

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 175, 176, 177, and 178

[Docket No. FDA-2016-F-1253]

Natural Resources Defense Council, et al.; Denial of Food Additive Petition; Denial Without Prejudice of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification; denial of petition.

SUMMARY: The Food and Drug Administration (FDA or we) is denying a food additive petition (FAP 6B4815) submitted by Natural Resources Defense Council, et al., requesting that we amend or revoke specified regulations to no longer provide for the food contact use of 28 *ortho*-phthalates. (We use the terms “phthalates” and “*ortho*-phthalates” interchangeably in this notification to refer to the subset of phthalates substituted in the “*ortho*” position).

DATES: This notification is applicable May 20, 2022, except as to any provisions that may be stayed by the filing of proper objections. Submit either electronic or written objections and requests for a hearing on the document June 21, 2022. See Section V for further information on the filing of objections.

ADDRESSES: You may submit objections and requests for a hearing as follows. Please note that late, untimely filed objections will not be considered. Electronic objections must be submitted on or before June 21, 2022. The <https://www.regulations.gov> electronic filing system will accept objections until 11:59 p.m. Eastern Time at the end of June 21, 2022. Objections received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic objections in the following way:

- *Federal eRulemaking Portal:* <https://www.regulations.gov>. Follow the instructions for submitting comments. Objections submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your objection will be made public, you are solely responsible for ensuring that your objection does not include any

confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your objection, that information will be posted on <https://www.regulations.gov>.

- If you want to submit an objection with confidential information that you do not wish to be made available to the public, submit the objection as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper objections submitted to the Dockets Management Staff, FDA will post your objection, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2016-F-1253 for “Natural Resources Defense Council, et al.; Denial of Food Additive Petition; Denial Without Prejudice of Food Additive Petition.” Received objections, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- *Confidential Submissions*—To submit an objection with confidential information that you do not wish to be made publicly available, submit your objections only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff.

If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT:

Jessica Urbelis, Center for Food Safety and Applied Nutrition (HFS-275), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-5187; or Meadow Platt, Office of Regulations and Policy (HFS-024), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-2378.

SUPPLEMENTARY INFORMATION:

I. Introduction

In a notice published in the **Federal Register** on May 20, 2016 (81 FR 31877), we announced that we filed a food additive petition (FAP 6B4815) (petition) submitted by Breast Cancer Fund (now Breast Cancer Prevention Partners), Center for Environmental Health, Center for Food Safety, Center for Science in the Public Interest, Clean Water Action, Consumer Federation of America, Earthjustice, Environmental Defense Fund, Improving Kids' Environment, Learning Disabilities Association of America, and Natural Resources Defense Council, c/o Mr. Thomas Neltner, 1875 Connecticut Ave. NW, Suite 600, Washington, DC 20009. In the May 2016 notice, FDA requested comments on the petition.

The petitioners initially requested that we amend or revoke specified food additive regulations under 21 CFR parts 175, 176, 177, and 178, to no longer provide for the food contact uses of 30 substances that the petition identified as *ortho*-phthalates. We filed this portion of the submission as a food additive

petition (81 FR 31877 at 31878). In addition, the petitioners requested that FDA amend regulations in 21 CFR part 181 related to prior-sanctioned uses of five *ortho*-phthalates and issue a new regulation in 21 CFR part 189 prohibiting the use of eight specific *ortho*-phthalates in food contact articles. We declined to file these portions of the submission as a food additive petition because those requests were not within the scope of a food additive petition (81 FR 31877 at 31878). Consequently, those portions of the petition are not the subject of this notice.

Following our May 20, 2016, announcement that we had filed the food additive petition, the petitioners provided supplementary information on October 8, 2016, and August 24, 2017 (Supp., October 8, 2016, and Supp., August 24, 2017, respectively). Included in the October 8, 2016, response, the petitioners also requested that FDA remove two substances (diphenylguanidine phthalate (CAS Reg No. 17573-13-6) and di(2-ethylhexyl) hexahydrophthalate (CAS Reg No. 84-71-9)) from the petitioners' original list of 30 substances, stating that they are not *ortho*-phthalates (Supp., October 8, 2016). Consequently, the subject of the petition is limited to food additive regulations for 28 *ortho*-phthalates.

The 28 subject *ortho*-phthalates are regulated as food additives under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The FD&C Act authorizes us to regulate "food additives" (see section 409(a) of the FD&C Act (21 U.S.C. 348(a))). The FD&C Act defines "food additive," in relevant part, as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of food or otherwise affecting the characteristics of any food (see section 201(s) of the FD&C Act (21 U.S.C. 321(s))). Food additives can include both substances added directly to food and indirectly and can also include "food contact substances." "Food contact substances" are substances intended for use in materials that come into contact with food, for instance in food packaging or manufacturing, but which are not intended to have any technical effect in the food (see § 170.3(e)(3) (21 CFR 170.3(e)(3))). Food additives are deemed unsafe and prohibited except to the extent that we permit their use (see, e.g., sections 301(a), 301(k), and 409(a) of the FD&C Act (21 U.S.C. 331(a), 331(k), and 348(a))). The FD&C Act provides a process through which persons who wish to use a food additive may submit a petition proposing the issuance of a regulation prescribing the conditions

under which the additive may be safely used (see section 409(b)(1) of the FD&C Act). Such a petition is referred to as a "food additive petition."

Under section 409(c)(3) of the FD&C Act, we will not establish a regulation for the use of a food additive if a fair evaluation of the data fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe. Any food additive regulation that we issue authorizes a specific use of the substance. Our regulations, at § 170.3(i), define safety as a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.

The FD&C Act provides that we must, by regulation, prescribe the procedure by which a food additive regulation may be amended or repealed (see section 409(i) of the FD&C Act). Our regulation specific to the administrative actions for food additives provides that the Commissioner of Food and Drugs, on his own initiative or on the petition of any interested person, may propose the issuance of a regulation amending or repealing a regulation pertaining to a food additive (see § 171.130(a) (21 CFR 171.130(a))). "When a food additive petition seeks to amend an existing regulation, the petitioner must include 'full information on each proposed change'" (*In re Natural Resources Defense Council*, 645 F.3d 400, 403 (D.C. Cir. 2011) (quoting § 171.1 (21 CFR 171.1))). Our regulation, at § 171.130(b), further provides that any such petition must include an assertion of facts, supported by data, showing that new information exists with respect to the food additive or that new uses have been developed or old uses abandoned, that new data are available as to toxicity of the chemical, or that experience with the existing regulation or exemption may justify its amendment or repeal. Under § 171.1(c), a petition must include full reports of investigations made with respect to the safety of the food additive. With respect to the showing that is required, a petition that seeks to amend or repeal existing regulations based on safety must contain sufficient data to establish the existence of safety questions significant enough to support a finding that there is no longer a reasonable certainty of no harm from the currently approved uses (see generally section 409(c) of the FD&C Act (describing the data requirements) and §§ 171.1 through 171.130 (food additive petition regulations)). Should FDA determine that there is sufficient data to raise safety concerns, FDA ensures that these concerns are addressed or that substances are no

longer used as food additives. The FD&C Act makes clear that food additives introduced into commerce must be shown to be safe (see generally sections 402 (21 U.S.C. 342) and 409 of the FD&C Act). If FDA determines that a food additive is no longer safe, FDA will revoke the approval or otherwise ensure that the food additive is no longer in use.

The petitioners requested that FDA amend parts 175, 176, 177, and 178 to no longer provide for the food contact use of 28 specified *ortho*-phthalates. The *ortho*-phthalates and corresponding regulations in parts 175, 176, 177, and 178 are as follows:

21 CFR 175.105 Adhesives

Butyl benzyl phthalate (Chemical Abstract Service (CAS) No. 85-68-7), Butyl decyl phthalate (CAS No. 89-19-0), Butyl octyl phthalate (CAS No. 84-78-6), Butyl phthalyl butyl glycolate (CAS No. 85-70-1), Di(butoxyethyl) phthalate (CAS No. 117-83-9), Dibutyl phthalate (CAS No. 84-74-2), Dicyclohexyl phthalate (CAS No. 84-61-7), Di(2-ethylhexyl) phthalate (CAS No. 117-81-7), Diethyl phthalate (CAS No. 84-66-2), Dihexyl phthalate (CAS No. 84-75-3), Dihydroabietyl phthalate (CAS No. 26760-71-4), Diisobutyl phthalate (CAS No. 84-69-5), Diisodecyl phthalate (CAS No. 26761-40-0), Diisooctyl phthalate (CAS No. 27554-26-3), Dimethyl phthalate (CAS No. 131-11-3), Dioctyl phthalate (CAS No. 117-84-0), Diphenyl phthalate (CAS No. 84-62-8), Ethyl phthalyl ethyl glycolate (CAS No. 84-72-0), Methyl phthalyl ethyl glycolate (CAS No. 85-71-2), Octyl decyl phthalate (CAS No. 119-07-3), and Diallyl phthalate (CAS No. 131-17-9).

21 CFR 175.300 Resinous and Polymeric Coatings

Dibutyl phthalate (CAS No. 84-74-2), Diethyl phthalate (CAS No. 84-66-2), Diisooctyl phthalate (CAS No. 27554-26-3), Di(2-ethylhexyl) phthalate (CAS No. 117-81-7), Diisodecyl phthalate (CAS No. 26761-40-0), Butyl phthalyl butyl glycolate (CAS No. 85-70-1), and Ethyl phthalyl ethyl glycolate (CAS No. 84-72-0).

