

ENVIRONMENTAL DEFENSE FUND | LEARNING DISABILITIES ASSOCIATION OF AMERICA | CENTER FOR FOOD SAFETY | CENTER FOR ENVIRONMENTAL HEALTH
CENTER FOR SCIENCE IN THE PUBLIC INTEREST | BREAST CANCER PREVENTION PARTNERS | DEFEND OUR HEALTH | ALASKA COMMUNITY ACTION ON TOXICS

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Dr. Robert M. Califf
Commissioner
U.S. Food & Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Ln., Rm. 601
Rockville, MD 20852

Via regulations.gov

PETITION FOR RECONSIDERATION
Docket No. FDA-2016-P-1171

Environmental Defense Fund, Learning Disabilities Association of America, Center for Food Safety, Center for Environmental Health, Center for Science in the Public Interest, Breast Cancer Prevention Partners, Defend Our Health, and Alaska Community Action on Toxics respectfully submit this petition for reconsideration of FDA’s May 19, 2022, decision denying the 2016 citizen petition to restrict specified uses of phthalates in food-contact materials, Docket No. FDA-2016-P-1171.¹

A. DECISION INVOLVED

The Response denied a citizen petition submitted by most of the parties to this reconsideration request and allied organizations on April 19, 2016, which asked FDA to take

¹ Letter from Leslie Kux, FDA, to Nancy Buermeyer, Breast Cancer Prevention Partners, Re: Docket Number FDA-2016-P-1171 (May 12, 2022) (the “Response”). Though the Response is dated May 12, 2022, FDA did not transmit the Response to the petitioners until May 19, 2022.

regulatory action to prohibit the use of certain phthalates in food packaging and food processing equipment.² Specifically, the Citizen Petition requested that FDA:

- (1) Add a new section to its regulations in 21 C.F.R. part 189 prohibiting food-contact uses of eight phthalates that the Consumer Product Safety Commission’s Chronic Hazard Advisory Panel (“CHAP”) determined are unsafe or likely to cause developmental harm: diisobutyl phthalate (DIBP), di-n-butyl phthalate (DBP), butyl benzyl phthalate (BBP), dicyclohexyl phthalate (DCHP), di-n-hexyl phthalate (DHEXP), diisooctyl phthalate (DIOP), di(2-ethylhexyl) phthalate (DEHP), and diisononyl phthalate (DINP); and
- (2) Revoke the prior sanctions codified at 21 C.F.R. § 181.27 authorizing the use of five phthalates “as plasticizers when migrating from food packaging material”: butylphthalyl butyl glycolate (BPPG), diethyl phthalate (DEP), ethylphthalyl ethyl glycolate (EPEG), DEHP (use on foods of high water content only), and DIOP (use on foods of high water content only).³

It took six years and a lawsuit by the petitioners for FDA to issue its Response to these requests.⁴

When FDA at last issued its Response to the Citizen Petition on May 19, 2022, it denied the petitioners’ requests in full. FDA denied the petitioners’ request to promulgate a regulation in 21 C.F.R. part 189 prohibiting food-contact uses of the eight phthalates found unsafe by the CHAP because, FDA asserted, “the administrative record does not contain information showing

² Breast Cancer Fund et al., Citizen Petition Requesting that FDA Remove its Prior Sanction of Five Ortho-Phthalates and Ban Eight Ortho-Phthalates (Apr. 19, 2016) (the “Citizen Petition”).

³ Citizen Petition 1–2.

⁴ See Complaint for Declaratory and Injunctive Relief, *Env’t Def. Fund v. FDA*, No. 21-3190 (D.D.C. Dec. 7, 2021).

that the Proposed part 189 Substances are never safe for use as food contact substances” and “cause food to be adulterated in any amount.”⁵ In reaching that conclusion, FDA failed to address substantial hazard and exposure evidence in the record and failed to consider whether any of the eight phthalates at issue and/or additional substances present in the diet are chemically or pharmacologically related within the meaning of the Food, Drug, and Cosmetic Act (the “Food Act”) such that a cumulative effects analysis is required.⁶

FDA also rejected the Citizen Petition’s request to revoke prior sanctions authorizing the use of five phthalates as plasticizers in food packaging.⁷ FDA asserted that the petitioners’ justification for this request, which was articulated in their related food additive petition and supporting materials,⁸ “is flawed” for the reasons explained in FDA’s decision denying the Food Additive Petition.⁹ FDA further claimed that the Citizen Petition did not provide “adequate legal grounds” for its request to revoke the prior sanctions for phthalates because the Citizen Petition purportedly did not address “why the Proposed Prior Sanction Revocation Substances are adulterated within the meaning of section 402(a)(1)” of the Food Act.¹⁰

At the same time, FDA asserted that if in the future it “become[s] aware of scientific evidence showing that any of the eight subject *ortho*-phthalates” for which the petitioners seek a

⁵ Response 10.

⁶ 21 U.S.C. § 348(c)(5)(B); *see* Response 4–10.

⁷ Response 10–11.

⁸ Nat. Res. Def. Council, et al., Food Additive Petition Regarding 30 Ortho-phthalates Submitted to FDA Pursuant to 21 U.S.C. § 348 (Mar. 18, 2016) (the “Food Additive Petition”).

⁹ Response 11; *see* Notification, Nat. Res. Def. Council, et al.; Denial of Food Additive Petition, 87 Fed. Reg. 31,066 (May 20, 2022) (denying food additive petition to revoke all food additive authorizations for phthalates based on safety concerns) (the “FAP Denial”).

¹⁰ Response 11.

part 189 prohibition “cause food to be adulterated, [FDA] will take appropriate action.”¹¹ In support of that assertion, FDA cited a “Request for Information” that the agency submitted for Federal Register publication on the same day it denied the Citizen Petition and related Food Additive Petition, in which FDA asked the public to submit “scientific data and information on current uses, use levels, dietary exposure, and safety data” pertaining to specified phthalates that remain approved for food-contact use following FDA’s issuance of the FAP Denial and simultaneous decision to grant an industry abandonment petition addressing phthalates.¹²

In its Request for Information, FDA acknowledged that the safety assessments supporting FDA’s current authorizations for food-contact uses of phthalates are “based on exposure and toxicological information and data provided during the period of 1961 through 1985,” *i.e., thirty-seven to sixty-one years ago*.¹³ FDA further acknowledged that relevant new information regarding the toxicity of phthalates and the extent of human exposure to these substances has amassed in the intervening decades, but said the agency is only “generally aware” of what this new information consists of or indicates.¹⁴

¹¹ *Id.* at 10 (footnote omitted).

¹² Notice, Ortho-phthalates for Food Contact Use; Request for Information, 87 Fed. Reg. 31,090, 31,091 (May 20, 2022); *see also* Final Rule, Indirect Food Additives: Adhesives and Components of Coatings; Paper and Paperboard Components; Polymers; Adjuvants, Production Aids, and Sanitizers, 87 Fed. Reg. 31,080 (May 20, 2022) (granting industry petition to revoke food additive authorizations for 25 phthalates based on assertion that the subject uses have been abandoned).

