



May 12, 2022

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c/o Tom Neltner
Environmental Defense Fund
1875 Connecticut Ave., NW, Suite 600
Washington, DC 20009

Re: Docket Number FDA-2016-P-1171

Dear Ms. Buermeyer:

This letter responds to your citizen petition¹ requesting that the Food and Drug Administration (FDA or we) prohibit the use of eight *ortho*-phthalates in food and revoke the prior sanctioned uses for five *ortho*-phthalates in food. Specifically, your citizen petition asks us to:

A) Add a new section to Part 189 of Title 21 prohibiting the use of eight *ortho*-phthalates as food contact substances that the Consumer Products Safety Commission's (CPSC) Chronic Health Advisory Panel on Phthalates (CHAP) concluded are unsafe or the evidence indicates developmental health effects are likely. These phthalates are:

Diisobutyl phthalate;
Di-n-butyl phthalate;
Butyl benzyl phthalate;
Dicyclohexyl phthalate;
Di-n-hexyl phthalate [also known as dihexyl phthalate];
Diisooctyl phthalate;
Di(2-ethylhexyl) phthalate [also known as DEHP]; and
Diisononyl phthalate.

¹ See Citizen Petition from Nancy Buermeyer, Breast Cancer Fund, et al., submitted to the Division of Dockets Management, Food and Drug Administration, dated April 19, 2016 ("petition").

B) Strike section 181.27 from Title 21 of FDA’s existing regulations. This section allows the use of five *ortho*-phthalates as prior-sanctioned substances. The regulation only authorizes their use “as plasticizers when migrating from food packaging material.” The petition proposes that the following *ortho*-phthalates no longer meet the reasonable certainty of no harm safety standard are:

Butylphthalyl butyl glycolate;
Diethyl phthalate;
Ethylphthalyl ethyl glycolate;
Di-(2-ethylhexyl) phthalate (use on foods of high water content only); and
Diisooctyl phthalate (use on foods of high water content only).

(Petition at pages 1-2).

In accordance with 21 CFR 10.30(e)(3), and for the reasons stated in section II of this response, we are denying your petition.

I. Procedural Background and Related Regulatory Actions

On April 19, 2016, you provided a submission requesting that: 1) FDA revoke and/or amend certain specified food additive and prior-sanctioned regulations in Title 21 of the Code of Federal Regulations to no longer provide for the food contact use of 30 *ortho*-phthalates; and 2) FDA prohibit the use of eight specific *ortho*-phthalates by adding a new section in 21 CFR part 189. You designated this submission as a food additive petition. With respect to the portion of your submission requesting that FDA revoke food additive uses of *ortho*-phthalates, FDA published in the Federal Register a notice of the filing of your food additive petition (FAP) on *ortho*-phthalates (81 FR 31877), on May 20, 2016.² In a separate document that we have finalized for publication in the Federal Register, we are denying that petition.³

With respect to the requests in your petition that FDA revoke prior sanctions and issue regulations under 21 CFR part 189, we declined to file those requests as a food additive petition, because those requests are not within the scope of requests that the food additive petition process is designed to address (see section 409(b) of the Federal Food, Drug, and Cosmetic Act (“FD&C Act”) (21 U.S.C. 348(b)) (referring to “a petition proposing the issuance of a regulation prescribing the conditions under which such [food] additive may be safely used”); section 201(s) of the FD&C Act (21 U.S.C. 321(s)) (exempting prior sanctioned materials from the definition of a food additive); see also FDA Letter from Francis S. Lin to Tom Neltner (April 12, 2016)).

Subsequently, you filed the instant citizen petition requesting that FDA take the above-mentioned actions. The statement of grounds in your petition provides, “See Food Additive

² FDA assigned this petition the tracking number FAP 6B4815. Following our May 20, 2016, announcement that we had filed the food additive petition, the petitioners provided supplementary information on October 8, 2016, that, among other things, 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. Consequently, the subject of the petition is limited to food additive regulations for 28 *ortho*-phthalates.

³ We incorporate by reference our final rule denying the FAP.