21 CFR 175.320 Resinous and Polymeric Coatings for Polyolefin Films

Butyl phthalyl butyl glycolate (CAS No. 85-70-1), Diethyl phthalate (CAS No. 84-66-2), and Ethyl phthalyl ethyl glycolate (CAS No. 84-72-0).

21 CFR 176.170 Components of Paper and Paperboard in Contact With Aqueous and Fatty Foods

Butyl benzyl phthalate (CAS No. 85–68–7), Dibutyl phthalate (CAS No. 84–74–2), Dicyclohexyl phthalate (CAS No. 84–61–7), and Diallyl phthalate (CAS No. 131–17–9).

21 CFR 176.180 Components of Paper and Paperboard in Contact With Dry Food

Butyl benzyl phthalate (CAS No. 85–68–7) and Diallyl phthalate (CAS No. 131–17–9).

21 CFR 176.210 Defoaming Agents Used in the Manufacture of Paper and Paperboard

Di(2-ethylhexyl) phthalate (CAS No. 117–81–7).

21 CFR 176.300 Slimicides

Dibutyl phthalate (CAS No. 84–74–2), Didecyl phthalate (CAS No. 84–77–5), and Dodecyl phthalate (CAS No. 21577–80–0).

21 CFR 177.1010 Acrylic and Modified Acrylic Plastics, Semirigid and Rigid

Di(2-ethylhexyl) phthalate (CAS No. 117–81–7) and Dimethyl phthalate (CAS No. 131–11–3).

21 CFR 177.1200 Cellophane

Castor oil phthalate with adipic acid and fumaric acid diethylene glycol polyester (CAS No. 68650–73–7), Castor oil phthalate, hydrogenated (FDA No. 977037–59–4), Dibutyl phthalate (CAS No. 84–74–2), Dicyclohexyl phthalate (CAS No. 84–61–7), Di(2-ethylhexyl) phthalate (CAS No. 117–81–7), Diisobutyl phthalate (CAS No. 84–69–5), and Dimethylcyclohexyl phthalate (CAS No. 1322–94–7).

21 CFR 177.1210 Closures With Sealing Gaskets for Food Containers

Diisodecyl phthalate (CAS No. 26761–40–0).

21 CFR 177.1460 Melamine-Formaldehyde Resins In Molded Articles

Diocetyl phthalate (CAS No. 117–84–0).

21 CFR 177.1590 Polyester Elastomers

Dimethyl phthalate (CAS No. 131–11–3).

21 CFR 177.2420 Polyester Resins, Cross-Linked

Butyl benzyl phthalate (CAS No. 85–68–7), Dibutyl phthalate (CAS No. 84–74–2), and Dimethyl phthalate (CAS No. 131–11–3).

21 CFR 177.2600 Rubber Articles Intended for Repeated Use

Amyl decyl phthalate (CAS No. 7493–81–4), Dibutyl phthalate (CAS No. 84–74–2), Didecyl phthalate (CAS No. 84–77–5), Diisodecyl phthalate (CAS No. 26761–40–0), Dioctyl phthalate (CAS No. 117–84–0), and Octyl decyl phthalate (CAS No. 119–07–3).

21 CFR 178.3740 Plasticizers in Polymeric Substances

Butyl benzyl phthalate (CAS No. 85–68–7), Dicyclohexyl phthalate (CAS No. 84–61–7), Diisononyl phthalate (CAS No. 28553–12–0), Dihexyl phthalate (CAS No. 84–75–3), and Diphenyl phthalate (CAS No. 84–62–8).

21 CFR 178.3910 Surface Lubricants Used in the Manufacture of Metallic Articles

Diisodecyl phthalate (CAS No. 26761–40–0), Di(2-ethylhexyl) phthalate (CAS No. 117–81–7), and Diethyl phthalate (CAS No. 84–66–2).

II. Evaluation of the Information Contained in the Petition

The petition concludes that the authorized food contact uses for the 28 specified *ortho*-phthalates no longer meet the safety standard of “reasonable certainty of no harm” and, therefore, the *ortho*-phthalates should no longer be authorized under the existing regulations.

The petition is premised on three distinct assertions (which for ease of reference we refer to as Assertions A, B, and C). Assertion A claims that the 28 subject *ortho*-phthalates are chemically and pharmacologically related and should therefore be treated as a class for purposes of evaluating their safety. Under Assertion B, the petition proposes applying a purported acceptable daily intake (ADI) for di(2-ethylhexyl) phthalate (DEHP) to all 28 *ortho*-phthalates that are the subject of the petition (*i.e.*, the petition proposes applying the proposed ADI to the entire purported class). Assertion C states that the estimated daily intake (EDI) for the asserted class of *ortho*-phthalates significantly exceeds the proposed ADI, thus rendering the purported class unsafe for their use as food contact substances.

We address each assertion in turn.

A. Assertion A: Ortho-Phthalates Are a Class of Chemically and Pharmacologically Related Substances for Purposes of Determining Safety Pursuant to Section 409 of the FD&C Act and § 170.18 (21 CFR 170.18)

The petition asserts that all 28 phthalates have similar chemical

structures and similar or related pharmacological effects sufficient to be treated as one class of compounds for the purposes of evaluating the safety of these compounds. The petition states that such an approach would be consistent with section 409(c)(5)(B) of the FD&C Act, which directs FDA to consider, among other factors, the cumulative effect of an additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet, and § 170.18(a), which states that 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.

1. Information Provided in the Petition To Support the 28 Ortho-Phthalates as Chemically Related Substances

The primary document the petition relies on to support the proposed grouping of the 28 *ortho*-phthalates as chemically related substances is the Organization for Economic Co-operation and Development (OECD) guidance on Grouping Chemicals (Ref. 1). The petition states that the OECD guidance lists five underpinning rationales in the category approach and asserts that the 28 *ortho*-phthalates “meet” two of the five rationales: (i) The common functional group rationale, and (iv) the likelihood of common precursors and/or breakdown products via physical or biological processes that result in structurally similar chemicals rationale.

While we note that the OECD guidance does not establish criteria for chemical grouping (rather, it provides guidance on how to ensure that any chemical categories selected are sufficiently robust), in the discussion that follows we nevertheless address each of the OECD rationales adopted by the petition.

2. FDA’s Evaluation of the Information Provided To Support the 28 Ortho-Phthalates as Chemically Related Substances

In support of the assertion that the 28 *ortho*-phthalates “meet” rationale (i) of the OECD guidance (*i.e.*, share a common functional group), the petition states that all 28 phthalates share a general 1,2-benzene diester chemical structural framework comprised of a benzene ring with two ester functional groups attached at adjacent carbons (referred to as *ortho* positions). A functional group is a part of an organic molecule that gives the molecule its characteristic physical and chemical

properties. The physical-chemical properties are one of many factors that may determine the toxicity of a substance for one or more given endpoints. Contrary to the petition's assertion that there is a similar structural framework shared by all 28 *ortho*-phthalates, we reviewed the chemical structures of the phthalates provided by the petitioner and determined that four of the 28 phthalates do not contain the framework described by the petition (*i.e.*, do not contain the framework of sharing a general 1,2-benzene diester chemical structural framework comprised of a benzene ring with two ester functional groups attached at adjacent carbons). Specifically, two compounds, dimethylcyclohexyl phthalate and dodecyl phthalate, contain only one ester side chain and are, therefore, considered mono- (not di-) esters of 1,2-benzenedicarboxylic acid and cannot be classified as *ortho*-phthalates. Two other phthalates (castor oil phthalate, hydrogenated and castor oil phthalate with adipic acid and fumaric acid-diethylene glycol) are polymeric in nature and, therefore, have many possible chemical structures (Ref. 3). Thus, the shared structural framework described in the petition is not, in fact, shared by these four *ortho*-phthalates.

In addition, the petition does not address the structural differences in the ester side chains across the 28 phthalates. Structural differences across substances may impact whether they share characteristic physical and chemical properties (*i.e.*, whether they possess a "common functional group" for the purposes of risk assessment). It is not appropriate to group substances into a class for the purposes of risk assessment based merely on the assertion that they have a common functional group. Rather, the common functional group rationale should be supported with a discussion of any structural variations within that common functional group definition and an explanation of why the chemical-structural differences between members would not impact the suitability of the category for risk assessment. Notably, OECD guidelines state that when structural variations across a category impact functionality, inclusion of such variances in a category should be limited (Ref. 1). Across the 28 phthalates, the number of carbon atoms in the ester side chains vary from one carbon atom (*e.g.*, dimethyl phthalate (DMP)) to as many as 10 carbon atoms (*e.g.*, diisodecyl phthalate (DIDP)). The ester side chains also differ by consisting of either branched or linear

carbon chains, and varying degrees of saturation and oxidation (Ref. 3). Indeed, the chemical-structural differences of the side chains among the *ortho*-phthalates are associated with differences in physical-chemical properties (*e.g.*, volatility). For example, phthalates with ester side chains with more than eight carbon atoms are generally less volatile than phthalates with ester side chains with eight or fewer carbon atoms. Also, phthalates that contain straight ester side chains are generally less volatile than their branched-chain counterparts. The petition does not discuss these structural differences nor does the petition discuss whether structural variances across substances would still allow for those substances to be grouped with a "common functional group" for the purposes of a risk assessment. The petition, therefore, does not provide adequate evidence to demonstrate that the asserted shared structural similarity (*i.e.*, a benzene ring attached to two ester functional groups) is sufficient to group the 28 substances into a single class.

