July 21, 2023

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Re: Docket Number FDA-2016-P-1171

Dear Ms. O'Brien:

This letter responds to your petition for reconsideration dated June 21, 2022 (Petition for Reconsideration submitted by Katherine K. O'Brien, Earthjustice, et al., to the Division of Dockets Management, Food and Drug Administration ("Reconsideration Petition")). The Reconsideration Petition requests that the Food and Drug Administration (FDA or we) reconsider our May 12, 2022, response denying a citizen petition submitted by you and others to FDA on April 16, 2016 ("Original Petition"). The Original Petition requested that FDA prohibit the use of eight *ortho*-phthalates in food and revoke the prior-sanctioned uses for five *ortho*-phthalates in food. Specifically, the Original Petition asked 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:
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> Diisobutyl phthalate;
> Di-n-butyl phthalate;
> Butyl benzyl phthalate;
> Dicyclohexylphthalate;
> Di-n-hexyl phthalate [also known as dihexyl phthalate];
> Diisooctyl phthalate;
> Di(2-ethylhexyl) phthalate [also known as DEHP]; and
> Diisononyl phthalate.
>
> 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 *ortho*- phthalates no longer meeting 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).

(Original Petition pages 1-2.)

The Reconsideration Petition asks the following:

> We ask that FDA reconsider its rejection of both requests advanced in the Citizen Petition based on a full and fair evaluation of the data and information in the administrative record for this proceeding and based on that review:
>
> (1) Publish a proposed regulation in 21 CFR part 189 to prohibit food-contact uses of DIBP, DBP, BBP, DCHP, DHEXP, DIOP, DEHP, and DINP; or any subset of these substances that FDA agrees satisfy the standard for such a regulatory prohibition; and
>
> (2) Revoke the prior sanctions authorizing the use of BPBG, DEP, EPEG, DEHP, and DIOP as plasticizers in food packaging material; or any subset of those prior sanctions for which FDA agrees revocation is justified.

(Reconsideration Petition at page 5.)

The Reconsideration Petition asserts, among other things, that FDA's response to the Original Petition failed to consider relevant information and views contained in the administrative record (Reconsideration Petition at page 5). We have considered the information submitted in the Reconsideration Petition and other relevant information in the administrative record. For reasons described below, we are denying your request for reconsideration.

I. STANDARD FOR RECONSIDERATION

Under 21 CFR § 10.33, an interested person may request reconsideration of part or all of FDA's decision on a petition submitted under 21 CFR § 10.25.[1] Our regulation at 21 CFR § 10.33(d) provides that FDA shall grant a petition for reconsideration if the Commissioner determines that *all* of the following apply:

(1) The petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered.

(2) The petitioner's position is not frivolous and is being pursued in good faith.

[1] An "[*i*]*nterested person* or *any person who will be adversely affected* means a person who submits a petition or comment or objection or otherwise asks to participate in an informal or formal administrative proceeding or court action." 21 CFR § 10.3(a).

(3) The petitioner has demonstrated sound public policy grounds supporting reconsideration.

(4) Reconsideration is not outweighed by public health or other public interests.[2]

The regulation also specifies that a petition for reconsideration may not be based on information and views not contained in the administrative record on which the decision was made.[3] As described more fully below, we have determined that you have not demonstrated that relevant information or views contained in the administrative record were not previously or not adequately considered. Therefore, we are denying your petition for reconsideration.

II. THE ORIGINAL PETITION AND FDA'S RESPONSE

In your Original Petition, you requested that we: 1) prohibit the use of eight *ortho*-phthalates under part 189 of our regulations for use in food; and 2) revoke the prior sanctions for five *ortho*-phthalates that exist under part 181 of our regulations for use as plasticizers in food packaging, as explained more fully above (Original Petition pages 1-2).

In our response dated May 12, 2022, we denied the Original Petition (Letter from Leslie Kux, Deputy Director for Nutrition, Regulatory Policy, and Engagement, Center for Food Safety and Applied Nutrition, to Nancy Buermeyer et al., dated May 12, 2022) (Original Petition Response). Please refer to our Original Petition Response for our analysis of and response to the points raised in the Original Petition. In addition, we posted to the docket for the Original Petition a Memorandum to the Administrative Record (FDA-2016-P-1171), dated May 11, 2022, from Jessica H. Urbelis, Ph.D. (FDA Memo to Administrative Record). The FDA Memo to Administrative Record describes FDA's review of the six comments that were submitted to the docket for the Original Petition, all received between April 14 – May 5, 2022, and FDA's analysis of how the studies attached to the comments impacted our evaluation of the requests in the Original Petition. In reviewing the comments and submitted studies, we considered the relevance of the scientific information provided to the specific requests in the Original Petition. As a result of this review, FDA concluded that the comments, individually and collectively, provided insufficient support for the actions requested in the Original Petition for the reasons set forth in the FDA Memo to Administrative Record.

On the same day that we issued the Original Petition Response, we also responded to a Food Additive Petition that you had previously submitted requesting that we revoke certain specified food additive regulations authorizing the use of certain *ortho*-phthalates.[4] We incorporated our final rule denying your Food Additive Petition into the Original Petition Response.[5]

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[2] 21 CFR § 10.33(d). In addition, we note that FDA has the discretion to grant a petition for reconsideration if it is in the public interest and in the interest of justice. *Id.*

[3] 21 CFR § 10.33(e) ("An interested person who wishes to rely on information or views not included in the administrative record shall submit them with a new petition to modify the decision under § 10.25(a).").

[4] FDA assigned this petition the tracking number FAP 6B4815. Our final rule denying the Food Additive Petition was published in the *Federal Register*. See 87 FR 31066 (May 20, 2022).

[5] Original Petition Response at page 2, footnote 3.

In sum, we concluded that the administrative record, which included the information contained in and relied upon by your Original Petition as well as the information contained in and relied upon by your Food Additive Petition, did 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, we concluded that the administrative record did not support a determination that any amount of the substances caused food to be adulterated, including under section 402(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and/or section 402(a)(1) of the FD&C Act (Original Petition Response page 10). Further, based on our consideration of the scientific evidence and other information submitted with your Original Petition, we concluded that the evidence was insufficient to support revoking the prior sanctions for the five *ortho*-phthalates that exist under part 181 (Original Petition Response at page 11). Therefore, in accordance with 21 CFR § 10.30(e)(3), we denied your petition.

III. DISCUSSION OF LEGAL ISSUES

In this section, we address your assertions regarding FDA's legal obligations.

A. Assertion regarding legal obligation to consider non-dietary sources of exposure

In discussing the FDA Memo to Administrative Record, you state:

> [T]o the extent FDA is asserting that it may ignore exposure to the phthalates at issue from sources additional to the diet, as reflected in biomonitoring data, that position also misconstrues the agency's legal obligations. Dietary exposure to substances used in food or food-contact materials is one factor 'among other relevant factors' that FDA must consider in evaluating whether such uses are safe.

(Reconsideration Petition at page 26 (quoting section 409(c)(5) of the FD&C Act).)

You further state that "[t]o rationally assess whether a substance is safe for use in food, FDA cannot rely on the erroneous assumption that diet is the only source of exposure where the available evidence demonstrates that people also are exposed from other sources." (Reconsideration Petition at pages 26-27.)

You state that "even low dose exposures may have a relevant biologic effect when combined with elevated background levels" (internal quotation omitted). (Reconsideration Petition at page 27.)

FDA Response: FDA disagrees with your assertion that, in evaluating requests to issue part 189 regulations or revoke prior sanctions, FDA is legally required to consider exposure to phthalates from non-dietary sources. In evaluating the requests in the Original Petition, we considered whether the information submitted demonstrates that each of the eight *ortho*-phthalates that are the subject of the request for the part 189 regulation cause 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 (21 U.S.C. § 342(a)(2)(C)); or (2) the substance causes food to be adulterated under section 402(a)(1) of the FD&C Act (21 U.S.C. § 342(a)(1)). With respect to the *ortho*-phthalates

that are the subject of the request to revoke the prior sanction authorizations, we considered whether the information submitted shows that the prior sanctioned uses may be injurious to health under section 402(a)(1) of the FD&C Act. We disagree with your assertion that these adulteration authorities require consideration of exposure from non-dietary sources.

Your only legal citation in support of this argument is to the phrase "among other relevant factors" in section 409(c)(5) of the FD&C Act (21 U.S.C. § 348(c)(5)(B)). In determining whether a food additive is safe under section 409 of the FD&C Act, FDA is to "consider among other relevant factors" the following: (A) Probable consumption of the additive; (B) 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 "generally recognized" by qualified experts "as appropriate for the use of animal experimentation data" (section 409(c)(5) of the FD&C Act). Section 409(c)(5) of the FD&C Act does not impose a "legal obligation" for FDA to consider exposure from non-dietary sources in determining safety. Rather, section 409(c)(5) of the FD&C Act makes clear that FDA has discretion to review a number of factors to determine whether a food additive is safe. Besides the factors enumerated in subparagraphs (A), (B), and (C), section 409(c)(5) of the FD&C Act gives FDA discretion to decide, in its scientific expertise, whether there are other factors that are "relevant" to the safety of a food additive in the context of a particular petition.

