by polymerization, condensation, and/or cross-linking without oxidation.
(3) Coatings prepared from prepolymerized substances.
(b) The coatings are formulated from optional substances that may include:
(1) Substances generally recognized as safe in food.
(2) Substances the use of which is permitted by regulations in this part or which are permitted by prior sanction or approval and employed under the specific conditions, if any, of the prior sanction or approval.
(3) Any substance employed in the production of resinous and polymeric coatings that is the subject of a regulation in subchapter B of this chapter and conforms with any specification in such regulation. Substances named in this paragraph (b)(3) and further identified as required:
(viii) Epoxy resins, catalysts, and adjuncts:
(*b*) Catalysts and cross-linking agents for epoxy resins:

~~Dibutyl phthalate, for use only in coatings for containers having a capacity of 1,000 gallons or more when such containers are intended for repeated use in contact with alcoholic beverages containing up to 8 percent of alcohol by volume.~~

(xxiv) Plasticizers:

~~Butyl phthalyl butyl glycolate.~~
~~Diethyl phthalate.~~
~~Diisooctyl phthalate.~~
~~Ethyl phthalyl ethyl glycolate.~~
~~di-2-Ethylhexyl phthalate.~~

(xxxii) Side seam cements: In addition to the substances listed in paragraph (b)(3) (i) to (xxx), inclusive, of this section, the following may be used.

~~Diisodecyl phthalate for use only as plasticizer in side seam cements for containers intended for use in contact with food only of the types identified in paragraph (d) of this section, table 1, under Categories I, II, and VI.~~

EXISTING Sec. 175.320 Resinous and polymeric coatings for polyolefin films.

Resinous and polymeric coatings may be safely used as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, in accordance with the following prescribed conditions:

(a) The coating is applied as a continuous film over one or both sides of a base film produced from one or more of the basic olefin polymers complying with 177.1520 of this chapter. The base polyolefin film may contain optional adjuvant substances permitted for use in polyolefin film by applicable regulations in parts 170 through 189 of this chapter.

(b) The coatings are formulated from optional substances which are:

(1) Substances generally recognized as safe for use in or on food.

(2) Substances the use of which is permitted under applicable regulations in parts 170 through 189 of this chapter, by prior sanctions, or approvals.

(3) Substances identified in this paragraph (b)(3) and subject to such limitations as are provided:

(ii) Plasticizers:

~~Butyl phthalyl butyl glycolate~~
~~Diethyl phthalate~~
~~Ethyl phthalyl ethyl glycolate~~

(c) The coating in the finished form in which it is to contact food, when extracted with the solvent or solvents characterizing the type of food, and under conditions of time and temperature characterizing the conditions of its intended use as determined from tables 1 and 2 of 176.170(c) of this chapter, shall yield net chloroform-soluble extractives not to exceed 0.5 milligram per square inch of coated surface.

(d) Acrylonitrile copolymers identified in this section shall comply with the provisions of 180.22 of this chapter.

21 CFR 176 INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS

EXISTING Sec. 176.170 Components of paper and paperboard in contact with aqueous and fatty foods.

Substances identified in this section may be safely used as components of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods, subject to the provisions of this section. Components of paper and paperboard in contact with dry food of the type

identified under Type VIII of table 1 in paragraph (c) of this section are subject to the provisions of 176.180.

(a) Substances identified in paragraph (a) (1) through (5) of this section may be used as components of the food-contact surface of paper and paperboard. Paper and paperboard products shall be exempted from compliance with the extractives limitations prescribed in paragraph (c) of this section: *Provided,* That the components of the food-contact surface consist entirely of one or more of the substances identified in this paragraph: *And provided further,* That if the paper or paperboard when extracted under the conditions prescribed in paragraph (c) of this section exceeds the limitations on extractives contained in paragraph (c) of this section, information shall be available from manufacturing records from which it is possible to determine that only substances identified in this paragraph (a) are present in the food-contact surface of such paper or paperboard.

