

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

June 21, 2022

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

Re: Objections and Request for Evidentiary Public Hearing Regarding FDA's Denial of Phthalates Food Additive Petition (FAP 6B4815), Docket No. FDA-2016-F-1253

Dear Commissioner Califf:

Pursuant to the Food, Drug, and Cosmetic Act (the "Food Act"), 21 U.S.C. § 348(f)(1), and its implementing regulations, 21 C.F.R. § 12.22, 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 (collectively, "Objectors") submit these objections to FDA's May 20, 2022, order denying Food Additive Petition 6B4815,¹ which requested in March 2016 that FDA revoke its existing approvals for food-additive uses of phthalates.²

As these objections describe, FDA's Order contains multiple material errors of law and fact and is contrary to the Food Act, the Administrative Procedure Act ("APA"), 5 U.S.C.

¹ Notification, Nat. Res. Def. Council, et al.; Denial of Food Additive Petition, 87 Fed. Reg. 31,066 (May 20, 2022) (the "Order").

² Nat. Res. Def. Council, et al., Food Additive Petition Regarding 30 Ortho-Phthalates (Mar. 18, 2016) (the "Petition").

§§ 551–559, and FDA’s regulations. Objectors request an evidentiary public hearing on material factual issues as specified below.

I. Factual and Legal Background

A. Factual Background³

Over the last sixty-plus years, FDA has authorized the use of more than two dozen ortho-phthalate esters (“phthalates”) in food packaging and food-production materials with evidence showing that these chemicals migrate out of the materials to which they are added into food and beverages.⁴ As a result, diet is the primary source of phthalate exposure for most people in the United States—including infants and children.⁵ Further, as FDA acknowledged in the Request for Information concerning food-contact uses of phthalates that it issued the same day as the Order addressed in these objections, the safety assessments supporting FDA’s 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*.⁶ FDA acknowledges that relevant new information regarding the toxicity of phthalates and the

³ For a complete recitation of the relevant factual background, see Petition for Writ of Mandamus 4–17, *In re Env’t Def. Fund*, No. 21-1255 (D.C. Cir. Dec. 7, 2021). As required by FDA’s regulations, Objectors are submitting to the online docket concurrently with these objections all reports, articles, and other documents cited in support of factual assertions in these objections, 21 C.F.R. § 12.22(a)(5)(i), excepting material that already is part of the docket for this proceeding.

⁴ See Expert Declaration of Russ B. Hauser, M.D., Sc.D., M.P.H., ¶¶ 14–15, *In re Env’t Def. Fund*, No. 21-1255 (D.C. Cir. Dec. 7, 2021) (“Hauser Decl.”) (provided in Petitioners’ Addendum of Declarations).

⁵ See *id.* ¶ 17; Expert Declaration of Ami R. Zota, Sc.D., M.S., ¶¶ 3, 16, *In re Env’t Def. Fund*, No. 21-1255 (D.C. Cir. Dec. 7, 2021) (“Zota Decl.”) (provided in Petitioners’ Addendum of Declarations).

⁶ Notice, Ortho-Phthalates for Food Contact Use; Request for Information, 87 Fed. Reg. 31,090, 31,091 (May 20, 2022).

extent of human exposure to these substances has amassed in the intervening decades, but says it is only “generally aware” of what this new information consists of or indicates.⁷

Recognizing that FDA’s safety assessments for phthalates used in food-contact materials are dangerously out of date, on March 18, 2016, Objectors Environmental Defense Fund, Learning Disabilities Association of America, Center for Food Safety, Center for Environmental Health, and Center for Science in the Public Interest, along with allied organizations, submitted the Petition asking FDA to revoke these authorizations based on a substantial body of new evidence raising significant questions about the safety of using phthalates in food packaging and production equipment.⁸ In response to FDA’s deficiency notice seeking further information to support the Petition, the petitioners submitted substantial additional data and analysis to the agency in August 2017.⁹

Despite FDA’s statutory duty to publish an order granting or denying the Petition within no more than 180 days,¹⁰ FDA did not issue its Order denying the Petition for more than six years after it accepted the Petition for filing. On the same day FDA published its Order denying the Petition, FDA granted a separate food additive petition submitted by the Flexible Vinyl Alliance requesting revocation of food additive authorizations for specified phthalates based on

⁷ *Id.*

⁸ Objector Breast Cancer Prevention Partners (previously known as Breast Cancer Fund) subsequently joined as a petitioner.

⁹ Letter from Tom Neltner, Env’t Def. Fund, to Dr. Kelly Randolph, FDA, Re: Food Additive Petition No. 6B4815 Regarding Ortho-phthalates/Response to Sept. 1, 2016 Request (Aug. 24, 2017) (“Deficiency Notice Response”).

¹⁰ 21 U.S.C. § 348(c)(2); *see also* 21 C.F.R. § 171.100(a), (c).

the assertion that the industry has abandoned those uses (the “abandonment petition”).¹¹ FDA concurrently issued a third order denying a related citizen petition submitted by most of the Objectors which asked FDA to revoke prior sanctions authorizing food-contact uses of five phthalates and promulgate new regulations in 21 C.F.R. part 189 prohibiting food-contact uses of eight phthalates.¹²

Following this trio of related decisions, the following nine phthalates remain approved for specific food-contact uses pursuant to food additive authorizations, prior sanctions, or both:

1. Di(2-ethylhexyl) phthalate, CAS No. 117-81-7 (DEHP)
2. Dicyclohexyl phthalate, CAS No. 84-61-7 (DCHP)
3. Diisononyl phthalate, CAS No. 28553-12-0 (DINP)
4. Diisodecyl phthalate, CAS No. 26761-40-0 (DIDP)
5. Diallyl phthalate, CAS No. 131-17-9 (DAP)
6. Diethyl phthalate, CAS No. 84-66-2 (DEP)
7. Butyl phthalyl butyl glycolate, CAS No. 85-70-1 (BPPG)
8. Diisooctyl phthalate, CAS No. 27554-26-3 (DIOP)
9. Ethyl phthalyl ethyl glycolate, CAS No. 84-72-0 (EPEG)

Accordingly—despite the Order’s inexplicable failure to acknowledge or account for FDA’s simultaneous decisions to grant the industry abandonment petition and deny the citizen petition—these objections focus on material factual and legal errors in FDA’s Order that require

¹¹ 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).

¹² Letter from Leslie Kux, FDA, to Nancy Buermeyer, Breast Cancer Prevention Partners, Re: Docket Number FDA-2016-P-1171 (May 12, 2022). Though this letter is dated May 12, 2022, FDA did not transmit it to the citizen petitioners or post it in the online docket until May 19, 2022. Objectors are concurrently submitting a petition for reconsideration of FDA’s decision denying the citizen petition.

immediate correction based on the current state of FDA’s authorizations for food-contact uses of phthalates and the current scientific information.¹³

B. Legal Background

Congress has charged FDA with “protect[ing] the public health by ensuring that . . . foods are safe.”¹⁴ As a core part of that mandate, FDA has a duty to ensure the safety of all food additives,¹⁵ which include substances added directly to food as well as substances used in food packaging and food production equipment that “may reasonably be expected” to migrate into food.¹⁶

Under the Food Act, all new food additives and new uses of existing additives are presumed unsafe and prohibited unless their proponent provides evidence to FDA establishing “that the proposed use of the food additive . . . will be safe.”¹⁷ To satisfy this standard, the evidence must be adequate to support “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use,”¹⁸ meaning it

¹³ At the same time, as discussed *infra*, Objection 6, the available data indicate that additional phthalates that are no longer approved for food-contact use are nonetheless present in the diet, whether due to environmental contamination or other causes. FDA must consider the cumulative effects of these related substances in the diet when evaluating the safety of the food-additive uses of phthalates that remain approved. 21 U.S.C. § 348(c)(5)(B).

¹⁴ *Id.* § 393(b)(2)(A); see *POM Wonderful LLC v. Coca-Cola Co.*, 573 U.S. 102, 108 (2014) (affirming that the Food Act’s primary purpose is “to protect the health and safety of the public at large”) (citations omitted).

¹⁵ 21 U.S.C. §§ 342(a)(2)(C), 348.

¹⁶ *Id.* § 321(s); see also 21 C.F.R. § 170.3(e)(1).

¹⁷ 21 U.S.C. § 348(a), (c)(3)(A).

¹⁸ 21 C.F.R. § 170.3(i).

will not “injure or otherwise damage the health of individuals consuming the additive.”¹⁹ In evaluating whether a substance satisfies this standard, FDA must consider, “among other relevant factors,” (1) “the probable consumption of the additive and of any substance formed in or on food because of the use of the additive”; (2) “the cumulative effect” of the additive in the diet, “taking into account any chemically or pharmacologically related substance or substances in [the] diet”; and (3) scientifically accepted “safety factors” to provide a margin of safety for human health where FDA is relying on animal studies.²⁰

FDA acknowledges that it has a “continuing obligation to monitor the safety of the food supply,” including the safety of additives already on the market.²¹ Thus, as FDA has explained, it must amend or revoke existing food additive regulations when presented with “sufficient data to establish the existence of safety questions significant enough to support a finding that there is no longer a reasonable certainty of no harm from the currently approved uses.”²²

¹⁹ Final Rule, Food Additives Permitted for Direct Addition to Food for Human Consumption; Olestra, 61 Fed. Reg. 3118, 3119 (Jan. 30, 1996).

²⁰ 21 U.S.C. § 348(c)(5); *see also* 21 C.F.R. § 170.3(i) (parroting statutory standard for “safe” additives).

²¹ 61 Fed. Reg. at 3169; *see* 21 U.S.C. § 348(b)(1), (i); 21 C.F.R. § 171.1 (providing for submission of food additive petitions that request issuance, amendment, or repeal of food additive authorizations); *In re Nat. Res. Def. Council*, 645 F.3d 400, 407 (D.C. Cir. 2011).

²² 87 Fed. Reg. at 31,067; *see also* Final Rule, Indirect Food Additives: Paper and Paperboard Components, 81 Fed. Reg. 5-01, 7 (Jan. 4, 2016) (revoking food-additive authorizations for certain long-chain perfluorinated compounds based on data raising “significant questions as to the safety of the authorized uses of the three [food-contact substances] subject to the petition” and “a lack of data” available “to address these questions”).

II. Interests of Objectors

Objectors and their members, staff, volunteers, board members, and supporters are adversely affected by FDA's Order denying the Petition.²³ Objectors Environmental Defense Fund, Learning Disabilities Association of America, Center for Food Safety, Center for Environmental Health, Center for Science in the Public Interest, and Breast Cancer Prevention Partners submitted the food additive petition at issue and are adversely affected by FDA's arbitrary and unlawful decision to deny it.²⁴ Further, each of the Objector organizations is dedicated to protecting human health from phthalates and other toxic chemicals; has engaged in substantial advocacy to FDA and other regulatory and legislative authorities to eliminate phthalates from food and consumer products; and has members, staff, volunteers, board members, and/or supporters who have suffered and continue to suffer from exposure to phthalates in their food that endangers their health and their children's health.²⁵

III. Objections and Requests for Public Hearing

As elaborated below, FDA's Order contains multiple material errors of law and fact, which each individually, and in concert, require FDA to promptly withdraw the Order.²⁶

Further, FDA must afford Objectors an evidentiary hearing on Objections 3, 5-A, 5-B, 5-C, 6,

²³ See 21 U.S.C. § 348(f)(1) (authorizing "any person adversely affected" by FDA order denying a food additive petition to submit administrative objections); 21 C.F.R. § 10.3 (defining "person" to include "an individual, partnership, corporation, association, or other legal entity").