The petition also cites FDA's previous evaluation of long-chain perfluorinated compounds (PFCs) in support of utilizing the rationale of a common functional group to constitute the 28 phthalates as a class of chemically related substances. FDA's evaluation of long-chain PFCs was limited to a set of compounds with very specific structural similarities in their designated common functional group. Due to the structural similarity, and in the absence of contrary data, FDA determined that data demonstrating reproductive developmental toxicity for some long-chain PFCs was applicable to the three long-chain PFCs under evaluation (81 FR 5 at 7, January 4, 2016). Across the three compounds at issue in FDA's action on long-chain PFCs, the only variance in the common functional group was the number of carbons in the linear perfluorinated alkyl chain. This contrasts with the 28 *ortho*-phthalates that are the subject of the current petition, where there are significant structural differences, and these differences result in large differences in chemical-structural properties (Refs. 3 and 4). The classification of the subject *ortho*-phthalates as chemically related would not be akin to FDA's previous evaluation of long-chain PFCs.

With respect to the petition's assertion that the *ortho*-phthalates subject to the petition "meet" rationale (iv) of the OECD guidance (*i.e.*, share common precursors and/or breakdown products via physical or biological processes that result in structurally similar chemicals), the petition asserts

that the *ortho*-phthalates share common metabolites and a common metabolic pathway (petition at 4).

We address the assertion of common metabolites first. The petition provides a list of 10 *ortho*-phthalates and their metabolites to support the claim that there are common metabolites (Supp., August 24, 2017, at 3–4). However, the data provided in the petition only demonstrate one common metabolite shared by only two parent phthalates (Ref. 4). As the petitioners were only able to provide metabolic data pertaining to 10 of the 28 phthalates, and that data does not support that these 10 *ortho*-phthalates share common metabolites, this information does not support common metabolites for the other 18 phthalates or the group of 28 phthalates as a whole.

In addition, the petition discusses a common metabolic pathway as support for the assertion that the subject 28 *ortho*-phthalates "meet" rationale (iv) of the OECD guidance. We note that rationale (iv) is not based on identification of shared steps in a metabolic pathway as described in the petition. Rather, the OECD guidance explains that this rationale is based on the applicability of data from a parent chemical to identify the hazards of its metabolites (or vice versa). The data between parent chemical and metabolite may be related because the toxicity induced by treatment with the parent chemical is likely due to the exposure to the metabolite(s). Likewise, under OECD rationale (iv), several different parent chemicals and their metabolite(s) could be considered as one class if a common metabolite is formed from these parent chemicals. Therefore, the assertion of a common metabolic pathway, without supporting information indicating that this pathway results in common metabolites, is not consistent with the approach to grouping in rationale (iv) of the OECD guidance.

Furthermore, FDA does not agree that the petition has demonstrated that the subject *ortho*-phthalates share a common metabolic pathway. While the petition purports to identify three common steps associated with the metabolism of all 28 phthalates, it also acknowledges that not all 28 phthalates follow the purported metabolic pathway (see Supp., August 24, 2017). The petition notes that phthalates that lack longer alkyl side chains either do not or might not follow steps two (oxidation) or three (glucuronidation) of the purported common metabolic pathway (*id.* at 2). The data cited to support the list of 10 *ortho*-phthalates and their metabolites provided in the petition also

demonstrate that for four phthalates (dimethyl phthalate (DMP), diethyl phthalate (DEP), butyl benzyl phthalate (BBP), and dicyclohexyl phthalate (DCHP)), only primary (hydrolytic) metabolites and no secondary (oxidized) metabolites were identified (see Supp., August 24, 2017, at 3–4). These four phthalates therefore differ from other phthalates in both the metabolic pathway (only undergoing step one of three) and the resulting metabolites from that pathway. Similar trends between chain length and metabolism were also observed in the three biomonitoring articles cited in the petition, which identified excreted metabolites that may result from phthalate exposure. The phthalates with shorter side chain length (e.g., DMP, DEP, and BBP) exhibit hydrolytic monoesters as the major urinary metabolites; however, for phthalates with longer side chain length (e.g., DEHP, di-isononyl phthalate (DINP), and DIDP)), the hydrolytic monoesters are predominantly further metabolized before excretion in urine (Ref. 4). The existence of different metabolic pathways among phthalates is also demonstrated by a 2008 National Academy of Science (NAS) report (Ref. 5). The NAS report notes that monoesters are the main detected metabolites of the low molecular weight phthalates, such as DEP and dibutyl phthalate (DBP). However, phthalate monoesters with five or more carbons in the ester side chain (i.e., not low molecular weight phthalates) are efficiently transformed further to oxidized metabolites arising mainly from oxidation at the terminal or penultimate carbon of the alkyl ester side chain. All of these examples demonstrate how the differences in chemical structure among phthalates studied give rise to differences in metabolism and resulting metabolites.

In addition to side chain length and molecular weight, the other structural differences among the 28 *ortho*-phthalates described earlier in this subsection suggest that it is unlikely common metabolites and/or breakdown products exist for the purported class. Phthalates with ester side chains containing different structural elements (e.g., double bonds, bulky side chain, and extra ester linkage) can be expected to metabolize differently than phthalates with saturated ester side chains. For example, available information suggests steric hindrance of the bulky side chain of dihydroabietyl phthalate may prevent hydrolysis (which is usually the first step in the metabolic pathway for phthalates with straight/branched side

chains). The bulky side chain may prevent hydrolysis by blocking the access of the esterases (which are the enzymes that perform this reaction) to the ester linkage, therefore reducing the likelihood of this reaction occurring (Ref. 1). Alternatively, methyl phthalyl ethyl glycolate (MPEG), ethyl phthalyl ethyl glycolate (EPEG), and butyl phthalyl butyl glycolate (BPBG) have extra ester linkages in their side chains that could subject them to an additional hydrolysis step and produce glycolyl phthalate (GP) that is not expected to generate from *ortho*-phthalates without the extra ester bond (e.g., DEHP) (Ref. 4). These examples further demonstrate how the chemical structure differences across these phthalates impact their metabolic pathway, and therefore result in different metabolites and/or breakdown products.

As discussed earlier in this section, the petition does not support the assertion of a common metabolic pathway for the subject *ortho*-phthalates. Furthermore, data cited in the petition as well as other available information contradict the claim of a common metabolite or group of metabolites for all 28 *ortho*-phthalates. The petition therefore does not justify the applicability of rationale (iv) of OECD's guidance for grouping chemicals to all 28 *ortho*-phthalates.

3. Information Provided in the Petition To Support the 28 *Ortho*-Phthalates as Pharmacologically Related Substances

In support of the proposed grouping of the 28 *ortho*-phthalates as pharmacologically related substances, the petition discusses the 2014 report from the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (the CHAP report) (Ref. 6) and the results of a literature search for toxicological information that yielded information on health effects for 12 of the 28 phthalates. The petition asserts that these data demonstrate that “[w]hen *ortho*-phthalates have been studied, similar or related pharmacological effects have been identified affecting children's health” (petition at 5). The petition also states that “[r]eproductive, developmental, and endocrine toxicity effects were among the health endpoints identified for multiple compounds” (petition at 5). The petition asserts that “while the specific effects associated with *ortho*-phthalate exposure may vary among some studies, these effects nonetheless are pharmacologically related because they result from the effects of *ortho*-phthalates on the endocrine system” (Supp., August 24, 2017, at 6). The petition also asserts that the 12

phthalates with available data have “at least some evidence of endocrine disruption” (id.) and that this information supports the conclusion that the 28 phthalates are therefore “pharmacologically related by endocrine disrupting effects” (id. at 13).

4. FDA's Evaluation of the Information Provided To Support the 28 *Ortho*-Phthalates as Pharmacologically Related Substances

In asserting that the 28 *ortho*-phthalates constitute a class of pharmacologically related substances for purposes of determining safety, the petition states that “eleven *ortho*-phthalate have reproductive, developmental and endocrine health effects.” The petition further points to “adverse effects on endpoints relevant to children's health,” as summarized in table 1, that the petition characterizes as showing “similar toxic effects.” However, reproductive, developmental, and endocrine effects are broad categorizations that cover a wide range of toxicological effects that are not necessarily similar and can be caused by a variety of different mechanisms. The petition's generalized assertion that all of the cited effects are pharmacologically related because they “result from the effects of *ortho*-phthalates on the endocrine system” (Supp., August 24, 2017, at 6) does not acknowledge that the endocrine system is a generic term that encompasses multiple organs and multiple hormonal pathways. A substance that exhibits activity in one hormonal pathway may not have any effect on a different hormonal pathway, and disruption of different hormonal pathways may not result in common health outcomes (Ref. 4).

The petition's assertion that all studied *ortho*-phthalates demonstrate similar effects on the endocrine system is also directly contradicted by data cited in the petition (see Supp., August 24, 2017). One of the most commonly studied pharmacological effects for phthalates is antiandrogenicity; antiandrogens affect the endocrine system by modulating the production of testicular testosterone pertaining to the development of the male reproductive system. The data cited in the petitioners' literature search indicates that, among the 12 phthalates with available toxicological information, 7 phthalates exhibit antiandrogenic effects (i.e., butyl benzyl phthalate (BBP), diisobutyl phthalate (DiBP), DBP, dicyclohexyl phthalate (DCHP), dihexyl phthalate (DHP), DEHP, and diisononyl phthalate (DINP)) (see Supp., August 24, 2017, Appendix B). Importantly, four of

the phthalates (*i.e.*, dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-octyl phthalate (DnOP), and DiDP) have been shown to not exhibit antiandrogenic effects. As the petitioners provide data for only 12 of the 28 *ortho*-phthalates, and those data do not support the 12 *ortho*-phthalates as having similar pharmacological effects on the endocrine system, this information does not support that the remaining 16 *ortho*-phthalates also exhibit similar pharmacological effects (see Supp., August 24, 2017). Similarly, the data do not support the notion that the group of 28 *ortho*-phthalates as a whole consists of phthalates with similar pharmacological effects (see Ref. 4).