Petition (FAP) No. 6B4815 and FDA’s filing letter for that petition issued on April 12, 2016,” and provides no additional data or analysis (see petition at page 2).⁴

While your citizen petition was pending, the Flexible Vinyl Alliance filed a food additive petition on the use of *ortho*-phthalates (see 83 FR 56750, November 18, 2018, (announcing the filing of FAP 8B4820)), requesting that FDA amend our food additive regulations to no longer provide for the use of certain *ortho*-phthalates because the uses have been abandoned (“the abandonment petition”). We have finalized for publication in the *Federal Register* a notice granting the abandonment petition FAP 8B4820 to no longer provide for the use of 25 plasticizers in various food contact applications. Appendix A includes a table of the *ortho*-phthalates affected by the final rule on this subject.⁵

Of the substances cited in your citizen petition, the following three *ortho*-phthalates will remain in our food additive regulations after our actions on petition FAP 8B4820: Dicyclohexyl phthalate (DCHP, Chemical Abstract Service (CAS) No. 84-61-7); Diisononyl phthalate (DINP, CAS No. 28553-12-0); and Di(2-ethylhexyl) phthalate (DEHP, CAS No. 117-81-7) (see Appendix A). These substances therefore will currently remain approved for the food additive uses specified in 21 CFR 175.105, 175.300, 176.170, 176.210, 177.1010, 177.1200, 178.3740, and 178.3910. Our actions on petition FAP 8B4820 will not have any bearing on prior-sanctioned authorizations. Furthermore, our actions on petition FAP 8B4820 will not result in any regulations prohibiting the use of food ingredients under 21 CFR part 189.

Regarding *ortho*-phthalates that are the subject of a marketing authorization (i.e., they remain approved as food additives or authorized as prior sanctioned substances), we have finalized a notice for publication in the *Federal Register* on this topic. That notice requests scientific data and information on current uses, use levels, dietary exposure, and safety data for DCHP, DINP, DEHP, DIDP, BPBG, DEP, EPEG, and DIOP. These substances comprise *ortho*-phthalates for which marketing authorizations will remain either as food additives or prior sanctioned substances or both.⁶ The purpose of this request is to encourage stakeholders to provide FDA with all sources of relevant information to support our review of the current use levels and safe use of these *ortho*-phthalates in food contact applications. We may use this information to update the dietary exposure estimates and safety assessments for the permitted food contact uses of *ortho*-phthalates.

II. Specific Responses to the Actions Requested in Your Petition

In your petition, you request that we A) prohibit the use of eight *ortho*-phthalates under part 189 of our regulations for use in food; and B) revoke the prior sanctions for five *ortho*-phthalates that exist under part 181 of our regulations for use as plasticizers in food packaging. For the reasons

⁴ “FDA’s filing letter” is FDA’s correspondence to Tom Neltner, dated April 12, 2016.

⁵ We also note that we are denying your food additive petition requesting that we amend or revoke specified regulations to no longer provide for the food contact use of the 28 *ortho*-phthalates that are the subject of that petition.

⁶ The notice requests this data and information for the four phthalates (DEHP, DCHP, DINP and DIDP) subject to FAP 6B4815 that remain in the food additive regulations as a result of the abandonment petition FAP 8B4820 final rule.

discussed below, we conclude that your petition does not contain information demonstrating that these requests should be granted.

A. Request to Prohibit Substances under 21 CFR Part 189

You have asked FDA to update its regulations in 21 CFR part 189 with the purpose of “prohibiting the use of” the following eight *ortho*-phthalates as food contact substances under part 189 of our regulations: Diisobutyl phthalate (DIBP); Di-n-butyl phthalate (DBP); Butyl benzyl phthalate (BBP); Dicyclohexyl phthalate (DCHP); Di-n-hexyl phthalate (DHexP) Diisooctyl phthalate (DIOP); Di(2-ethylhexyl) phthalate (DEHP); and Diisononyl phthalate (DINP) (collectively, “the Proposed part 189 Substances”).⁷ In addition to the food additive uses of the Proposed part 189 Substances, both DIOP and DEHP also have prior sanctioned uses.

Under 21 CFR 189.1(a), food ingredients that are listed as prohibited substances result from a “determination that they present a potential risk to the public health or have not been shown by adequate scientific data to be safe for use in human food.” Substances that are the subject of part 189 prohibitions are generally not permitted at any added or detectable level, as specified by regulation (see generally 21 CFR part 189, subparts B-D). The regulation further states that “[u]se of any of these substances in violation of this section causes the food involved to be adulterated in violation of the act” (21 CFR 189.1(a)). In previous cases where FDA has issued part 189 regulations, FDA has issued such regulations upon finding the substance causes adulteration, for example, because: 1) use of the substance would cause food to be adulterated under section 402(a)(2)(C) of the FD&C Act (21 U.S.C. 342(a)(2)(C)),⁸ i.e., it is an unsafe food additive; or 2) the substance that comes in contact with the food packaging may cause the food to be injurious to health and thus adulterated under section 402(a)(1) of the FD&C Act.⁹

Based on our regulations, we reviewed your citizen petition to determine if it demonstrates that each of the eight *ortho*-phthalates at issue cause adulteration, for example, either because: 1) the substance causes food to be adulterated under section 402(a)(2)(C) of the FD&C Act; or 2) the substance causes food to be adulterated under section 402(a)(1) of the FD&C Act.