Moreover, the text of subparagraphs (A) and (B), which contemplate FDA considering *food-related* uses in assessing safety, provides additional support that it is not necessary for FDA to consider exposure from non-dietary sources as a relevant factor. Specifically, subparagraph (A) states that in determining safety, the Secretary shall consider "the probable *consumption* of the additive and of *any substance formed in or on food because of the use of the additive*," and subparagraph (B) refers to the *diet* of man or animals" (emphasis added). Additionally, subparagraph 409(c)(5)(C) of the FD&C Act, which directs FDA to consider safety factors that "are generally recognized as appropriate for the use of animal experimentation data," does not suggest that FDA must consider exposure from non-dietary sources. Therefore, your argument that non-dietary exposure must be part of the safety analysis under section 409(c)(5) of the FD&C Ac is incorrect.[6]

B. **Assertion regarding legal obligation to consider "cumulative effects"**

You assert that "FDA also must reconsider its refusal to promulgate the requested part 189 prohibitions because FDA failed to consider its legal duty to assess the cumulative effects of chemically and pharmacologically related phthalates and substantial record evidence that the proposed part 189 substances are related." As support for this asserted deficiency, you state that FDA was incorrect "in faulting the petitions for failing to 'analyze each of the Proposed part 189 Substances individually' and establish that each one is unsafe in any amount" (quoting Original

[6] Further, as explained in our response to your Food Additive Petition, 87 FR 31066 at 31068-31072, we do not agree with your conclusion that the substances are chemically or pharmacologically related such that even their *dietary* exposures should be taken into account under Section 409(c)(5)(B) of the FD&C Act. *See also* Original Petition Response at page 10 (referring to Food Additive Petition's failure to demonstrate relatedness and lack of additional evidence regarding the eight specific proposed part 189 substances in the Original Petition); *infra* section III.B.

Petition Response at page 10). You state that FDA thereby "disregarded the Food Act's[7] direction to consider as part of its safety assessments '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'" (quoting section 409(c)(5)(B) of the FD&C Act). In addition, your citation to section 409(c)(5)(B) of the FD&C Act includes a "see also" citation to "21 C.F.R. § 170.3(i); *id.* § 170.18(a) (requiring FDA to 'consider[] as related food additives' substances 'that cause similar or related pharmacological effects' and assume such substances 'hav[e] additive toxic effects' absent contrary evidence)." (Reconsideration Petition pages 27-28.)

FDA Response: Your comment that FDA "failed to consider its legal duty to assess the cumulative effects" of the proposed part 189 substances reflects a misunderstanding of the basis for FDA's denial of your Original Petition. While our Original Petition Response does note that your "submission does not analyze each of the Proposed part 189 Substances individually," the Original Petition Response goes on to explain that "[w]e 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."

We reached that conclusion because the record did not contain sufficient factual evidence showing the presence of the Proposed part 189 Substances in any amount cause food to be adulterated, not because we "disregarded" any "legal obligation" related to section 409(c)(5)(B) of the FD&C Act. *See infra* section III.D. (responding to your assertions that FDA applied the incorrect legal standards for issuing part 189 regulations and/or revoking prior sanctions); section III.B. (discussing biomonitoring data and cumulative effects). As we noted in our Original Petition Response, the only justification offered by your Original Petition to support your request that FDA "[a]dd a new section to [21 CFR part 189] prohibiting the use of [DIBP, DBP, BBP, DCHP, DHEXP, DIOP, DEHP, and DINP]" was a reference to your Food Additive Petition (FAP), which addressed these eight *ortho*-phthalates and twenty others. The core premise of your FAP was that these twenty-eight *ortho*-phthalates should be considered chemically- and pharmacologically-related, and therefore treated as a single class for safety evaluation.[8] Our notice denying your FAP explained why we did not find a sufficient basis to treat the twenty-eight *ortho*-phthalates as a class for safety evaluation, and our Original Petition Response explained that your Original Petition did not fill the data gaps in your FAP by demonstrating that the Proposed part 189 Substances cause food to be adulterated. *See* Original Petition Response at 10. A showing of adulteration would require, for example, an adequately-supported analysis of toxicology data establishing an acceptable intake level and evaluation of exposure data to account for whether the population would be exposed in excess of the acceptable level.[9] Your

[7] Throughout your Petition for Reconsideration, you reference the "Food Act." We assume you are referring to the FD&C Act.

[8] From this premise, you argued that a single purported acceptable daily intake (ADI) for DEHP should be applied to the purported class of twenty-eight *ortho*-phthalates, and that certain published dietary exposure estimates for particular *ortho*-phthalates in the purported class of twenty-eight, as well as for the cumulative exposure to all twenty-eight, significantly exceeded the purported ADI for DEHP, thereby rendering food additive use of the entire purported class unsafe.

[9] While your Food Additive Petition included some data proposing an acceptable daily intake value for DEHP and exposure estimates, these values were not adequately supported (as explained in detail in our final rule denying your

Petition for Reconsideration identifies no information in the Original Petition's administrative record that we overlooked in concluding that you failed to demonstrate adulteration. As we explain *infra*, section VI.A.viii, a grouping analysis is not a safety analysis; safety analyses must be supported by other types of data, such as relevant and appropriate toxicity and exposure data, which were not present here.

C. **Assertion regarding FDA consideration of the comments**

Quoting the FDA Memo to Administrative Record, you state that "FDA criticized the comments for purportedly failing to 'provide further analysis' of how studies commenters submitted 'relate to the requests in the citizen petition.'" You state "FDA is an expert agency with a statutory obligation to determine whether, based on 'a fair evaluation of the data before [FDA],' a chemical is safe for use in food" (quoting section 409(c)(3)(A) of the FD&C Act). You state, "FDA cannot dismiss relevant scientific information provided by members of the public on the basis that these public commenters have not completed FDA's analysis themselves." (Reconsideration Petition at page 25.)

FDA Response: Your Original Petition requested that FDA issue two types of regulations: one that would prohibit the use of *ortho*-phthalates under 21 CFR part 189, and one that would revoke certain prior sanctions in accordance with 21 CFR part 181. "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)). Our Original Petition Response and our FDA Memo to Administrative Record explain why we concluded that the administrative record, which includes the comments, did not set forth an adequate scientific basis for amending our regulations.

You assert in your Petition for Reconsideration that it is FDA's responsibility to "complete[] [the safety] analysis" and then conclude that the proposed part 189 substances adulterate food under, for example, section 402(a)(1) of the FD&C Act. This argument ignores that under our regulations, a petitioner bears the burden of justifying the requested action. See 21 CFR § 10.30(b) (citizen petition must include a "Statement of Grounds"); see also *Natural Resources Defense Council, Inc. v. FDA*, 2022 WL 1094790 at *7 (April 12, 2022) (stating that when an interested party submits a citizen petition "[t]he burden is undoubtedly on the petitioner. . . to propose its requested form of relief and to provide the necessary supporting information").[10] Our regulations concerning part 189 prohibitions and prior sanction revocations require that we take those actions only when there is adequate scientific support. See 21 CFR § 189.1(c); 21

Food Additive Petition). *See* 87 FR 31066 at 31072-75; *see also* T-F. Chang to J. Urbelis, FAP 6B4815 Toxicology Memorandum dated May 11, 2022; R. Briñas to J. Urbelis, FAP 6B4815 Chemistry Memorandum dated May 11, 2022. The Food Additive Petition did not provide the requisite information for either the selected No Observed Adverse Effect Level (NOAEL) or the proposed Acceptable Daily Intake level for DEHP. Similarly, the Food Additive Petition did not justify the application of the proposed ADI for DEHP to the purported class of subject *ortho*-phthalates. Likewise, the Food Additive Petition did not adequately support its proposed exposure estimates. Your Original Petition provided no further support for the values proposed in the Food Additive Petition. *See id.*

[10] Moreover, this argument essentially faults FDA for declining to grant the requested relief, even though your Original Petition failed to identify a basis for the requested relief with any meaningful particularity. *See* Food Additive Petition (containing no references to adulteration or citations to section 402 of the FD&C Act or 21 U.S.C. § 342); Original Citizen Petition (same).

CFR § 181.1(b). Here, with your Original Petition, the administrative record did not set forth such scientific support. This conclusion reflects our assessment of the administrative record; it does not reflect any notion that we would expect outside entities to "complete[]" our own work.