¹³ 87 Fed. Reg. at 31,091.

¹⁴ *Id.*

B. ACTION REQUESTED

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 C.F.R. 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.

C. STATEMENT OF GROUNDS

FDA's regulations dictate that the Commissioner of Food and Drugs "shall grant" a petition for reconsideration where:

- (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.
- (3) The petitioner has demonstrated sound public policy grounds supporting reconsideration.
- (4) Reconsideration is not outweighed by public health or other public interests.¹⁵

For the reasons explained below, this reconsideration petition satisfies these four requirements regarding both aspects of the Response.

1. In Denying the Requested Part 189 Prohibitions, FDA Failed to Consider Relevant Information and Views Contained in the Administrative Record

FDA should reconsider its rejection of the Citizen Petition's request to establish a new regulation in 21 C.F.R. part 189 prohibiting food-contact uses of DIBP, DBP, BBP, DCHP,

¹⁵ 21 C.F.R. § 10.33(d).

DHEXP, DIOP, DEHP, and DINP. The Response demonstrates that FDA failed to consider substantial information and views in the administrative record that are material to this determination and support the petitioners' request.

A. FDA did not consider and apply the correct legal standard

The regulations codified in 21 C.F.R. part 189 establish “a partial list of substances prohibited from use in human food.”¹⁶ FDA may add a substance to this list if it determines that the substance’s use in food or food-contact materials “present[s] a potential risk to the public health or ha[s] not been shown by adequate scientific data to be safe for use in human food.”¹⁷ For FDA to find that a substance is safe for food or food-contact use requires “reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use,”¹⁸ considering the three factors enumerated in the Food Act and implementing regulations and “other relevant factors.”¹⁹ As FDA has explained, a substance is not harmful if will not “injure or otherwise damage the health of individuals consuming” it.²⁰ A petition to establish or modify a part 189 prohibition, like the Citizen Petition at issue here, must “include an adequate scientific basis to support the petition . . . and will be published for comment if it contains reasonable grounds.”²¹

¹⁶ *Id.* § 189.1(b).

¹⁷ *Id.* § 189.1(a).

¹⁸ *Id.* § 170.3(i).

¹⁹ 21 U.S.C. § 348(c)(5); *see also* 21 C.F.R. § 170.3(i).

²⁰ Final Rule, Food Additives Permitted for Direct Addition to Food for Human Consumption; Olestra, 61 Fed. Reg. 3118, 3119 (Jan. 30, 1996).

²¹ 21 C.F.R. § 189.1(c).

In the Response, FDA acknowledged that a part 189 prohibition is appropriate when FDA determines that a substance does not satisfy the Food Act’s safety standard for food additives or where the substance may cause food to be injurious to health, *i.e.*, adulterated.²² But in evaluating the petitioners’ request to promulgate such prohibitions for the eight phthalates at issue, FDA failed to consider adequately and apply the correct legal standard.

First, FDA erroneously asserted that the requested part 189 prohibitions would be justified only if the petitioners proved that each of the eight phthalates is “unsafe at *any* level” and irrationally suggested 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.²³ This position 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.”²⁴ Further, the fact that toxicological studies on a substance may support a NOAEL in no way indicates that “the substance is not harmful *under the conditions of its intended use*”²⁵ and does not account for required safety factors.²⁶

FDA’s position is also 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

²² Response 4.

²³ *Id.* at 6–7.

²⁴ 21 C.F.R. § 189.1(a) (emphasis added).

²⁵ *Id.* § 170.3(i) (emphasis added).

²⁶ 21 U.S.C. § 348(c)(5)(C); 21 C.F.R. § 170.3(i)(3).

substance” in food “which may render it injurious to health.”²⁷ These standards are precautionary; by their terms, they do not require *proof* of harm to support regulatory protections. Accordingly, these standards do not require petitioners—or FDA—to prove a substance would be harmful at any level to support a ban. Instead, they focus on whether the substance “will be safe” under the intended “conditions of use.”²⁸ Indeed, elsewhere in its Response FDA contradicted its assertion that petitioners must prove the eight phthalates would be harmful at any level, observing that a part 189 prohibition “may be *especially* justified if it is shown that a substance cannot be safely consumed at any level.”²⁹

The judicial decisions FDA cited in the Response do not support its position.³⁰ *Anderson Seafoods* held that an added substance causes food to be adulterated if it “pose[s] a reasonable possibility of injury to anyone’s health.”³¹ While FDA cannot determine that a food is adulterated merely by finding that it is “physically possible for one to consume enough of [the substance] to harm oneself” under “the most extreme circumstances,”³² the adulteration standard does not require proof that an added substance will be harmful at any level of consumption

²⁷ 21 U.S.C. § 342(a)(1), (a)(2)(C)(i); *id.* § 348(c)(3)(A), (h)(1). As FDA recently affirmed, “[t]here is not a substantive difference” between the Food Act’s safety and adulteration standards. FDA Informal Responses to Cosmetics-Related Questions from May 6, 2022, HELP Majority Email Request 1 (May 6, 2022) (attached as **Exhibit 1**); *see also id.* (stating that the phrases “not injurious to health” and “reasonable certainty of no harm” are “effectively equivalent” under the Food Act).

²⁸ 21 U.S.C. § 348(c)(3)(A).

²⁹ Response 6 (emphasis added).

³⁰ *See id.* at 6 nn. 11–12 (citing *United States v. Anderson Seafoods*, 447 F. Supp. 1151 (N.D. Fl. 1978), *aff’d* 622 F.2d 157 (5th Cir. 1980), and *United States v. Lexington Mill & Elevator Co.*, 232 U.S. 399 (1914)).

³¹ *Anderson Seafoods*, 447 F. Supp. at 1156.

³² *Id.* at 1155.

before FDA may act to protect public health. *Lexington Mill* is in accord. There, the Court affirmed the plain meaning of the Food Act, which provides that food is adulterated when “added poisonous or deleterious substances . . . may render” it harmful to health, and explained that this standard is met by evidence that a food may “injure the health of *any*” consumer, including those who are more susceptible to harm due to age, illness, or other factors.³³ Like the text of the Food Act and FDA’s regulations, these decisions do not support FDA’s position that a food must be proven harmful at any level for FDA to conclude that it is not safe.

FDA also failed to consider and apply the governing legal standards in asserting that petitioners had to quantify a safe level of exposure to each of the eight phthalates to justify the requested part 189 prohibitions.³⁴ Placing this burden on the petitioners is contrary to the safety standards established in the Food Act and FDA’s regulations, which, as noted, establish a presumption that additives are not safe and, therefore, prohibited unless FDA possesses evidence that affirmatively establishes safety.³⁵ Further, requiring petitioners to quantify a safe level of 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,” and to assign to such a class the lowest acceptable exposure level, or tolerance, applicable to any individual substance within that class.³⁶ As explained *infra*, point C.1.C, FDA

³³ *Lexington Mill*, 232 U.S. at 411.