Furthermore, the petition's approach to class grouping is not consistent with the approach taken by other regulatory and scientific bodies. Other regulatory and scientific bodies have not grouped phthalates based on broad criteria such as non-specific effects on the endocrine system. Instead, other regulatory and scientific bodies have focused on common health outcomes that result from a discrete mechanism of action. Specifically, reports from regulatory or scientific bodies cited in the petition (*i.e.*, the 2014 CHAP report and the NAS report) as well as other reviews conducted by OECD (Ref. 7), the European Food Safety Authority (EFSA) (Ref. 8), and the Government of Canada (Ref. 9), grouped small subsets of *ortho*-phthalates for cumulative risk assessment based on specific related health (*i.e.*, pharmacological) effects. These assessments relied on defined toxicological endpoints with a common mechanism of action to conduct grouping, and also relied on specific and well-defined similarities in chemical structure. For example, the CHAP report concluded that phthalates with three to eight carbon atoms in the backbone of the alkyl side chain have the same endpoint of antiandrogenicity, while phthalates with alkyl side chains having carbon atoms outside of this range are not antiandrogenic and therefore should not be considered in the same class for a safety assessment (Ref. 6). The CHAP report did not group together these different categories of phthalates. Similarly, the NAS report noted that phthalates with ester chains of four to six carbon atoms are most potent in causing effects on the development of the male reproductive system (*i.e.*, antiandrogenicity), but phthalates with shorter or longer chains typically exhibit less severe or no effects (see Ref. 5). While the petition states that the NAS report "recommends that

effects of *ortho*-phthalates should be considered additive" (petition at 6), the relevant point in the NAS report only pertains to those *ortho*-phthalates that cause common adverse outcomes of antiandrogenicity (Ref. 5). The NAS report similarly did not group together the different categories of phthalates.

Additionally, a 2004 OECD report grouped phthalates for the purpose of assessing human health and ecotoxicity endpoints but only did so with respect to seven high molecular weight phthalates consisting of esters with an alkyl carbon backbone with seven carbon atoms or greater. OECD noted that the seven phthalates in the group produce little (if any) effects of developmental or reproductive toxicity, and only phthalates with alkyl carbon backbones of four to six carbon atoms cause adverse effects in development and reproduction (Ref. 4).

Since the petition was filed, EFSA and the Government of Canada also conducted their own assessments of phthalates. Both regulatory bodies grouped phthalates using defined toxicological endpoints. EFSA considered five *ortho*-phthalates commonly used in food contact materials, but only grouped four based on the common mechanism of fetal testosterone reduction and excluded the fifth (*i.e.*, DiDP) due to not sharing this effect (Ref. 8 at 1). The Government of Canada conducted a "screening assessment" of 28 *ortho*-phthalates but only grouped those with ester side-chains of three to seven carbons for the purposes of cumulative risk assessment based on the observation of antiandrogenic effects for this group (Ref. 9 at 7). Thus, the approach proposed in the petition (*i.e.*, grouping a large number of phthalates together despite data showing that those phthalates do not share the same toxic endpoints), is not consistent with the approach taken in the scientific literature, including reports cited in the petition. The petition also cites FDA's previous decision on PFCs as support for grouping the 28 *ortho*-phthalates as pharmacologically related substances. As discussed previously in section II.A.2, our grouping of long-chain PFCs was limited to a strict subset of structurally similar compounds, distinguishable from the wide structural differences in the 28 *ortho*-phthalates that are the subject of the current petition.

The petition also specifically invokes § 170.18 as support for its proposed class grouping approach. In accordance with § 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. Our regulation, at § 170.18(b), states that tolerances established for such related food additives may limit the amount of a common component that may be present or may limit the amount of biological activity that may be present, or may limit the total amount of related food additives that may be present. Section 170.18(c) provides that where 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 (§ 170.18(c)).

The petition asserts that § 170.18 is applicable to the evaluation of the 28 *ortho*-phthalates subject to the petition. Specifically, the petition asserts that the toxicokinetic and toxicodynamic properties of the *ortho*-phthalates "may be comparable" and "similar or related pharmacological effects have been identified affecting children's health." The petition further states that "[r]eproductive, developmental and endocrine toxicity effects were among the health endpoints identified for multiple compounds and at low exposure." Based on what the petition describes as "similar toxicity effects" from 13 *ortho*-phthalates, the petition states that *ortho*-phthalates are "pharmacologically related food additives for purposes of 21 CFR 170.18." (Note that the August 2017 supplement refers to data only for 12 *ortho*-phthalates). Further, the petition states that "we found several publications reporting on additive mixtures of four and five *ortho*-phthalates on developmental and reproductive endpoints" and that the NAS report "recommends that effects of *ortho*-phthalates should be considered additive" (petition at 6).

The petition has not demonstrated that § 170.18 is applicable because the petition has not shown that the 28 *ortho*-phthalates cause similar or related pharmacological effects. By its terms, § 170.18 only provides that food additives are to be regarded as a class if it has been shown that the food additives cause similar or related

pharmacological effects. However, as the petitioners concede, they only have submitted data on the effects of 12 of the 28 *ortho*-phthalates that are the subject of the petition and have not submitted data addressing the effects of 16 of the 28 *ortho*-phthalates. Furthermore, as discussed in the previous paragraphs, the data for the 12 phthalates provided by the petition do not demonstrate that all 12 phthalates have similar or related pharmacological effects; therefore, this data also does not support that all 28 *ortho*-phthalates have similar or related pharmacological effects. Thus, the petition has not put forward the threshold evidence that is necessary to apply § 170.18.

In arguing for grouping all 28 phthalates into one class, the petition also points to section 409(c)(5)(B) of the FD&C Act. The FD&C Act provides that a food additive cannot be approved for use unless the data presented to FDA establish that the food additive is safe for that use (section 409(c)(3)(A) of the FD&C Act). To determine whether a food additive is safe, section 409(c)(5) of the FD&C Act requires FDA to consider among other relevant factors the following: (1) Probable consumption of the additive; (2) 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; and (3) safety factors recognized by experts as appropriate for the use of animal experimentation data (section 409(c)(5) of the FD&C Act). As a preliminary matter, the petition has not presented evidence to show that section 409(c)(5)(B) of the FD&C Act is even applicable to the proposed class grouping. With respect to section 409(c)(5)(B) of the FD&C Act, we note as a preliminary matter that the petition has not presented sufficient evidence to show that all 28 *ortho*-phthalates are in fact chemically or pharmacologically related substances (see discussion in the previous paragraphs). As an additional matter, we note that section 409(c)(5)(B) of the FD&C Act does not direct FDA to group food additives in a class in the manner proposed in the petition. If it is established that substances are chemically or pharmacologically related to a food additive under consideration, FDA is directed to “tak[e] into account” such substances in considering the cumulative effect of the food additive in the diet of man or animals. Chemically or pharmacologically related substances can be taken into account for this purpose in any number of scientifically valid ways that are distinct from the class grouping approach proposed by

the petition (*e.g.*, considering chemically related substances in an exposure analysis or considering toxicity data from one pharmacologically related substance to evaluate possible toxic effects of another pharmacologically related substance, as appropriate). To the extent that the petition interprets section 409(c)(5) of the FD&C Act to compel FDA to adopt the petition’s approach to class grouping, the petition is incorrect. The petition proposes grouping a chemically diverse group of substances together, applying a proposed ADI value for one substance to all the substances in the purported class, and comparing the exposure of all the substances against that single proposed ADI. The FD&C Act sets forth no requirement to analyze the safety of a food additive in this manner.

5. Conclusion for Assertion A: *Ortho*-Phthalates Are Not a Class of Chemically and Pharmacologically Related Substances for Purposes of Determining Safety Pursuant to Section 409 of the FD&C Act and § 170.18

After our review of the relevant information, we conclude that the petition’s arguments for treating the 28 *ortho*-phthalates as a class are not supported. The petition points to two rationales in the OECD guidance to support its argument but fails to demonstrate that grouping all 28 phthalates is in fact consistent with those rationales. The 28 phthalates do not have a common functional group, do not have similar or related pharmacological effects, do not share a “common metabolic pathway” or even a common mechanism of action, and do not have effects on the same or similar target or system (*i.e.*, the reproductive system of male rodents). To the extent the petition suggests that the proposed class grouping is required by section 409(c)(5)(B) of the FD&C Act and/or § 170.18, the petition is incorrect.

B. Assertion B: *The ADI for DEHP Should Be Assigned to All 28 Ortho-Phthalates*

To establish with reasonable certainty that a food additive is not harmful under its intended conditions of use, FDA considers the projected human dietary exposure to the food additive, the additive’s toxicological data, and other available relevant information (such as published literature). To determine safety, one approach FDA may utilize is to compare the EDI of the food additive to an ADI level established by appropriate toxicological data. Following the argument contained in Assertion A that all 28 phthalates should be grouped as a single class, the

petition asserts that a single ADI should be established for the class and also asserts that the ADI should be used to set the upper exposure limit for cumulative exposure to all 28 phthalates.