As we stated in our Original Petition Response, while we denied your requests, we are nevertheless committed to ensuring that any *ortho*-phthalates allowed for food contact uses are safe. If we become aware of information showing that the approved uses of *ortho*-phthalates cause food to be adulterated, we will take appropriate action. Indeed, we issued a notice on this subject in the *Federal Register* (87 FR 31090, May 20, 2022) requesting scientific data and information on current uses, use levels, dietary exposure, and safety data of certain *ortho*-phthalates. 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.

D. Assertions that FDA applied incorrect legal standards for issuing part 189 regulations and/or revoking prior sanctions

You assert that FDA was incorrect to consider that "part 189 prohibitions would be justified only if the petitioners proved that each of the eight phthalates is 'unsafe at *any* level,'" and that "a part 189 prohibition is inappropriate for substances for which a 'no observed adverse effect level,' or NOAEL, has been identified in the scientific literature." You argue that this view "is contrary to the plain language of FDA's regulations, which state that FDA may promulgate a part 189 prohibition when the available information indicates that a substance "present[s] *a potential risk* to the public health or [has] not been shown by adequate scientific data to be safe for use in human food.'" Reconsideration Petition at page 7 (emphasis in original).

You also assert that "FDA's position is contrary to the safety and adulteration standards in the Food Act, which establish a presumption that substances proposed for direct or indirect addition to food are unsafe and prohibited unless the evidence demonstrates that they are reasonably certain to cause no harm under their intended conditions of use and prohibit 'any poisonous or deleterious substance' in food 'which may render it injurious to health.'" (Reconsideration Petition at page 7). You argue that "[t]hese standards are precautionary; by their terms, they do not require proof of harm to support regulatory protections." (Reconsideration Petition pages 7-8). You further argue that neither petitioners nor FDA is required "to prove a substance would be harmful at any level to support a ban," but rather, "they focus on whether the substance 'will be safe' under the intended 'conditions of use.'" (Reconsideration Petition at page 8.)

You assert that the judicial decisions cited in our Original Petition Response "do not support FDA's position that a food must be proven harmful at *any* level to conclude that it is not safe." (Reconsideration Petition at page 9). You also assert "the adulteration standard does not require proof that an added substance will be harmful at any level of consumption before FDA may act to protect public health" and that "*Lexington Mill* is in accord." (Reconsideration Petition pages 8-9).

You further assert that FDA applied an incorrect legal standard to your requests to revoke the prior sanctions, raising the same arguments as you have made elsewhere regarding cumulative effects and legal support. (Reconsideration Petition at page 31.)

You also specifically assert that:

> In criticizing the Citizen Petition for reportedly failing to address how the substances at issue violate the Food Act's adulteration standard, FDA contradicted its own recent acknowledgement that '[t]here is not a substantive difference' between the Food Act's adulteration standard and its safety standard, which the petitioners indisputably addressed.

(Reconsideration Petition at page 31; see also *id*. at 8 n. 27.)

FDA Response: We disagree with your argument that FDA applied an incorrect legal standard to your request for proposed part 189 regulations. Because a part 189 regulation amounts to a prohibition on use of a substance for *all* intended uses, the inquiry for promulgating such a prohibition is different from the inquiry for authorizing or revoking the authorization for a specific use (or specific uses) of a food additive. As we previously explained, when we have entirely prohibited use of a substance in food by issuing a part 189 regulation, we have generally concluded that its presence *at any added or detectable level* would cause food to be adulterated (Original Petition Response at pages 4, 6; see generally 21 CFR part 189, subparts B-D); in contrast, to issue or revoke authorization for a food additive under section 409 of the FD&C Act, we evaluate the *specific conditions* of use to determine whether the substance can be safely used in food for those uses (see section 409(a) of the FD&C Act (21 U.S.C. § 348(a)).[11]

First, you misapprehend the action FDA can take against adulterated food under section 402(a)(1) of the FD&C Act with a prohibition under part 189. You contend that the "adulteration standard does not require proof that an added substance will be harmful at any level of consumption before FDA may act to protect public health" and as such, "*Lexington Mill* is in

[11] We note that the Original Petition's request for FDA to issue regulations under Part 189 is a request for FDA to engage in rulemaking, an activity to which FDA would need to assign a significant amount of its limited resources and for which the courts have recognized that agencies have broad discretion in deciding whether to undertake. *See Massachusetts v. EPA*, 549 U.S. 497, 527–28 (2007) (noting that when an agency exercised its discretion by refusing to promulgate proposed regulations, the Court's review "is extremely limited and highly deferential") (internal quotations and citations omitted); *WWHT, Inc. v. FCC*, 656 F.2d 807, 818-19 (D.C. Cir. 1981) (stating that judicial review of an agency's decision denying a petition for rulemaking is "extremely narrow," and explaining that such decisions should be overturned "only in the rarest and most compelling of circumstances" because they "are essentially legislative … and are thus committed to the discretion of the agency"). In particular, rulemakings under 21 CFR part 189 are historically rare. Of the numerous substances that may potentially come into contact with food, only a handful are the subject of regulations under 21 CFR part 189. Most recently, in 2004, FDA issued an interim final rule regarding prohibited cattle material linked to bovine spongiform encephalopathy (BSE), a fatal neurodegenerative disorder transmissible to humans after finding that a cow testing positive for BSE had been imported into the United States (69 Fed. Reg. 42256). (That rule was subsequently finalized and amended on several occasions.) The FDA response to BSE was consistent with actions taken by international regulators to address the severe public health concerns posed by BSE in the food supply, and FDA's rulemaking under 21 CFR part 189 recognized this acute concern. Importantly, rulemakings under 21 CFR part 189 are only *one* tool that the Agency may use if it finds a substance in the food supply to be unsafe. Among its various tools, FDA can take action under section 409 of the FD&C Act by revoking a food additive approval when appropriate; issue action levels to address contaminants (see 21 CFR part 109, establishing the procedures and standards for action levels); and provide other types of guidance to industry (see 21 CFR 10.115, establishing the regulatory framework for guidance generally).

accord." (Reconsideration Petition pages 8-9) (referring to *United States v. Lexington Mill & Elevator Co.*, 232 U.S. 399, 411 (1914)). Your reliance on *Lexington Mill* is misplaced. *Lexington Mill* addressed the adulteration standard under section 402(a)(1) of the FD&C Act in the context of enforcement action against a specific food. It did not address the standards for promulgating regulations under 21 CFR part 189. When our Original Petition Response stated that the Original Petition did not demonstrate that the proposed part 189 substances cause adulteration in "any amount,"[12] we were not asserting that demonstrating adulteration under section 402(a)(1) of the FD&C Act requires an "any amount" analysis. Rather, we were referring to the showing that would justify issuance of a regulation under part 189. As we previously explained, when we have entirely prohibited use of a substance in food by issuing a part 189 regulation, we have generally concluded that its presence *at any added or detectable level* would cause food to be adulterated. Indeed, 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. As your Original Petition merely referenced your FAP, whose argument that the 28 subject *ortho*-phthalates were unsafe for their specific authorized uses was predicated on treating those 28 *ortho*-phthalates as a single class, your Original Petition failed to provide sufficient information to justify part 189 regulations prohibiting use of the 8 proposed substances at any added or detectable level.

Second, you misapprehend the requirement for pre-market approval as a food additive with a prohibition under part 189. You assert that "FDA's position is also contrary to the safety and adulteration standards in the Food Act," which you describe as establishing "a presumption that substances proposed for direct or indirect addition to food are unsafe and prohibited unless the evidence demonstrates that they are reasonably certain to cause no harm under their intended conditions of use" (Reconsideration Petition at page 7). However, there is no contradiction. Here, your Reconsideration Petition refers to the FD&C Act's pre-market review framework for food additives. Under that statutory framework, 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 food additive petition process through which persons may submit a petition proposing the issuance of a regulation that would prescribe the conditions under which the additive may be safely used. *See* section 409(b)(1) of the FD&C Act. The positions in our Original Petition Response are consistent with this framework. Our Original Petition Response explains why the administrative record does not support the specific *post*-market remedy requested by the Original Petition—namely, promulgating regulations under part 189 prohibiting the use of certain *ortho*-phthalates that FDA has permitted to be food additives under specified conditions of use. Our conclusion that this *post*-market remedy was not justified because the record failed to show that any amount of the subject *ortho*-phthalates causes food to be adulterated, including under sections 402(a)(1) and 402(a)(2)(C) of the FD&C Act, does not conflict with the statutory *pre*-market review framework for food additives.

You also assert that FDA's Original Petition Response is "contrary" to the statutory prohibition on "any poisonous or deleterious substance in food which may render it injurious to health" (Reconsideration Petition pages 7-8, internal quotations omitted). Here, too, there is no contradiction. The Reconsideration Petition refers to the adulteration standard under section

[12] See Original Petition Response pages 9-10.