²⁴ See 21 C.F.R. § 10.3 (defining "any person . . . adversely affected" to include "a person who submits a petition").

²⁵ See Declarations of Margaret Yellow Wolf Tarrant, Debra Cole, Lisette van Vliet, Susan L. Chiang, Rachel Doughty, Sally J. Drew, Jaydee Hanson, Jean Bissell, Peter Lurie, Michael Belliveau, Laura Seaton, Paul Ames, Tom Neltner, Frank Wissler, Tracy Gregoire, and Alexandra Moulton, *In re Env't Def. Fund*, No. 21-1255 (D.C. Cir. Dec. 7, 2021) (provided in Petitioners' Addendum of Declarations).

²⁶ 21 C.F.R. § 12.26; see *id.* § 12.24(a).

and 8 because these objections raise genuine issues of material fact affecting the validity of FDA's Order and satisfy the procedural requirements for a public hearing established in the Food Act and implementing regulations, as elaborated in the specific public hearing requests below.²⁷

Objection 1: FDA unlawfully placed on the petitioners the burden of proving that the approved food-additive uses of phthalates are not safe. (Objection to Order § II)

Section II of FDA's Order reflects a fundamental misunderstanding of the evidentiary burden borne by parties who petition FDA to revoke food-additive authorizations based on safety concerns. Read as a whole, section II indicates that FDA placed on the petitioners the burden of proving that the food-additive uses at issue are unsafe, contrary to the Food Act and its implementing regulations. For this reason alone, FDA must withdraw the Order and evaluate the safety of the food-additive authorizations for phthalates that remain in effect under the correct legal standard. As explained below, that standard requires FDA to revoke approval for food additives where, as here, the available evidence raises significant questions about the safety of the approved uses and, upon reevaluation of the additives' safety, FDA cannot conclude with reasonable certainty that the additives' continued use will cause no harm to human health.

As FDA acknowledged in the Order, the Food Act "makes clear that food additives introduced into commerce must be shown to be safe,"²⁸ and the burden of proving safety rests

²⁷ See 21 U.S.C. § 348(f)(1) (directing that FDA "*shall*" hold, "as promptly as possible," "[a] public hearing for the purpose of receiving evidence relevant and material to the issues raised by . . . objections" to an order denying a food additive petition if those objections are timely, "specify[] with particularity the provisions of the order deemed objectionable, stat[e] reasonable grounds therefor, and request[] a public hearing upon such objections") (emphasis added); 21 C.F.R. §§ 10.20, 12.22.

²⁸ 87 Fed. Reg. at 31,067 (citations omitted).

with the proponent of an additive's use.²⁹ As a necessary corollary, when FDA becomes aware of "sufficient data *to raise safety concerns*" about existing food additives, the agency must take action to "ensure[] that these concerns are addressed or that [the] substances are no longer used as food additives."³⁰

Accordingly, parties petitioning FDA to revoke approval of a food additive on safety grounds do not bear the burden of proving that the additive is unsafe, *i.e.*, that it will cause harm to human health under the intended conditions of use. Placing this burden of proof on petitioners raising safety concerns would be inconsistent with the Food Act's central premise for food-additive regulation, namely, that food additives are presumptively unsafe and may not be used unless the available evidence establishes with "reasonable certainty"³¹ that their use "*will be safe*."³² In the context of a petition to revoke existing food-additive authorizations, this means that FDA must revoke an additive's approval where a petitioner raises "significant questions as to the safety of the authorized uses" that FDA cannot rationally dispel based on the available evidence.³³

²⁹ 21 U.S.C. § 348(a), (c)(3)(A); *see also, e.g., Fmali Herb, Inc. v. Heckler*, 715 F.2d 1385, 1391 (9th Cir. 1983) ("As the overriding purpose of the Food, Drug, and Cosmetic Act is to protect the public health, the burden of proof of safety to be borne by a proponent of an ingredient is heavy.") (citation omitted).

³⁰ 87 Fed. Reg. at 31,067 (emphasis added); *see also* 81 Fed. Reg. at 7 (revoking food-additive authorizations for certain long-chain perfluorinated compounds based on data raising "significant questions as to the safety of the authorized uses" and "a lack of data" available "to address these questions").

³¹ 21 C.F.R. § 170.3(i).

³² 21 U.S.C. § 348(c)(3)(A) (emphasis added).

³³ 81 Fed. Reg. at 7.

FDA’s regulations implementing the Food Act reinforce this conclusion. The regulation governing petitions that “propose the issuance of a regulation amending or repealing a regulation pertaining to a food additive”—like the Petition at issue here— do not require the petitioner to provide proof that an approved food additive is unsafe.³⁴ Instead, such petitions must

include an assertion of facts, supported by data, showing that new information exists with respect to the food additive or that new uses have been developed or old uses abandoned, that new data are available as to toxicity of the chemical, or that experience with the existing regulation . . . may justify its amendment or repeal.³⁵

This language establishes that petitioners seeking revocation of a food-additive regulation bear a burden of production—specifically, the burden of tendering new information regarding a food additive’s toxicity or otherwise demonstrating that amendment or repeal of the additive’s authorization may be justified—not the burden of persuasion on the ultimate question of an additive’s safety.

The U.S. Court of Appeals for the Ninth Circuit reached the same conclusion regarding substantially similar Food Act regulations governing petitions to repeal pesticide tolerances, which establish the level of pesticide residue permitted in food. The court rejected the agency’s argument that a petitioner seeking revocation of an established pesticide tolerance bears “a burden of persuasion . . . to . . . affirmatively demonstrate that the tolerances are unsafe.”³⁶ Instead, the court held that the governing regulations—which, like the regulation at issue here, require petitioners to provide “an assertion of facts” with supporting data “showing . . . that new data are available as to the toxicity of the chemical, or that experience with the application of the [existing regulation] . . . may justify its modification or revocation”—impose only “a

³⁴ 21 C.F.R. § 171.130(a).

³⁵ *Id.* § 171.130(b).

³⁶ *League of United Latin Am. Citizens v. Regan*, 996 F.3d 673, 695 (9th Cir. 2021).

burden of *production*” on the petitioner.³⁷ As the court emphasized, imposing on petitioners the burden of proof regarding safety would be contrary to this regulatory language and at odds with the Food Act’s health-protective purpose—a conclusion that applies with equal force here.³⁸

Indeed, FDA has stated plainly that when FDA is in the position of raising concerns about the safety of a food additive or other product that it has previously authorized, the agency bears only an initial burden of producing new information that calls into question its previous safety finding; the burden of persuasion on the ultimate question of safety lies with the party advocating for continued authorization of the product. For example, in its decision authorizing food-additive uses of olestra, FDA stated that to revoke or limit that authorization in the future “FDA would not be required to show that [the additive] is unsafe. Rather, the agency would only need to show that based upon new evidence, FDA is no longer able to conclude that the approved use . . . is safe, i.e., that there is no longer a reasonable certainty of no harm from the use of the additive.”³⁹ In support of this position, FDA cited its regulations governing public hearings on revocation petitions, which state explicitly that “the participant who is contending that the product is safe . . . and who is . . . contesting withdrawal of approval has the burden of proof in establishing safety.”⁴⁰ The same principle governs here.

³⁷ *Id.* at 694–95 (emphasis added) (quoting 40 C.F.R. § 180.32(b)).

³⁸ *Id.*; *see also id.* at 692 (explaining that the Food Act is “a remedial statute, which . . . must be given a liberal construction consistent with the Act’s overriding purpose to protect the public health”) (quotation omitted).

³⁹ 61 Fed. Reg. at 3169.

⁴⁰ 21 C.F.R. § 12.87(d); *see also Nat. Res. Def. Council v. FDA*, 884 F. Supp. 2d 127, 139 (S.D.N.Y. 2012) (holding that at hearing initiated by FDA under § 12.87 to revoke animal drug approval, “the FDA has the initial burden of producing evidence that the drug has not been shown to be safe . . . However, the drug sponsor has the burden of persuasion on the ultimate question of whether [the drug] is shown to be safe.”) (quotation omitted) (alteration in original); Notice, Deprol; Final Decision Following Formal Evidentiary Public Hearing, 58 Fed. Reg.

Yet in the Order at issue, FDA unlawfully placed the burden of proof regarding the phthalate additives' safety on the petitioners, asserting that FDA need only revoke a food additive authorization if presented with new evidence that "approved additives *are in fact unsafe*."⁴¹ Indeed, FDA did not assess in the Order whether the petitioners provided "new information" regarding the "toxicity of the chemical[s]" at issue, as its regulations require,⁴² nor whether that information "establish[es] the existence of safety questions significant enough to support a finding that there is no longer a reasonable certainty of no harm from the currently approved uses."⁴³ Instead, proceeding from its incorrect position that any action to revoke the approved uses requires proof that those uses "are in fact unsafe,"⁴⁴ FDA's analysis was limited to evaluating whether the petitioners proved that the food-additive uses of the 28 phthalates addressed in the petitioners' 2016 Petition harm human health based on their evaluation as a class.⁴⁵

FDA's approach is absurd given the agency's simultaneous publication of an order granting the industry abandonment petition, which significantly altered the scope of food-additive authorizations for phthalates that remain in effect, and for which a safety evaluation is still required. And this approach reflects FDA's erroneous position that it may leave the extant

50,929-03, 50,939 (Sept. 29, 1993) (explaining, in decision revoking drug approval, that § 12.87(d) places "the burden of proof in establishing safety" on "the participant who is contending that the product is safe . . . and who is . . . contesting withdrawal of approval").

⁴¹ 87 Fed. Reg. at 31,077 (emphasis added).

⁴² 21 C.F.R. § 171.130(b).

⁴³ 87 Fed. Reg. at 31,067 (citations omitted).

⁴⁴ *Id.* at 31,077.

⁴⁵ *See id.* at 31,068–75.

food-additive authorizations in effect unless and until petitioners prove that they are in fact unsafe. This legal error infected FDA’s entire analysis and requires FDA to withdraw the Order.

Objection 2: FDA unlawfully failed to evaluate the safety of the food-additive uses of phthalates that remain authorized (Objection to Order § II).

A distinct but related defect in FDA’s Order, which also necessitates its withdrawal, is the agency’s failure to evaluate the safety of the food-additive authorizations that remain in effect for DAP, DCHP, DEHP, DINP, and DIDP following FDA’s May 20, 2022 decisions.⁴⁶ Stunningly, neither the Order nor the FDA technical memoranda in the docket contain an analysis of whether these authorized uses are safe. Instead, as discussed above, FDA confined its analysis to determining that the Petition purportedly “does not provide adequate support for grouping the 28 phthalates”—*i.e.*, the set of substances that formerly constituted all FDA-approved phthalate food additives, but no longer do—as a single class, and therefore, “the research pertaining to individual phthalates or specific mixtures of phthalates cannot be applied to all 28 phthalates that are the subject of the petition.”⁴⁷

This is unlawful. Setting aside that FDA irrationally confined its analysis to addressing a question that it had effectively rendered moot by deciding to grant the industry abandonment petition, FDA failed to discharge its “continuing obligation to oversee the safety of the food

⁴⁶ As explained below, this safety analysis must account for the cumulative effects of related phthalates that remain approved for food-contact use under prior sanctions as well as additional related phthalates that are appear in the diet regardless of their regulatory status. 21 U.S.C. § 348(c)(5)(B).