³⁴ Response 7; *see also id.* at 10 (asserting that the petitioners must show that “each of the Proposed part 189 substances individually” is not safe to consume in any amount).

³⁵ 21 U.S.C. § 348(a), (c)(3)(A); 21 C.F.R. § 189.1(a).

³⁶ 21 C.F.R. § 170.18(a), (c); *see also* 21 U.S.C. § 348(c)(5)(B) (requiring FDA, in evaluating food additive safety, to “consider . . . the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet”); 21 C.F.R. § 170.3(i)(2) (same).

failed to consider evidence in the administrative record that the eight phthalates are pharmacologically related such that their safety must be evaluated as a class.

In sum, FDA must reconsider its denial of the Citizen Petition to apply the correct legal standard to the Petition's request for a part 189 prohibition on food-contact uses of DIBP, DBP, BBP, DCHP, DHEXP, DIOP, DEHP, and DINP.

B. FDA failed to adequately consider hazard and exposure information in the administrative record indicating that the eight phthalates are not safe for food-contact use

FDA must also reconsider its decision refusing to promulgate part 189 prohibitions for any of the eight phthalates at issue because FDA did not adequately consider substantial evidence in the administrative record demonstrating that these substances are not safe for food-contact use.

First, 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."³⁷ 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.³⁸ 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,

³⁷ Response 7.

³⁸ See U.S. Consumer Prod. Safety Comm'n, *Rep. by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives* 19–33, 69–70 (2014) ("CHAP Report").

which apply equally to an evaluation of whether these substances are safe to consume in food. FDA must address this evidence on reconsideration.

Further, the CHAP evaluated the extent of human exposure to the eight phthalates from all documented sources—not just toys and child care articles.³⁹ 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”⁴⁰ Moreover, the CHAP specifically concluded that diet is the primary exposure source for several of the phthalates for which the Citizen Petition requests a part 189 prohibition, as well as related phthalates that remain approved for food-contact use:

- The CHAP identified DINP as having “the maximum potential of exposure for infants, toddlers, and older children,” and concluded that this exposure occurs “primarily from food.”⁴¹
- “The highest estimated phthalate exposures to women were associated with DEP, DINP, DIDP, and DEHP. The main source of phthalate exposure for pregnant women/women of reproductive age were from food, beverages, and drugs via direct ingestion.”⁴²

³⁹ See *id.* at 3 (explaining that “[t]he CHAP used two different approaches to assess human phthalate exposure”: (1) an analysis of biomonitoring data, which provides “an integrated measure of exposure from multiple sources and routes but does not provide information on the contributions of individual exposure sources and routes,” and (2) “scenario-based exposure assessment estimates . . . for individual sources such as toys, personal care products, and household products,” which were based on “information on phthalate concentrations in products and environmental media, frequency and duration of contact with products and environmental media, and physiological information”).

⁴⁰ *Id.*; see also *id.* at 52–53, 59.

⁴¹ *Id.* at 53.

⁴² *Id.* at 52.

- “Infants were primarily exposed to DINP, DEHP, DIDP, DEP, DNOP, . . . and BBP, with DINP, DEHP, and DIDP being the highest contributors. The exposure to DINP was the highest in infants primarily from diet”⁴³
- “Toddlers were primarily exposed to DINP, DIDP, and DEHP Exposure to toddlers from DIDP, DIBP, and DINP was via food and beverages.”⁴⁴

That the CHAP recommended prohibitions on many of these substances in toys and childcare articles, despite concluding that uses within FDA’s jurisdiction are the primary threat to children’s health, only underscores the need for FDA to act.

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.⁴⁵ Accordingly, Dr. Hauser explained that

[t]he Consumer Product Safety Commission’s conclusions about the dangers associated with phthalates found in toys and other children’s products apply with equal force to the dangers of exposure to phthalates in foods and beverages. The need to remove these chemicals from the food supply is critical given how widespread and substantial dietary phthalate exposures are among the U.S. population, including at developmentally critical periods in early life.⁴⁶

FDA must address these conclusions on reconsideration and reverse its determination that the requested part 189 prohibitions are not justified, or else rationally explain how a fair evaluation

⁴³ *Id.*

⁴⁴ *Id.*

⁴⁵ Expert Declaration of Russ B. Hauser, M.D., Sc.D., M.P.H., ¶ 31, *In re Env’t Def. Fund*, No. 21-1255 (D.C. Cir. Dec. 7, 2021) (“Hauser Decl.”).

⁴⁶ *Id.* ¶ 32.

of the record evidence supports a determination that the eight phthalates are in fact safe for use in food.

In this regard, FDA’s critique of certain data sources underlying the CHAP’s dietary exposure assessments in FDA’s FAP Denial does not rationally support FDA’s Response.⁴⁷ 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.”⁴⁸ 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.

Second, FDA failed to address recent analyses in the administrative record supporting the CHAP’s conclusions regarding the primacy of dietary exposure to relevant phthalates. For example, 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 of normal testosterone production in the developing male fetus.”⁴⁹ 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

⁴⁷ 87 Fed. Reg. at 31,074–75.

⁴⁸ *Id.* at 31,072.

⁴⁹ Expert Declaration of Ami R. Zota, Sc.D., M.S. ¶ 16, *In re Env’t Def. Fund*, No. 21-1255 (D.C. Cir. Dec. 7, 2021) (“Zota Decl.”).

regarding the unique importance of diet as a source of exposure to DEHP.⁵⁰ Indeed, ATSDR found that “[t]he principal route of human exposure to DEHP is oral” and in both children and adults, “ingestion of food (including food from containers that leach DEHP) accounts for *approximately 95%* of total oral exposure.”⁵¹ For infants and toddlers, ATSDR estimated that roughly half of oral exposure to DEHP comes from food.⁵² FDA must consider these assessments on reconsideration, as they are directly relevant to FDA’s safety assessments for the eight phthalates and—in the context of the overwhelming evidence of human health hazards contained in the record—preclude a rational finding that these substances are safe for use in food.

Third, 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. 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,⁵³ or in the petitioners’ 2017 deficiency notice response.⁵⁴ FDA’s FAP Denial

⁵⁰ ATSDR, *Toxicological Profile for Di(2-ethylhexyl)Phthalate (DEHP)* (2022) (“DEHP Tox. Profile”).

⁵¹ *Id.* at 2 (emphasis added).

⁵² *Id.*

⁵³ Food Additive Petition 7–8 and App. III.