. . .

(b) Substances identified in paragraphs (b) (1) and (2) of this section may be used as components of the food-contact surface of paper and paperboard, provided that the food-contact surface of the paper or paperboard complies with the extractives limitations prescribed in paragraph (c) of this section.

(1) Substances identified in 175.300(b)(3) of this chapter with the exception of those identified in paragraphs (b)(3) (v), (xv), (xx), (xxvi), (xxxi), and (xxxii) of that section and paragraph (a) of this section.

(2) Substances identified in this paragraph (b)(2) follow:

~~Butylbenzyl phthalate~~	~~Complying with 178.3740 of this chapter.~~
~~Dibutyl phthalate~~	
~~Dicyclohexyl phthalate~~	
~~Vinyl acetate copolymers produced by copolymerizing vinyl acetate with one or more of the monomers acrylamide, acrylic acid, acrylonitrile, bicyclo [2.2.1]*hept*-2-ene-6-methylacrylate, butyl acrylate, crotonic acid, decyl acrylate, diallyl fumarate, diallyl maleate, diallyl phthalate, dibutyl fumarate, dibutyl itaconate, dibutylmaleate, di(2-ethylhexyl) maleate, divinyl benzene, ethyl acrylate, 2-ethyl-hexyl acrylate, fumaric acid, itaconic acid, maleic acid, methacrylic acid, methyl acrylate, methyl methacrylate, mono(2-ethylhexyl) maleate, monoethyl maleate, styrene, vinyl butyrate, vinyl crotonate, vinyl hexoate, vinylidene chloride, vinyl pelargonate, vinyl propionate, vinyl pyrrolidone, vinyl stearate, and vinyl sulfonic acid. The finished copolymers shall contain at least 50 weight percent of polymer units derived from vinyl acetate and shall contain no more than 5 weight percent of total polymer units derived from acrylamide, acrylic acid, crotonic acid, decyl acrylate, dibutyl itaconate, di(2-ethylhexyl) maleate, fumaric acid, itaconic acid, maleic acid, methacrylic acid, mono(2-ethylhexyl) maleate, monoethyl maleate, vinyl butyrate, vinyl hexoate, vinyl pelargonate, vinyl propionate, vinyl stearate, and vinyl sulfonic acid~~	

EXISTING Sec. 176.180 Components of paper and paperboard in contact with dry food.

The substances listed in this section may be safely used as components of the uncoated or coated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding dry food of the type identified in 176.170(c), table 1, under Type VIII, subject to the provisions of this section.

(a) The substances are used in amounts not to exceed that required to accomplish their intended physical or technical effect, and are so used as to accomplish no effect in food other than that ordinarily accomplished by packaging.
(b) The substances permitted to be used include the following:
  (1) Substances that by 176.170 and other applicable regulations in parts 170 through 189 of this chapter may be safely used as components of the uncoated or coated food-contact surface of paper and paperboard, subject to the provisions of such regulation.
  (2) Substances identified in the following list:
  ~~Butyl benzyl phthalate.~~
  ~~Diallyl phthalate.~~

EXISTING Sec. 176.210 Defoaming agents used in the manufacture of paper and paperboard.
Defoaming agents may be safely used in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food in accordance with the following prescribed conditions:
(a) The defoaming agents are prepared from one or more of the substances named in paragraph (d) of this section, subject to any prescribed limitations.
(b) The defoaming agents are used to prevent or control the formation of foam during the manufacture of paper and paperboard prior to and during the sheet-forming process.
(c) The quantity of defoaming agent or agents added during the manufacturing process shall not exceed the amount necessary to accomplish the intended technical effect.
(d) Substances permitted to be used in the formulation of defoaming agents include substances subject to prior sanctions or approval for such use and employed subject to the conditions of such sanctions or approvals, substances generally recognized as safe for use in food, substances generally recognized as safe for use in paper and paperboard, and substances listed in this paragraph, subject to the limitations, if any, prescribed.
  (3) Miscellaneous:
  ~~Di-(2-ethylhexyl) phthalate.~~