⁴⁷ 87 Fed. Reg. at 31,076.

supply” by assessing “whether there continues to be reasonable certainty of no harm from the use of” the additives that remain approved.⁴⁸

As FDA has previously recognized, this obligation requires the agency, when responding to a revocation petition like the one at issue here, “to evaluate whether new data are available as to the toxicity of the subject [chemicals] that justify amendment” of the applicable authorizations, which in turn requires FDA to assess both “the data and information in the petition and other available relevant material.”⁴⁹ So, for example, in evaluating a food additive petition to revoke approval for certain perfluorinated compounds used in food-contact materials, FDA reviewed the safety information the petitioners submitted and “also conducted its own updated critical review of the literature database” for relevant toxicity studies—the results of which FDA documented in the record—“in order to assess whether the overall weight of the evidence still supports FDA’s conclusions” from a prior assessment and, in conjunction with the petitioners’ submissions, “indicated that there are significant, unanswered questions regarding the safety of exposure” to the additives at issue.⁵⁰

In contrast, the Order at issue here claims without elaboration that “FDA is aware of the research that has been conducted with respect to phthalates” and that FDA considered, in an undisclosed manner, “the research in its evaluation of the petition.”⁵¹ But neither the Order nor the underlying technical memoranda in FDA’s docket identify what constitutes “the research”

⁴⁸ 61 Fed. Reg. at 3168; *see* 21 U.S.C. § 348(a), (c)(3) (providing that all food additive uses are presumptively unsafe and unlawful unless “a fair evaluation of the data before [FDA]” proves that the additive’s use “will be safe”).

⁴⁹ 81 Fed. Reg. at 7.

⁵⁰ Mem. from Dr. Penelope A. Rice, FDA, to Dr. Paul Honigfort, FDA, Re: FAP 4B4809, at 7 (July 27, 2015).

⁵¹ 87 Fed. Reg. at 31,076.

relevant to FDA’s safety evaluation nor document this evaluation. Thus, there is no analysis in the record demonstrating that the food-additive uses that remain subject to the agency’s authorization “will be safe.”⁵²

Further, FDA’s claim that it has adequately assessed “the research that has been conducted with respect to phthalates” cannot be credited given the agency’s statements in the Request for Information concerning food-contact uses of phthalates that FDA issued on the same day it published the Order. In that Request, FDA acknowledged that its safety evaluations for food-contact uses of phthalates are based on “information and data provided during the period of 1961 through 1985,” and admitted that it is only “generally aware” of current information regarding the toxicity of and exposure to the phthalates that remain approved.⁵³ These statements belie any claim that FDA adequately evaluated the safety of these substances before publishing its Order denying the Petition.

Moreover, FDA’s Request for Information makes plain that the agency is unlawfully attempting to defer its evaluation of whether the agency’s current authorizations for food-contact uses of phthalates are in fact safe. The request asks the public to submit “all updated information regarding the food contact uses, use levels, and dietary exposure and safety data” for the phthalates that remain approved (except for DAP, which FDA excluded from the Request for Information) and asserts that FDA “*may* use this information to update the dietary exposure estimates and safety assessments for the permitted food contact uses of ortho-phthalates.”⁵⁴ But these are the very issues that FDA was required to address—years ago—in response to the

⁵² 21 U.S.C. § 348(c)(3)(A).

⁵³ 87 Fed. Reg. at 31,091.

⁵⁴ *Id.* (emphasis added).

Petition.⁵⁵ FDA’s attempt to kick the proverbial can down the road by stating that it might address the safety questions concerning food-contact uses of phthalates that the Petition raised more than six years ago is irresponsible and unlawful.

To the extent FDA believes it was not required to conduct a safety assessment in this proceeding because the petitioners did not proffer sufficient new information to trigger that duty, that position is unsupported and incorrect. As discussed *supra*, Objection 1, FDA disregarded that the petitioners bear only an initial burden of production to tender new information regarding toxicity or other factors that call into question the safety of the approved food additives, and FDA failed even to consider whether the petitioners met that burden. In this regard, FDA inexplicably ignored the substantial toxicity information presented with the 2016 Petition and supplemented in the petitioners’ 2017 deficiency notice response.⁵⁶ This information alone satisfied the petitioners’ burden of “showing that new information exists with respect to the food additive[s]” at issue or “that new data are available as to toxicity of the chemical[s]” and triggered FDA’s obligation to assess whether there remains a reasonable certainty of no harm from the uses that remain authorized.⁵⁷ And as discussed *infra*, Objection 3, substantial toxicity information generated since 2017 further supports the significant safety questions raised in the Petition and obligates FDA to evaluate fully—in *this proceeding*—whether the extant food-additive authorizations for phthalates are safe.

⁵⁵ See 21 U.S.C. § 348(c)(2) (requiring FDA to issue order granting or denying food additive petition within 180 days).

⁵⁶ Petition 7–8 and app. III; Deficiency Notice Response.

⁵⁷ 21 C.F.R. § 171.130(b).

Objection 3: FDA’s Order fails to address new toxicity information that raises significant questions about the safety of the approved food-additive uses of phthalates (Objection to Order §§ II.B.2, II.D).

Petitioners object to FDA’s decision to deny the Petition and maintain its food-additive authorizations for DAP, DCHP, DEHP, DINP, and DIDP without addressing the substantial body of relevant toxicity information published since the petitioners submitted their 2017 Deficiency Notice Response, which supplemented the Petition’s presentation of relevant toxicity information up to that point in time. Despite FDA’s unsubstantiated claim that it considered “the research that has been conducted with respect to phthalates” in evaluating the Petition,⁵⁸ neither the Order nor FDA’s supporting memoranda even acknowledge most of this information, let alone explain how FDA can rationally conclude that the approved uses will be safe based on a “fair evaluation of the data before [FDA].”⁵⁹ FDA must do so in response to these objections and modify its decision accordingly.⁶⁰

This body of relevant toxicity information includes dozens of peer-reviewed animal, *in vitro*, and epidemiological studies that underscore the toxicity of the phthalates that remain approved for food-contact use.⁶¹ For example, in the last two years alone, roughly 50 peer-reviewed animal studies were published citing associations between DEHP exposure and developmental toxicity,ⁱ developmental neurotoxicity,ⁱⁱ adult neurotoxicity,ⁱⁱⁱ reproductive toxicity,^{iv} endocrine disruption,^v hepatotoxicity,^{vi} metabolic toxicity,^{vii} immunotoxicity,^{viii} and

⁵⁸ 87 Fed. Reg. at 31,076.

⁵⁹ 21 U.S.C. § 348(c)(3).

⁶⁰ The relevance of the toxicity information regarding phthalates that are chemically or pharmacologically related to the five that remain approved for food-additive use is addressed *infra*, Objections 5–6.

⁶¹ Due to the volume of materials cited in support of this objection, we provide references for the scientific papers cited in this section in endnotes to this document.

even epigenetic alterations.^{ix} Collectively, these studies provide evidence for a number of DEHP-related adverse health outcomes, including altered adult sex behavior,^x delayed puberty,^{xi} reduced insulin sensitivity,^{xii} obesity,^{xiii} hypothyroidism,^{xiv} cognitive impairment,^{xv} and even depressive-like behaviors.^{xvi} Several *in vitro* studies confirmed associations between DEHP and hepatotoxicity,^{xvii} immunotoxicity,^{xviii} and male reproductive toxicity.^{xix}

Recent animal studies also linked DINP exposure to hepatotoxicity^{xx} and exacerbated nerve cell damage and decline in learning and memory when combined with artificial light.^{xxi} One animal study additionally linked DCHP exposure to elevated cholesterol.^{xxii}

Most notably, two dose-response studies examining the cumulative effects of several phthalates (including DCHP and DEHP) found that phthalate mixtures induced reproductive tract malformations in male rats at doses well below those associated with harm from individual chemicals.^{xxiii}

In addition, there are more than a dozen recent peer-reviewed epidemiological studies providing relevant toxicity information that undercuts FDA's outdated safety determinations, but which FDA has not addressed. Many of 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,^{xxiv} altered lipid metabolism,^{xxv} insulin resistance and diabetes,^{xxvi} delayed onset of puberty in boys,^{xxvii} thyroid hormone disruption,^{xxviii} reduced levels of critical reproductive hormones in women undergoing fertility treatment,^{xxix} 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.^{xxx}

Similar adverse health outcomes were linked to urinary DINP metabolites, including insulin resistance^{xxxii} and delayed puberty onset in boys.^{xxxii} Also included in this body of evidence are birth cohort studies that found associations between gestational urinary DEHP and DINP metabolites and adverse health outcomes in both pregnant mothers and their children. For example, several studies linked gestational DEHP exposure to preterm birth^{xxxiii} and neurodevelopmental harm, including ADHD, social problems, lower vocabulary scores, and lower IQ, in children exposed *in utero*.^{xxxiv} One of these studies also linked ADHD to *in utero* DINP exposure.^{xxxv}

In addition to peer-reviewed publications, FDA must also address recent hazard and/or risk assessments released by federal and European agencies, including the recent “Toxicological Profile for DEHP” released by the Agency for Toxic Substances and Disease Registry (“ATSDR”),⁶² the “Technical Report on the Toxicology and Carcinogenesis Studies of Di(2-ethylhexyl) Phthalate” released by the National Toxicology Program (“NTP”),⁶³ and an updated risk assessment of DEHP, DBP, BBP, DINP, and DIDP for use in food contact materials released by the European Food Safety Authority (“EFSA”).⁶⁴ These assessments, among others, provide novel insights and weight of evidence analyses that are relevant to the safety reevaluations that FDA must conduct for the approved phthalate food additives.

⁶² Agency for Toxic Substances and Disease Registry, *Toxicological Profile for Di(2-ethylhexyl)phthalate (DEHP)* (2022) (“DEHP Tox. Profile.”).

⁶³ NTP, NTP TR 601, *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Di(2-ethylhexyl) Phthalate Administered in Feed to Sprague Dawley Rats* (2021).

⁶⁴ EFSA Panel on Food Contact Materials et al., *Update of the Risk Assessment of Di-butylphthalate (DBP), Butyl-benzylphthalate (BBP), Bis(2-ethylhexyl)phthalate (DEHP), Diisononylphthalate (DINP) and Diisodecylphthalate (DIDP) for Use in Food Contact Materials* (2019).

Further, in December 2021 the Objectors presented FDA with declarations and supporting studies prepared by two preeminent experts in the health effects of phthalates who concluded from their own direct research experience and an updated review of the published literature that FDA’s failure to revoke all food-additive authorizations for phthalates has caused “unnecessary and avoidable harm to the health of children, women, and men in the United States”⁶⁵ by causing them “to be exposed to levels of phthalates in their food that are damaging to their health.”⁶⁶ 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.⁶⁷ For some of these health hazards, such as adult male reproductive harms associated with antiandrogenic phthalates, “[t]he link [to] phthalate exposures . . . is well established” based on nearly twenty years’ worth of peer-reviewed studies.⁶⁸

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.”⁶⁹ Further, as Dr. Ami Zota explained, certain subpopulations—including infants and children, Black and Latina women of

⁶⁵ Hauser Decl. ¶ 3.