⁵⁴ Letter from Breast Cancer Prevention Partners et al. to Dr. Kelly Randolph, FDA, Re: Food Additive Petition No. 6B4815 Regarding Ortho-phthalates / Response to Sept. 1, 2016 Request (Aug. 24, 2017).

does not fill this gap.⁵⁵ As explained in the objections to the FAP Denial filed concurrently with this reconsideration request, FDA’s decision denying the food additive petition applies the wrong legal standard for assessing safety, ignores a wealth of relevant hazard and exposure information, and fails to conduct the safety analysis for the relevant phthalates that the Food Act requires.⁵⁶

Nor did FDA adequately address the substantial hazard information submitted with comments on the Citizen Petition. Among other pertinent material, 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.⁵⁷ Dr. Zota and Dr. Hauser concluded that FDA’s failure to revoke all authorizations for food-contact uses of phthalates and adopt the requested Part 189 prohibitions has caused “unnecessary and avoidable harm to the health of children, women, and men in the United States”⁵⁸ by causing people “to be exposed to levels of phthalates in their food that are damaging to their health.”⁵⁹ 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

⁵⁵ See Response 10 (asserting that FDA’s “notice denying your food additive petition . . . explain[s] why you have not demonstrated lack of safety for the 28 *ortho*-phthalates that are the subject of the food additive petition”).

⁵⁶ See Env’t Def. Fund et al., *Objections and Request for Evidentiary Public Hearing Regarding FDA’s Denial of Phthalates Food Additive Petition (FAP 6B4815) (June 21, 2022)* (attached as **Exhibit 2**). Because FDA expressly relies on the FAP Denial to support its Response denying the Citizen Petition, it cannot ignore the objections addressing material legal and factual errors in the FAP Denial that require FDA to withdraw that decision.

⁵⁷ See generally Zota Decl.; Hauser Decl.

⁵⁸ Hauser Decl. ¶ 3.

⁵⁹ Zota Decl. ¶ 31; see also *id.* at ¶¶ 7, 30–32.

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.⁶⁰ Ultimately, these experts were unequivocal in their conclusion that FDA’s ongoing authorization for uses of phthalates in food packaging and food production equipment is exposing the United States population to “serious health harms.”⁶¹

Further, 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.⁶² On reconsideration, FDA must reassess its denial of the requested part 189 prohibitions in light of this analysis and evidence indicating that the phthalates at issue are not safe for food-contact use and threaten the health of the general population and higher-risk groups.⁶³

FDA must also reconsider its determination that the requested prohibitions are not justified in light of the dozens of peer-reviewed animal, *in vitro*, and epidemiological studies submitted with comments on the Citizen Petition that link exposure to the eight phthalates and related substances with a range of adverse health effects. For example, commenters submitted

⁶⁰ Hauser Decl. ¶¶ 18–25, 28–30, 32; Zota Decl. ¶¶ 4, 29.

⁶¹ Hauser Decl. ¶ 37.

⁶² Zota Decl. ¶¶ 5–7, 23–25.

⁶³ See 21 U.S.C. §§ 342(a), 348(a), 348(c)(3)(A); see also *Lexington Mill*, 232 U.S. at 410–11 (explaining that the Food Act’s prohibition against “adulterated” food applies to any food containing a poisonous or deleterious substance that may “injure the health of *any*” consumer, including those who are more susceptible to harm due to age, illness, or other factors) (emphasis added).

dozens of peer-reviewed animal studies from the last two years alone citing associations between DEHP exposure and serious health hazards, including:

- developmental toxicity,⁶⁴

⁶⁴ Josephine Bou Dagher et al., *Independent and Combined Effects of Bisphenol A and Diethylhexyl Phthalate on Gestational Outcomes and Offspring Development in Sprague-Dawley Rats*, 263 *Chemosphere*, art. no. 128307 (2021); Xiyu Ge et al., *Prenatal Exposure to the Phthalate DEHP Impacts Reproduction-related Gene Expression in the Pituitary*, 108 *Reprod. Toxicology* 18 (2022); Jing-Cai Liu et al., *DEHP Exposure to Lactating Mice Affects Ovarian Hormone Production and Antral Follicle Development of Offspring*, 416 *J. Hazardous Materials*, art. no. 125862 (2021); Wan Xu et al., *Gene expression in Rat Placenta After Exposure to Di(2-ethylhexyl) Phthalate*, 40 *Human & Experimental Toxicology* 504 (2021); Yukiko Tando et al., *Epi-mutations for Spermatogenic Defects by Maternal Exposure to Di(2-ethylhexyl)phthalate*, 10 *eLife*, art. no. e70322 (2021); Ping-Chi Hsu et al., *Transgenerational Effects of Di(2-Ethylhexyl) Phthalate on Anogenital Distance, Sperm Functions and DNA Methylation in Rat Offspring*, 22 *Int'l J. of Molecular Sci.*, art. no. 4131 (2021); Soheila Safarpour et al., *Prenatal and Breastfeeding Exposure to Low Dose of Diethylhexyl Phthalate Induces Behavioral Deficits and Exacerbates Oxidative Stress in Rat Hippocampus*, 154 *Food & Chem. Toxicology*, art. no. 12322 (2021).

- developmental neurotoxicity,⁶⁵
- adult neurotoxicity,⁶⁶
- reproductive toxicity,⁶⁷

⁶⁵ Jia Lv et al., *Maternal Exposure to Bis(2-ethylhexyl) Phthalate During the Thyroid Hormone-Dependent Stage Induces Persistent Emotional and Cognitive Impairment in Middle-Aged Offspring Mice*, 163 *Food & Chem. Toxicology*, art. no. 112967 (2022); Daphne Capela et al., *Effects of Pubertal Exposure to Low Doses of Di-(2-ethylhexyl)Phthalate on Reproductive Behaviors in Male Mice*, 263 *Chemosphere*, art. no. 128191 (2021); Jae Soon Kang et al., *Ingestion of Bis(2-ethylhexyl) Phthalate (DEHP) During Adolescence Causes Depressive-like Behaviors Through Hypoactive Glutamatergic Signaling in the Medial Prefrontal Cortex*, 289 *Env't Pollution*, art. no. 117978 (2021); Yao Li et al., *Autism Spectrum Disorder-Like Behavior Induced in Rat Offspring by Perinatal Exposure to Di(2ethylhexyl) Phthalate*, *Env't Sci. & Pollution Rsch.* (Mar. 7, 2022); Ahmed Nadeem et al., *Exposure to the Plasticizer, Di-(2-ethylhexyl) Phthalate During Juvenile Period Exacerbates Autism-like Behavior in Adult BTBR T +tf/J Mice Due to DNA Hypomethylation and Enhanced Inflammation in Brain and Systemic Immune Cells*, *Progress in Neuropsychopharmacology & Biological Psychiatry*, art. no. 110249 (2021); Jianan Wang et al., *Exposure to Di-(2-ethylhexyl) Phthalate Reduces Secretion of GDNF Via Interfering With Estrogen Pathway and Downregulating ERK/c-fos Signaling Pathway in Astrocytes*, 158 *Food & Chem. Toxicology*, art. no. 12592 (2021); Anil Yirun et al., *Neuroendocrine Disruption by Bisphenol A and/or Di(2-ethylhexyl)phthalate after Prenatal, early Postnatal and Lactational Exposure*, 28 *Env't Sci. & Pollution Rsch.* 26961 (2021); Xiong Zhang et al., *Prenatal Exposure to Di(2-ethylhexyl) Phthalate Causes Autism-like Behavior Through Inducing Nischarin Expression in the Mouse Offspring*, 585 *Biochemical & Biophysical Rsch. Comm'cns* 29 (2021); Safarpour et al. (2021).