402(a)(1) of the FD&C Act, which 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. Our Original Petition Response is not "contrary" to the requirement that food not bear or contain any poisonous or deleterious substance which may render it injurious to health. Rather, our Original Petition Response explains that the administrative record did not show that any amount of the proposed part 189 substances causes adulteration within the meaning of section 402(a)(1) of the FD&C Act.

You assert that "requiring petitioners to quantify a safe level or exposure for each of the eight phthalates is at odds with FDA's obligation to consider food additives 'that cause similar or related pharmacological effects . . . as a class' with 'additive toxic effects.'" (Reconsideration Petition at page 9). However, as we have noted above, our Original Petition Response explained that your Original Petition did not fill in the data gaps in your FAP by demonstrating that the proposed part 189 substances cause food to be adulterated, and your Petition for Reconsideration identifies no information in the Original Petition's administrative record that we overlooked in reaching these conclusions. See supra section III.B.

We also disagree with your argument as to the legal standard for revoking a prior sanction. As explained in our Original Petition Response at page 11, 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)). Our regulations at 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." FDA's Original Petition Response appropriately noted that your Original Petition failed to explain 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. Citizen petitions must contain information to support the requested action. (See 21 CFR § 10.30(b)(3) (requiring a "statement of grounds" in a citizen petition)). It was appropriate for FDA to evaluate your citizen petition request regarding prior sanctions to determine whether you demonstrated that the prior sanctioned uses may cause food to be adulterated under section 402(a)(1) of the FD&C Act.

Further, with respect to your argument that FDA contradicted itself by stating "[t]here is not a substantive difference" between the FD&C Act's adulteration and safety standards, we note that you are citing a May 6, 2022 document that FDA provided to members of the U.S. Senate Committee on Health, Education, Labor and Pensions ("HELP Committee") entitled "FDA's Informal Responses to Cosmetics-related Questions from the May 6, 2022 HELP Majority Email Request." Your comment regarding FDA's Informal Responses to Cosmetics-related Questions from the May 6, 2022 HELP Majority Email Request misreads that document. The question concerned draft legislative text to amend FDA's authorities with respect to cosmetic products that would have proposed a definition of "safe" for purposes of the draft cosmetics legislation

that was not ultimately adopted and that does not match any of the legal standards relevant to your Original Petition. Neither section 402(a)(1) nor 409(c)(5) of the FD&C Act uses the phrase that was the subject of the question concerning the draft cosmetics legislation: "not injurious."

IV. DISCUSSION OF FACTUAL ISSUES

You have not demonstrated that we failed to adequately consider relevant information or views in the administrative record. Indeed, our Original Petition Response contains an extensive discussion of the scientific issues that were relevant to the actions requested in the Original Petition. Our Original Petition Response also notes that we incorporated by reference the final rule denying your Food Additive Petition.[13] (The statement of grounds in the Original Petition stated, "See Food Additive Petition (FAP) No. 6B4815 and FDA's filing letter for that petition issued on April 12, 2016," and provided no additional data or analysis.) Under FDA's regulations, the administrative record for the citizen petition includes all comments received on the petition (21 CFR § 10.30(i)), and our FDA Memo to Administrative Record describes FDA's review of the comments that were submitted to the docket for the Original Petition.[14] Thus, the record supporting our Original Petition Response shows that we considered all relevant information and views, including those submitted as part of the Original Petition, the Food Additive Petition, and the comments.

In the below paragraphs, we address your assertions about factual information or views that FDA allegedly failed to consider.

A. Denial of the requested part 189 prohibitions

Your Reconsideration Petition makes the following specific points:

i. Assertions regarding Chronic Hazard Advisory Panel (CHAP) report

You assert that "FDA arbitrarily dismissed the CHAP's conclusions on the basis that '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.'" (Reconsideration Petition at page 10.)

You further state, "As an initial matter, the fact that the CHAP's recommendations addressed the subject phthalates' uses in toys and childcare articles does not affect the relevance of the CHAP's hazard evaluation, which by definition was not use-specific. FDA's Response does not address—let alone refute—the CHAP's thorough evaluation of the animal and epidemiological studies on the eight phthalates and its attendant conclusions about the human health hazards of these substances, which apply equally to an evaluation of whether these substances are safe to consume in food." (Reconsideration Petition at pages 10-11.)

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[13] Original Petition Response at page 2, footnote 3.

[14] The subject for this Memorandum is "Review of comments submitted to FDA-2016-P-1171," and we placed this Memorandum in the public docket for the citizen petition.

You next assert that "the CHAP evaluated the extent of human exposure to the eight phthalates from all documented sources—not just toys and child care articles. And it concluded that "food, beverages, and drugs via direct ingestion, and not children's toys and their personal care products, constituted the highest [source of] phthalate exposures to all subpopulations. . ." (Reconsideration Petition at page 11.)

You further assert that "FDA did not dispute the CHAP's conclusions regarding the primacy of diet as an exposure source for relevant phthalates or, as noted, the CHAP's hazard analyses. Moreover, as FDA acknowledged in the FAP Denial, comparing a quantified estimated daily intake (EDI) value to the acceptable daily intake (ADI) for a substance is only 'one approach FDA may utilize' to 'determine safety.' Therefore, FDA's critique of certain inputs to the CHAP's dietary exposure estimates does not provide a reasoned basis to reject the CHAP's conclusions regarding the primacy of dietary exposure to relevant phthalates or the health hazards associated with that exposure." (Reconsideration Petition at page 13.)

FDA Response: In considering your Original Petition, FDA did consider data and information in the administrative record regarding the CHAP report's scientific evaluation.[15] Your Reconsideration Petition takes issue with *how* we evaluated the CHAP report and does not dispute the fact that we did evaluate the CHAP report. Our record supporting the Original Petition Response explains our analysis of the CHAP report, including statements in the CHAP report about the role of dietary exposure to *ortho*-phthalates.[16] While you assert that the CHAP report was not "use-specific" and that its "conclusions about the human health hazards of these substances . . . apply equally to an evaluation of whether these substances are safe to consume in food," the CHAP report did not analyze the safety of food contact uses under the FD&C Act. In addition, your Original Petition did not explain 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. Our Original Petition Response explains the text of section 409(c)(5) of the FD&C Act contemplates FDA considering *food-related* uses in assessing safety, *see infra* section III.A, and also explains how FDA recommends specific testing protocols for assessing migration and resulting dietary exposure that reflects the intended use of the substance.[17] Assessments conducted for the purpose of evaluating the safety of a use that does not result in dietary exposure (i.e., the use of a substance in children's toys and child care articles) would have a different set of parameters to account for the different intended use and possibly different route of exposure. You did not provide an explanation in your Original Petition as to why the CHAP report's assessments of phthalates in children's toys and child care articles should apply directly to the safety of the dietary exposure to phthalates as a result of their food contact uses. Your Reconsideration Petition does not contradict or otherwise engage with the example provided in our response to the Original Petition that the specific testing protocols we recommend for assessing migration and dietary exposure are important for evaluating the safety of food contact

[15] The toxicology memorandum was part of the record for the final rule denying your Food Additive Petition, which we incorporated by reference in our response to your Original Petition.

[16] Examples of our discussion of the CHAP report's statements about dietary exposure include: Original Petition Response pages 7-9; our final rule denying your food additive petition (87 FR 31066 at 31074-31076); chemistry memorandum pages 8-12; Observation 8 in the FDA Memo to the Administrative Record. These documents demonstrate that we analyzed the data discussed in the CHAP report in the context of the requested actions in the petitions.

[17] *See* Original Petition Response pages 8-9.

uses, and it does not identify any information in the administrative record for your Original Petition that would call that view into question.[18]

Additionally, you assert that FDA "d[id] not address-let alone refute—the CHAP's thorough evaluation of the animal and epidemiological studies on the eight phthalates and its attendant conclusions about the human health hazards of these substances, which apply equally to an evaluation of whether these substances are safe to consume in food." Your Reconsideration Petition does not identify specific "animal and epidemiological studies" that FDA purportedly failed to consider, but in any event, FDA's duty in responding to the Original Petition was not to list and evaluate (or list and refute) the CHAP report's evaluation of each and every study discussed in the CHAP report. Rather, our burden was to assess whether there was an adequate scientific and legal basis for the Original Petition's requested actions, based on the CHAP report and other information in the administrative record. 21 CFR § 10.30. Our Original Petition Response shows that, in reaching our conclusions, we did consider the CHAP report and studies cited therein. For example, the Original Petition Response notes that the CHAP report refers to scientific studies showing that all eight of the proposed part 189 substances can be administered at levels that do not cause toxic effects.[19] We explained that this is relevant because when FDA has issued a part 189 regulation, we have generally concluded that its presence *at any added or detectable level* would cause food to be adulterated (Original Petition Response page 4, 6; *see generally* 21 CFR part 189, subparts B-D).[20] In addition, while the Food Additive Petition relied on a NOAEL for DEHP that was listed in the CHAP report, we noted that the Food Additive Petition did not explain why that NOAEL for DEHP was appropriate for human risk assessment of dietary exposure.[21] To the extent you are arguing that our burden was to list and evaluate (or list and refute) the CHAP report's evaluation of each scientific study because 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, for the reasons outlined above, we disagree that this is appropriate.

ii. Assertion regarding "recent analyses in the administrative record"

You assert that FDA failed to address recent analyses in the administrative record supporting the CHAP's conclusions regarding the primacy of dietary exposure to relevant phthalates. Specifically, you assert that "Dr. Russ Hauser, a member of the CHAP, reinforced the relevance of the CHAP Report to FDA's safety analysis in an expert declaration in the administrative record, explaining that although the CHAP's investigation 'was focused on children's toys and childcare articles, the report clearly raised the issue of exposure from foods and beverages as a critically important source' of phthalate exposure for children." (Reconsideration Petition at page 12.)