EXISTING Sec. 176.300 Slimicides.
(a) Slimicides may be safely used in the manufacture of paper and paperboard that contact food, in accordance with the following prescribed conditions:
  (1) Slimicides are used as antimicrobial agents to control slime in the manufacture of paper and paperboard.
  (2) Subject to any prescribed limitations, slimicides are prepared from one or more of the slime-control substances named in paragraph (c) of this section to which may be added optional adjuvant substances as provided for under paragraph (d) of this section.
  (3) Slimicides are added to the process water used in the production of paper or paperboard, and the quantity added shall not exceed the amount necessary to accomplish the intended technical effect.
(b) To insure safe usage, the label or labeling of slimicides shall bear adequate directions for use.
(c) Slime-control substances permitted for use in the preparation of slimicides include substances subject to prior sanction or approval for such use and the following:
(d) Adjuvant substances permitted to be used in the preparation of slimicides include substances generally recognized as safe for use in food, substances generally recognized as safe for use in paper and paperboard, substances permitted to be used in paper and paperboard by other regulations in this chapter, and the following:
  ~~Dibutyl phthalate.~~
  ~~Didecyl phthalate.~~
  ~~Dodecyl phthalate.~~

21 CFR 177 <u>INDIRECT FOOD ADDITIVES: POLYMERS</u>

EXISTING Sec. 177.1010 Acrylic and modified acrylic plastics, semirigid and rigid.
Semirigid and rigid acrylic and modified acrylic plastics may be safely used as articles intended for use in contact with food, in accordance with the following prescribed conditions. The acrylic and modified acrylic polymers or plastics described in this section also may be safely used as components of articles intended for use in contact with food.

(a) The optional substances that may be used in the formulation of the semirigid and rigid acrylic and modified acrylic plastics, or in the formulation of acrylic and modified acrylic components of articles, include substances generally recognized as safe in food, substances used in accordance with a prior sanction or approval, substances permitted for use in such plastics by regulations in parts 170 through 189 of this chapter, and substances identified in this paragraph. At least 50 weight-percent of the polymer content of the acrylic and modified acrylic materials used as finished articles or as components of articles shall consist of polymer units derived from one or more of the acrylic or methacrylic monomers listed in paragraph (a)(1) of this section.

8) Miscellaneous materials:
~~Di(2-ethylhexyl) phthalate, for use only as a flow promoter at a level not to exceed 3 weight-percent based on the monomers.~~
~~Dimethyl phthalate.~~

EXISTING Sec. 177.1200 Cellophane.
Cellophane may be safely used for packaging food in accordance with the following prescribed conditions:

(a) Cellophane consists of a base sheet made from regenerated cellulose to which have been added certain optional substances of a grade of purity suitable for use in food packaging as constituents of the base sheet or as coatings applied to impart desired technological properties.

(b) Subject to any limitations prescribed in this part, the optional substances used in the base sheet and coating may include:
(1) Substances generally recognized as safe in food.
(2) Substances for which prior approval or sanctions permit their use in cellophane, under conditions specified in such sanctions and substances listed in 181.22 of this chapter.
(3) Substances that by any regulation promulgated under section 409 of the act may be safely used as components of cellophane.
(4) Substances named in this section and further identified as required.

(c) *List of substances:*

List of substances	Limitations (residue and limits of addition expressed as percent by weight of finished packaging cellophane)
~~Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol polyester~~	~~As the basic polymer.~~
~~Castor oil phthalate, hydrogenated~~	~~Alone or in combination with other phthalates where total phthalates do not exceed 5 percent.~~
~~Dibutylphthalate~~	~~Alone or in combination with other phthalates where total phthalates do not exceed 5 percent.~~
~~Dicyclohexyl phthalate~~	~~Do.~~
~~Di(2-ethylhexyl) phthalate~~	~~Alone or in combination with other phthalates where total phthalates do not exceed 5 percent.~~
~~Diisobutyl phthalate~~	~~Do.~~
~~Dimethylcyclohexyl phthalate~~	~~Do.~~

EXISTING Sec. 177.1210 Closures with sealing gaskets for food containers.