1. Information Provided in the Petition To Support Assertion B

To establish a proposed ADI for all 28 *ortho*-phthalates, the petition cites no observed adverse effect levels (NOAELs) for specific phthalates that are published in a variety of sources. The petition then picks a NOAEL for DEHP as the basis to derive an ADI for the purported class because it is the lowest of the listed NOAEL values. The petition then proposes safety factors to be applied to that NOAEL to derive the proposed ADI. In the discussion that follows, we evaluate the petition’s approach for deriving the proposed ADI for DEHP, as well as the applicability of the proposed ADI to all 28 phthalates.

2. FDA’s Evaluation of the Information Provided To Support Assignment of the ADI for DEHP to All 28 *Ortho*-Phthalates

An ADI is the amount of a substance that is considered safe to consume each day over the course of a person’s lifetime (Ref. 10). The ADI is typically based on an evaluation of toxicological studies to determine the highest appropriate experimental exposure dose level in animal studies that was shown to cause no adverse effect (also known as the no-observed-adverse-effect level, or NOAEL), multiplied by an appropriate safety factor (Ref. 10). Accordingly, the lower the NOAEL for a specific substance, the lower the resulting ADI for the substance. A calculated dietary exposure to the food additive (*i.e.*, the estimated daily intake, or EDI) at or below the ADI is considered consistent with a reasonable certainty of no harm (Ref. 10). Therefore, a lower ADI requires a lower dietary exposure to the food additive to meet the burden of safety than a food additive with a higher ADI.

To establish a proposed ADI for all 28 phthalates, the petition identifies NOAELs for nine phthalates that are included in the 2014 CHAP report. The petition also identifies NOAELs for 15 phthalates that are included in the 1973 paper by Shibko, et al. (the 1973 paper, Ref. 2). Together, this makes for a total of 24 NOAEL values for 17 different phthalates. The petition does not provide NOAEL values for the remaining 11 phthalates that are the subject of the petition. The petition adopts the NOAEL provided for DEHP in the 2014 CHAP report because it was

the lowest of the cited values. To calculate the ADI, the petition applies a total safety factor of 1,000 to the cited NOAEL for DEHP, resulting in a proposed ADI of 3 micrograms per kilogram of body weight per day ($\mu\text{g}/\text{kg bw}/\text{d}$) (petition at 11). However, the petition fails to provide any discussion or supplementary information to justify why any of these NOAEL values are appropriate for assessing risk of dietary exposure to *ortho*-phthalates.

Our regulation, at § 171.1(c), requires that a petition provide full reports of investigations made with respect to the safety of a food additive and not omit, without explanation, any reports of investigations that would bias an evaluation of the safety of the food additive. Such information is necessary so that FDA can independently evaluate and verify the relevant evidence. However, the petition merely lists values published in the CHAP report and the 1973 paper and does not evaluate the underlying evidence supporting the NOAEL values listed in those publications. Although the CHAP report is the result of considerable scientific analysis, it was not designed to assess the safety of food additive uses and does not provide a comprehensive discussion of evidence that would be sufficient to permit FDA to independently evaluate the evidence used to determine the NOAELs (Refs. 10 and 11). Similarly, the 1973 paper provides only a truncated summary of literature available at the time of publication. Furthermore, the NOAELs in the 1973 paper were derived from either subacute or chronic animal studies, which only tested phthalates in weanling animals. These studies have limitations to assess antiandrogenicity as an endpoint (Refs. 4 and 6) and therefore are not appropriate to determine NOAELs for those phthalates that are known antiandrogens. Most importantly, the petition does not provide additional information that would allow FDA to fill the gaps.

Typically, to determine appropriate NOAEL values, FDA considers a wide array of information, including the results of a comprehensive literature search, so that we can evaluate the most relevant studies and their methods, determine the most appropriate endpoint(s), and consider the appropriateness of the animal species selected for study (Refs. 10 and 11). However, the petition provides no such wide array of information with respect to the NOAEL. Rather, the petition merely lists the NOAEL value that is included in the CHAP report. The petition does not explain why this NOAEL for DEHP is appropriate for

human risk assessment of dietary exposure. FDA is aware of the existence of studies on DEHP in non-human primates that identify NOAELs based on testicular effects that are at least two orders of magnitude higher than the level derived from studies conducted in rats cited by the petitioners (Refs. 12 to 15). Results in primates are generally considered more applicable to human risk assessment than results in rats, and these non-human primate studies were not included in the assessment in the CHAP report. As the petition does not address these studies or others that may impact the appropriateness of the cited NOAEL for human risk assessment of exposure to DEHP itself, the petition has not provided an adequate scientific rationale to justify the selected NOAEL for DEHP. Thus, the information submitted in the petition does not amount to a full report of investigations made with respect to safety, as required by § 171.1(c), and the petition has not provided adequate scientific justification for the proposed NOAEL for DEHP.

In addition to lacking sufficient support for the appropriateness of the selected NOAEL for evaluation of DEHP itself, the petition also lacks scientific support to justify applying the cited NOAEL for DEHP to all 28 *ortho*-phthalates. Although the petition cites the 1973 paper in support of applying a single substance's ADI to a group of phthalates, that paper discussed this approach based on the assumption that the toxicity for an *ortho*-phthalate may be related to the toxicity of the alcohol moiety (which is not antiandrogenic). The paper describes the alcohol moiety as a common metabolite for these substances, when in fact more current scientific information does not support that all 28 phthalates share a common metabolite. Accordingly, the recommendation in the 1973 paper is based on a scientific assumption that has since been contradicted. The 1973 paper therefore does not support the petition's requested action.

Furthermore, the petition's proposed NOAEL for DEHP is based on an antiandrogenic endpoint. Recent scientific data, including information contained in the petition, demonstrate that not all phthalates are antiandrogenic. Recent data also demonstrate that antiandrogenicity may not be the most sensitive endpoint for all 28 *ortho*-phthalates, including some which also demonstrate antiandrogenicity (Ref. 4). NOAELs serve to identify the highest dosages of a particular substance in which toxic effects were not observed, but a NOAEL is not useful for determining safe

exposure levels if it is not in fact based on toxic effects that may result from the substance. Also, as discussed in our response to Assertion A, the petition has not provided sufficient information to demonstrate that the pharmacological effects for all 28 *ortho*-phthalates are similar or related. Therefore, it is not appropriate to apply a NOAEL based on the effect of antiandrogenicity to substances that are not antiandrogenic.

In addition, with respect to converting the NOAEL to an ADI, the petition has not sufficiently supported the application of additional safety factors to the proposed NOAEL. In general, the use of a safety factor is intended to provide an adequate margin of safety for consumers by accounting for variability, such as differences between animals and humans (*i.e.*, interspecies variability) and differences in sensitivity among humans (*i.e.*, intraspecies variability) (Ref. 10). In accordance with § 170.22, a safety factor of 100 will be used as a general rule in applying animal test data for the purposes of safety assessment for human consumers.

However, exceptions to a safety factor of 100 are permitted in accordance with the nature and extent of data available and the circumstances of use of the food additive. For reproductive and developmental endpoints, FDA recommends the use of a safety factor of 1,000 if the observed effects are severe or irreversible (*e.g.*, decrease in the number of pups born live) (Ref. 10). Otherwise, FDA recommends a safety factor of 100. Additional adjustments may be appropriate when considered on a case-by-case basis (Refs. 4 and 11). The petition proposes dividing the cited NOAEL for DEHP by a safety factor of 1,000 to derive the proposed ADI. In support of the application of an additional 10x safety factor for the severity of effects, the petition makes a general assertion that "developmental, reproductive and endocrine toxicity effects observed after prenatal and postnatal exposure also represent severe findings due to their likely irreversibility" (Supp., August 24, 2017, at 9). Because the petition does not provide critical information about the studies (*e.g.*, study design, animal species, animal numbers, dosing regime, dosing duration, examined endpoints, and statistical methods) to support the selected NOAEL for DEHP, the petition fails to adequately justify an exception to a safety factor of 100. This absence of information means that the proposed ADI for DEHP lacks scientific justification.

3. Conclusion for Assertion B: The ADI Proposed in the Petition Should Not Be Assigned to All 28 *Ortho*-Phthalates

The petition has not provided the requisite information for either the selected NOAEL or the proposed ADI for DEHP. Similarly, the petition has not justified the application of the proposed ADI for DEHP to all 28 phthalates. To the extent that the petition relies on § 170.18 for applying a single ADI to all 28 phthalates, there is no support for such an approach because, as discussed in section II.A, the petition has not demonstrated that the criteria in § 170.18 for treating food additives as a class are met.

C. Assertion C: The EDI for *Ortho*-Phthalates Exceeds the Proposed ADI and, Therefore, the Intentional Use of *Ortho*-Phthalates as Food Contact Substances Are Not Safe

The argument in Assertion C is predicated on the underlying premise of the petition (*i.e.*, the establishment of a single class for all 28 phthalates). The petition asserts that certain published dietary exposure estimates for several of the individual subject phthalates, as well as the cumulative exposure to all 28 phthalates, significantly exceeds the ADI proposed in the petition for the purported class. From this comparison between published dietary exposure estimates and the proposed ADI, the petition states that “the intentional use of *ortho*-phthalates as food contact substances are not safe as defined by FDA’s regulations” (petition at 11).