FDA, on its own initiative or on behalf of any interested person who has submitted a citizen petition under 21 CFR 10.25 and 10.30, may publish a proposal to establish a regulation prohibiting the use of a substance in human food under 21 CFR part 189 on the basis of new scientific evaluation or information (see 21 CFR 189.1(c)). “When seeking to ban a substance from use in food, a petition must include ‘an adequate scientific basis.’” *In re Natural Resources Defense Council*, 645 F.3d 400, 403 (D.C. Cir. 2011) (quoting § 189.1(c)). Under 21 CFR 10.30, citizen petitions are to be resolved based on information in the administrative record (see 21 CFR 10.30(j)). Under 21 CFR 10.30(i), the record consists of: 1) the petition, including all information on which it relies, filed by the Division of Dockets Management (now called the Dockets Management Staff); 2) all comments received on the petition, including all information

⁷ As noted above, the abandonment final rule removes many of these substances from our food additive regulations.

⁸ See, for example, the Federal Register notices supporting our part 189 prohibition of tin coated lead foil capsules for wine bottles, *available at* 57 FR 55485 and 61 FR 4816.

⁹ See, for example, the Federal Register notices supporting our part 189 prohibition on lead-soldered food cans, *available at* 58 FR 33860, 60 FR 33106.

submitted as a part of the comments; 3) if the petition resulted in a proposal to issue, amend, or revoke a regulation, all of the documents specified in 21 CFR 10.40(g); 4) the record, consisting of any transcripts, minutes of meetings, reports, Federal Register notices, and other documents resulting from certain optional procedures; 5) the Commissioner’s decision on the petition, including all information identified or filed by the Commissioner with the Dockets Management Staff as part of the record supporting the decision; and 6) all documents filed with the Dockets Management Staff under § 10.65(h).

For the reasons outlined below, we have concluded that the administrative record, which includes the information contained in and relied upon by your petition, does not set forth a sufficient showing that the scientific evidence supports amending our regulations to prohibit the use of these substances under part 189. Specifically, the administrative record does not support a determination that the substances caused food to be adulterated, for example either because: 1) the substance causes food to be adulterated under section 402(a)(2)(C) of the FD&C Act; and/or 2) the substance causes food to be adulterated under section 402(a)(1) of the FD&C Act.

1. Regulatory Framework

The FD&C Act authorizes us to regulate “food additives” (see section 409(a) of the FD&C Act). 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). Food additives can include both substances added directly to food and indirectly and may 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 (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), (k), and 409(a) of the FD&C Act (21 U.S.C. 331(a), (k), and 348(a))). 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. Our regulations at 21 CFR 170.3(h)(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 creates an exception to the “food additive” definition for substances that are generally recognized as safe (“GRAS”). If a substance is GRAS, it is not a “food additive” and therefore is not subject to the mandatory premarket review requirement in section 409 of the FD&C Act. A substance cannot be classified as GRAS under the conditions of its intended use if the available data and information do not satisfy the safety standard for a food additive under the FD&C Act (see 21 CFR 170.30). General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances directly or indirectly added to food, that there is a reasonable certainty that the substance is not harmful under the conditions of its intended use (see *id.*). “Common knowledge” can be based

on either scientific procedures or on experience based on common use of a substance in food prior to January 1, 1958 (see *id.*).

To establish with reasonable certainty that a food additive is not harmful under its intended conditions of use such that it meets the safety standard under section 409 of the FD&C Act, 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). One method that FDA may use is to compare the Estimated Daily Intake (EDI) of the food additive to an Acceptable Daily Intake (ADI) level established by applying appropriate safety factors to applicable toxicological data. 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: A) Probable consumption of the additive; B) 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 C) safety factors recognized by experts as appropriate for the use of animal experimentation data (section 409(c)(5) of the FD&C Act).

