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Comments of Consumers Union to the Food and Drug Administration on the Food Additive Petition Filed by the Breast Cancer Fund, Center for Environmental Health, Center for Food Safety, Center for Science in the Public Interest, Clean Water Action, Consumer Federation of America, Earthjustice, Environmental Defense Fund, Improving Kids' Environment, Learning Disabilities Association of America, and Natural Resources Defense Council
Docket No. FDA-2016-F-1253

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Summary

Consumers Union, the policy and mobilization arm of Consumer Reports,[1] welcomes the opportunity to comment on the Food Additive Petition filed by the Breast Cancer Fund, Center for Environmental Health, Center for Food Safety, Center for Science in the Public Interest, Clean Water Action, Consumer Federation of America, Earthjustice, Environmental Defense Fund, Improving Kids' Environment, Learning Disabilities Association of America, and Natural Resources Defense Council asking the Food and Drug Administration (FDA) to amend or revoke the approvals of 30 ortho-phthalates as indirect food additives in food contact articles. We strongly support this petition, and urge FDA to ban all 30 ortho-phthalates for use in production, storage, and packaging of food.

We agree with the petitioners that all 30 ortho-phthalates are chemically related and pharmacologically related and therefore they should be considered as a class, and further agree that the toxicity should be considered additive, e.g., FDA should consider the cumulative risks posed by exposure to multiple chemicals that are chemically or pharmacologically related based on the best available data. Data also show that virtually everyone in the United States is exposed to phthalates and the major route of exposure is through the diet. Of the 30 ortho-phthalates, 13 have been found to have adverse reproductive, developmental, and/or endocrine effects, while the other 17 have enough data gaps for reproductive, developmental, and/or endocrine effects such that their safety cannot adequately be determined. In addition, there is a lack of exposure

[1] Consumers Union is the policy and mobilization arm of Consumer Reports. Consumers Union is an expert, independent, nonprofit organization whose mission is to work for a fair, just, and safe marketplace for all consumers and to empower consumers to protect themselves. It conducts this work in the areas of food and product safety, telecommunications reform, health reform, financial reform, and other areas. Consumer Reports is the world's largest independent product-testing organization. Using more than 50 labs, auto test center, and survey research center, the nonprofit organization rates thousands of products and services annually. Founded in 1936, Consumer Reports has over 7 million subscribers to its magazine, website, and other publications.

information for 21 of the 30 ortho-phthalates. Given the lack of safety data for 17 of 30 ortho-phthalates, we agree with the petitioners that it should be presumed that all the ortho-phthalates have the hazard of the most toxic one, which is di-2-ethyhexyl phthalate (DEHP) and that an additional 10-fold safety factor, on top of the normal 100-fold safety factor (for interspecies differences and intraspecies differences), should be used when calculating and acceptable daily intake (ADI) to take into account risk to developing fetuses and children resulting in an ADI of 3 µg/kg bw/day. Thus, the ADI for the total amount of the 30 ortho-phthalates should be 3 µg/kg bw/day. We also agree with petitioners that the estimated daily intake (EDI) for all ortho-phthalates significantly exceeds the ADI, so that there is no longer a reasonable certainty of no harm for the food contact use of the 30 ortho-phthalates, which means that the indirect food additive uses of all of them should be revoked.

Our more detailed comments follow.