⁶⁶ Zota Decl. ¶ 31; *see also id.* at ¶¶ 7, 30–32.

⁶⁷ Hauser Decl. ¶¶ 18–25, 28–30, 32; Zota Decl. ¶¶ 4, 29.

⁶⁸ Hauser Decl. ¶ 20; *see also id.* ¶¶ 19, 28.

⁶⁹ *Id.* ¶ 37.

reproductive age, and economically insecure people—experience greater exposure to phthalates and are more likely to suffer from health harms associated with that exposure.⁷⁰ FDA cannot lawfully retain food-additive authorizations for phthalates without grappling with the expert analyses and scientific literature presented here.⁷¹

Request for Public Hearing:

Objectors request, and are entitled to, a public hearing on this objection.⁷² The foregoing discussion provides “a detailed description and analysis of the factual information” supporting the objection and demonstrates that “[t]here is a genuine and substantial issue of fact for resolution at a hearing,”⁷³ namely, whether the many years’ worth of data and information regarding the human health hazards of phthalates found in the diet presented in support of the Petition and Objections raise significant questions regarding the safety of the authorized food-additive uses of DAP, DCHP, DEHP, DINP, and DIDP. Excepting the report from the Consumer Product Safety Commission’s Chronic Hazard Advisory Panel on phthalates and

⁷⁰ Zota Decl. ¶¶ 5–7, 23–29.

⁷¹ See 21 U.S.C. § 348(a), (c)(3)(A); *Motor Vehicle Mfrs. Ass’n of U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (holding that an agency rule is “arbitrary and capricious” in violation of the APA “if the agency ... entirely failed to consider an important aspect of the problem [or] offered an explanation for its decision that runs counter to the evidence before the agency”). See also *United States v. Lexington Mill & Elevator Co.*, 232 U.S. 399, 410–11 (1914) (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 one who is more susceptible to harm due to age, illness, or other factors).

⁷² 21 U.S.C. § 348(f)(1) (directing that FDA “shall” hold a public hearing when requested “for the purpose of receiving evidence relevant and material to the issues raised by ... objections”); 21 C.F.R. § 12.22(a)(4)–(5) (requiring objectors to specify the objections for which a hearing is requested and provide a detailed description and analysis of supporting information); *id.* § 12.24(b) (providing that a hearing request “will be granted” if the objection raises a genuine issue of material fact capable of resolution in the objector’s favor based on the information submitted).

⁷³ 21 C.F.R. §§ 12.22(a)(5), 12.24(b)(1).

phthalate alternatives (the “CHAP”),⁷⁴ FDA largely ignored this information in the Order and did not explain why the information is inadequate to undermine FDA’s safety determinations for the food additives at issue. At a public hearing, Objectors would offer expert testimony regarding the human health harms associated with consumption of the phthalates approved for food-additive use and related substances at levels experienced by the general population and higher-risk subpopulations and why the available toxicological and epidemiological data do not support a reasonable certainty that the approved uses are safe. Because Objectors have “identifie[d] . . . a material issue of fact” regarding the validity of FDA’s Order, they are “entitled to a public hearing.”⁷⁵

Objection 4: FDA applied an erroneous interpretation of “chemically or pharmacologically related” substances for which the Food Act mandates a cumulative effects analysis (Objection to Order § II.A).

As FDA’s Order acknowledged, in evaluating the safety of a food additive, section 409 of the Food Act requires FDA to “consider among other relevant factors . . . the cumulative effect of such additive in the diet of man or animals, taking into account any *chemically or pharmacologically related substance or substances* in such diet.”⁷⁶ This mandate is broad on its face. As FDA explained in the Order, it may require FDA to account for related substances in the diet in a number of ways to validly assess an additive’s safety, such as by utilizing toxicological data from one substance to fill gaps in the hazard profile for a related substance

⁷⁴ U.S. Consumer Prod. Safety Comm’n, *Report by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives* (2014) (“CHAP Report”).

⁷⁵ *Marshall Minerals, Inc. v. FDA*, 661 F.2d 409, 425 (5th Cir. Unit B 1981).

⁷⁶ 21 U.S.C. § 348(c)(5)(B) (emphasis added); 21 C.F.R. § 170.3(i)(2); *see* 87 Fed. Reg. at 31,072.

and/or accounting for cumulative exposure to related substances in the diet.⁷⁷ Though FDA purported to recognize this statutory obligation, it ultimately applied a cramped interpretation of “related” substances that is contrary to the Food Act and implementing regulations. This interpretation must be corrected to support a reasoned safety assessment for the food-additive uses of phthalates that remain approved.

The Order does not articulate FDA’s interpretation of what constitutes a “related” substance within the meaning of section 409. But FDA’s rationale indicates that the agency interpreted “related” substances in a manner at odds with that provision’s plain language. Specifically, FDA appeared to interpret section 409 as requiring FDA to account only for the cumulative effects of substances that are known to share with the additive under review (1) “well-defined similarities in chemical structure,” and (2) a common “defined toxicological endpoint[,]” and (3) “a common mechanism of action” associated with that common endpoint.⁷⁸ But requiring all three common elements for substances to be considered “related” is at odds with the plain language of section 409, which requires FDA to account for the cumulative effects of all chemicals in the diet that are “chemically *or* pharmacologically related” to the additive under review.⁷⁹

Further, regarding pharmacologically related substances specifically, nothing in the Food Act or FDA’s regulations requires FDA to identify a common mechanism of action to conclude

⁷⁷ 87 Fed. Reg. at 31,072.

⁷⁸ *Id.* at 31,071; *see also* Mem. from Dr. Tsu-Fan Cheng, FDA, to Dr. Jessica Urbelis, FDA, Re: Food Additive Petition (FAP) 6B4815 – DFCS Toxicology Phthalate Petition Memorandum 10 (May 11, 2022) (faulting the Petition for failing to address that asserted health effects may be “induced through separate pathways (*i.e.*, not a common pathway)” and purported inconsistency with other scientific and regulatory assessments that grouped phthalates based on “common health outcomes (*i.e.*, antiandrogenicity) as a result of a discrete mechanism of action”).

⁷⁹ 21 U.S.C. § 348(c)(5)(B) (emphasis added).

that substances are pharmacologically related.⁸⁰ FDA’s regulations make the focus on common effects, as opposed to a common mechanism of action, more explicit, dictating that the agency must treat as related any additives that cause “similar or related pharmacological effects,” full stop.⁸¹ Indeed, it would be irrational and contrary to the Food Act’s safety mandate to ignore the cumulative effects of substances in the diet that are known to contribute to the same adverse health effect because the mechanism of action is not known to be the same for both substances or is not known at all. This approach would also be inconsistent with the current scientific literature, which “support[s] ... the idea that cumulative assessment groups need to include all chemicals that produce common adverse effects in an assessment of chemical risk and not narrowly limited to those with identical modes of action.”⁸²

Similarly, FDA erred in asserting that it is only required to consider the cumulative effects of substances that would be suitable for grouping into a single “category for risk assessment.”⁸³ As FDA acknowledged elsewhere in the Order, “[c]hemically or pharmacologically related substances can be taken into account,” as section 409 requires, “in any

⁸⁰ *Id.* Where Congress intended to limit the requirement for a cumulative effects analysis to substances with a common mechanism of action, it said so. *See* 21 U.S.C. § 346a(b)(2)(C)(i)(III), (D)(v) (requiring EPA, when evaluating pesticide tolerances, to consider the cumulative effects of “other substances *that have a common mechanism of toxicity*” with the pesticide at issue); *Russello v. United States*, 464 U.S. 16, 23 (1983) (affirming that “where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.”) (quotation and alteration omitted).

⁸¹ 21 C.F.R. § 170.18(a).

⁸² Justin M. Conley et al., *A Mixture of 15 Phthalates and Pesticides Below Individual Chemical No Observed Adverse Effects Levels (NOAELs) Produces Reproductive Tract Malformations in the Male Rat*, 156 *Env’t Int’l*, art. no. 106615 (2021); *see also* Nat’l Rsch. Council, *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* 4 (2008).

⁸³ 87 Fed. Reg. at 31,069.

number of scientifically valid ways.”⁸⁴ As noted above, this may involve combining the estimated dietary exposure to related substances or using read-across approaches to fill data gaps concerning the toxicity of related substances.⁸⁵ And it is well established that not all these modes of analysis depend upon finding structural similarity and a common toxicological endpoint with a known common mechanism of action. For example, as explained further *infra*, Objection 5-A, OECD guidance explains that validly grouped chemicals may have varying hazards, which may warrant subcategorization based on hazard.

In sum, FDA’s interpretation of “related” substances for which section 409 requires a cumulative effects analysis is contrary to the plain language of the statute and FDA’s regulations and inconsistent with current scientific practice. And in the context of evaluating phthalates’ safety, this error is grave. As Dr. Hauser’s declaration explains, biomonitoring data reveal that most people in the United States are exposed repeatedly to multiple phthalates on a daily basis, and toxicological studies demonstrate that this

exposure to multiple phthalates will, at a minimum, have additive health effects, if not synergistic health effects, that can magnify the health harms associated with individual phthalates. In addition, subpopulations exposed to other chemical and non-chemical stressors can experience an even greater risk of health harms from phthalate exposures.⁸⁶

As discussed in the following objection, proper application of section 409’s relatedness standard supports multiple valid groupings of the phthalates that remain approved for food-contact use. In addition, proper application of the statutory relatedness standard requires FDA to consider the cumulative effects of additional phthalates that are no longer approved for food-contact use but appear to be present in the diet, whether due to environmental contamination or other reasons.

⁸⁴ *Id.* at 31,072.

⁸⁵ *Id.*

⁸⁶ Hauser Decl. ¶¶ 33, 35.

To conduct the safety evaluations the Food Act demands, FDA must withdraw the Order and properly apply the statutory standard for chemically or pharmacologically related substances to account for the cumulative effects of all related phthalates in the diet.

Objection 5: FDA failed to rationally consider whether the nine phthalates that remain approved for food-contact use, and/or any subset(s) of those chemicals, are chemically or pharmacologically related (Objection to Order § II.A).

In addition to applying an erroneous interpretation of “related” substances under section 409 of the Food Act, FDA acted arbitrarily and unlawfully by failing to assess whether the nine phthalates that remain approved for food-contact use after the agency’s May 2022 decisions—and/or any subset of those substances—are “chemically or pharmacologically related” such that FDA must consider their cumulative effects.⁸⁷

Despite FDA’s decision to coordinate the simultaneous publication of its two orders (1) denying the Petition to revoke approved food-additive uses of phthalates on safety grounds and (2) granting the industry abandonment petition,⁸⁸ the Order denying the safety-based Petition does not acknowledge FDA’s concurrently-issued order granting the abandonment petition and considers only whether the petitioners established that the 28 phthalates *formerly* approved for food-additive use are chemically or pharmacologically related within the meaning of section 409.⁸⁹ This is irrational on its face, and by failing to address in the Order the relatedness—and safety—of the substances that remain authorized for food-contact use FDA has unlawfully

⁸⁷ 21 U.S.C. § 348(c)(5)(B).