Section 402(a)(1) of the FD&C Act provides, in relevant part, that a food shall be deemed adulterated if it bears or contains any poisonous or deleterious substance which may render it injurious to health.¹⁰ Courts have interpreted this language to mean that a food is adulterated when it contains enough of an added poisonous or deleterious substance to pose a reasonable possibility of injury to health.¹¹ Without such a possibility, the mere presence of an added poisonous or deleterious substance does not render food adulterated under section 402(a)(1) of the FD&C Act. Moreover, courts have concluded that a reasonable possibility of injury to health does not exist solely because it is physically possible for a person to consume enough of a food to harm themselves if ingested in extreme amounts.¹²

2. *Relevant Scientific Evidence*

You have not demonstrated that it is appropriate to prohibit the use of the eight *ortho*-phthalates that are the subject of your request under part 189. In evaluating safety, it is important to identify both whether the substance can cause an adverse effect and, if so, at what levels.¹³ A prohibition may be especially justified if it is shown that a substance cannot be safely consumed at any level.¹⁴ But for the Proposed part 189 Substances, you have not demonstrated that they

¹⁰ If a substance is not an added substance, section 402(a)(1) of the FD&C Act provides that the food shall not be considered adulterated under this provision if the quantity of such substance in such food does not ordinarily render it injurious to health. However, this provision for substances that are not added is not relevant to the discussion of *ortho*-phthalates, which are added substances for purposes of the uses subject to this petition.

¹¹ See, e.g., *United States v. Anderson Seafoods, Inc.*, 447 F. Supp. 1151, 1156 (N.D. FL 1978), *aff'd*, 622 F.2d 157 (5th Cir. 1980); *United States v. Lexington Mill & Elevator Co.*, 232 U.S. 399, 411 (1914).

¹² See *Anderson Seafoods*, 447 F. Supp. at 1155.

¹³ FDA guidance for industry, *Guidance for Industry and other Stakeholders. Toxicological Principles for the Safety Assessment of Food Ingredients: Redbook 2000* (July 2000, revised July 2007). We update guidances periodically. To ensure that you have the most recent version of a guidance, check the FDA Guidances Web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

¹⁴ But if a substance does not have a safe level, and also cannot be avoided, there may be more appropriate regulatory tools for limiting exposure to the substance other than a part 189 prohibition. Action levels issued under 21 CFR part 109, for example, may take into account both public health needs and the fact that the substance cannot

are unsafe at *any* level. To the contrary, two of the publications you rely on in your food additive petition 6B4815 (the CHAP report and the 1973 Shibko publication) refer to scientific studies showing that all eight of the Proposed part 189 Substances can be administered at levels that do not cause toxic effects.¹⁵ Indeed, your food additive petition cites no-observed-adverse-effect-level (NOAELs) from the CHAP report. Thus, the scientific evidence you have provided indicates that there are in fact exposure levels that do not cause adverse effects.

In addition, you have not justified that each of the eight Proposed part 189 Substances are unsafe at any particular level.¹⁶ The food additive framework under section 409 of the FD&C Act requires that FDA assess safety under the intended conditions of use (section 409(b)(2)(B) of the FD&C Act) and also provides that a food additive may not be permitted at levels above those required to achieve its technical effect (section 409(c)(4) of the FD&C Act). FDA may permit the use of a food additive for a specified use and use level at which reliable and sufficient data demonstrate that the additive has been shown to be safe under the intended conditions of use. FDA uses risk assessment to appropriately determine whether there is a reasonable certainty that no harm will result from the proposed use of an additive at its specified level. FDA's regulations provide us the option to establish prohibitions under part 189 when the science justifies such an approach, but notably do not provide that such prohibitions are the only path for managing risk.¹⁷ Your petition does not explain why a prohibition is justified based on the available scientific data.

We also note that as justification for your part 189 request, you state that the “Consumer Product Safety Commission’s (CPSC) Chronic Health Advisory Panel on Phthalates (CHAP) concluded” that eight specific *ortho*-phthalates “are unsafe or evidence indicates developmental health effects are likely” (Petition at page 1). However, the CHAP report’s scientific evaluation was primarily conducted for the purpose of evaluating the safety of phthalates for use in children’s toys and child care articles—not in food contact substances.¹⁸ In evaluating the safety of

be avoided. FDA makes case-by-case assessments on how best to manage risks from contaminants that cannot be avoided. Thus, if a substance is not safe at any level and also cannot be avoided, a part 189 prohibition is not necessarily the best approach.