⁶⁶ Delnia Ahmadpour et al., *Disruption of the Blood-Brain Barrier and its Close Environment Following Adult Exposure to Low Doses of Di(2-ethylhexyl)phthalate Alone or in an Environmental Phthalate Mixture in Male Mice*, 282 *Chemosphere*, art. no. 131013 (2021); Delnia Ahmadpour et al., *Effects and Underlying Cellular Pathway Involved in the Impairment of the Neurovascular Unit Following Exposure of Adult Male Mice to Low Doses of Di(2-ethylhexyl) Phthalate Alone or in an Environmental Phthalate Mixture*, 207 *Env't Rsch.* (2022).

⁶⁷ Nolwenn Adam et al., *Exposure of Adult Female Mice to Low Doses of di(2-ethylhexyl) Phthalate Alone or in an Environmental Phthalate Mixture: Evaluation of Reproductive Behavior and Underlying Neural Mechanisms*, 129 *Env't Health Persps.*, art. no. 17008 (2021); Xufeng Fu et al., *Di-(2-ethylhexyl) Phthalate Exposure Induces Female Reproductive Toxicity and Alters the Intestinal Microbiota Community Structure and Fecal Metabolite Profile in Mice*, 36 *Env't Toxicology* 1226 (2021); Lindong Han et al., *Stereological Analysis and Transcriptome Profiling of Testicular Injury Induced by Di-(2-ethylhexyl) Phthalate in Prepubertal Rats*, 220 *Ecotoxicology & Env't Safety*, art. no. 112326 (2021); Yifan Hong et al., *Exposure to DEHP*

- endocrine disruption,⁶⁸
- hepatotoxicity,⁶⁹

Induces Testis Toxicity and Injury Through the ROS/ mTOR/NLRP3 Signaling Pathway in Immature Rats, 227 *Ecotoxicology & Env't Safety*, art. no. 112889 (2021); Lian Kang et al., *Multiple Transcriptomic Profiling: Potential Novel Metabolism-Related Genes Predict Prepubertal Testis Damage Caused by DEHP Exposure*, 29 *Env't Sci. & Pollution Rsch.* 13478 (2022); Roberta Tassinari et al., *Metabolic, Reproductive and Thyroid Effects of Bis(2-ethylhexyl) Phthalate (DEHP) Orally Administered to Male and Female Juvenile Rats at Dose Levels Derived from Children Biomonitoring Study*, 449 *Toxicology*, art. no. 152653 (2021); Junke Wang et al., *Multiple Transcriptomic Profiling: p53 Signaling Pathway is Involved in DEHP-Induced Prepubertal Testicular Injury Via Promoting Cell Apoptosis and Inhibiting Cell Proliferation of Leydig Cells*, 46 *J. Hazardous Materials*, art. no. 124316 (2021); Yuhao Wu et al., *Di-(2-ethylhexyl) Phthalate Exposure Leads to Ferroptosis Via the HIF-1 α / HO-1 Signaling Pathway in Mouse Testes*, 426 *J. Hazardous Materials*, art. no. 127807 (2022); Bin-Bin Zhu et al., *Di-(2-ethylhexyl) Phthalate Induces Testicular Endoplasmic Reticulum Stress and Germ Cell Apoptosis in Adolescent Mice*, 28 *Env't Sci. & Pollution Rsch.* 21696 (2021).

⁶⁸ Shahzad Ahmad et al., *mRNA Expression and Protein-Protein Interaction (PPI) Network Analysis of Adrenal Steroidogenesis in Response to Exposure to Phthalates in Rats*, 89 *Env't Toxicology & Pharmacology*, art. no. 103780 (2022); Di Sun et al., *Effect of Di-(2-ethylhexyl) Phthalate on the Hypothalamus-Pituitary-Thyroid Axis in Adolescent Rat*, 65 *Endocrine J.* 261 (2022); Sang-Yon Kim et al., *The Impairment of Thyroid Hormones Homeostasis after Short-Term Exposure to Di(2-ethylhexyl)phthalate in Adolescent Male Rats*, 25 *Dev. & Reprod.* 293 (2021); Bo Young Lee et al., *A Chronic-Low-Dose Exposing of DEHP with OECD TG 443 Altered the Histological Characteristics and Steroidogenic Gene Expression of Adrenal Gland in Female Mice*, 25 *Dev. & Reprod.* 257 (2021); Pablo A. Perez et al., *Perinatal DEHP Exposure Modulates Pituitary Estrogen Receptor α and β Expression Altering Lactotroph and Somatotroph Cell Growth in Prepuberal and Adult Male Rats*, *Food & Chem. Toxicology*, art. no. 112649 (2021); Tassinari et al. (2021); Junke Wang et al. (2021).

⁶⁹ SJ An et al., *Perinatal Exposure to Di-(2-ethylhexyl)phthalate Induces Hepatic Lipid Accumulation Mediated by Diacylglycerolacyltransferase 1*, 40 *Human & Experimental Toxicology* 1698 (2021); Yangyang Ding et al., *Di-(2-ethylhexyl) Phthalate-Induced Hepatotoxicity Exacerbated Type 2 Diabetes Mellitus (T2DM) in Female Pubertal T2DM Mice*, 149 *Food & Chem. Toxicology* 112003 (2021); Yan Yang et al., *Postnatal Exposure to DINP Was Associated With Greater Alterations of Lipidomic Markers for Hepatic Steatosis than DEHP in Postweaning Mice*, 758 *Sci. of the Total Env't* (2021); Tassinari et al. (2021); Gang Li et al., *Integrated Metabolomics and Transcriptomics Reveal Di(2-ethylhexyl) Phthalate-Induced Mitochondrial Dysfunction and Glucose Metabolism Disorder Through Oxidative Stress in Rat Liver*, 228 *Ecotoxicology & Env't Safety*, art. no. 112988 (2021).

- metabolic toxicity,⁷⁰
- immunotoxicity,⁷¹ and
- epigenetic alterations.⁷²

Collectively, these studies provide evidence for a number of DEHP-related adverse health outcomes, including:

- altered adult sex behavior,⁷³
- delayed puberty,⁷⁴

⁷⁰ Shuang Ding et al., *Relationships Between di-(2-ethylhexyl) Phthalate Exposure and Lipid Metabolism in Adolescents: Human Data and Experimental Rat Model Analyses*, 286 *Env't Pollution* 117570 (2021); Jhih-Wei Hsu et al., *Di(2-ethylhexyl)phthalate Exposure Exacerbates Metabolic Disorders in Diet-induced Obese Mice*, 156 *Food & Chem. Toxicology*, art. no. 112439 (2021); Henghai Su et al., *Long-term Chronic Exposure to Di-(2-ethylhexyl)-phthalate Induces Obesity via Disruption of Host Lipid Metabolism and Gut Microbiota in Mice*, 287 *Chemosphere*, art. no. 132414 (2022); Zhen Yu et al., *DEHP Induces Cholesterol Imbalance Via Disturbing Bile Acid Metabolism by Altering the Composition of Gut Microbiota in Rats*, 263 *Chemosphere*, art. no. 127959 (2021); Tassinari et al. (2021); Yangyang Ding et al. (2021); Gang Li et al. (2021).