⁸⁸ See Mem. from Dr. Jessica H. Urbelis, FDA, to Admin. File, FAP 6B4815, Re: Food Additive Petition (FAP) 6B4815 Supplementary Memorandum 2 (May 11, 2022) (“Supplementary Memo”) (explaining that “FDA intends to respond to [the industry abandonment petition] concurrently with its response to [the Petition seeking revocation based on safety concerns] by amending its food additive regulations to no longer provide for the food additive use of 23 of the 28 phthalates covered by [the Petition raising safety concerns]”).

⁸⁹ 87 Fed. Reg. at 31,068–72.

“failed to consider an important aspect of the problem.”⁹⁰ FDA cannot fulfill its “continuing obligation to monitor the safety of the food supply,” without evaluating the safety of the uses that remain approved.⁹¹ And this evaluation must account for, “among other relevant factors,” the cumulative effects of any of the approved substances that are chemically or pharmacologically related.⁹²

FDA’s Supplementary Memo supporting the Order does not cure this defect in FDA’s analysis because it only addressed whether the relatedness arguments advanced in the 2016 Petition support grouping four of the nine phthalates that remain approved for food-contact use.⁹³ This is arbitrary, first, because it ignores four additional phthalates that remain approved for food-contact use pursuant to prior sanctions only, namely, DEP, EPEG, BPBG, and DIOP. Under the Food Act, FDA must consider the cumulative effects of any substances in the diet that are chemically or pharmacologically related to the approved food additives in evaluating the safety of those additives; that these four substances are authorized pursuant to prior sanctions does not exempt them from the cumulative effects analysis required by section 409.⁹⁴ Further, as

⁹⁰ *State Farm*, 463 U.S. at 43.

⁹¹ 61 Fed. Reg. at 3169.

⁹² 21 U.S.C. § 348(c)(5)(B).

⁹³ Supplementary Memo 2, 6–8. In the Supplementary Memo, FDA took the position that it need not consider the relatedness of DAP to the other phthalates that remain approved as food additives because DAP is authorized only for use as a monomer in polymer production and supposedly is “structurally unique.” *Id.* at 2. The assertion that DAP lacks sufficient structural similarity with the other approved phthalates is wrong for the reasons described in Objection 5-A, and the nature of the approved food-contact use is not relevant to determining whether DAP is “chemically or pharmacologically related” to approved food additives or other substances in the diet. 21 U.S.C. § 348(c)(5)(B).

⁹⁴ *See* 21 U.S.C. § 348(c)(5)(B) (requiring FDA, in evaluating the safety of a food additive, to consider the cumulative effect of “*any* chemically or pharmacologically related *substance or substances* in [the] diet,” not only those classified legally as food additives) (emphasis added).

explained in the following objections, there are multiple valid groupings for the nine phthalates that remain approved for food-contact use, requiring FDA to consider their cumulative effects in evaluating the safety of the substances that remain approved as food additives.⁹⁵

Objection 5-A: Contrary to FDA’s conclusion, OECD guidance supports grouping the nine approved phthalates as chemically related substances, requiring FDA to consider their cumulative effects in evaluating safety (Objection to Order § II.A.1–2, 5).

First, contrary to FDA’s conclusion in the Order and supporting memoranda, OECD guidance supports grouping all nine phthalates that remain approved for food-contact use as chemically related substances based on the common presence of the Ph-C-CO-OR functional groups that are characteristic of all ortho-phthalate esters.⁹⁶

In a 2014 guidance document on grouping chemicals for hazard assessment, OECD recommended that chemicals may be grouped based on one or more criteria, including the presence of “common functional group(s).”⁹⁷ Thus, contrary to FDA’s conclusion,⁹⁸ the OECD guidance supports grouping the nine approved phthalates based on the common presence of the Ph-C-CO-OR functional groups. In fact, OECD itself recognizes the “obvious structural similarities” of ortho-phthalate esters based on these shared functional groups.⁹⁹

FDA erred in concluding that differences in physical-chemical properties and R-group chemistry among the phthalates evaluated preclude a single grouping based on the shared Ph-C-

⁹⁵ *Id.*

⁹⁶ See Memorandum from Dr. Raymond P. Briñas, FDA, to Dr. Jessica Urbelis, FDA, Re: FAP 6B4815 Chemistry Memorandum 3 (May 11, 2022) (“Chemistry Memo”) (describing this cluster of functional groups as “diesters of 1,2-dicarboxy-benzene with two alkyl groups containing a carbon chain of at least one carbon”).

⁹⁷ OECD, *Guidance on Grouping of Chemicals* 12 (2d. ed. 2017) (“OECD Guidance”).

⁹⁸ 87 Fed. Reg. at 31,069.

⁹⁹ OECD Guidance 69.

CO-OR functional groups.¹⁰⁰ Contrary to FDA’s conclusion, OECD recommends that robust characterization of chemicals within a category and justification for their inclusion will require *disclosure* of differences in physical-chemical properties, adverse health outcomes, and/or mechanism of action,¹⁰¹ but it does not dictate that such differences preclude grouping chemicals into a category. In fact, OECD acknowledges that one or more of these additional factors can “be present or follow a trend for some but not all members of the category.”¹⁰² In such cases, differences in physical-chemical properties, adverse health outcomes, and/or mechanism of action among chemicals within a category can be used to identify candidates for sub-categorization.¹⁰³ For example, due to the established anti-androgenic potential of ortho-phthalate esters with an R-group alkyl side chain length of 3-8 carbon atoms,¹⁰⁴ a sub-

¹⁰⁰ 87 Fed. Reg. at 31,068–69; Chemistry Memo 3-7.

¹⁰¹ OECD Guidance 109-114.

¹⁰² *Id* at 17.

¹⁰³ *Id* at 17-18.

¹⁰⁴ CHAP Report 16; Nat’l Acad. of Scis., Eng’g, & Medicine, *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals* (2017); Maryam Zarean et al., *The Role of Exposure to Phthalates in Variations of Anogenital Distance: A Systematic Review and Meta-Analysis*, 247 *Env’t Pollution* 172 (2019); Richard Grady & Sheela Sathyanarayana, *An Update on Phthalates and Male Reproductive Development and Function*, 13 *Current Urology Reports* 307 (2012); Vickie S. Wilson et al., *Diverse Mechanisms of Anti-Androgen Action: Impact on Male Rat Reproductive Tract Development*, 31 *Int’l J. Andrology* 178 (2008); Yayoi Suzuki et al., *Foetal Exposure to Phthalate Esters and Anogenital Distance in Male Newborns*, 35 *Int’l J. Andrology* 236 (2012); Shanna H. Swan, *Environmental Phthalate Exposure in Relation to Reproductive Outcomes and Other Health Endpoints in Humans*, 108 *Env’t Rsch.* 177 (2008); Shanna H. Swan et al., *Decrease in Anogenital Distance Among Male Infants With Prenatal Phthalate Exposure*, 113 *Env’t Health Persps.* 1056 (2005); Shanna H. Swan et al., *First Trimester Phthalate Exposure and Anogenital Distance in Newborns*, 30 *Human Reprod.* 963 (2015); A.J. Martino-Andrade et al., *Timing of Prenatal Phthalate Exposure in Relation to Genital Endpoints in Male Newborns*, 4 *Andrology* 585 (2016); Kembra L. Howdeshell et al., *Cumulative Effects of Antiandrogenic Chemical Mixtures and Their Relevance to Human Health Risk Assessment*, 220 *Int’l J. Hygiene & Env’t Health* 179 (2017).

categorization of this group of ortho-phthalate esters for the purposes of risk and/or hazard assessment would be consistent with the OECD guidelines, but it would not preclude the broader grouping of all ortho-phthalate esters as a category based on shared functional groups.

Accordingly, all nine phthalates that remain approved for food-contact use are “chemically . . . related” such that FDA must take into account their cumulative effects in evaluating the safety of the phthalates subject to food additive authorizations.¹⁰⁵ Under the statute, FDA need not identify a further pharmacological relationship among these substances to trigger the requirement for a cumulative effects analysis; to the contrary, such an analysis is required for substances that are “chemically *or* pharmacologically related.”¹⁰⁶ FDA’s apparent approach of requiring evidence of both a structural relationship and an established common health hazard before considering the cumulative effects of different substances in the diet is contrary to the OECD guidance and the plain language of the Food Act.

Request for Public Hearing:

Objectors request, and are entitled to, a public hearing on this objection.¹⁰⁷ The foregoing discussion provides “a detailed description and analysis of the factual information” supporting the objection and demonstrates that “[t]here is a genuine and substantial issue of fact

¹⁰⁵ 21 U.S.C. § 348(c)(5)(B).

¹⁰⁶ *Id.* (emphasis added).

¹⁰⁷ *Id.* § 348(f)(1) (directing that FDA “shall” hold a public hearing when requested “for the purpose of receiving evidence relevant and material to the issues raised by . . . objections”); 21 C.F.R. § 12.22(a)(4)–(5) (requiring objectors to specify the objections for which a hearing is requested and provide a detailed description and analysis of supporting information); *id.* § 12.24(b) (providing that a hearing request “will be granted” if the objection raises a genuine issue of material fact capable of resolution in the objector’s favor based on the information submitted).

for resolution at a hearing,”¹⁰⁸ namely, whether the nine phthalates that remain approved for food-contact use are “chemically or pharmacologically related” under section 409 of the Food Act such that FDA must consider their cumulative effects in assessing the safety of the approved food additives within this group. FDA did not address this issue in the Order, and it is an integral component of the statutorily required safety assessment. At a public hearing, Objectors would offer expert testimony regarding the structural relationship among the nine substances at issue and the approach or approaches FDA could take to appropriately account for the cumulative effects of these substances in evaluating the safety of the five phthalates that remain approved for use as food additives. Because Objectors have “identifie[d] . . . a material issue of fact” regarding the validity of FDA’s Order, they are “entitled to a public hearing.”¹⁰⁹

Objection 5-B: Contrary to FDA’s conclusion, seven of the nine approved phthalates are pharmacologically related substances based on their common effect of developmental toxicity, requiring FDA to consider their cumulative effects in evaluating safety (Objection to Order § II.A.3–5).

Second, even assuming for the sake of argument that the nine approved phthalates lacked sufficient structural similarity to constitute “chemically . . . related” substances within the meaning of section 409, FDA would still be required to consider the cumulative effects of seven of the nine phthalates that remain approved for food-contact use because they are pharmacologically related substances on account of their common effect of developmental toxicity.¹¹⁰ These substances are DEP, DAP, DCHP, DEHP, DIOP, DINP, and DIDP.

¹⁰⁸ 21 C.F.R. §§ 12.22(a)(5), 12.24(b)(1).

¹⁰⁹ *Marshall Minerals*, 661 F.2d at 425.

¹¹⁰ 21 U.S.C. § 348(c)(5)(B); *see also* 21 C.F.R. § 170.18(a) (dictating that “[f]ood additives that cause *similar or related* pharmacological effects will be regarded as a class” and assumed to have additive toxic effects absent contrary evidence) (emphasis added).

FDA defines developmental toxicity as the “adverse effects on the developing organism that result from exposure prior to conception, during the prenatal period, or postnatally up to the time of sexual maturity.”¹¹¹ FDA further defines the “major manifestations” of developmental toxicity to include mortality, dysmorphogenesis (structural abnormalities), alterations to growth, and/or functional impairment to the developing fetus.¹¹²

Exposure to each of these seven phthalates has been associated with various manifestations of developmental toxicity that are consistent with FDA’s definition. For example, prenatal exposures to DINP, DCHP, DIOP, and DEHP have been strongly linked to reduced fetal testis testosterone production during fetal development,¹¹³ a functional impairment that leads to irreversible structural abnormalities in the developing male reproductive tract, including reduced

¹¹¹ FDA, *Guidance for Industry, Reproductive and Developmental Toxicities—Integrating Study Results to Assess Concerns* 4 (2011), <https://www.fda.gov/media/72231/download>.