You assert "FDA must address these conclusions on reconsideration and reverse its determination that the requested part 189 prohibitions are not justified, or else rationally explain

[18] See Original Petition Response at page 9.
[19] Original Petition Response at page 7.
[20] Original Petition Response at page 6.
[21] 87 FR 31066 at 21073.

how a fair evaluation of the record evidence supports a determination that the eight phthalates are in fact safe for use in food." (Reconsideration Petition pages 12-13.)

You further assert "FDA did not address the conclusion of Dr. Ami Zota, stated in a December 2021 expert declaration in the administrative record, that 'diet is the main source of exposure to most phthalates, particularly to phthalates that have been associated with disruption or normal testosterone production in the developing male fetus.'" (Reconsideration Petition at page 13.)

You further state "FDA disregarded the declarations of Dr. Zota and Dr. Hauser, who are preeminent experts in the human health effects of phthalates and specifically evaluated the impacts of FDA's failure to take the actions requested in the Citizen Petition and related Food Additive Petition." (Reconsideration Petition at page 15.)

You further assert "as Dr. Zota explained, certain subpopulations—including infants and children, Black and Latina women of reproductive age, and economically insecure people—experience greater exposure to phthalates and are more likely to suffer from health harms associated with that exposure." (Reconsideration Petition at page 16.)

You state, "These declarations discussed, with citations to supporting toxicological and epidemiological studies, the links between phthalates approved for food-contact use and a long list of serious adverse health effects, including male and female infertility, miscarriage, preterm birth, harm to the developing female and male reproductive organs, neurodevelopmental harm manifesting in reduced IQ and behavioral disorders, uterine fibroids, reduced follicular count and ovarian reserve, and exacerbation of menopausal symptoms." (Reconsideration Petition pages 15-16.)

You also assert "FDA criticized the comments for purportedly failing to 'provide further analysis' of how studies commenters submitted 'relate to the requests in the citizen petition.' But FDA ignored such analysis where it was provided, as in the expert declarations from Drs. Hauser and Zota, which analyzed both the studies cited therein and the significance of the studies' findings to the regulatory issues before FDA." (Reconsideration Petition at page 25.)

FDA Response: In considering your Original Petition, FDA did consider all relevant data and information contained in the administrative record, including the information and views from the Expert Declaration of Russ B. Hauser and the Expert Declaration of Ami R. Zota that you assert FDA overlooked. With respect to the view that the CHAP report "clearly raised the issue of exposure from foods and beverages as a critically important source," please see our response to your assertion above. See IV.A.i. (discussing the CHAP report). We analyzed the data discussed in the CHAP report within the context of the requested actions in the petitions, including statements in the CHAP report about the role of dietary exposure to *ortho*-phthalates.[22]

[22] For examples of our discussion of the CHAP report's statements about dietary exposure, we refer you to the examples identified in the previous response (section IV.A.i): Original Petition Response at 7-9; our final rule denying your food additive petition (87 FR 31066 at 31074-76); chemistry memorandum at 8-12; Observation 8 in our FDA Memo to Administrative Record.

With respect to your assertion that "FDA did not address the conclusion of Dr. Ami Zota, stated in a December 2021 expert declaration in the administrative record, that 'diet is the main source of exposure to most phthalates, particularly to phthalates that have been associated with disruption or normal testosterone production in the developing male fetus," we did review this statement in the declaration. However, the declaration and corresponding literature citations[23] did not identify data or other information to support the statement that "diet is the main source of exposure" to all phthalates subject to the petition, or any information regarding the amount of exposure resulting from the food contact use of those phthalates.[24] To this end, in Observation 5 of the FDA Memo to Administrative Record, we explain "migration of food contact substances

[23] The portion of Dr. Zota's declaration describing "diet as the main source of exposure to most phthalates" cites two literature articles. However, these articles do not adequately support that conclusion. Varshavsky et al. reported that dining out may increase cumulative exposure to phthalates compared to food consumption solely at home (i.e., food purchased from a grocery store). The study examined urine metabolites of participants and the percent of their dietary intake from food consumed outside the home, and thus provides information about a potential causal relationship between dining out and phthalates metabolites. Wittassek et al. claimed food is the primary pathway for long chain phthalates (e.g., DEHP) but acknowledges that for short chain phthalates (e.g., DiBP and DBP), other sources of exposure are relevant. Both publications rely on biomonitoring studies which use quantification of urine metabolites that result from exposure to the body, but do not differentiate sources of exposure (i.e., dietary, dermal or inhalation) and therefore do not represent exposure resulting solely from the diet. We addressed the use of biomonitoring studies in Observation 7 of the FDA Memo to Administrative Record. *See also infra* section IV.A.iv. (discussing biomonitoring studies). Our Original Petition Response considered these views and sources of information.

[23] The portion of Dr. Zota's declaration describing "diet as the main source of exposure to most phthalates" cites two literature articles. However, these articles do not adequately support that conclusion. Varshavsky et al. reported that dining out may increase cumulative exposure to phthalates compared to food consumption solely at home (i.e., food purchased from a grocery store). The study examined urine metabolites of participants and the percent of their dietary intake from food consumed outside the home, and thus provides information about a potential causal relationship between dining out and phthalates metabolites. Wittassek et al. claimed food is the primary pathway for long chain phthalates (e.g., DEHP) but acknowledges that for short chain phthalates (e.g., DiBP and DBP), other sources of exposure are relevant. Both publications rely on biomonitoring studies which use quantification of urine metabolites that result from exposure to the body, but do not differentiate sources of exposure (i.e., dietary, dermal or inhalation) and therefore do not represent exposure resulting solely from the diet. We addressed the use of biomonitoring studies in Observation 7 of the FDA Memo to Administrative Record. *See also infra* section IV.A.iv. (discussing biomonitoring studies). Our Original Petition Response considered these views and sources of information.

[24] Dr. Zota's declaration did not provide comprehensive exposure data regarding the food contact use of the *ortho*-phthalates that are the subject of the Original Petition. We acknowledge that select studies cited in the declaration did provide estimates of dietary exposure to a single phthalate, or a mixture of phthalates. However, all of these studies were based on biomonitoring studies (urine metabolite analysis) and did not differentiate sources of exposure. For example, Zota cites Sathyanarayana et. al., to support the statement that "contamination of food occurs at multiple stages of the food supply chain, including during manufacturing, processing, storing, transporting, and handling...." The authors provided a dietary the estimate by using a "no plastic" intervention trial period intended to minimize DEHP exposure. However, the study reported that DEHP exposure was higher during this period of "no plastic" compared to baseline or post-intervention period. This suggests that the source of DEHP exposure was not from the food contact surfaces of the packaging or handling equipment that was avoided during the "no plastic" intervention. Further, the study did not provide a representative estimate of dietary exposure to DEHP for the general population. Nor did it provide exposure estimates for the other seven phthalates that are the subject of the Original Petition.

into food is expected and that evidence of migration into food, in-and-of itself, is not sufficient to demonstrate that the use of a food contact substance may be unsafe."

Your statement that "FDA disregarded the declarations of Dr. Zota and Dr. Hauser" is incorrect. We considered the scientific views expressed in the declarations and discussed our evaluation of them in our FDA Memo to Administrative Record. For example, Observation 7 in our FDA Memo to Administrative Record describes FDA's evaluation of the biomonitoring data discussed in Dr. Zota's declaration. In addition, Observation 4 of the FDA Memo to Administrative Record addresses FDA's evaluation of assertions that *ortho*-phthalates cause harm and our assessment that, while some of the evidence pointing to identifying the types of adverse health effects is a helpful starting point, the information in the comments were not adequate to serve as a basis for conducting a safety analysis. You go on to assert that Drs. Zota and Hauser "specifically evaluated the impacts of FDA's failure to take the actions requested in the Citizen Petition and related Food Additive Petition." Drs. Zota and Hauser were addressing the fact that, at the time of their declarations, FDA had not yet responded to the pending petitions.[25] We did so on May 12, 2022.