¹⁵ See 2014 Chronic Hazard Advisory Panel (CHAP) on Phthalates and Phthalate Alternatives Final Report, Table 2.1, page 81; see also Shibko, S. I.; Blumenthal, H., 1973, “Toxicology of phthalic acid esters used in food packaging material,” *Environmental health perspectives*, 3:131-137.

¹⁶ Although your food additive petition 6B4815 proposes an ADI for DEHP and proposed to apply it to all 28 phthalates, our response to that petition explains why the proposed ADI for DEHP is not justified and also why it is not justified to apply that ADI to the entire proposed class of 28 *ortho*-phthalates.

¹⁷ See *supra* note 15.

¹⁸ Notably, CPSC’s handling of phthalates is more complex and goes beyond the CHAP. For example, section 108 of the Consumer Product Safety Improvement Act (15 U.S.C. 2057c) established a permanent prohibition on manufacture, sale, distribution, or importation of any children’s toy or child care article containing more than 0.1 percent of di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), or benzyl butyl phthalate (BBP). The same section also created an “interim” prohibition with respect to the manufacture, sale, distribution, or importation of “any children’s toy that can be placed in a child’s mouth or child care article that contains concentrations of more than 0.1 percent of diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), or di-n-octyl phthalate (DnOP).” The statute charged the CHAP with conducting an examination of “the full range of phthalates that are used in products for children” and to:

substances for food contact uses, FDA is required by statute to consider the safety of a substance for the particular food contact use,¹⁹ and we are directed by statute to consider *dietary* exposure

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- (i) examine all of the potential health effects (including endocrine disrupting effects) of the full range of phthalates;
 - (ii) consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates;
 - (iii) examine the likely levels of children’s, pregnant women’s, and others’ exposure to phthalates, based on a reasonable estimation of normal and foreseeable use and abuse of such products;
 - (iv) consider the cumulative effect of total exposure to phthalates, both from children’s products and from other sources, such as personal care products;
 - (v) review all relevant data, including the most recent, best-available, peer-reviewed, scientific studies of these phthalates and phthalate alternatives that employ objective data collection practices or employ other objective methods;
 - (vi) consider the health effects of phthalates not only from ingestion but also as a result of dermal, hand-to-mouth, or other exposure;
 - (vii) consider the level at which there is a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals and their offspring, considering the best available science, and using sufficient safety factors to account for uncertainties regarding exposure and susceptibility of children, pregnant women, and other potentially susceptible individuals; and
 - (viii) consider possible similar health effects of phthalate alternatives used in children’s toys and child care articles.

15 U.S.C. 2057c(b)(2)(B)(i) through (viii).

The CHAP recommended no further action on DBP, BBP, and DEHP due to the statutory prohibition in children’s toys and child care articles at levels greater than 0.1% (see “Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives,” dated July 2014, (CHAP Report) at page 7). It also recommended that the interim ban on DINP in children’s toys and child care articles at levels greater than 0.1% be made permanent (*id.*), but that the interim bans on DNOP and DIDP be lifted (*id.* at page 8). It also recommended no action on dimethyl phthalate or diethyl phthalate (*id.*), although the CHAP recommended that U.S. agencies responsible for dealing with DEP exposures from food, pharmaceuticals, and personal care products “conduct the necessary risk assessments with a view to supporting risk management steps” (*id.*).

The CHAP report also discussed other phthalates, such as dimethyl phthalate (DMP), diethyl phthalate (DEP), di(2-propylheptyl) phthalate (DPHP), diisobutyl phthalate (DIBP), di-*n*-pentyl phthalate (DPENP), di-*n*-hexyl phthalate (DHEXP), dicyclohexyl phthalate (DCHP), and diisooctyl phthalate (DIOP) and recommended permanent bans for DIBP, DPENP, DHEXP, and DCHP in children’s toys and child care articles at levels greater than 0.1% and an interim ban on DIOP in children’s toys and child care articles at levels greater than 0.1% until sufficient toxicity and exposure data are available to assess potential risks (*id.*).