⁷¹ Adam Schwendt et al., *Acute Exposure to Phthalates During Recovery From a Myocardial Infarction Induces Greater Inflammasome Activation in Male C57bl/6N Mice*, 440 *Toxicology & Applied Pharmacology*, art. no. 115954 (2022).

⁷² Epigenetic alterations are changes to certain markings on DNA that are heritable across generations. These DNA markings are collectively referred to as the epigenome. The studies cited here involve alterations in DNA methylation—a type of epigenetic marking. See Siyu Liu et al., *Perinatal DEHP Exposure Induces Sex- and Tissue-Specific DNA Methylation Changes in Both Juvenile and Adult Mice*, 7 *Env't Epigenetics*, art. no. dvab004 (2021); David López-Rodríguez et al., *Multi- and Transgenerational Outcomes of an Exposure to a Mixture of Endocrine-Disrupting Chemicals (EDCs) on Puberty and Maternal Behavior in the Female Rat*, 129 *Env't Health Persps.*, art. no. 087003 (2021); Oladele A. Oluwayiose et al., *Paternal preconception phthalate exposure alters sperm methylome and embryonic programming*, 155 *Env't Int'l*, art. no. 106693 (2021); Yukiko Tando et al. (2021); Ping-Chi Hsu et al. (2021).

⁷³ Adam et al. (2021); Capela, et al. (2021).

⁷⁴ López-Rodríguez et al. (2021); Tassinari, et al. (2021).

- reduced insulin sensitivity,⁷⁵
- obesity,⁷⁶
- hypothyroidism,⁷⁷
- cognitive impairment,⁷⁸ and
- depressive-like behaviors.⁷⁹

Several *in vitro* studies confirmed associations between DEHP and hepatotoxicity,⁸⁰ immunotoxicity,⁸¹ and male reproductive toxicity.⁸²

⁷⁵ Yangyang Ding et al. (2021).

⁷⁶ Su et al. (2022).

⁷⁷ Kim et al. (2021); Lv et al. (2022).

⁷⁸ Lv et al. (2022); Safarpour et al. (2021).

⁷⁹ Lv et al. (2022); Jae Soon Kang et al. (2021).

⁸⁰ Yuezhu Zhang et al., *MEHP Promotes Liver Fibrosis by Down-Regulating STAT5A in BRL-3A Hepatocytes*, 295 *Chemosphere*, art. no. 133925 (2022).

⁸¹ Akiko Honda et al., *Di-(2-ethylhexyl) Phthalate Enhances Cytokine Release From Group 2 Innate Lymphoid Cells in the Presence of Interleukin-33*, 87 *Env't Toxicology & Pharmacology*, art. no. 103726 (2021).

⁸² Kassim Traore et al., *MEHP Induces Alteration of Mitochondrial Function and Inhibition of Steroid Biosynthesis in MA-10 Mouse Tumor Leydig Cells*, 463 *Toxicology* 152985 (2021); Junke Wang et al. (2021); Yuhao Wu et al. (2022).

Recent animal studies in the record also linked DINP exposure to hepatotoxicity⁸³ and exacerbated nerve cell damage and decline in learning and memory when combined with artificial light.⁸⁴ One animal study additionally linked DCHP exposure to elevated cholesterol.⁸⁵

In addition, recent peer-reviewed epidemiological studies in the record provide relevant toxicity information that FDA must address. 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,⁸⁶ altered lipid metabolism,⁸⁷ insulin resistance and diabetes,⁸⁸ delayed onset of puberty in boys,⁸⁹ thyroid hormone disruption,⁹⁰

⁸³ Yang et al. (2021).

⁸⁴ Peng Song et al., *Continuous Artificial Light at Night Exacerbates Diisononyl Phthalate-Induced Learning and Memory Impairment in Mice: Toxicological Evidence*, 151 *Food & Chem. Toxicology*, art no. 112102 (2021).

⁸⁵ Yipeng Sui et al., *Effects of Dicyclohexyl Phthalate Exposure on PXR Activation and Lipid Homeostasis in Mice*, 129 *Env't Health Persps.*, art no. 127001 (2021).

⁸⁶ Tsung-Hua Hsieh et al., *DEHP Mediates Drug Resistance by Directly Targeting AhR in Human Breast Cancer*, 145 *Biomedicine & Pharmacotherapy*, art no. 112400 (2022).

⁸⁷ Shuang Ding et al. (2021).

⁸⁸ Hong Zhang et al., *Phthalate Exposure and Risk of Diabetes Mellitus: Implications From a Systematic Review and Meta-Analysis*, 204 *Env't Rsch.*, art. no. 112109 (2022); Elizabeth G. Radke et al., *Phthalate Exposure and Metabolic Effects: a Systematic Review of the Human Epidemiological Evidence*, 132 *Env't Int'l*, art. no. 104768 (2019).

⁸⁹ Jane S. Burns et al., *Associations of Prepubertal Urinary Phthalate Metabolite Concentrations with Pubertal Onset Among a Longitudinal Cohort of Boys*, 212 *Env't Rsch.*, art. no. 113218 (2022).

⁹⁰ Irene Souter et al., *Urinary Concentrations of Phthalate Metabolite Mixtures in Relation to Serum Biomarkers of Thyroid Function and Autoimmunity among Women from a Fertility Center*, 128 *Env't Health Persps.*, art. no. 067007 (2020); Wei Wu et al., *Urinary Phthalate Metabolites in Pregnant Women: Occurrences, Related Factors, and Association with Maternal Hormones*, 29 *Env't Sci. & Pollution Rsch.* 33372 (2022).

reduced levels of critical reproductive hormones in women undergoing fertility treatment,⁹¹ and even increased risk of mortality in adults, which could account for approximately 100,000 premature deaths and more than \$40 billion in lost economic productivity annually among 55-64 year-olds in the United States.⁹²

Similar adverse health outcomes were linked to urinary DINP metabolites, including insulin resistance⁹³ and delayed puberty onset in boys.⁹⁴ Also included in this body of evidence is a birth cohort study that found associations between gestational urinary DEHP metabolites and preterm birth.⁹⁵

In addition, FDA must address ATSDR's establishment of a 0.10 µg/kg bw/d intermediate minimal risk level (MRL) for oral exposure to DEHP,⁹⁶ which is substantially lower than the ADI FDA considered.⁹⁷ This determination by FDA's peer agency substantially strengthens the case that DEHP is not safe for use in food, particularly in conjunction with ATSDR's conclusion that nearly 100% of DEHP exposure among children and adults, and

⁹¹ Caitlin R. Sacha et al., *Urinary Phthalate Metabolite Concentrations Are Negatively Associated with Follicular Fluid Anti-Müllerian Hormone Concentrations in Women Undergoing Fertility Treatment*, 157 *Env't Int'l*, art. no. 106809 (2021).