With respect to your assertion that we failed to consider information in Dr. Zota's declaration that "certain subpopulations . . . are more likely to suffer from health harms associated with that exposure," we note that the declaration cites two publications to support this statement. The first, McHale, et. al (2018), discusses a general approach to epidemiological research targeting the assessment of extrinsic and intrinsic factors and their potential interactions. However, this publication does not provide data or analysis for phthalates, so it was not relevant to the requests in the Original Petition. The second publication, Varshavsky, et al (2018), uses biomonitoring data. Observation 7 in our FDA Memo to Administrative Record describes our assessment of biomonitoring studies, including Varshavsky, et al (2018), as they relate to the requests in the Original Petition. *See also infra* section IV.A.iv. (discussing biomonitoring studies). Your assertion that we failed to consider this information is incorrect. Your Reconsideration Petition also notes that the declarations submitted by Drs. Hauser and Zota discuss a variety of health effects, "including male and female infertility, miscarriage, preterm birth, harm to the developing female and male reproductive organs, neurodevelopmental harm manifesting in reduced IQ and behavioral disorders, uterine fibroids, reduced follicular count and ovarian reserve, and exacerbation of menopausal symptoms." To the extent that you are asserting that we did not adequately consider this information, we disagree. As stated above, Observation 7 in the FDA Memo to Administrative Record describes our review of the claims in Drs. Hauser and Zota's declarations of health effects observed from biomonitoring studies, and Observation 4 in the FDA Memo to Administrative Record describes our review of information related to studies discussed in the declarations that used animal models to assess behavioral outcomes and explore possible underlying mechanisms. Some of these studies are useful for evaluating additional hypotheses as they may be helpful for hazard identification for future research. In other words, some of these studies may be useful in describing the potential types of effects or responses the body may have from exposure to a substance. Such hazard identification is the first step in a risk assessment, but the existence of a possible effect does not necessarily mean that the effect is the appropriate endpoint to use for a risk assessment, or that the substance in fact is unsafe. As the

[25] *See* page 2 of Hauser Decl. (referring to "FDA's failure to act on these petitions"); Page 5 of Zota Decl. (referring to "FDA's failure to act on EDF's 2016 petitions").

studies were not designed to establish the underlying mechanisms that caused the observed health effects, and dose-response relationships were not appropriately examined, these data are not adequate for identifying a point of departure (e.g., NOAEL, LOAEL, etc.) to perform a risk assessment. On pages 6-7 of our Original Petition Response, we explain that the petition does not demonstrate that the Proposed Part 189 substances are not safe at any level. *See also supra* section III.D. Observation 4 in the FDA Memo to Administrative Record explains that some studies cited in the declaration and the comments examined known health effects (i.e., antiandrogenicity),[26] but the studies involved doses substantially higher than expected human exposure and therefore do not demonstrate that there is "no safe level." The studies cited in these declarations therefore do not support the requested actions in the Original Petition. You have not demonstrated that we failed to adequately consider this information.

Regarding your assertion that FDA failed to consider analysis from the expert declarations from Drs. Hauser and Zota, we note that their declarations do not include risk assessments or other types of safety analyses that we would need to conclude the actions requested in the Original Petition are scientifically justified. For example, the declarations do not address the adulteration standards that are relevant to determining whether a regulation under 21 CFR part 189 is justified or whether revoking certain prior sanctions is justified. *See supra* section III.D.

iii. Assertions regarding the Agency for Toxic Substances and Disease Registry (ATSDR)

You assert that "FDA also did not address the 2022 toxicological profile for DEHP published by the Agency for Toxic Substances and Disease Registry (ATSDR), which provides very recent affirmation of the CHAP's conclusions regarding the unique importance of diet as a source of exposure to DEHP." You state, "For infants and toddlers, ATSDR estimated that roughly half of oral exposure to DEHP comes from food." (Reconsideration Petition pages 13-14.)

You further assert "FDA must address ATSDR's establishment of a 0.10 μg/kg bw/d intermediate minimal risk level (MRL) for oral exposure to DEHP, which is substantially lower than the ADI FDA considered." (Reconsideration Petition at page 23.)

FDA Response: You have not demonstrated that FDA failed to adequately consider this information. In considering your Original Petition, FDA did consider all relevant data and information contained in the administrative record, including the ATSDR Toxicological Profile (identified in footnotes 50 and 96 in your Reconsideration Petition). The MRL cited in the report was determined based on a single study that used only one dose level and only a limited number of animals (not statistically significant). Due to the use of a single dose and limited animals, there is not enough supporting information to rely on this value in our safety assessment of DEHP, or to apply it as a value for risk assessments of the other substances that are the subject of the Original Petition. As discussed in Observation 4 of the FDA Memo to Administrative Record, studies that report effects using an insufficient number of animals compared to

[26] As stated in our toxicology memo for FAP 6B4815, antiandrogens effect the endocrine system by modulating the production of testicular testosterone pertaining to the development of male reproductive systems. This endpoint would include the claim by Zota of "harm to developing male reproductive organs."

established Organization for Economic Co-operation and Development (OECD) guidelines, reduce the statistical significance of the reported findings. Our comments in Observation 4 of the FDA Memo to Administrative Record addressed the MRL, among other studies included in the comments to the petition.[27] With respect to the ATSDR statement regarding the diet as a source of exposure to DEHP, these statements are based on biomonitoring studies which are discussed in Observation 7 of the FDA Memo to Administrative Record. Human biomonitoring studies can be part of an appropriate post-market approach to determine dietary exposure for a substance that is already authorized for use as a food contact substance. However, there are many factors that should be addressed in assessing the suitability of any given dataset for determining dietary exposure outcomes as biomonitoring studies do not differentiate sources of exposure. As we explained in the Final Rule, these factors include "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." (87 FR 31066 at 31074.) Nothing in the administrative record for the Original Petition explains how the ATSDR statement regarding the diet as a source of exposure to DEHP provides justification for the particular actions requested in the Original Petition. See also our discussion regarding your assertions about biomonitoring studies, below (section IV.A.vii.).

iv. **Assertion regarding "hazard information"**

You assert "FDA did not adequately consider the wealth of additional hazard information in the record concerning the human health effects of the eight phthalates and related substances in the diet." (Reconsideration Petition at page 14.)

You state, "Indeed, aside from the CHAP Report and the Shibko and Blumenthal paper, FDA's Response does not acknowledge or address any of the hazard information presented by the petitioners in their related food additive petition, which was incorporated as support for the Citizen Petition, or in the petitioners' 2017 deficiency notice response. FDA's FAP Denial does not fill this gap." (Reconsideration Petition at page 14.)

You state, "FDA disregarded the declarations of Dr. Zota and Dr. Hauser . . . these declarations discussed, with citations to supporting toxicological and epidemiological studies, the links between phthalates approved for food-contact use and a long list of serious adverse health effects, including male and female infertility, miscarriage, preterm birth, harm to the developing female and male reproductive organs, neurodevelopmental harm manifesting in reduced IQ and behavioral disorders, uterine fibroids, reduced follicular count and ovarian reserve, and exacerbation of menopausal symptoms." (Reconsideration Petition pages 15-16.)

[27] You assert that the MRL is "substantially lower than the ADI FDA considered." We are not sure what ADI you are referring to because there is no established ADI for DEHP. In any case, your claim with respect to the Reconsideration Petition is that FDA "must address" the ATSDR. Our response explains our assessment of the MRL reported in the ASTDR report, which was documented in Observation 4 of the FDA Memo to Administrative Record. To the extent you are asserting that FDA failed to consider an ADI, Observation 1 in the FDA Memo to Administrative Record states that the comments do not discuss or provide a proposed ADI.

You state, "commenters submitted dozens of peer-reviewed animal studies from the last two years alone citing associations between DEHP exposure and serious health hazards, including: developmental toxicity, developmental neurotoxicity, adult neurotoxicity, reproductive toxicity, endocrine disruption, hepatoxicity, metabolic toxicity, immunotoxicity, and epigenetic alterations." (Reconsideration Petition pages 16-20.)

You assert that all these studies "provide evidence for a number of DEHP-related adverse health outcomes, including: altered sex behavior, delayed puberty, reduced insulin sensitivity, obesity, hypothyroidism, cognitive impairment, and depressive-like behaviors." (Reconsideration Petition pages 20-21.)

You also assert that "[s]everal *in vitro* studies confirmed associations between DEHP and hepatoxicity, immunotoxicity, and male reproductive toxicity." (Reconsideration Petition at page 21.)