In short, the CPSC’s handling of phthalates reflects a mixture of permanent and temporary statutory restrictions (as stated in section 108 of the Consumer Product Safety Improvement Act) and recommendations for permanent or temporary restrictions on certain phthalates. The CPSC, pursuant to section 8 of the Consumer Product Safety Improvement Act, was to use the CHAP’s findings and recommendations to “declare any children’s products containing any phthalates to be a banned hazardous substance...as the Commission determines necessary to protect the health of children” (15 U.S.C. 2057c(3)(B)). (The CPSC issued its final rule on phthalates on October 27, 2017 (82 FR 49938).)

¹⁹ See 409(b) and 409(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 determining safety.²⁰ For example, FDA recommends specific testing protocols for assessing migration and resulting dietary exposure that reflects the intended use of the substance.²¹ Migration of a substance may vary due to the physiochemical properties of the substance, the time and temperature conditions of its intended use (e.g., oven baking at 400 degrees Fahrenheit for one hour), and the types of food (e.g., aqueous foods, fatty foods, etc.) in contact with the food-contact article.²² Accordingly, FDA’s safety assessments consider the specific intended conditions of use at issue. Assessments conducted for the purpose of evaluating the safety of a use that does not result in dietary exposure (for example, the use of a substance in children’s toys and articles) would use a different set of parameters as is expected for a different intended use and possibly different route of exposure. Therefore, assessments conducted for the purpose of evaluating children’s toys and child care article uses do not necessarily apply to the safety of food contact uses due to the different conditions of use, and you have not provided an explanation in your petition for why the CHAP report’s assessments of phthalates in children’s toys and child care articles should apply directly to the safety of phthalates for food contact uses. As appropriate, FDA may consider the underlying evidence reviewed in such assessments. 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.

In evaluating requests to issue a regulation prohibiting a substance under 21 CFR part 189, we may also consider whether an added ingredient is poisonous or deleterious and may render a food injurious to health, such that the food would be adulterated under section 402(a)(1) of the FD&C Act. However, you have not provided any explanation as to why the 402(a)(1) standard is implicated. You have not explained why a food would be adulterated within the meaning of section 402(a)(1) of the FD&C Act whenever it contains any amount of the Proposed part 189 Substances. As stated above, courts have interpreted the standard of section 402(a)(1) of the FD&C Act to mean that a food is adulterated when it contains enough of an added poisonous or deleterious substance to pose a reasonable possibility of injury to health.²³ Without such a possibility, the mere presence of an added poisonous or deleterious substance does not render food adulterated under section 402(a)(1) of the FD&C Act. You have not provided any explanation or evidence that addresses this standard.

As an additional matter, you have not presented evidence that the specific Proposed part 189

²⁰ See section 409(c)(5) of the FD&C Act (21 U.S.C. 348(c)(5) (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”). See also FDA guidance for industry, *Estimating Dietary Intake of Substances in Food* (August 2006).

²¹ See FDA guidance for industry, *Preparation of Premarket Submissions for Food Contact Substances (Chemistry Recommendations)* (December 2007).

²² FDA then applies this migration information to an 100% market capture assumption (*i.e.*, FDA assumes that all products of the particular type authorized will utilize the FCS at the highest authorized use level, even though other competing FCSs that serve the same function may be used instead or the FCS may be used at lower use levels in some products). Using a migration protocol that reflects the “worst-case” conditions of the intended use (e.g., highest temperature and use level) and assuming 100% market capture ensures that dietary exposure estimates do not underestimate potential dietary exposure to the substance under its intended condition of use (see FDA guidance for industry, *Preparation of Premarket Submissions for Food Contact Substances (Chemistry Recommendations)* (December 2007)).

²³ See, e.g., *United States v. Anderson Seafoods, Inc.*, 447 F. Supp. 1151, 1156 (N.D. FL 1978), *aff’d*, 622 F.2d 157 (5th Cir. 1980); *United States v. Lexington Mill & Elevator Co.*, 232 U.S. 399, 411 (1914).

Substances are not GRAS and do not meet the food additive safety standard in any amount, thereby causing food to be adulterated under section 402(a)(2)(C) of the FD&C Act. Instead, the scientific evidence you have provided is a reference to your food additive petition (FAP 6B4815). This petition proposes a grouping of 28 *ortho*-phthalates for the purpose of assessing their safety, but the submission does not analyze each of the Proposed part 189 Substances individually. In our notice denying your food additive petition that we have finalized for publication in the *Federal Register*, we explain why you have not demonstrated lack of safety for the 28 *ortho*-phthalates that are the subject of the food additive petition. Your citizen petition does not fill in any of those gaps to provide evidence regarding the specific Proposed part 189 Substances.