1. Information Provided in the Petition To Support Assertion C

The petition concedes that it does not provide exposure data for all 28 *ortho*-phthalates, asserting that a cumulative exposure to all 28 phthalates cannot be determined based on the limited information available (see petition at 14). Instead, the petition compares estimated exposures to individual phthalates for specific subpopulations (as reported in various published data sources) to the proposed ADI for the purported class. Specifically, the petition asserts that the following dietary exposures are all greater than the proposed ADI for the purported class: The average women’s dietary exposures to DINP and DIDP, as estimated in the CHAP report; the 95th percentile exposure for women to DEHP, as listed in the CHAP report; and the infant exposure to DEHP, as listed in a 2013 publication by Schecter et al. (Ref. 16). Turning to biomonitoring data, the petition also relies on this type of data to assert that the following additional

exposures exceed the proposed ADI: The median and 95th percentile exposures for pregnant women and women of reproductive age to DEHP; and the 95th percentile exposures for pregnant women and women of reproductive age to DBP and DINP. This biomonitoring data comes from National Health and Nutrition Examination Survey (NHANES) survey results covering different years.

We have previously discussed in sections II.A and II.B that the petition does not demonstrate that all 28 phthalates should be considered as a single class, and that the petition does not demonstrate that the proposed ADI for DEHP should be applied to the purported class. Therefore, our discussion below is not focused on comparing published exposure estimates for members of a purported *ortho*-phthalate class to a proposed ADI for that purported class. Rather, our discussion below evaluates the relevance of the cited data for estimating U.S. dietary exposure.

2. FDA’s Evaluation of the Information Provided To Support Assertion C

Food surveys, total diet studies, and human biomonitoring studies can all be part of an appropriate postmarket approach to determine dietary exposure for a substance that is already authorized for use as a food contact substance. However, many factors should be addressed to determine the suitability of any given dataset for determining dietary exposure. These factors can include suitability of sample preparation and data analysis, relevance of the data to the current market, specific population or geographic region, and whether it is sufficiently robust in both sample breadth (number of different types of foods sampled) and size (number of samples within a given food type) to be representative. In determining sample breadth, it may be appropriate to consider dietary exposure from a number of sources, such as uses that are authorized through the food contact notification process or food additive regulations and uses that are determined to be generally recognized as safe. Rather than analyze the relevance or suitability of the data cited, the petition simply lists any reported value from any dataset that is higher than the proposed ADI for the purported class.

In general, dietary exposure values for a substance can be calculated using the level of the substance in food (taken from food surveys) and the daily food consumption rate (taken from food categorization systems). Food categorization systems divide the daily

diet into distinct food types. This allows for surveying consumption of individual foods within those food types to be representative of exposure from overall consumption of those types of foods by the consumer. Food categorization systems provide for a tiered grouping of foods first based on a broad category (*i.e.*, aquatic animals, land animals, plants, and other) all the way down to differences in processing (*e.g.*, pasteurized or not pasteurized). These subdivisions allow for assignment of foods to a specific category for purposes of determining consumption rates of individual foods or larger food categories (*e.g.*, all forms of dairy). Food surveys analyze the foods in the average diet of the whole population in a country (*i.e.*, Total Diet Study (TDS) approach), or by analyzing select foods in the diet of a given population within a limited geographical area (*e.g.*, the data in Schecter et al. (Ref. 16)). When determining whether a particular food survey is relevant and suitable for estimating levels of a substance in the total diet of a specific population, multiple factors should be considered to ensure scientific validity. These include, among others, whether the types of food, number of samples, and location of where food samples were obtained represent the diet of the target population, the appropriateness of the sample preparation and analytical methods, and whether a particular food categorization system is suitable to calculate exposure from the levels in food obtained from the survey.

As previously stated, the petition relies on dietary exposure estimates that are provided in the CHAP report and Schecter et al. study. Although the CHAP report described and supported its dietary exposures estimates, there are still data gaps that raise questions about the petition’s reliance on estimated dietary exposure values that are derived from the CHAP report. Specifically, the CHAP report relies on a TDS conducted in the United Kingdom (UK). This survey may not reflect U.S. dietary exposures, as different supply chains in different continents may result in different exposures. In addition, this data was almost 10 years old at the time the petition was submitted to FDA (see Ref. 6). Further, while the data in Schecter et al. is from a segment of the U.S. population (*i.e.*, food sampled in Albany, NY, in 2011), the dataset is less robust than the UK TDS. Schecter et al. analyzed for 9 phthalates in 72 commonly consumed foods, compared with the UK TDS that analyzed for 15 phthalate diesters and 9 phthalate esters, as well as phthalic acid in 261

retail food items in the UK. The studies also differ in the food categorization systems used to calculate exposure. An appropriate way to utilize the Schecter et al. study in the context of the CHAP report would be to examine if the results from these studies reinforce each other while accounting for the different parameters used by each. However, the petition provides no such examination or analysis and instead adopts any exposure to any phthalate from either analysis that is over the proposed ADI for the purported class. As such, the petition does not address the results from the CHAP report and the Schecter et al. study that are contradictory for select reported values. For example, the average exposure to DEHP for women in the CHAP report is 4.8 µg/kg bw/d (over the ADI of 3 µg/kg bw/d proposed in the petition), while the average exposure to DEHP for adults (which should be comparable to women) in Schecter et al. is only 0.67 µg/kg bw/d (lower than the proposed ADI) (Refs. 6 and 16). Further analysis is needed to determine which, if either, of these contradictory values is suitable for the purpose of a safety assessment.

We note that other available dietary survey/TDS data that are only briefly discussed in the petition (Canadian TDS and Australian TDS studies published in 2015 and 2014, respectively) could potentially address several of the data gaps. These data sets are more recent than the CHAP report and Schecter et al. study. They are also more robust than the Schecter et al. study. In addition, the Canadian TDS may be more directly relevant to the U.S. population than the UK TDS used in the CHAP report, in that Canadian and U.S. diet and packaging and processing supply chains may be more similar than UK and U.S. diet and packaging and processing supply chains. Although exposure estimates were not calculated in the Canadian and Australian TDS reports, the data from these studies could be applied to an appropriate food categorization system and used to calculate exposure estimates. The petition provides no such examination or analysis.

With respect to the petition's reliance on biomonitoring data, we note that biomonitoring studies are used in assessing human exposure to a chemical by measuring the level of the biomarker (e.g., the chemical itself, its metabolite(s), or reaction product(s) in a biological matrix such as human blood or urine) from individuals and then analyzing the data collectively. The exposure values calculated from biomonitoring data include contributions not just from the ingestion

of food (i.e., diet), but also from inhalation and dermal contact. However, using exposure values from biomonitoring studies without discussion and supporting information to determine the specific contribution from dietary sources is not appropriate in the context of a food additive petition, as the overall exposure value in a biomonitoring study may not be an appropriate proxy for the probable dietary exposure value (see section 409(c)(5)(B) of the FD&C Act (directing that FDA consider the cumulative effect of a food additive "in the diet of man or animals") (emphasis added); 21 CFR 171.3(i)(2) (providing that in determining a food additive's safety "the cumulative effect of the substance in the diet" shall be considered) (emphasis added)).

As to the specific biomonitoring data cited in the petition, the NHANES data and resultant exposure values are relevant in that they reflect relatively recent dietary patterns and are generated from the U.S. population. However, the approach of directly comparing biomonitoring-based exposure values to a proposed ADI for the purpose of assessing the safety of a food additive is not scientifically appropriate. As discussed in the previous paragraph, relying on biomonitoring data alone does not differentiate the amount of exposure that results from the diet compared to environmental and other sources. We note that NHANES and other biomonitoring data do not differentiate specific sources or routes of exposure, such as exposure from dietary sources. Because the petition does not account for these limitations by addressing how the biomonitoring data accounts for dietary exposure, the petition's direct comparison of biomonitoring-based exposure values to the purported ADI is scientifically flawed.

3. Conclusion for Assertion C: The EDI Approach in the Petition Is Not Valid

As discussed in sections II.A and II.B, the petition does not support the establishment of a single class for all 28 phthalates, nor does it support the proposed ADI for DEHP or the application of the proposed ADI to the purported class. As Assertion C is predicated on Assertions A and B, the approach in Assertion C of comparing published exposure estimates to the proposed ADI for the purported class is therefore scientifically flawed. In addition, the petition does not adequately support its proposed exposure estimates. The petition does not justify its approach of adopting any reported single phthalate exposure

estimate that is over the proposed ADI for the purported class. Specifically, the petition does not account for: (1) The imprecision of relying on exposures estimates derived from biomonitoring studies to assess dietary exposure; (2) the diverse parameters used in the cited dietary exposure analyses to determine which analysis, if any, most accurately reflects true U.S. dietary exposure; and (3) the contradiction in reported dietary exposure values between those analyses.

D. Summary Conclusion of FDA's Review of the Petition

As discussed in section II.A, the petition does not support the establishment of a proposed class for all 28 phthalates. In light of the differences in the chemical structures and toxicity profiles among the 28 phthalates, the petition does not provide adequate scientific support for grouping chemicals for the purpose of assessing safety. Section II.B explains that the petition's approach of applying the proposed ADI to the purported class is also flawed, in that the proposed ADI is not adequately supported, and it is not scientifically appropriate to apply the proposed ADI to the purported class of 28 *ortho*-phthalates. Section II.C explains that, as it is not valid to group all 28 *ortho*-phthalates as a class of chemically or pharmacologically related substances for the purpose of assessing safety, it is also not valid to compare exposures for these *ortho*-phthalates to a proposed ADI for the purported class. In addition, the petition's approach for estimating exposure to *ortho*-phthalates is not adequately supported. For all these reasons, the petition does not contain sufficient data to support a finding that there is no longer a reasonable certainty of no harm from the currently approved uses.