You also state that "[r]ecent animal studies in the record also linked DINP to hepatotoxicity and excaberated nerve cell damage and decline in learning and memory when combined with artificial light. One animal study additionally linked DCHP exposure to elevated cholesterol. (Reconsideration Petition at page 22.)

FDA Response: In considering your Original Petition, FDA did consider all relevant data and information contained in the administrative record related to effects attributed to *ortho*-phthalates. Just because a study has identified a possible effect that a substance may have in the body (what you refer to as "hazard information"), that does not mean that the possible effect is an appropriate endpoint for risk assessment, or that the substance is unsafe under the intended conditions of use. To the extent that you are asserting that we did not adequately consider this information, we disagree. Observation 4 in the FDA Memo to Administrative Record describes our review of information in the docket related to health endpoints and explains our reasoning for our conclusion that the information did not provide an adequate basis for performing risk assessment.[28] See also our discussion on biomonitoring data, below (section IV.A.viii.). Some of these studies are useful for evaluating additional hypotheses as they may be helpful for hazard identification for future research. However, as the studies did not identify the underlying mechanism for observed health effects and dose-response relationships were not appropriately examined, this data is not adequate for identifying a point of departure (e.g., NOAEL, LOAEL) that would enable FDA to perform a risk assessment, and there was nothing in the administrative record to fill this gap. In addition to describing our evaluation of the health effects data generally, the FDA Memo to Administrative Record also addresses why the data submitted that was relevant to the prior sanction authorizations did not support the action requested in the Original Petition related to the prior sanctions. For example, page 8 of the FDA Memo to

[28] In addition, the majority of the health effects that the comments describe are based on biomonitoring studies. As Observation 7 in the FDA Memo to Administrative Record explains, there are important limitations to how such biomonitoring studies can be interpreted. As we explained in the Final Rule, using exposure values from biomonitoring studies without discussion and supporting information to ascertain dietary exposure "may not be an appropriate proxy of the probable dietary exposure value." 87 FR 31066 at 31075. However, Observation 7 documents that we did consider this information. We adequately considered the information and views in the administrative record related to health effects, including health effects presented in the context of biomonitoring studies.

Administrative record explains that while a significant number of literature studies provided in the comments looked at the toxicology of DEHP, there was no information on the specific exposure levels for the prior-sanctioned use of DEHP. In addition, the final rule responding to your Food Additive Petition (87 FR 31066 at 31074-75) describes our review of many studies related to health endpoints and shows that we reviewed and evaluated studies and information related to health effects in the context of our review of the Food Additive Petition. Your Reconsideration Petition does not contradict or otherwise engage with our views on the scientific limitations of the studies discussed here.

v. Assertion regarding epidemiological studies

You assert that "recent peer-reviewed epidemiological studies in the record provide relevant toxicity information that FDA must address." (Reconsideration Petition at page 22.) You state, "These studies cite associations between urinary metabolites of DEHP and a number of adverse health outcomes in humans, including cancer recurrence and poor survival in breast cancer patients, altered lipid metabolism, insulin resistance and diabetes, delayed onset of puberty in boys, thyroid hormone disruption, reduced levels of critical reproductive hormones in women undergoing fertility treatment, and even increased risk of mortality in adults, which could account for 100,000 premature deaths and more than $40 billion in lost economic productivity annually among 55-64 year-olds in the United States." (Reconsideration Petition pages 22-23.)

You further state, "Similar adverse health outcomes were linked to urinary DINP metabolites, including insulin resistance and delayed puberty onset in boys. Also included in this body of evidence is a birth cohort study that found associations between gestational urinary DEHP metabolites and preterm birth." (Reconsideration Petition at page 23.)

FDA Response: In evaluating the epidemiological studies, in Observation 7 of the FDA Memo to Administrative Record and in our response to FAP 6B4815, we explain that exposures reported and evaluated from biomonitoring data and urinary metabolites cannot differentiate sources of exposure and include contributions not just from the ingestion of food (i.e., diet), but also from inhalation and dermal contact. Therefore, the adverse effects reported from these studies may be the result of contributions to exposure from sources outside of the diet. See our discussion of biomonitoring data, below, (IV.A.viii.). Observation 7 of the FDA Memo to Administrative Record shows that we reviewed and considered the information in the administrative record that was based on urinary metabolite data and also explains our evaluation of this information. Observation 7 of the FDA Memo to Administrative Record explains the limitations of urine metabolite data generally, including the limitations of data regarding mixtures of phthalates. For example, if a study analyzes urine metabolites of phthalate mixtures (i.e., more than one phthalate), the study cannot provide safety information about individual phthalates. Observation 2 of the FDA Memo to Administrative Record shows our review of studies, such as epidemiological studies that assessed associational evidence, but that lack evidence regarding causation and did not provide further analysis or context for how they relate to the requests in the Original Petition. In Observation 2 of the FDA Memo to Administrative Record, we explain that these studies are general toxicological studies, or association studies. These are not causation studies, which require statistical rigor and protocol design that is absent. In addition, on page 9 of our toxicology memorandum denying your Food Additive Petition, we explain that an

epidemiology study may only provide suggestion of correlation, not causation, and additional data would be needed to draw any conclusion of causation for a specific adverse effect.[29] Your Reconsideration Petition does not contradict or otherwise engage with our views on the scientific limitations of the studies discussed here.

vi. Assertions regarding U.S. dietary exposure

You assert "FDA's memo also irrationally dismisses studies in the record that 'determine levels of phthalates in food or food packaging obtained outside the U.S.' on the basis that these studies 'may not reflect U.S. dietary exposures.' But the fact that these studies may not reflect with perfect precision the levels of phthalates in U.S. foods is not a rational justification for rejecting them wholesale. Indeed, in the FAP Denial FDA itself advocated for the use of foreign dietary surveys to assess the safety of phthalates approved as food additives. FDA's opportunistic adoption of the opposite position in reviewing the Citizen Petition comments does not rationally support the agency's decision and, instead, illustrates the insufficiency of FDA's memo to fill critical gaps in the agency's analysis of the record evidence." (Reconsideration Petition at page 25.)

FDA Response: Your Reconsideration Petition acknowledges that FDA considered studies in the record that addressed phthalate exposure outside the U.S., but disagrees with our assessment that several of these studies may not reflect U.S. dietary exposure as different supply chains in different countries may result in different exposures. See Observation 6 from FDA Memo to Administrative Record. In our final rule denying your Food Additive Petition, we similarly described our concern that the Total Diet Study supporting the CHAP report conducted in the United Kingdom (UK) "may not reflect U.S. dietary exposures" for this very reason. 87 FR 31066 at 31074. We then contrasted the UK and other foreign data (from Australia) with Canadian data, which we stated "could potentially address several of the data gaps" with further analysis, in part because "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." 87 FR 31066 at 31075. In other words, the U.S. and Canada may be similar enough to each other in terms of relevant considerations to allow for greater use of Canadian data than data from other countries. The studies submitted as part of the comments determined levels of select phthalates in food or food packaging obtained outside of the U.S and Canada. The information submitted to the administrative record did not explain how these non-U.S. and non-Canada levels of select phthalates in food or food packaging provide a basis for estimating dietary exposures of the phthalates included in the Original Petition for the U.S. population resulting from their uses as food contact substances. Additionally, the studies did not address exposure to all of the phthalates that are the subject of the Original Petition, and so did not purport to provide complete exposure data. Accordingly, you have not demonstrated that we failed to adequately consider the information from studies related to levels of phthalates in non-U.S. food and food packaging. In considering your Original Petition, FDA did consider all relevant data and information contained in the administrative record related to U.S. dietary exposure to *ortho*-phthalates.

[29] This statement is part of the discussion of an epidemiological study that reported the health effect of insulin resistance to be associated with diemthyl pthalate (DMP) exposure. While DMP is not included in the Original Petition, our explanation regarding the appropriateness of epidemiological studies to perform a risk assessment is directly applicable.

vii. Assertions regarding biomonitoring data

You assert "FDA's memo irrationally disregards studies that associate levels of phthalate metabolites in urine with specific adverse health outcomes on the basis that such 'biomonitoring data cannot differentiate sources of exposure and include contributions not just from the ingestion of food.' This critique ignores the specific purpose for which these studies presumably were offered, and for which they undoubtedly are useful, i.e., to support an assessment of the substances' health hazards. That these studies do not, in themselves, establish the role of dietary exposure in the associated health outcomes is not a basis to ignore them." (Reconsideration Petition at page 26.)

You assert that because "information in the record establishes that diet is a predominant source of exposure to relevant phthalates[,]" therefore "even if FDA could permissibly disregard non-dietary sources of phthalate exposure in assessing safety, it still could not rationally disregard biomonitoring data or studies that rely on such data on that basis, since it is well established that a major-to overwhelming proportion of phthalate intake reflected in biomonitoring data comes from the diet." (Reconsideration Petition pages 26-27.)