We are denying your request for part 189 prohibitions because the administrative record does not contain information showing that the Proposed part 189 Substances are never safe for use as food contact substances. The administrative record does not contain sufficient information showing that the Proposed part 189 Substances cause food to be adulterated in any amount, including under sections 402(a)(1) and 402(a)(2)(C) of the FD&C Act. Although we are denying your request, we note that we are nevertheless committed to ensuring that any *ortho*-phthalates allowed for food contact uses are safe. If we become aware of scientific evidence showing that any of the eight subject *ortho*-phthalates cause food to be adulterated,²⁴ we will take appropriate action. Here, with your citizen petition, you have not adduced evidence to support your requested action.

B. Request to Revoke Prior Sanctions

You have asked us to revoke the prior sanctions for five *ortho*-phthalates that are codified under part 181 of our regulations for use in food or food packaging: Butylphthalyl butyl glycolate (BPBG); Diethyl phthalate (DEP); Ethylphthalyl ethyl glycolate (EPEG); Di-(2-ethylhexyl) phthalate (DEHP) (use on foods of high water content only); and Diisooctyl phthalate (DIOP) (use on foods of high water content only) (the “Proposed Prior Sanction Revocation Substances”).

A “prior sanction” is “an explicit approval granted with respect to use of a substance in food prior to September 6, 1958,” by FDA or the United States Department of Agriculture (USDA), pursuant to the FD&C Act, the Poultry Products Inspection Act, or the Meat Inspection Act (21 CFR 170.3(l)). The term “prior sanction” derives from section 201(s)(4) of the FD&C Act, which exempts from the definition of a food additive any substance “used in accordance with a sanction or approval granted prior to” September 6, 1958, the date of enactment of the Food Additives Amendment to the FD&C Act. Before that date, FDA had approved specific uses of various food-contact materials or food ingredients by issuing letters and other statements that stated that in FDA’s view these substances were “not considered unsafe,” that they did “not present a hazard,” or that FDA “did not object to their use.” The existence of a prior sanction exempts sanctioned uses from the food additive provisions of the FD&C Act but not from the other adulteration or the misbranding provisions of the FD&C Act (21 CFR 181.5(b)). The prior sanction exists “only for a specific use(s) of a substance in food, i.e., the level(s), condition(s),

²⁴ We note that we are issuing a notice on this subject in the *Federal Register* requesting scientific data and information on current uses, use levels, dietary exposure, and safety data of certain *ortho*-phthalates.

product(s), etc., for which there was explicit approval” by FDA or USDA before September 6, 1958 (21 CFR 181.5(a)). Some prior sanctioned substances are codified in 21 CFR part 181.

Notably, 21 CFR 181.1(b) states: “Based upon scientific data or information that shows that use of a prior-sanctioned food ingredient may be injurious to health, and thus in violation of section 402 of the [FD&C] Act, the Commissioner will establish or amend an applicable prior sanction regulation to impose whatever limitations or conditions are necessary for the safe use of the ingredient, or to prohibit use of the ingredient.” Furthermore, 21 CFR 181.5(c) allows for the revocation of a regulation of a prior sanctioned substance “to prohibit use of the ingredient, in order to prevent the adulteration of food in violation of section 402 of the [FD&C] Act.” We therefore evaluate your citizen petition’s request regarding prior sanctions to determine whether it shows that the use of the prior sanctioned use may be injurious to health under section 402(a)(1) of the FD&C Act.

The only evidence you submitted in support of this request is your food additive petition, which proposes to treat a large, diverse number of *ortho*-phthalates as a class for purposes of a safety assessment, apply a proposed ADI value for one phthalate to all the phthalates in the purported class, and compare the exposure of all the phthalates against that single proposed ADI. This approach is flawed for the reasons outlined in our notice denying your food additive petition that is finalized for publication in the *Federal Register*.

In submitting your citizen petition, you did not provide any additional evidence beyond what you submitted in your food additive petition. Neither your food additive petition nor your citizen petition explains any basis for concluding that the Proposed Prior Sanction Revocation Substances cause food to be regarded as adulterated within the meaning of section 402(a)(1) of the FD&C Act. Furthermore, neither your food additive petition nor your citizen petition addresses the safety of the specific uses for which the Proposed Prior Sanction Revocation Substances have received prior sanction.