⁹² Leonardo Trasande et al., *Phthalates and Attributable Mortality: A Population-Based Longitudinal Cohort Study and Cost Analysis*, 292 *Env't Pollution*, art. no. 118021 (2022).

⁹³ Radke et al. (2019).

⁹⁴ Burns et al. (2022).

⁹⁵ Jennifer J. Yland et al., *Phthalate and DINCH Urinary Concentrations Across Pregnancy and Risk of Preterm Birth*, 292 *Env't Pollution*, art. no. 118476 (2022).

⁹⁶ DEHP Tox. Profile 14.

⁹⁷ See Food Additive Petition 10 (proposing, based on then-available information, ADI of 3 µg/kg bw/d).

roughly 50% of exposure among infants and toddlers, comes from the diet.⁹⁸ This conclusion is strengthened further by properly accounting for the cumulative effects of related antiandrogenic phthalates in the diet, as discussed further below.

FDA's May 11, 2022, memo purporting to address the comments and supporting material submitted to the Citizen Petition docket does not fill this gap.⁹⁹ The memo broadly summarizes "characteristics FDA found across the comments" that purportedly render them "insufficient" to support the requests in the Citizen Petition.¹⁰⁰ However, the memo does not identify any particular study that supposedly exhibits any of these disfavored "characteristics," making it impossible to respond with specificity to FDA's critique. Nonetheless, statements in the memo make plain that FDA failed to rationally consider relevant material in the record. For example, FDA asserts that the comments "do not discuss or provide a proposed ADI for any of the phthalates in the petition."¹⁰¹ Setting aside that comparing an ADI to the estimated daily intake ("EDI") for a substance is only "one approach FDA may utilize" to "determine safety,"¹⁰² FDA's memo ignores the MRL for DEHP established by ATSDR in an assessment submitted to the docket, which is appropriate to compare to intake estimates to conduct this type of safety evaluation and, as discussed further below, must be applied to all the antiandrogenic phthalates for which the petitioners seek regulatory restrictions.

⁹⁸ DEHP Tox. Profile 2.

⁹⁹ Memorandum from Dr. Jessica H. Urbelis to Admin. Record, Review of Comments Submitted to FDA-2016-P-1171 (May 11, 2022) ("Urbelis Memo").

¹⁰⁰ *Id.* at 4.

¹⁰¹ *Id.* at 5.

¹⁰² 87 Fed. Reg. at 31,072.

Similarly, FDA criticized the comments for purportedly failing to “provide further analysis” of how studies commenters submitted “relate to the requests in the citizen petition.”¹⁰³ 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. More fundamentally, 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.¹⁰⁴ 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.

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.”¹⁰⁵ 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.¹⁰⁶ 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.

¹⁰³ Urbelis Memo 5.

¹⁰⁴ 21 U.S.C. § 348(c)(3)(A).

¹⁰⁵ Urbelis Memo 6.

¹⁰⁶ *See* 87 Fed. Reg. at 31,075 (advocating for consideration of total diet studies from Canada and Australia, which FDA said “could potentially address several ... data gaps” that FDA perceived in evidence supporting the related Food Additive Petition).

In addition, 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.”¹⁰⁷ 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. Further, as the CHAP explained, biomonitoring data are “an integral measure of exposure [to chemicals] from multiple sources and routes and permit[] an integrated exposure assessment even when the quantity and quality of external exposures are unknown and/or if the significance of the contribution of different routes of exposure is ambiguous.”¹⁰⁸ In addition, biomonitoring results “can be used to reliably extrapolate to the daily intakes of the respective parent phthalate (and compared with health benchmarks for the individual phthalates as well as on a cumulative basis . . .).”¹⁰⁹

Further, to 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.¹¹⁰ To rationally assess whether a substance is safe for

¹⁰⁷ Urbelis Memo 7.

¹⁰⁸ CHAP Report 34 (citations omitted).

¹⁰⁹ *Id.* at 37.

¹¹⁰ 21 U.S.C. § 348(c)(5).

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. As the National Academy of Sciences has emphasized, it is critical to evaluate “background exposures” to chemicals of concern because even low dose exposures “may have a relevant biologic effect” when combined with elevated background levels.¹¹¹ And here, the contribution of dietary sources to total exposure is not at all low. To the contrary, as discussed above, information in the record establishes that diet is a predominant source of exposure to relevant phthalates. Thus, 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.

In sum, on reconsideration FDA must thoroughly and rationally address the hazard and exposure information in the record, which supports the conclusion that the eight phthalates are not safe for use in food and should be banned under part 189. FDA may not defer this analysis to some future proceeding, as the agency suggested in the Request for Information it issued concurrently with its Response to the Citizen Petition. As described above, FDA’s Request for Information solicited updated hazard and exposure information for eight phthalates that have active food-additive authorizations and/or prior sanctions—including DEHP, DINP, and DCHP—and stated that the agency “*may* use this information to update the dietary exposure estimates and safety assessments” for these substances.¹¹² But as this reconsideration request

¹¹¹ Nat’l Rsch. Council, *Science and Decisions: Advancing Risk Assessment* 130, 132 (2009).

¹¹² 87 Fed. Reg. at 31,091 (emphasis added).

illustrates, FDA already possesses in the administrative record for the Citizen Petition substantial hazard and exposure information indicating that these and related phthalates are not safe for use in food, which FDA has a legal obligation to address and act on *in the current proceedings*.

C. FDA failed to consider the cumulative effects of related phthalates, as the Food Act requires

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.

First, in faulting the petitioners for failing to “analyze each of the Proposed part 189 Substances individually” and establish that each one is unsafe in any amount,¹¹³ FDA disregarded the Food Act’s 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.”¹¹⁴ Contrary to FDA’s assertion that each of the part 189 substances must be proven unsafe in isolation, the Food Act and implementing regulations require FDA to evaluate a substance’s safety in a manner that accounts for the cumulative effects of related substances in the diet.

Further, 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

¹¹³ Response 10.

¹¹⁴ 21 U.S.C. § 348(c)(5)(B); *see also* 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).

antiandrogenic and fall within a structural subclass of 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).¹¹⁵ These phthalates have been strongly linked to irreversible structural abnormalities in the developing male reproductive tract, including reduced anogenital distance, hypospadias,¹¹⁶ and undescended testes.¹¹⁷ In animal studies, this combination of developmental harms together with other abnormalities is referred to as “phthalate syndrome.”¹¹⁸ In addition, it is well-established that these phthalates induce antiandrogenic effects via a common mechanism of action of reduced fetal testis testosterone production,¹¹⁹ which underscores the importance of a cumulative effects analysis in considering the requested part 189 prohibitions.

In addition, 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.¹²⁰ This methodology is also supported by authoritative scientific bodies. For example, the National Research Council of the National Academy of Sciences recommends conducting a cumulative risk assessment for phthalates that contribute to common adverse health outcomes, and in doing

¹¹⁵ CHAP Report 2, 7–8, 15–16.