¹¹² *Id.*; FDA, *Redbook 2000: IV.C.9.b. Guidelines for Developmental Toxicity Studies* (2000), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivc9b-guidelines-developmental-toxicity-studies>.

¹¹³ CHAP Report 2, 8, 16; Nat’l Acad. of Scis. (2017); Zarean et al. (2019); Howdeshell et al. (2017); Grady & Sathyanarayana (2012); Wilson et al. (2008); Anne-Marie Saillenfait et al., *Adverse Effects of Diisooctyl Phthalate on the Male Rat Reproductive Development Following Prenatal Exposure*, 42 *Reprod. Toxicology* 192 (2013); Bethany R. Hannas et al., *Dose-Response Assessment of Fetal Testosterone Production and Gene Expression Levels in Rat Testes Following in Utero Exposure to Diethylhexyl Phthalate, Diisobutyl Phthalate, Diisoheptyl Phthalate, and Diisononyl Phthalate*, 123 *Toxicological Scis.* 206 (2011).

anogenital distance (“AGD”),¹¹⁴ hypospadias,¹¹⁵ and “phthalate syndrome” in animal studies.¹¹⁶ Gestational and early life exposures to DEHP and DEP have been linked to neurodevelopmental harm to the developing fetus, resulting in functional impairment later in life, including “lower IQ and problems with attention, hyperactivity, and poorer social communication.”¹¹⁷ Finally, prenatal exposures to DIDP and DAP have been associated with skeletal abnormalities¹¹⁸ and weight changes in exposed offspring; *in utero* DAP exposure was associated with reduced fetal body weight,¹¹⁹ and *in utero* DIDP exposure was linked to reduced pup survival and weight gain following birth.¹²⁰ These outcomes evidence developmental toxicity consistent with FDA’s

¹¹⁴ CHAP Report 15–16; Nat’l Acad. of Scis. (2017); Zarean et al. (2019); Grady & Sathyanarayana. (2012); Wilson et al. (2008); Suzuki et al. (2012); Swan (2008); Swan et al. (2015); Martino-Andrade et al. (2016); Consumer Prod. Safety Comm’n, *Toxicity Review of Dicyclohexyl phthalate (DCHP)* (2010).

¹¹⁵ 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. Ajay Thankamony et al., *Anogenital Distance and Penile Length in Infants with Hypospadias or Cryptorchidism: Comparison with Normative Data*, 122 *Env’t Health Persps.* 207 (2014); Michael H. Hsieh et al., *Associations Among Hypospadias, Cryptorchidism, Anogenital Distance, and Endocrine Disruption*, 9 *Current Urology Reports* 137 (2008). See also CHAP Report 15–16; Wilson et al. (2008); Grady & Sathyanarayana (2012).

¹¹⁶ CHAP Report 15–16; Wilson et al. (2008); Grady & Sathyanarayana (2012).

¹¹⁷ Stephanie M. Engel et al., *Neurotoxicity of Ortho-phthalates: Recommendations for Critical Policy Reforms to Protect Brain Development in Children*, 111 *Am. J. Pub. Health* 687, 690 (2021); see also Day et al. (2021); van den Dries et al. (2020); Engel et al. (2018); Daniel et al. (2020); Olesen et al. (2018); Kamai et al. (2021); Li et al. (2019).

¹¹⁸ Anne-Marie Saillenfait et al., *Evaluation of the Developmental Toxicity of Diallyl Phthalate Administered Orally to Rats*, 46 *Food & Chem. Toxicology* 2150 (2008); CHAP Report 102–103.

¹¹⁹ Saillenfait et al. (2008).

¹²⁰ CHAP Report 102–103.

definition and constitute “similar or related pharmacological effects” requiring treatment of DEP, DAP, DCHP, DEHP, DIOP, DINP, and DIDP as a class for purposes of FDA’s safety review.¹²¹

Request for Public Hearing:

Objectors request, and are entitled to, a public hearing on this objection.¹²² The foregoing discussion provides “a detailed description and analysis of the factual information” supporting the objection and demonstrates that “[t]here is a genuine and substantial issue of fact for resolution at a hearing,”¹²³ namely, whether seven of the phthalates that remain approved for food-contact use are “pharmacologically related” under section 409 of the Food Act and FDA’s regulations such that FDA must consider their cumulative effects in assessing the safety of the approved food additives within this group. FDA did not address this issue in the Order. And in the event that FDA rejects the preceding argument that all nine phthalates that remain approved for food-contact use are related, the pharmacological relatedness of the seven substances addressed in this objection is an integral component of FDA’s statutorily required safety assessment. At a public hearing, Objectors would offer expert testimony regarding the pharmacological relationship among the seven substances at issue and the approach or approaches FDA could take to appropriately account for the cumulative effects of these substances in evaluating the safety of the phthalates that remain approved for use as food

¹²¹ 21 C.F.R. § 170.18(a).

¹²² 21 U.S.C. § 348(f)(1) (directing that FDA “shall” hold a public hearing when requested “for the purpose of receiving evidence relevant and material to the issues raised by ... objections”); 21 C.F.R. § 12.22(a)(4)–(5) (requiring objectors to specify the objections for which a hearing is requested and provide a detailed description and analysis of supporting information); *id.* § 12.24(b) (providing that a hearing “will be granted” if the objection raises a genuine issue of material fact capable of resolution in the objector’s favor based on the information submitted).

¹²³ 21 C.F.R. §§ 12.22(a)(5), 12.24(b)(1).

additives. Because Objectors have “identifie[d] . . . a material issue of fact” regarding the validity of FDA’s Order, they are “entitled to a public hearing.”¹²⁴

Objection 5-C: Contrary to FDA’s conclusion, four of the nine approved phthalates are pharmacologically related based on their structural similarity and common antiandrogenic effect, requiring FDA to consider their cumulative effects in evaluating safety (Objection to Order § II.A).

Third, even assuming for the sake of argument that FDA could decline to proceed with an analysis considering the broader groupings discussed above, FDA would still be required at a minimum to consider the cumulative effects of DEHP, DINP, DCHP, and DIOP based on their structural similarity and common antiandrogenic effects associated with the mechanism of action of reduced fetal testosterone production. Indeed, this grouping (DEHP, DINP, DCHP, and DIOP) satisfies even FDA’s unlawfully restrictive interpretation of “related” substances as requiring a common (1) structural relationship, (2) toxicological endpoint, and (3) mechanism of action.

As discussed above, there is sufficient conclusive scientific evidence that DEHP, DINP, DCHP, and DIOP are 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).¹²⁵ These phthalates have been strongly shown to cause permanent structural abnormalities of the developing male reproductive tract, including reduced anogenital distance (“AGD”), hypospadias, and undescended testes.¹²⁶ In animal

¹²⁴ *Marshall Minerals*, 661 F.2d at 425.

¹²⁵ CHAP Report 2, 8, 16.

¹²⁶ CHAP Report 15–16; Nat’l Acad. of Scis. (2017); Zarean et al. (2019); Grady & Sathyanarayana. (2012); Wilson et al. (2008); Saillenfait et al. (2013); Suzuki et al. (2012); Swan. (2008); Swan et al. (2015); Martino-Andrade et al. (2016); Consumer Prod. Safety Comm’n (2010).

studies, this combination of developmental harms together with other abnormalities is referred to as “phthalate syndrome.”¹²⁷ In addition, it is well-established that these phthalates induce antiandrogenic effects via a common mechanism of action of reduced fetal testis testosterone production.¹²⁸

Further, as discussed *infra*, Objection 8, antiandrogenic phthalates have been shown to have cumulative effects in dose-response studies.¹²⁹ Indeed, the CHAP recommended a permanent ban on DEHP, DINP, and DCHP in children’s toys and childcare articles based on these substances’ ability to induce cumulative effects via anti-androgenicity. The CHAP further concluded that due to the likely antiandrogenic potential of DIOP, which was later empirically confirmed,¹³⁰ it should be subject to an interim ban.¹³¹

The chemical and pharmacological relationship among these four phthalates supports FDA’s application of the same acceptable exposure value for *at least* these four substances—specifically, the minimal risk level (MRL) for intermediate oral exposure established for DEHP by ATSDR in 2022.¹³² FDA’s regulations require this approach.¹³³ This methodology is also

¹²⁷ CHAP Report 15-16; Wilson et al. (2008); Grady & Sathyanarayana (2012).

¹²⁸ CHAP Report 2, 8, 16; Nat’l Acad. of Scis. (2017); Zarean et al. (2019); Howdeshell et al. (2017); Wilson et al. (2008); Grady & Sathyanarayana (2012); Saillenfait et al. (2013); Hannas et al. (2011).

¹²⁹ Howdeshell et al. (2017); Conley et al. (2021); Conley et al. (2018); Hannas et al. (2011); A. Kortenkamp & M. Faust, *Combined Exposures to Anti-androgenic Chemicals: Steps Towards Cumulative Risk Assessment*, 33 Int’l J. Andrology 463 (2010).

¹³⁰ Saillenfait et al. (2013).

¹³¹ CHAP Report 7–8.

¹³² DEHP Tox. Profile 14.

¹³³ 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).

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, including DEHP, DINP, DCHP, and DIOP, and in doing 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.¹³⁴ As explained below, adopting this approach in the context of the available biomonitoring data strongly supports the conclusion that food-additive uses of these and related substances are unsafe. Because FDA did not address the propriety of grouping, at a minimum, these established antiandrogens and applying the most up-to-date acceptable intake level developed by its peer agency, FDA must withdraw the Order and address these issues in response to these objections.

Request for Public Hearing:

Objectors request, and are entitled to, a public hearing on this objection.¹³⁵ The foregoing discussion provides “a detailed description and analysis of the factual information” supporting the objection and demonstrates that “[t]here is a genuine and substantial issue of fact for resolution at a hearing,”¹³⁶ namely, whether four of the phthalates that remain approved for food-contact use are “chemically or pharmacologically related” such that FDA must consider their cumulative effects and apply the MRL for DEHP to all food additives within this class.

¹³⁴ Nat'l Rsch. Council (2008) at 74-78.

¹³⁵ 21 U.S.C. § 348(f)(1) (directing that FDA “shall” hold a public hearing when requested “for the purpose of receiving evidence relevant and material to the issues raised by . . . objections”); 21 C.F.R. § 12.22(a)(4)–(5) (requiring objectors to specify the objections for which a hearing is requested and provide a detailed description and analysis of supporting information); *id.* § 12.24(b) (providing that a hearing “will be granted” if the objection raises a genuine issue of material fact capable of resolution in the objector’s favor based on the information submitted).

¹³⁶ 21 C.F.R. §§ 12.22(a)(5), 12.24(b)(1).