Closures with sealing gaskets may be safely used on containers intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food in accordance with the following prescribed conditions:

(a) Closures for food containers are manufactured from substances generally recognized as safe for contact with food; substances that are subject to the provisions of prior sanctions; substances authorized by regulations in parts 174, 175, 176, 177, 178 and 179.45 of this chapter; and closure-sealing gaskets, as further prescribed in this section.

(b) Closure-sealing gaskets and overall discs are formulated from substances identified in 175.300(b) of this chapter, with the exception of paragraph (b)(3) (v), (xxxi), and (xxxii) of that section, and from other optional substances, including the following:

(1) Substances generally recognized as safe in food.

(2) Substances used in accordance with the provisions of a prior sanction or approval within the meaning of section 201(s) of the act.

(3) Substances that are the subject of regulations in parts 174, 175, 176, 177, 178 and 179.45 of this chapter and used in accordance with the conditions prescribed.

(4) Substances identified in paragraph (b)(5) of this section, used in amounts not to exceed those required to accomplish the intended physical or technical effect and in conformance with any limitation provided; and further provided that any substance employed in the production of closure-sealing gasket compositions that is the subject of a regulation in parts 174, 175, 176, 177, 178 and 179.45 of this chapter conforms with the identity or specifications prescribed.

(5) Substances that may be employed in the manufacture of closure-sealing gaskets include:

Table 1

List of substances	Limitations (expressed as percent by weight of closure-sealing gasket composition)
~~Diisodecyl phthalate~~	~~No limitation on amount used but for use only in closure-sealing gasket compositions used in contact with non-fatty foods containing no more than 8 percent of alcohol.~~

EXISTING Sec. 177.1460 Melamine-formaldehyde resins in molded articles.

Melamine-formaldehyde resins may be safely used as the food-contact surface of molded articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food in accordance with the following prescribed conditions:

(a) For the purpose of this section, melamine-formaldehyde resins are those produced when 1 mole of melamine is made to react with not more than 3 moles of formaldehyde in water solution.

(b) The resins may be mixed with refined woodpulp and the mixture may contain other optional adjuvant substances which may include the following:

List of substances	Limitations
~~Dioctyl phthalate~~	~~For use as lubricant.~~

(c) The molded melamine-formaldehyde articles in the finished form in which they are to contact food, when extracted with the solvent or solvents characterizing the type of food and under the conditions of time and temperature as determined from tables 1 and 2 of 175.300(d) of this chapter, shall yield net chloroform-soluble extractives not to exceed 0.5 milligram per square inch of food-contact surface.

EXISTING Sec. 177.1590 Polyester elastomers.

The polyester elastomers identified in paragraph (a) of this section may be safely used as the food-contact surface of articles intended for use in contact with bulk quantities of dry food of the type identified in 176.170(c) of this chapter, table 1, under Type VIII, in accordance with the following prescribed conditions:

(a) For the purpose of this section, polyester elastomers are those produced by the ester exchange reaction when one or more of the following phthalates--dimethyl terephthalate, ~~dimethyl orthophthalate~~, and dimethyl isophthalate--is made to react with alpha-hydroomega-hydroxypoly (oxytetramethylene) and/or 1,4-butanediol such that the finished elastomer has a number average molecular weight between 20,000 and 30,000.

(b) Optional adjuvant substances employed in the production of the polyester elastomers or added thereto to impart desired technical or physical properties may include the following substances:

(c) An appropriate sample of the finished polyester elastomer in the form in which it contacts food when subjected to ASTM method D968-81, "Standard Test Methods for Abrasion Resistance of Organic Coatings by the Falling Abrasive Tester," which is incorporated by reference (Copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*), using No. 50 emery abrasive in lieu of Ottawa sand, shall exhibit an abrasion coefficient of not less than 100 liters per mil of thickness.