¹¹⁶ Hypospadias is a birth defect in which a male infant’s urethra is located typically at the underside of the penis rather than the tip. Surgery is often necessary to correct hypospadias when the infant is between six and twelve months old.

¹¹⁷ CHAP Report 2, 7–8, 15–16.

¹¹⁸ *Id.* at 15-16; *see also* Nat’l Rsch. Council, *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (2008).

¹¹⁹ Nat’l Rsch. Council (2008); CHAP Report 15–19.

¹²⁰ *See* 21 C.F.R. § 170.18(a), (c) (providing that “[f]ood additives that cause similar or related pharmacological effects will be regarded as a class” and that FDA will apply the lowest numerical tolerance established for any member of that class to the entire class when multiple substances from the class are present in food).

so, relying on health-protective toxicity values that are relevant for hazard endpoint and exposure duration, even if that means applying a single toxicity value for multiple phthalates.¹²¹

In short, FDA's Response ignored its legal obligation to consider the cumulative effects of related substances in evaluating the safety of the part 189 substances, and it took an unjustified all-or-nothing approach by considering only whether the 28 phthalates formerly approved for food-contact use satisfy the statutory definition of "related substance[s]."¹²² On reconsideration, FDA must rationally account for the cumulative effects of the part 189 substances, which supports the conclusion that they are not safe for use in food.¹²³

2. In Denying the Request to Revoke Prior Sanctions for Five Phthalates, FDA Failed to Consider Relevant Information and Views Contained in the Administrative Record

FDA should also reconsider its decision to maintain the prior sanctions authorizing the use of DEP, EPEG, BPBG, DIOP, and DEHP as plasticizers in food packaging.¹²⁴ This aspect of the Response largely incorporates or otherwise repeats erroneous analysis in FDA's FAP Denial and/or the portion of the Response rejecting the request for part 189 prohibitions.

First, this aspect of FDA's Response expressly incorporates the FAP Denial to justify FDA's decision to maintain the five prior sanctions for phthalates.¹²⁵ As explained in the concurrently filed objections to the FAP Denial, that decision contains multiple material errors of law and fact and cannot sustain the agency's Response to the Citizen Petition.

¹²¹ Nat'l Rsch. Council (2008) at 74-78.

¹²² 21 U.S.C. § 348(c)(5)(B).

¹²³ *Id.*; 21 C.F.R. § 170.18.

¹²⁴ Response 10-11.

¹²⁵ *Id.* at 11.

Second, as discussed above, 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. 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.”¹²⁶ That FDA characterized the record this way only underscores that the agency failed to consider adequately what is in the record.

Third, FDA failed to consider and apply the correct legal standard in evaluating the petitioners’ request to revoke the prior sanctions. In criticizing the Citizen Petition for purportedly failing to address how the substances at issue violate the Food Act’s adulteration standard,¹²⁷ 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,¹²⁸ which the petitioners indisputably addressed.¹²⁹ Accordingly, FDA erred in claiming that the Citizen Petition’s request to revoke prior sanctions lacked adequate legal support.¹³⁰ Further, as discussed above, under the governing standard FDA cannot confine its safety assessment solely to the prior-sanctioned uses “in a vacuum” without accounting for the cumulative effects from all

¹²⁶ *Id.*

¹²⁷ *Id.*

¹²⁸ Ex. 1 at 1.

¹²⁹ *See* Food Additive Petition 1– 3, 17.

¹³⁰ Response 11.

approved uses of the prior-sanctioned substances and related substances in the diet.¹³¹ On reconsideration, FDA must rationally address the evidence in the record, which undermines its conclusion that the prior-sanctioned uses are safe, and take prompt action to withdraw those authorizations.

3. The Petitioners' Position is Not Frivolous and is Being Pursued in Good Faith

For the reasons provided above and in the Citizen Petition and supporting materials, the positions advanced in the Citizen Petition and this reconsideration request are not frivolous and they are pursued in good faith. The organizations making this reconsideration request are non-profit, public-interest organizations with longstanding commitments to protecting people from dangerous exposure to toxic chemicals such as phthalates in food and other sources. Collectively, these organizations have a long track record of advocating for health-protective changes to federal and state laws governing phthalates in food and other products, pressing companies to eliminate phthalates from their supply chains, and educating their members and the broader public about the health risks from phthalate exposure and strategies to reduce that exposure. The organizations make this reconsideration request on behalf of their members and supporters who are concerned about exposure to phthalates in food and drinks and the threats this exposure poses to their health and their children's health.

4. Sound Public Policy Grounds Support Reconsideration, and Reconsideration is Not Outweighed by Public Health or Other Public Interests

Finally, sound public policy grounds support reconsideration and are not outweighed by countervailing public health or other public interests. The need to eliminate phthalates from the food supply—an objective the Citizen Petition's requests would substantially advance—is

¹³¹ *Id.*

urgent. As Dr. Zota has explained, FDA’s failure to eliminate authorized uses of phthalates in food-contact materials “has created a serious public health problem of great magnitude.”¹³² “For every year that FDA fails to act” by implementing the requests in the Citizen Petition and related Food Additive Petition, “more people continue to be exposed to levels of phthalates in their food that are damaging to their health”—including children, infants, and developing fetuses who are acutely vulnerable to harm.¹³³ “The effects of these early-life exposures on health and development can alter a person’s entire life trajectory.”¹³⁴ Further, as Dr. Zota explained,

Until FDA reverses course, the health burdens of exposure to phthalates in food will continue to harm the United States population and will disproportionately harm people of color, people of low wealth, and babies and young children undergoing critical periods of growth and development. The health and economic implications resulting from the continued use of phthalates in food packaging and food-processing materials will not only harm those who have been consuming phthalates . . . but also the next generation.¹³⁵

Further, as discussed in this request, there is a wealth of scientific evidence and information in the administrative record that FDA has not addressed, and which compels immediate action to restrict the use of phthalates that are strongly linked to human health harms in food-contact applications.

Finally, FDA has not articulated any public health or other public interests that outweigh the substantial public health interests supporting reconsideration, and we are aware of none. In this regard, both FDA and the public have had ample opportunity—to the tune of six years—to develop and evaluate data and information relevant to the requests in the Citizen Petition and

¹³² Zota Decl. ¶ 32.

¹³³ *Id.* ¶ 31.

¹³⁴ *Id.*

¹³⁵ *Id.* ¶ 32.

provide input on the agency's approach. There is no legitimate basis to delay further in deference to FDA's new Request for Information or for any other reason.

Respectfully submitted June 21, 2022.



Katherine K. O'Brien
Earthjustice
P.O. Box 2297
South Portland, ME 04116
(212) 284-8036
kobrien@earthjustice.org

Attorney for Environmental Defense Fund, Learning Disabilities Association of America, Center for Food Safety, Center for Environmental Health, Center for Science in the Public Interest, Breast Cancer Prevention Partners, Defend Our Health, and Alaska Community Action on Toxics

Rashmi Joglekar, Ph.D.
Earthjustice
1001 G St., N.W., 10th Floor
Washington, D.C. 20001
rjoglekar@earthjustice.org