FDA did not address these issues in the Order. And in the event that FDA rejects the preceding arguments that a larger number of the phthalates that remain approved for food-contact use are related within the meaning of section 409, the relatedness of these four established antiandrogens is an integral component of FDA’s statutorily required safety assessment. At a public hearing, Objectors would offer expert testimony regarding the chemical and pharmacological relationship among DEHP, DINP, DCHP, and DIOP, the relevance of the DEHP MRL, and the approach or approaches FDA could take to appropriately account for the cumulative effects of these substances in evaluating the safety of the food-additive authorizations for phthalates that remain in effect. Because Objectors have “identifie[d] . . . a material issue of fact” regarding the validity of FDA’s Order, they are “entitled to a public hearing.”¹³⁷

Objection 6: FDA failed to consider the cumulative effects of all pharmacologically related phthalates in the diet, regardless of their regulatory status (Objection to Order § II.A).

FDA also acted contrary to the Food Act and its regulations by failing to account for the cumulative effects of dietary exposure to all chemically or pharmacologically related phthalates that available data show are present in the diet, including those for which FDA has recently revoked food-additive authorization in response to the industry abandonment petition. Specifically, data show that the phthalates BBP, DBP, DIBP, and DnHP are antiandrogenic¹³⁸ and are likely present in the diet,¹³⁹ meaning FDA should treat them as a class with DEHP,

¹³⁷ *Marshall Minerals*, 661 F.2d at 425.

¹³⁸ CHAP Report 2, 8, 15–16; Nat’l Acad. of Scis. (2017); Zarean et al. (2019); Howdeshell et al. (2017); Grady & Sathyanarayana (2012); Wilson et al. (2008); Hannas et al. (2011); Swan (2008).

¹³⁹ See Env’t Def. Fund, et al., *Objections to FDA’s Decision to Partially Grant the Flexible Vinyl Alliance Ortho-Phthalates Abandonment Food Additive Petition at Docket No. FDA-2018-F-3757* for “Indirect Food Additives: Adhesives and Components of Coatings; Paper and

DINP, DCHP, and DIOP.¹⁴⁰ Indeed, a recent study based on sampling conducted in 2017–2018 detected BBP, DBP, and DIBP in common menu items purchased from popular fast-food restaurants in San Antonio, Texas.¹⁴¹ Accordingly, whether these substances are present in food and drinks due to environmental contamination or some other reason, their cumulative effects must be taken into account when FDA evaluates whether DEHP, DINP, DCHP, and DIOP are safe for use as food additives.¹⁴² This is because the Food Act and FDA’s regulations require the agency to take into account “any chemically or pharmacologically related *substance or substances in [the] diet*,” not only substances authorized as food additives.¹⁴³

Request for Public Hearing:

Objectors request, and are entitled to, a public hearing on this objection.¹⁴⁴ The foregoing discussion and attached materials provide “a detailed description and analysis of the factual information” supporting the objection and demonstrate that “[t]here is a genuine and substantial issue of fact for resolution at a hearing,”¹⁴⁵ namely, whether FDA unlawfully failed to

Paperboard Components; Polymers; Adjuvants, Production Aids, and Sanitizers 3–6 (June 19, 2022) (“Abandonment Petition Objections”).

¹⁴⁰ 21 C.F.R. § 170.18; *see supra*, Objection 5-C.

¹⁴¹ Lariah Edwards et al., *Phthalate and Novel Plasticizer Concentrations in Food Items From U.S. Fast Food Chains: a Preliminary Analysis*, 32 J. Expo. Sci. & Env’t Epidemiology 366 (2022).

¹⁴² 21 U.S.C. § 348(c)(5)(B); 21 C.F.R. § 170.3(i)(2).

¹⁴³ 21 U.S.C. § 348(c)(5)(B) (emphasis added); 21 C.F.R. § 170.3(i)(2).

¹⁴⁴ 21 U.S.C. § 348(f)(1) (directing that FDA “shall” hold a public hearing when requested “for the purpose of receiving evidence relevant and material to the issues raised by . . . objections”); 21 C.F.R. § 12.22(a)(4)–(5) (requiring objectors to specify the objections for which a hearing is requested and provide a detailed description and analysis of supporting information); *id.* § 12.24(b) (providing that a hearing “will be granted” if the objection raises a genuine issue of material fact capable of resolution in the objector’s favor based on the information submitted).

¹⁴⁵ 21 C.F.R. §§ 12.22(a)(5), 12.24(b)(1).

consider the cumulative effects of phthalates in the diet that are “chemically or pharmacologically related” to phthalates that remain approved for food-additive use. FDA did not address this issue in the Order, and whether FDA accounted fully for the cumulative effects of all related substances in the diet is integral to its statutorily required safety assessment for the phthalates still approved as food additives. At a public hearing, Objectors would offer expert testimony regarding the presence of BBP, DBP, DIBP and DnHP in the diet; the chemical and pharmacological relationship among these substances and DEHP, DINP, DCHP, and DIOP; and the approach or approaches FDA could take to appropriately account for the cumulative effects of these substances. Because Objectors have “identifie[d] . . . a material issue of fact” regarding the validity of FDA’s Order, they are “entitled to a public hearing.”¹⁴⁶

Objection 7: FDA erred in requiring the petitioners to adduce exposure data and prove that current exposure to the substances at issue exceeds safe levels (Objection to Order § II.C–D).

As discussed *infra*, Objection 8, FDA erred in concluding that “the information currently available” does not provide “a basis to conclude that dietary exposure levels from approved ortho-phthalates exceed a safe level.”¹⁴⁷ At the outset, however, FDA erred insofar as it required the petitioners to prove that current dietary exposure to the approved phthalates exceeds safe levels.

While FDA is required to consider exposure to an existing food additive in evaluating its safety,¹⁴⁸ FDA’s regulation governing petitions to amend or repeal food additive regulations

¹⁴⁶ *Marshall Minerals*, 661 F.2d at 425.

¹⁴⁷ 87 Fed. Reg. at 31,075.

¹⁴⁸ *See* 21 U.S.C. § 348(c)(5)(A) (requiring FDA to consider, when evaluating an additive’s safety, “the probable consumption of the additive and of any substance formed in or on food because of the use of the additive”); 21 C.F.R. § 170.3(i)(1) (requiring FDA to consider this factor in determining safety).

does not require the petitioner to tender exposure data. To the contrary, the regulations state explicitly that such petitions may be based solely on “new data . . . as to the *toxicity* of the chemical,” “or” other “new information” showing “that experience with the existing regulation . . . may justify its amendment or repeal.”¹⁴⁹ The regulation states that this new data must be presented in a manner consistent with the formal requirements of 21 C.F.R. § 171.1, which governs food additive petitions generally.¹⁵⁰ To the extent that the substantive requirements of section 171.1 are applicable to petitions seeking revocation or repeal of food additive regulations, that provision also does not require exposure data. While section 171.1 requires “full reports of adequate tests reasonably applicable to show whether or not the food additive will be safe for its intended use,” it notes that the requisite reports “ordinarily should include detailed data derived from appropriate animal and other biological experiments”—*i.e.*, toxicological data.¹⁵¹ And to the extent that FDA interprets this provision to require exposure information, it must apply that requirement in a manner that comports with the burden of production the Food Act places on petitioners seeking revocation of food additive authorizations based on safety concerns, as discussed *supra*, Objection 1. For this reason, too, FDA cannot lawfully require such petitioners to tender data proving that existing exposure to the additives at issue and related substances is unsafe.

FDA’s 2016 decision granting a petition to revoke food additive authorizations for certain perfluorinated compounds reflects the proper role of exposure data when FDA evaluates petitions seeking revocation of existing food-additive authorizations, as well as the distinction

¹⁴⁹ 21 C.F.R. § 171.130(b) (emphasis added).

¹⁵⁰ *Id.*

¹⁵¹ *Id.* § 171.1(c)(E).

between the evidentiary showing that may be required to prove an additive is safe in the first instance versus the showing required to support revocation based on significant safety concerns. There, FDA affirmed that its “regulations specific to the administrative actions for food additives,” codified at 21 C.F.R. § 171.130(a), provide that

a petitioner may propose that [FDA] amend a food additive regulation if the petitioner can demonstrate that new data are available *as to the toxicity* of the food additive that may justify amendment of the food additive regulation In order for FDA to grant a petition that seeks an amendment to a food additive regulation *based upon new data concerning the toxicity of the food additive*, such data must be adequate for FDA to conclude that there is no longer a reasonable certainty of no harm for the intended use of the substance.¹⁵²

Further, FDA correctly concluded that “the available data demonstrating reproductive and developmental toxicity” for the class of chemicals to which the substances at issue belong, in combination with evidence of biopersistence, sufficiently undermined FDA’s finding that these substances are safe for food-contact use, notwithstanding that the “available migration information d[id] not allow a quantitative assessment of the safety of exposure to these [food-contact substances].”¹⁵³

In contrast, in the Order at issue here FDA faulted the petitioners for purportedly failing to provide a sufficiently precise quantification of dietary exposure to each of the approved phthalates.¹⁵⁴ For the reasons stated, that approach is contrary to the applicable statutory and regulatory provisions, the proper burden of proof, and FDA’s past practice. Moreover, as discussed in the following objection, the available exposure information—interpreted consistent

¹⁵² 81 Fed. Reg. at 6–7 (emphases added).

¹⁵³ *Id.* at 7.

¹⁵⁴ 87 Fed. Reg. at 31,075. Objectors specifically address FDA’s critique of the Petition’s reliance on biomonitoring data *infra*, Objection 8.

with the applicable burden of proof—is sufficient to raise significant questions concerning the safety of the approved food-additive uses of phthalates and justify revocation of those approvals.

Objection 8: Contrary to FDA’s conclusion, the available exposure information raises serious safety questions regarding the approved food-additive uses of phthalates (Objection to Order § II.C).

In addition to unlawfully requiring the petitioners to prove unsafe dietary exposure to each of the phthalates at issue, FDA’s assessment of the available exposure information is arbitrary and unsupported, necessitating withdrawal of the Order.

At the outset, FDA inexplicably ignored multiple authoritative analyses concluding that diet is a major, if not primary, source of exposure to the phthalates at issue. For example, Dr. Zota’s declaration explains 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.”¹⁵⁵ The CHAP’s conclusions are in accord. Based on its thorough analysis of both biomonitoring data and scenario-based exposure estimates, the CHAP 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”¹⁵⁶ The CHAP specifically concluded that diet is the primary exposure source for multiple phthalates that remain approved for food-contact use, as well as related antiandrogenic phthalates present in the diet, stating for example that:

- For DINP, which the CHAP identified as having “the maximum potential of exposure for infants, toddlers, and older children,” “exposures were primarily from food.”¹⁵⁷

¹⁵⁵ Zota Decl. ¶ 16.

¹⁵⁶ CHAP Report 3, 53; *see also id.* at 59.

¹⁵⁷ *Id.* at 53.

- “The highest estimated phthalate exposures to women were associated with DEP, DINP, DIDP, and DEHP. The main sources of phthalate exposure for pregnant women/women of reproductive age were from food, beverages, and drugs via direct ingestion.”¹⁵⁸
- “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.”¹⁵⁹
- “Toddlers were primarily exposed to DINP, DIDP, and DEHP Exposure to toddlers from DIDP, DIBP, and DINP was via food and beverages.”¹⁶⁰

Dr. Hauser, a member of the CHAP, reinforced the relevance of the CHAP Report to FDA’s safety analysis in his declaration, 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.¹⁶¹

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.¹⁶²

¹⁵⁸ *Id.* at 52.