EXISTING Sec. 177.2420 Polyester resins, cross-linked.

Cross-linked polyester resins may be safely used as articles or components of articles intended for repeated use in contact with food, in accordance with the following prescribed conditions:

(a) The cross-linked polyester resins are produced by the condensation of one or more of the acids listed in paragraph (a)(1) of this section with one or more of the alcohols or epoxides listed in paragraph (a)(2) of this section, followed by copolymerization with one or more of the cross-linking agents listed in paragraph (a)(3) of this section:

(b) Optional adjuvant substances employed to facilitate the production of the resins or added thereto to impart desired technical or physical properties include the following, provided that the quantity used does not exceed that reasonably required to accomplish the intended physical or technical effect and does not exceed any limitations prescribed in this section:

List of substances	Limitations (limits of addition expressed as percent by weight of finished resin)
4. Solvents for inhibitors, accelerators, and catalysts:	
~~Butyl benzyl phthalate (containing not more than 1.0 percent by weight of dibenzyl phthalate)~~	
~~Dibutyl phthalate~~	
~~Dimethyl phthalate~~	

EXISTING Sec. 177.2600 Rubber articles intended for repeated use.

Rubber articles intended for repeated use may be safely used in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, subject to the provisions of this section.

(a) The rubber articles are prepared from natural and/or synthetic polymers and adjuvant substances as described in paragraph (c) of this section.

(b) The quantity of any substance employed in the production of rubber articles intended for repeated use shall not exceed the amount reasonably required to accomplish the intended effect in the rubber article and shall not be intended to accomplish any effect in food.
(c) Substances employed in the preparation of rubber articles include the following, subject to any limitations prescribed:
  (1) Substances generally recognized as safe for use in food or food packaging.
  (2) Substances used in accordance with the provisions of a prior sanction or approval.
  (3) Substances that by regulation in parts 170 through 189 of this chapter may be safely used in rubber articles, subject to the provisions of such regulation.
  (4) Substances identified in this paragraph (c)(4), provided that any substance that is the subject of a regulation in parts 174, 175, 176, 177, 178 and 179.45 of this chapter conforms with any specification in such regulation.
    (ii) *Vulcanization materials*
      (*b*) *Accelerators (total not to exceed 1.5 percent by weight of rubber product).*
        ~~Diphenylguanidine phthalate.~~
    (iv) *Plasticizers (total not to exceed 30 percent by weight of rubber product unless otherwise specified).*
    ~~*n*-Amyl *n*-decyl phthalate.~~
    ~~Dibutyl phthalate.~~
    ~~Didecyl phthalate.~~
    ~~Diisodecyl phthalate.~~
    ~~Dioctyl phthalate.~~
    ~~*n*-Octyl *n*-decyl phthalate.~~

21 CFR 178 INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS

EXISTING Sec. 178.3740 Plasticizers in polymeric substances.
Subject to the provisions of this regulation, the substances listed in paragraph (b) of this section may be safely used as plasticizers in polymeric substances used in the manufacture of articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.
(a) The quantity used shall not exceed the amount reasonably required to accomplish the intended technical effect.
(b) List of substances:

Substances	Limitations
~~Butylbenzyl phthalate~~	~~For use only: 1. As provided in 175.105 and 176.180 of this chapter. 2. In polymeric substances used in food-contact articles complying with 175.300, 175.320, or 176.170 of this chapter: Provided, That the butyl benzyl phthalate contains not more than 1 percent by weight of dibenzyl phthalate. 3. In polymeric substances used in other permitted food-contact articles: Provided, That the butyl benzyl phthalate contains not more than 1 percent by weight of dibenzyl phthalate; and Provided further, That the finished food-contact article, when extracted with the solvent or solvents characterizing the type of food and under the conditions of time and temperature characterizing the conditions of its intended use as determined from tables 1 and 2 of 175.300(d) of this chapter, shall yield net chloroform-soluble extractives not to exceed 0.5 mg. per square inch, as determined by the methods prescribed in 175.300(e) of this chapter.~~