As an additional matter, based on the information currently available to FDA, we do not have a basis to conclude that dietary exposure levels from approved *ortho*-phthalates exceed a safe level. As new information becomes available to us, we will continue to examine such data as appropriate to assess whether there remains a reasonable certainty of no harm.

III. Comments on the Filing Notice

Overall, we received multiple comments in support of the petitioners' request that we amend or revoke the specified regulations to no longer provide for the food contact use of the 28 *ortho*-phthalates. Other comments, such as those from a coalition composed of trade organizations, materials suppliers, compounders, formulators, molders, and fabricators, oppose the

petition. Additionally, some comments addressed matters that are outside the scope of the petition, and some comments were duplicate submissions.

In this section, we discuss the issues raised in the comments. We preface each comment discussion with a numbered “Comment” and each response by “Response” to make it easier to identify comments and our responses. We have numbered each comment to help distinguish among different topics. The number assigned is for organizational purposes only and does not signify the comment’s value, importance, or the order in which it was received.

(Comment 1) Many comments, primarily form letters, stated that phthalates are hormone disrupting chemicals linked to a wide variety of adverse health outcomes such as: Reduced anogenital distance in male infants; reduced sperm quality; infertility; genital birth defects in boys; impaired mental and/or psychomotor development; attention deficit disorder and behavioral symptoms; obesity and insulin resistance; rhinitis; eczema; asthma; endometriosis; and renal, hepatic, thyroid, and hormone-dependent cancers. The comments stated that, given the available research, FDA should take quick action to reduce exposure to these chemicals in our food supply.

(Response 1) FDA is aware of the research that has been conducted with respect to phthalates. While FDA considered the research in its evaluation of the petition, including the research identified in the comments, most of the research considered individual phthalates or mixtures of phthalates. The petition is based on the idea that the 28 subject phthalates should be considered as a class and deemed unsafe as a class. For the reasons described previously, the petition does not provide adequate support for grouping the 28 phthalates as a single class, and therefore, the research pertaining to individual phthalates or specific mixtures of phthalates cannot be applied to all 28 phthalates that are the subject of the petition.

(Comment 2) Many comments cited the CHAP report and pointed to the Consumer Product Safety Commission’s (CPSC’s) final rule prohibiting children’s toys and childcare articles that contain more than 0.1 percent of five specific *ortho*-phthalates (82 FR 49938, October 27, 2017). Other comments also cited the CHAP report’s finding that the diet (separate from exposure from children’s toys and childcare articles) is a major route of exposure to phthalates as a reason why

FDA should also address the use of phthalates. These comments argued that, because maximum use levels of certain phthalates in toys have been used to assess risk to children during early development, FDA should take action against uses of phthalates in food contact applications that contribute to exposure for pregnant women and the developing fetus, as well as for nursing mothers and babies.

(Response 2) The CHAP report included a risk assessment regarding the use of 14 phthalates and 6 phthalate alternatives in children’s toys and childcare articles. While the report was a result of significant scientific analysis, the report was conducted primarily for the purpose of evaluating the safety of certain phthalates and phthalate alternatives in children’s toys and childcare articles, and the regulatory recommendations in that report apply to those particular uses of phthalates. Notably, the CHAP report was not designed to evaluate the safety of phthalates for food contact uses, which is the subject of this petition. In evaluating the safety of substances for food contact uses, FDA is required by statute to consider the safety of a substance for the particular food contact use (see sections 409(b) and (h)(1) of the FD&C Act (providing that sponsors may submit petitions or notifications with respect to the “intended use” of the substance)). In addition, we are directed by statute to consider food-related uses in assessing safety (see section 409(c)(5) of the FD&C Act) (providing that in determining safety, the Secretary shall consider among other relevant factors “the probable consumption of the additive and of any substance formed in or on food because of the use of the additive”). Accordingly, safety assessments conducted for purposes other than evaluating the safety of food contact uses cannot directly determine the safety of food contact uses. As appropriate, FDA may consider the underlying evidence reviewed in such assessments. But FDA’s statutory responsibility is to evaluate safety in accordance with the FD&C Act and in consideration of the specific intended uses for which we have jurisdiction.

(Comment 3) Some comments discussed actions taken with regard to phthalates by other government entities (such as CPSC’s final rule prohibiting phthalates in children’s toys and childcare articles if they contain more than 0.1 percent of five *ortho*-phthalates (82 FR 49938) and the European Union’s (EU’s) plastic regulation (Commission Regulation 10/2011, Plastic Materials and Articles Intended to Come into Contact with Food, 2011 O.J. (L 12)).

Some comments referred to the EU regulation as an unequivocal ban on the use of almost all *ortho*-phthalates in food contact materials intended for fatty and infant foods. In addition, the comments pointed to FDA’s Center for Drug Evaluation and Research’s (CDER’s) removal of two phthalates from its inactive ingredients database (77 FR 72869, December 6, 2012), and FDA’s Center for Devices and Radiological Health’s (CDRH’s) draft guidance on medical devices made with polyvinyl chloride (PVC) containing DEHP (67 FR 57026, September 6, 2002). The comments argued that FDA should take similar action by banning the use of all phthalates in contact with food.

(Response 3) Each of the governmental actions described in the comments were taken based on different applicable legal standards, and the safety considerations and assessments that supported those actions were not conducted in accordance with FDA’s food additive safety standards under section 409 of the FD&C Act. In this action, FDA is responding to the specific claims made in the petition about the applicability of the safety standard in section 409 of the FD&C Act to a purported class of 28 *ortho*-phthalates, and we have evaluated those claims in accordance with the requirements for food additive petitions and applicable regulations.

We also note that other regulatory actions and government bodies identified in the comments have not limited or banned the use of all 28 *ortho*-phthalates that are the subject of the petition. For example, the actions taken by Congress and CPSC to limit the use of eight phthalates (DEHP, DBP and BBzP, DINP, di-n-pentylphthalate (DPENP), dihexyl phthalate (DHEXP), dicyclohexyl phthalate (DCHP), and diisobutyl phthalate (DIBP)) in children’s toys and childcare articles was not a total ban on the use of these substances, but a ban above the specific use level of 0.1 percent in the articles. While Congress also put an interim ban on DINP, DIDP, and DnOP, the CHAP report later recommended to lift the interim ban for DnOP and DIDP as these compounds are not likely to be antiandrogenic. The CHAP report also recommended that no action be taken on dimethyl phthalate (DMP) and diethyl phthalate (DEP).

The EU’s plastic regulation (Commission Regulation 10/2011, 2011 O.J. (L 12)) authorizes six phthalates (DBP, BBP, DEHP, DINP, diallyl phthalate (DAP), and DIDP) for use in food contact plastic materials and articles. These phthalates have different

use restrictions, specific migration limits, and specific type(s) of food the articles containing these substances may contact. The EU's regulation authorizes certain phthalates and does not ban the use of all other phthalates for food contact applications.

The removal of DEHP and DBP from CDER's database of inactive ingredients in drug products followed the publication of CDER's guidance document, "Limiting the Use of Certain Phthalates as Excipients in Center for Drug Evaluation and Research-Regulated Products" (77 FR 72869). While CDER's guidance was informed by concerns about the safety of DBP and DEHP, the guidance was limited to the use of those substances as excipients in drug and biologic products, and the guidance specifically states that the recommendations in the document do not address the use of DBP or DEHP in other types of FDA-regulated products. As an additional matter, the guidance document—like all FDA guidance documents—is non-binding and sets forth policy and regulatory recommendations only (see 21 CFR 10.115). In addition, the CDRH draft guidance is not a ban on the use of DEHP. Instead, the draft guidance (which was never finalized and has since been withdrawn) would have suggested labeling DEHP content and would have recommended that device manufacturers consider replacing DEHP for a small subset of medical devices where PVC containing DEHP may come in contact with the tissue of a sensitive patient population in a manner and for a period of time that may result in concerns about aggregate exposure to DEHP. The draft guidance did not address exposure to DEHP from any other use of PVC, such as food contact applications.

(Comment 4) Most comments supported banning all 28 *ortho*-phthalates even in the absence of scientific evidence of harm because of concern that banning only some phthalates could lead to substitution with other phthalates or alternatives that may carry unknown risks.

(Response 4) Consistent with section 409 of the FD&C Act, FDA evaluates the safety of all food additives against the same safety standard of reasonable certainty of no harm and does not make safety determinations based on the comparison of one chemical to its potential substitute. The 28 *ortho*-phthalates that are the subject of the petition were approved via the food additive petition process and included an evaluation using the same safety standard as other food contact substances. Any "substitute" phthalate

used as a food contact substance would also undergo any required premarket safety review and would be required to meet FDA's safety standard.

In response to the comments arguing that FDA should take action even if there is uncertainty about the data, FDA regulates food additives in accordance with the FD&C Act. Under the FD&C Act, food additives may not be used unless it can be demonstrated that there is a reasonable certainty that no harm will result from their use.