¹⁵⁹ *Id.*

¹⁶⁰ *Id.*

¹⁶¹ Hauser Decl. ¶ 31.

¹⁶² *Id.* ¶ 32.

While FDA’s Order critiques certain data sources underlying the CHAP’s dietary exposure assessments, FDA does not dispute the CHAP’s conclusions regarding the primacy of diet as an exposure source for multiple approved phthalates and related substances. Further, as FDA acknowledged in the Order, 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.”¹⁶³ As a result, FDA’s critique of certain inputs to the CHAP’s dietary exposure estimates does not rationally justify its disregard of the CHAP’s conclusions regarding the primacy of dietary exposure to relevant phthalates.

ATSDR’s 2022 toxicological profile of DEHP further reinforces these conclusions. ATSDR affirmed 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.”¹⁶⁴ For infants and toddlers, ATSDR estimated that roughly half of oral exposure to DEHP comes from food.¹⁶⁵ At a minimum, FDA must qualitatively consider ATSDR’s conclusions concerning the role of diet in exposure to DEHP, along with the conclusions from the CHAP, Dr. Hauser, and Dr. Zota that diet is a critically important source of exposure to DEHP and other phthalates at issue in this proceeding.

One way FDA must do so is in interpreting the available human biomonitoring data on relevant phthalate metabolites. Despite acknowledging that “human biomonitoring studies can . . . be part of an appropriate postmarket approach to determine dietary exposure for a substance,” FDA irrationally dismissed the relevance of biomonitoring data from the CDC’s

¹⁶³ 87 Fed. Reg. at 31,072.

¹⁶⁴ DEHP Tox. Profile 2.

¹⁶⁵ *Id.*

National Health and Nutrition Examination Survey (“NHANES”), which tracks metabolites of DEHP, DCHP, DEP, and DINP, among other phthalates, in human urine.¹⁶⁶ FDA faulted the petitioners for purportedly “relying on biomonitoring data alone” without “differentiat[ing] the amount of exposure that results from the diet compared to environmental and other sources.”¹⁶⁷ This response fails, first, because the petitioners did not “rely[] on biomonitoring data alone” to support their safety concerns about the approved phthalates.¹⁶⁸ As explained above, evidence presented with the Petition as well as more recent analyses establish the primacy of diet as a source of exposure to multiple phthalates at issue in this proceeding, including the widely used substances DEHP and DINP. The NHANES biomonitoring data must be evaluated in light of this evidence that most human exposures to these phthalates come from the diet.

Further, FDA misconstrued its statutory obligations in asserting that it may ignore “overall exposure” to phthalates approved as food additives in evaluating their safety.¹⁶⁹ Dietary exposure to a food additive and related substances is one factor that FDA must consider in evaluating an additive’s safety, “among other relevant factors.”¹⁷⁰ To rationally assess whether a substance can be used safely as a food additive, FDA cannot make the erroneous assumption that diet is the only source of exposure to the substance where the available evidence demonstrates that people are also exposed from other sources. By evaluating the Petition as if diet were the sole source of exposure to the approved phthalates, FDA acted contrary to the Food Act and understated the harm that food-contact uses of these substances cause in the real world. FDA’s

¹⁶⁶ 87 Fed. Reg. at 31,074.

¹⁶⁷ *Id.* at 31,075.

¹⁶⁸ *Id.*

¹⁶⁹ *Id.*

¹⁷⁰ 21 U.S.C. § 348(c)(5).

approach is also inconsistent with the recommendations of the National Academy of Sciences, which has emphasized the “[n]eed for [e]valuation of [b]ackground [e]xposures” because even low dose exposures to a chemical “may have a relevant biologic effect” when combined with elevated background levels.¹⁷¹ And here, as discussed, the contribution of dietary sources to total exposure is by no means low. Other federal agencies frequently consider background exposures when evaluating and regulating harmful chemicals, even if a portion of those exposures fall beyond their respective regulatory jurisdiction.¹⁷² FDA’s refusal to do so here was legally, scientifically, and factually unsupported.

FDA must properly consider the available NHANES data, in conjunction with the other evidence characterizing the role of diet in exposure to relevant phthalates, in response to these objections. Such an analysis strongly indicates that current exposure to the phthalates that remain approved as food additives is not safe, taking into account cumulative exposure to related substances in the diet.¹⁷³ Using the latest NHANES biomonitoring data for urinary metabolite concentrations corresponding to ten ortho-phthalate parent compounds (DEHP, BBP, DBP, DIBP, DCHP, DEP, DIDP, DINP, DMP, and DnOP), we calculated estimated daily intake values

¹⁷¹ Nat’l Rsch. Council, *Science and Decisions: Advancing Risk Assessment* 130, 132. Washington, DC: The Nat’l Academies Press (2009).

¹⁷² For instance, when establishing drinking water standards for pollutants, EPA applies a “relative source contribution factor” to account for air, dermal, and other non-drinking water exposure sources. U.S. Gov’t Accountability Off., GAO-11-254, *Safe Drinking Water Act: EPA Should Improve Implementation of Requirements on Whether to Regulate Additional Contaminants* 13–14 (2011), <https://www.gao.gov/assets/gao-11-254.pdf>. Similarly, EPA considered non-pesticidal exposures to sulfuryl fluoride, such as toothpaste, when calculating and regulating the risks from pesticidal uses. *See Sulfuryl Fluoride; Proposed Order Granting Objections to Tolerances and Denying Request for a Stay*, 76 Fed. Reg. 3,422, 3,435–36, 3,440, 3,446–47 (Jan. 19, 2011).

¹⁷³ This includes antiandrogenic phthalates that are not approved for food-contact use but for which there is evidence of ongoing presence in the diet. *See Abandonment Petition Objections* 3–6.

(“EDIs” in $\mu\text{g}/\text{kg bw}/\text{d}$) for all parent compounds apart from DCHP, for which corresponding metabolites were only measured once through NHANES, and levels were below the limit of detection.¹⁷⁴ The EDIs calculated for DEHP alone (at the 90th and 95th percentiles) were above the $0.10 \mu\text{g}/\text{kg bw}/\text{d}$ intermediate MRL for oral exposure established by ATSDR in 2022, indicating unsafe exposure levels across the U.S. population.¹⁷⁵

Considering that metabolites for eight additional ortho-phthalate parent compounds were detected in the urine of people living in the United States, and that four of these compounds (in addition to DEHP) are considered antiandrogenic (BzBP, DBP, DIBP, and DINP), the findings support significant safety concerns when accounting for the additive exposure to these other structurally- and pharmacologically-related substances found in food.¹⁷⁶ In addition, recent dose-response studies examining cumulative phthalate exposures indicate that phthalates with similar anti-androgenic effects act cumulatively. EPA scientists have documented the magnitude of the cumulative effect of mixtures of anti-androgenic ortho-phthalates¹⁷⁷ and mixtures of anti-androgenic ortho-phthalates and other substances with similar anti-androgenic effects.¹⁷⁸ Collectively, these studies found that ortho-phthalates in mixtures with structurally and pharmacologically-related substances induced anti-androgenic effects at doses that were orders of magnitude lower than those associated with anti-androgenic effects of individual phthalates.

¹⁷⁴ See Memorandum from Maricel Maffini to Tom Neltner, Env’t Def. Fund, Re: Estimated Intake Calculation Using NHANES Ortho-Phthalates Biomonitoring Data (June 20, 2022).

¹⁷⁵ DEHP Tox. Profile. 14.

¹⁷⁶ 21 U.S.C. § 348(c)(5)(B); 21 C.F.R. § 170.18.

¹⁷⁷ Howdeshell et al. (2017).

¹⁷⁸ Conley et al. (2021); Conley et al. (2018).

These findings, which are in accord with earlier studies,¹⁷⁹ underscore the need for FDA to consider the available exposure information in response to these objections, and the importance of cumulative effects analysis to that assessment.

Request for Public Hearing:

Objectors request, and are entitled to, a public hearing on this objection.¹⁸⁰ The foregoing discussion provides “a detailed description and analysis of the factual information” supporting the objection and demonstrates that “[t]here is a genuine and substantial issue of fact for resolution at a hearing,”¹⁸¹ namely, whether the NHANES biomonitoring data and other available exposure information together establish significant questions concerning the safety of the food-additive uses of phthalates that remain approved. FDA did not address this issue in its Order; instead, it dismissed the NHANES biomonitoring data provided with the Petition based on arguments that are legally and factually unsupported, and it did not evaluate the most recent NHANES data in conjunction with ATSDR’s MRL for DEHP. At a public hearing, Objectors would offer expert testimony regarding the interpretation and significance of the NHANES data and other exposure information discussed here as well as the applicability and significance of the ATSDR MRL for DEHP. Because Objectors have “identifie[d] . . . a material issue of fact” regarding the validity of FDA’s Order, they are “entitled to a public hearing.”¹⁸²

¹⁷⁹ Kortenkamp and Faust (2010).

¹⁸⁰ 21 U.S.C. § 348(f)(1) (directing that FDA “shall” hold a public hearing when requested “for the purpose of receiving evidence relevant and material to the issues raised by . . . objections”); 21 C.F.R. § 12.22(a)(4)–(5) (requiring objectors to specify the objections for which a hearing is requested and provide a detailed description and analysis of supporting information); *id.* § 12.24(b) (providing that a hearing “will be granted” if the objection raises a genuine issue of material fact capable of resolution in the objector’s favor based on the information submitted).

¹⁸¹ 21 C.F.R. §§ 12.22(a)(5), 12.24(b)(1).

¹⁸² *Marshall Minerals*, 661 F.2d at 425.

IV. Conclusion

For the foregoing reasons, FDA must address these objections and public hearing requests “as soon as possible” by withdrawing the Order and convening the requested public hearing.¹⁸³

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¹⁸³ 21 C.F.R. § 12.24(a).

ⁱ 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).

ⁱⁱ 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).

ⁱⁱⁱ 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).

^{iv} 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 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).

^v 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).

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^{viii} 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).

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^x Adam et al. (2021); Capela et al. (2021).

^{xi} López-Rodríguez et al. (2021); Tassinari, et al. (2021).

^{xii} Yangyang Ding et al. (2021).

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- ^{xiii} Su et al. (2022).
- ^{xiv} Kim et al. (2021); Lv et al. (2022).
- ^{xv} Lv et al. (2022); Safarpour et al. (2021).
- ^{xvi} Lv et al. (2022); Jae Soon Kang et al. (2021).
- ^{xvii} Yuezhu Zhang et al., *MEHP Promotes Liver Fibrosis by Down-Regulating STAT5A in BRL-3A Hepatocytes*, 295 *Chemosphere*, art. no. 133925 (2022).
- ^{xviii} 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)
- ^{xix} 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).
- ^{xx} Yang et al. (2021).
- ^{xxi} 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. 112101 (2021).
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- ^{xxiv} Tsung-Hua Hsieh et al., *DEHP Mediates Drug Resistance by Directly Targeting AhR in Human Breast Cancer*, 145 *Biomedicine & Pharmacotherapy*, art. no. 112400 (2022).
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- ^{xxvi} 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).
- ^{xxvii} 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).

^{xxviii} 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).

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^{xxx} 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).

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^{xxxiii} 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); Kelly K. Ferguson et al., *Joint Impact of Phthalate Exposure and Stressful Life Events in Pregnancy on Preterm Birth*, 133 *Env't Int'l*, art. no. 105254 (2019).

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