~~Dicyclohexyl phthalate~~	~~For use only: 1. As provided in 175.105, 176.170, 176.180, and 177.1200 of this chapter. 2. Alone or in combination with other phthalates, in plastic film or sheet prepared from polyvinyl acetate, polyvinyl chloride, and/or vinyl chloride copolymers complying with 177.1980 of this chapter. Such plastic film or sheet shall be used in contact with food at temperatures not to exceed room temperature and shall contain no more than 10 pct by weight of total phthalates, calculated as phthalic acid.~~
~~Diisononyl phthalate~~	~~For use only at levels not exceeding 43 pct by weight of permitted vinyl chloride homo- and/or copolymers used in contact with food only of the types identified in 176.170(c) of this chapter, table 1, under Categories I, II, IV-B, and VIII, at temperatures not exceeding room temperature. The average thickness of such polymers in the form in which they contact food shall not exceed 0.005 inch.~~
~~Dihexyl phthalate~~	~~For use only: 1. As provided in 175.105 of this chapter. 2. In articles that contact food only of the types identified in 176.170(c) of this chapter, table 1, under Categories I, II, IV-B, VI-B, and VIII.~~
~~Diphenyl phthalate~~	~~For use only: 1. As provided in 175.105 of this chapter. 2. Alone or in combination with other phthalates, in plastic film or sheet prepared from polyvinyl acetate, polyvinyl chloride, and/or vinyl chloride copolymers complying with 177.1980 of this chapter. Such plastic film or sheet shall be used in contact with food at temperatures not to exceed room temperature and shall contain no more than 10 pct by weight of total phthalates, calculated as phthalic acid.~~

EXISTING Sec. 178.3910 Surface lubricants used in the manufacture of metallic articles.
The substances listed in this section may be safely used in surface lubricants employed in the manufacture of metallic articles that contact food, subject to the provisions of this section.

(a) The following substances may be used in surface lubricants used in the rolling of metallic foil or sheet stock provided that total residual lubricant remaining on the metallic article in the form in which it contacts food does not exceed 0.015 milligram per square inch of metallic food-contact surface:
   (1) Substances identified in paragraphs (b)(1) and (2) of this section.
   (2) Substances identified in this paragraph.

List of substances	Limitations
~~Diisodecyl phthalate~~	
~~Di(2-ethylhexyl)phthalate~~	
~~Diethyl phthalate~~	

21 CFR § 181.27 PRIOR-SANCTIONED FOOD INGREDIENTS

EXISTING Sec. 181.27 Plasticizers.
Substances classified as plasticizers, when migrating from food-packaging material shall include:

~~Butylphthalyl butyl glycolate.~~
~~Di-(2-ethylhexyl) phthalate (for foods of high water content only).~~
~~Diethyl phthalate.~~
~~Diisooctyl phthalate (for foods of high water content only).~~
~~Ethylphthalyl ethyl glycolate.~~

21 CFR § 189.302 SUBSTANCES PROHIBITED FOR USE IN HUMAN FOOD

NEW Sec. 189.302 Ortho-Phthalates.

The following ortho-phthalates are not allowed to be used as an additive to food contact articles:

- Diisobutyl phthalate (DIBP).
- Di-n-butyl phthalate (DBP).
- Butyl benzyl phthalate (BBP).
- Dicyclohexyl phthalate (DCHP).
- Di-n-hexyl phthalate (DHEXP).
- Diisooctyl phthalate (DIOP).
- Di(2-ethylhexyl) phthalate (DEHP).
- Diisononyl phthalate (DINP).