FDA Response: 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. 87 FR 31066 at 31075.

In evaluating the biomonitoring studies, Observation 7 in the FDA Memo to Administrative Record acknowledges that human biomonitoring studies can be part of an appropriate post-market approach to determine dietary exposure, but also explains that many factors should be addressed to determine the suitability of any given dataset for determining outcomes from dietary exposure. This information was not provided or discussed in the comments. As the FDA Memo to Administrative Record explains, we considered the biomonitoring data that was submitted in the comments, but we concluded that the comments did not establish the suitability of the data for assessing the requests in the Original Petition. In addition, in our final rule denying your food additive petition we discuss biomonitoring data. We state that using exposure values from biomonitoring studies without discussion and supporting information to determine the specific contribution from dietary sources is not appropriate for determining dietary exposure values when the overall exposure value in a biomonitoring study may not be an appropriate proxy for the probable dietary exposure (87 FR 31066 at 31075). As explained in our final rule, biomonitoring exposure values do not distinguish "the amount of exposure that results from the diet compared to environmental and other sources." (87 FR 31066 at 31075). Our Original Petition Response further explains[30] that FDA is required by statute to consider the safety of a substance for the particular food contact use,[31] and that section 409(c)(5) of the FD&C Act

[30] See Original Petition Response pages 8-9.

[31] See section 409(b) and section 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).

contemplates evaluating dietary exposure in determining a substance's safety for the food-contact use.[32] Thus, without a discussion and supporting information that establishes the suitability of biomonitoring data for analyzing dietary exposure, biomonitoring data cannot identify the source of exposure; and without reliable information about the source of the exposure, the agency cannot determine whether a particular food-contact use causes unsafe levels of exposure in the diet. Your Petition for Reconsideration asserts that FDA's "critique ignores the specific purpose for which these studies presumably were offered, and for which they undoubtedly are useful, i.e., to support an assessment of the substances' health hazards." But for all of the above-described reasons, the biomonitoring data that was provided was not sufficient to determine the safety of the specific food-contact uses that were the subject of the Original Petition. *See also supra* section IV.A.iv.

Thus, we did consider the information and provided our assessment of the information.

viii. Assertions that FDA failed to consider the cumulative effects of related phthalates

You assert that "while FDA asserted that the petitioners failed to demonstrate that all twenty-eight phthalates formerly approved for food-contact uses are related, it failed even to consider evidence in the record that DIBP, DBP, BBP, DCHP, DHEXP, DIOP, DEHP, and DINP are all antiandrogenic and fall within a structural subclass phthalates that are associated with, and predicted to induce, antiandrogenic effects based on the length of the R-group alkyl side chain (3-8 carbon atoms)." Your supporting footnote for this assertion refers to the CHAP report. (Reconsideration Petition pages 28-29.)

You further assert "FDA failed to consider that the chemical and pharmacological relationship among these phthalates requires FDA to apply the same acceptable exposure value to all of them—specifically, the minimal risk level (MRL) established for DEHP by ATSDR." (Reconsideration Petition at page 29.)

FDA Response: To the extent that you are asserting we did not consider information in the administrative record from the CHAP report, we disagree. As described above in section IV.A.i, we discuss the CHAP report in the Original Petition Response; the final rule denying your Food Additive Petition; our FDA Memo to Administrative Record; our chemistry memorandum supporting the final rule denying your Food Additive Petition; and our toxicology memorandum denying your Food Additive Petition. For further reference to our analysis, please see footnote 16. These documents demonstrate that we analyzed the CHAP report in the context of the requested actions in the petitions. To the extent that you are asserting that our responsibility was to adopt the CHAP report's grouping without regard to how the report's grouping applies to the specific requests in your Original Petition, we disagree. In pages 6-7 of the Original Petition Response, we explain that your Original Petition does not explain how the CHAP report supports the requested action involving DIBP, DBP, BBP, DCHP, DHEXP, DIOP, DEHP, and DINP (i.e.,

[32] 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).

the CHAP report does not support the requested part 189 regulation for DIBP, DBP, BBP, DCHP, DHEXP, DIOP, DEHP, and DINP). The fact that the Proposed part 189 Substances were grouped in the CHAP report does not mean that regulations under part 189 are justified. In evaluating your Original Petition, we evaluated whether the administrative record showed that any amount of the Proposed part 189 Substances caused food to be adulterated, including under section 402(a)(2)(C) of the FD&C Act and/or section 402(a)(1) of the FD&C Act (Original Petition Response page 10). As we explained in the Original Petition Response, we concluded that the administrative record did not show that the Proposed part 189 Substances caused food to be adulterated in any amount. A grouping analysis is not a safety analysis[33]; safety analyses must be supported by other types of data, such as relevant and appropriate toxicity and exposure data, which were not present here. To the extent that you assert that we failed to consider the MRL proposed by ATSDR, please see our discussion above, section IV.A.iii. In sum, this assertion does not show that we failed to adequately consider information or views in the administrative record.

B. Denial of the Request to Revoke Prior Sanctions for Five Phthalates

Your Reconsideration Petition states that "in denying the request to revoke prior sanctions for five phthalates, FDA failed to consider relevant information and views contained in the administrative record" (Reconsideration Petition at page 30) and focuses on several issues that you contend we did not adequately consider.

i. Assertion Regarding Hazard and Exposure Information

You assert "the Response fails to acknowledge or rationally address substantial hazard and exposure information in the administrative record—including, as relevant here, a wealth of recent toxicity studies on DEHP and the 2022 ATSDR Toxicological Profile for DEHP, which affirmed that 50-95% of human exposure to DEHP (depending on age group) comes from the diet and established a substantially lower acceptable intake estimate (in the form of an intermediate MRL for oral exposure) than FDA considered in the Response or related FAP Denial." (Reconsideration Petition at page 31.)

FDA Response: The Reconsideration Petition does not make clear what exposure or hazard information FDA allegedly failed to consider. However, we explain in section IV.A that we did adequately consider relevant information in the administrative record, including the ATSDR information (section IV.A.iii.). You have not demonstrated that we failed to consider relevant information in the administrative record.

ii. Assertion Regarding the Evidence Considered

[33] As explained in our response to your FAP, in addition to disagreeing with your argument concerning (A) the proposed classification of 28 *ortho*-phthalates, we also disagreed with your arguments that (B) your purported acceptable daily intake (ADI) for DEHP should be assigned to all 28 *ortho*-phthalates, and (C) the estimated daily intake for *ortho*-phthalates exceeds the proposed ADI for DEHP, rendering the intentional use of all 28 *ortho*-phthalates as food contact substances unsafe. See 87 FR 31066.

After asserting that we failed to adequately consider certain hazard and exposure information submitted to the docket by others, which we discuss immediately above in section IV.B.i, you assert "the Response is incorrect in asserting that '[t]he only evidence . . . submitted in support of' the petitioners' request to revoke the prior sanctions for DEHP and four other phthalates 'is [the] food additive petition.' That FDA characterized the record this way only underscores that the agency failed to consider adequately what is in the record." (Reconsideration Petition at page 31.)

FDA Response: Your response is quoting the following statement from Page 11 of our Original Petition Response: "The only evidence **you** submitted in support of **this request** is **your** food additive petition[.]" (Emphasis added.) Your elided quotation misleadingly suggests that FDA's statement excluded from consideration any information submitted to the docket by others. As discussed above in section IV.B.i, we did consider such information. Additionally, we are not aware of any other information you submitted that was relevant to your request to revoke the prior sanctions. While there were numerous comments submitted to the docket for the citizen petition, only two were submitted by signatories to the citizen petition,[34] and these comments did not include any data or information specific to the request to revoke the prior sanctions or support the assertion that the specific prior-sanctioned use of these substances renders food injurious to health (see page 8 of FDA Memo to Administrative Record). Your Reconsideration Petition does not identify other information that you submitted that we allegedly overlooked.

V. CONCLUSION

As mentioned above, FDA must grant a petition for reconsideration only if all four criteria for reconsideration, which are provided in § 10.33(d)(1) through (4), apply. As explained above, we find that you have failed to demonstrate that relevant information or views contained in the administrative record were not previously or adequately considered as required by § 10.33(d)(1). Because you have failed to demonstrate this criterion, we need not address the other criteria identified in §10.33(d)(2) through (4). Therefore, we are denying your request for reconsideration.

Sincerely,

Lauren Roth -S

Digitally signed by Lauren Roth -S
Date: 2023.07.21 11:28:04 -04'00'

Lauren Roth
Associate Commissioner for Policy

[34] Specifically, comments were submitted by Earth Justice and Lisa Lefferts.