As described above, FDA does not evaluate safety in a vacuum. Rather, to assess the safety of a food contact substance, FDA evaluates the particular intended use of a substance. You have not demonstrated that the Proposed Prior Sanction Revocation Substances may render food injurious to health at any level of exposure, or even at specified levels of exposure caused by the prior sanctioned uses. By failing to demonstrate health risks at levels of exposure linked to the prior sanctioned uses, you have failed to provide a record showing that the prior sanction uses cause food to be regarded as adulterated within the meaning of section 402(a)(1) of the FD&C Act. Your citizen petition request therefore lacks scientific support.

In addition, by not addressing why the Proposed Prior Sanction Revocation Substances are adulterated within the meaning of section 402(a)(1) of the FD&C Act, your citizen petition request lacks legal support. Consequently, you have not provided adequate legal grounds for your requested action (see 21 CFR 10.30(b)(3) (requiring citizen petitions to set forth the legal grounds on which the petition relies)).

III. Conclusion

Based on our consideration of the scientific evidence and other information submitted with your petition, we conclude that the evidence is insufficient to support the actions that you request. Therefore, in accordance with 21 CFR 10.30(e)(3), we are denying your petition.

Sincerely,

Leslie Kux, J.D.
Deputy Director for Nutrition, Regulatory Policy,
and Engagement
Center for Food Safety and Applied Nutrition

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APPENDIX A

Table 1: <i>Ortho</i> -phthalates Affected by Final Rule on FAP 8B4820	
Food additive	CAS No.
Dimethyl phthalate (dimethyl <i>ortho</i> -phthalate)	131-11-3
Diphenyl phthalate	84-62-8
Methyl phthalyl ethyl glycolate (1,2-Benzenedicarboxylic acid, 1-(2-ethoxy-2-oxoethyl) 2-methyl ester)	85-71-2
Diethyl phthalate	84-66-2
Diphenylguanidine phthalate ¹	17573-13-6
Ethyl phthalyl ethyl glycolate (Ethyl carbethoxymethyl phthalate)	84-72-0
Diisobutyl phthalate	84-69-5
Butyl benzyl phthalate ²	85-68-7
Di- <i>n</i> -butyl phthalate ³	84-74-2
Butyl phthalyl butyl glycolate ⁴ (Butyl carbobutoxymethyl phthalate)	85-70-1
Dihexyl phthalate (Di- <i>n</i> -hexyl phthalate)	84-75-3
Di(butoxyethyl) phthalate (Bis(2- <i>n</i> -butoxyethyl) phthalate)	117-83-9
Dimethylcyclohexyl phthalate	1322-94-7
Diisooctyl phthalate	27554-26-3
Dioctyl phthalate (Di- <i>n</i> -octyl phthalate)	117-84-0
Butyloctyl phthalate (<i>n</i> -butyl <i>n</i> -octyl phthalate)	84-78-6
Di(2-ethylhexyl) hexahydrophthalate ¹	84-71-9
Amyl decyl phthalate (<i>n</i> -amyl <i>n</i> -decyl phthalate)	7493-81-4
Butyl decyl phthalate ⁵ (<i>n</i> -butyl <i>n</i> -decyl phthalate)	89-19-0
Decyl octyl phthalate (Octyldecyl phthalate / <i>n</i> -octyl <i>n</i> -decyl phthalate)	119-07-3
Didecyl phthalate (Di- <i>n</i> -decyl phthalate)	84-77-5
Dodecyl phthalate	21577-80-0
Dihydroabietyl phthalate	26760-71-4
Castor oil phthalate, hydrogenated	None Available
Castor oil phthalate with adipic acid and fumaric acid-diethylene glycol ⁶	68650-73-7

¹We note that while these substances are not chemically classified as *ortho*-phthalates, they are included in FAP 8B4820.



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 [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], 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 by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. 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 [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept objections until 11:59 p.m. Eastern Time at the end of [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. 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, D.C. 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 Schechter 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 Schechter 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 Schechter 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 Schechter 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. Schechter 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 Schechter 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 Schechter 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 $\mu\text{g}/\text{kg bw}/\text{d}$ (over the ADI of 3 $\mu\text{g}/\text{kg bw}/\text{d}$ proposed in the petition), while the average exposure to DEHP for adults (which should be comparable to women) in Schechter et al. is only 0.67 $\mu\text{g}/\text{kg bw}/\text{d}$ (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 Schechter et al. study. They are also more robust than the Schechter 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 estimated 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>.

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- *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>).

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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.

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