(Comment 5) Several comments supported the petitioners' position that all 28 phthalates should be considered and regulated as a single class because, in the commentors' view, the phthalates are chemically and pharmacologically related. The comments also stated that exposure to phthalates should be considered cumulatively based on the antiandrogenic effects seen in rats treated with certain phthalates and that a single ADI should be established for the asserted class. The comments agreed with the petition's argument that adverse effects and the 3 µg/kg bw/day ADI proposed for DEHP should be attributed to the entire asserted class, and that current exposure levels for phthalates exceeds this level.

Conversely, one comment stated that the antiandrogenic effect identified is species-specific and that some studies have reported that, unlike the observations made in studies testing rat fetus tissue, antiandrogenicity is not observed in human fetus tissue when exposed to phthalates in the same way.

(Response 5) FDA has addressed the petitioners' three assertions in sections II (A, B, and C). FDA has also addressed the human relevance to the antiandrogenicity effect reported from rat studies in section II.B and in Ref. 4.

(Comment 6) Some comments stated that FDA should consider purported economic costs of human health impacts (such as healthcare expenses due to illness and lost productivity) associated with exposure to chemicals generally, including phthalates.

(Response 6) FDA does not agree that it is necessary to evaluate the potential economic impact of the regulated uses of the 28 *ortho*-phthalates that are the subject of the petition. The economic costs for which the comment wants FDA to conduct estimates are health related (*i.e.*, costs to the healthcare system that result from asserted health problems caused by phthalates). At the time FDA authorized the 28 *ortho*-phthalates that are the subject of the petition, FDA found them to be safe. The comments did not explain why FDA is under an ongoing obligation to develop cost estimates for substances that FDA has

found to be safe. If new data and information accrue such that FDA determines that any approved additives are in fact unsafe, FDA will take appropriate action by revoking the approvals for such additives or otherwise ensuring that the additives are not used.

(Comment 7) Several comments stated that if FDA does not grant the petition, we should require disclosure of the use of phthalates in food packaging directly on the label so consumers who wish to avoid or limit exposure to phthalates are able to make an informed decision.

(Response 7) The petition did not request that FDA establish requirements for the labeling of products manufactured with phthalates. We note that manufacturers may voluntarily label their products as phthalate-free, as long as such labeling is truthful and not misleading.

For FDA to require labeling on food packages regarding the use of phthalates, FDA would consider the standards in: (1) Section 409(c)(1)(A) of the FD&C Act, providing that regulations for food additives prescribe the conditions necessary to provide for the safe use of the ingredient, and (2) the standard under section 201(n) of the FD&C Act that any such declaration constitutes a material fact with respect to the consequences that may result from the use of the food. The comments did not provide evidence to address either of these standards, and based on the current record, we do not find it appropriate to take such action in response to these comments.

(Comment 8) Some comments urged FDA to consider the effects phthalates have on the environment and wildlife. The comments stated that the use of these chemicals could result in the contamination of soil, air, and drinking water.

(Response 8) The comments did not provide any information or relevant data to substantiate the asserted environmental effects of phthalates from their use as food additives. Therefore, these comments are unsupported. To the extent the comments suggested that FDA conduct an environmental assessment or impact statement under the National Environmental Policy Act (NEPA), 42 U.S.C. 4321 *et seq.*, we note that NEPA does not require Agencies to conduct such assessments or impacts unless there is a major Federal action. Agency decisions that maintain the status quo do not constitute major Federal actions (see, *e.g.*, 40 CFR 1508.1(q); *Fund for Animals, Inc. v. Thomas*, 127 F.3d 80 (D.C. Cir. 1997); *Defenders of Wildlife v. Andrus*, 627 F.2d 1238, 1243–46 (D.C. Cir. 1980)).

Our denial of this food additive petition maintains the status quo. To the extent that the comments suggested that environmental effects can be a basis for withdrawing a food additive petition, we are unaware of any such authority under the FD&C Act and the comments did not identify any.

(Comment 9) Some comments agreed with the petitioners' exposure estimation that considers cumulative exposure using four datasets from different sources, while others disagreed with the approach used to estimate exposure. One comment stated that one of petitioners' sources for estimating exposure, the 2014 CHAP report, overestimates exposure levels because it used outdated NHANES biomonitoring data that does not reflect a more recent decline in exposure, as evidenced by a reduction in urinary metabolite levels observed in the most recent NHANES data (2009–2010 CDC NHANES data, published September 2012).

(Response 9) As discussed in section II.C, the petition does not adequately support the proposed exposure values. We have addressed the petitioners' use of exposure data in section II.C.

(Comment 10) Many comments agreed with the petitioner regarding the additional safety factor applied to the NOAEL for DEHP to calculate the ADI. The comments stated that a safety factor of 1,000 should be used. Conversely, one comment stated that the available data does not support the use of a safety factor of 1,000 because the effects identified for DEHP in the reference studies are "mild" and do not warrant an adjustment for severity.

(Response 10) As discussed in section II.B.2, FDA cannot determine the appropriate safety factor without more information than what was provided in the petition.

IV. Conclusion

FAP 6B4815 requested that the food additive regulations be amended to provide for the removal of 28 authorized phthalates listed for use in contact with food. After reviewing the petition, as well as additional data and information relevant to the petitioners' request, we determine that the petition provides insufficient information to support a finding that there is no longer a reasonable certainty of no harm for the proposed class of *ortho*-phthalates. Therefore, FDA is denying FAP 6B4815 in accordance with § 171.100(a).

V. Objections

Any persons that may be adversely affected by this notice may file with the Dockets Management Staff (see **ADDRESSES**) either electronic or written

objections. You must separately number each objection, and within each numbered objection you must specify with particularity the provision(s) to which you object, and the grounds for your objection. Within each numbered objection, you must specifically state whether you are requesting a hearing on the particular provision that you specify in that numbered objection. If you do not request a hearing for any particular objection, you waive the right to a hearing on that objection. If you request a hearing, your objection must include a detailed description and analysis of the specific factual information you intend to present in support of the objection in the event that a hearing is held. If you do not include such a description and analysis for any particular objection, you waive the right to a hearing on the objection.

It is only necessary to send one set of documents. Identify documents with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>. We will publish notice of the objections that we have received or lack thereof in the **Federal Register**.

VI. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time. In addition, Reference A is also part of the administrative record and is on display at the Dockets Management Staff. This reference is also available electronically at <https://www.regulations.gov>.

*1. 2014 Organization for Economic Co-operation and Development (OECD) Guidance on Grouping of Chemicals.

*2. Shibko, S.I. and H. Blumenthal (1973) "Toxicology of Phthalic Acid Esters Used in Food Packaging Material," *Environmental Health Perspectives*, 3:131–137.

*3. FDA Memorandum from R. Briñas to J. Urbelis, May 11, 2022.

*4. FDA Memorandum from T–F. Cheng to J. Urbelis, May 11, 2022.

*5. Phthalates and Cumulative Risk Assessment: The Tasks Ahead; National Research Council (US) Committee on the Health Risks of Phthalates (NAS Report): Washington (DC): *National Academies Press* (US); 2008.

*6. 2014 Chronic Hazard Advisory Panel (CHAP) on Phthalates and Phthalate Alternatives Final Report.

*7. OECD: Screening Information Dataset (SIDS) Initial Assessment Meeting (SIAM) 19), 19–22 October 2004.

*8. European Food Safety Authority (EFSA) Panel on Food Contact Materials, Enzymes and Processing Aids (2019) "Update of the Risk Assessment of di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and di-isodecylphthalate (DIDP) for Use in Food Contact Materials," *EFSA Journal*, 17(12):5838.

*9. Canada: Screening Assessment—Phthalate Substance Grouping. Environment and Climate Change Canada, Health Canada. December 2020. Cat. No.: En14–393/2019E–PDF; ISBN 978–0–660–32979–6.

*10. FDA, Guidance for Industry, "Toxicological Principles for the Safety Assessment of Food Ingredients: Redbook 2000," July 2007 (available at: <https://www.fda.gov/media/79074/download>).

*11. FDA, Guidance for Industry, "Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations," October 2021 (available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-preparation-food-contact-substance-notifications-toxicology-recommendations>).

*12. FDA, (2001) "Safety Assessment of Di(2-ethylhexyl) phthalate (DEHP) Released from PVC Medical Devices," (available at: <https://www.fda.gov/media/114001/download>).

13. Kurata, Y., F. Kidachi, M. Yokoyama, et al. (1998) "Subchronic Toxicity of Di(2-ethylhexyl)phthalate in Common Marmosets: Lack of Hepatic Peroxisome Proliferation, Testicular Atrophy, or Pancreatic Acinar Cell Hyperplasia," *Toxicological Sciences*, 42:49–56.

*14. Rhodes, C., T.C. Orton, S. Pratt, et al. (1986) "Comparative Pharmacokinetics and Subacute Toxicity of Di-(2-ethylhexyl) Phthalate (DEHP) in Rats and Marmosets: Extrapolation of Effects in Rodents to Man," *Environmental Health Perspectives*, 65, 299–307.

15. Pugh, G. Jr., J.S. Isenberg, L.M. Kamendulis, et al. (2000) "Effects of Di-isononyl Phthalate, Di-2-ethylhexyl Phthalate, and Clofibrate in Cynomolgus Monkeys," *Toxicological Sciences*, 56(1):181–188.

*16. Schecter, A., M. Lorber, Y. Guo, et al. (2013) "Phthalate Concentrations and Dietary Exposure from Food Purchased in New York State," *Environmental Health Perspectives*, 121(4): 473–494.

*A. FDA Supplementary Memorandum for Food Additive Petition (FAP) 6B4815, J. Urbelis, May 11, 2022.

Dated: May 11, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

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