Ortho-phthalate exposure is ubiquitous and main route of exposure is dietary

Ortho-phthalates are chemically and pharmacologically related substances that are found in cellophane, paper, and plastics that come into contact with food. FDA has approved thirty ortho-phthalates for use as plasticizers, adhesives, coating agents, defoaming agents, lubricants, or slimicides, or in gasket closures, cellophane, or paper in food packaging materials and processing equipment.[2] Since ortho-phthalates are not part of the plastic structure, they can leach out of products and be inhaled, ingested or absorbed through the skin. According to the Centers for Disease Control and Prevention[3] (CDC) and the Consumer Product Safety Commission[4] (CPSC), human exposure to ortho-phthalates is virtually ubiquitous in the United States. The 2014 report of the Chronic Hazard Advisory Panel (CHAP) to the CPSC looked at ortho-phthalate levels in 261 food items and compared them to exposure from other sources, and concluded that food, beverages and drugs via direct ingestion constituted the highest phthalate exposure sources for the total population, and specifically for pregnant women and women of reproductive age.[5] Food and beverages were the main source for four particular phthalates: diisobutyl phthalate (DiBP), butylbenzyl phthalate (BBzP), di-n-octyl phthalate (DnOP), and DEHP.[6] Other studies have also found diet to be a major source of exposure to DEHP, diisonoyl phthalate (DiNP) and diisodecyl phthalate (DiDP).[7] [8] [9]

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[2] Federal Register Vol. 81, No. 98. May 20, 2016. Food and Drug Administration, 21 CFR Parts 175, 176, 177, and 178 [Docket No. FDA–2016–F–1253] Breast Cancer Fund, Center for Environmental Health, Center for Food Safety, Center for Science in the Public Interest, Clean Water Action, Consumer Federation of America, Earthjustice, Environmental Defense Fund, Improving Kids' Environment, Learning Disabilities Association of America, and Natural Resources Defense Council; Filing of Food Additive Petition. At: http://docs.regulations.justia.com/entries/2016-05-20/2016-11866.pdf

[3] CDC. 2015. *National Report on Human Exposure to Environmental Chemical Updated Tables*, February 2015. Centers for Disease Control and Prevention, Atlanta, GA. At: http://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf

[4] CPSC. 2014. *Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. U.S. Consumer Product Safety Commission, Bethesda, MD. At: http://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/The-Consumer-Product-Safety-Improvement-Act/Phthalates/Chronic-Hazard-Advisory-Panel-CHAP-on-Phthalates/

[5] *Id.*

[6] *Id.*

[7] Serrano SE, Braun J, Trasande L, Dills R, and S Sathyanarayana. 2014. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environmental Health*, 13(1): 43

Ortho-phthalates are chemically and pharmacologically related and have additive effects

Ortho-phthalates are chemically related

The Federal Food, Drug, and Cosmetic Act directs the FDA, in determining the safety of a food additive, to consider "the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in the diet."[10] Furthermore, the regulations on tolerances for related food additives state that "[f]ood additives that cause **similar or related pharmacological effects will be regarded as a class**, and in the absence of evidence to the contrary, as **having additive toxic effects** and will be considered as related food additives," **bold** added.[11]

Although the statute does not define "chemically-related" or "pharmacologically-related," the approach FDA took when it approved Food Additive Petition No. 4B4809 to remove the agency's approval of three perfluoroalkyl ethyl containing substances (PFCs)[12] was to use the Organization for Economic Co-operation and Development (OECD) *Guidance on Grouping of Chemicals*.[13] According to the OECD Guidance, there are five rationales for grouping chemicals into the same class.[14] Ortho-phthalates meet two of these five rationales: **Common functional group(s)** (e.g., aldehyde, epoxy, ester, specific metal ion); and the **likelihood of common precursors and/or breakdown products** via physical or biological processes that result in structurally similar chemicals (e.g., the "metabolic pathway approach" of examining related chemicals such as acid/ester/salt).

In terms of the common functional group, the ortho-phthalates are diesters of 1,2-dicarboxy-benzene with two alkyl groups (R and R') with a carbon chain of at least one carbon (see Figure 1), so they meet this rationale.

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http://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/The-Consumer-Product-Safety-Improvement-Act/Phthalates/Chronic-Hazard-Advisory-Panel-CHAP-on-Phthalates/

[8] Serrano SE, Karr CJ, Seixas NS, Nguyen RH, Barrett ES et al. 2014. *International Journal of Environmental Research and Public Health*, 11(6): 6193-6215. At: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4078574/pdf/ijerph-11-06193.pdf

[9] Schecter A, Lorber M, Guo Y, Wu Q, Yun SH et al. 2013. Phthalate Concentrations and Dietary Exposure from Food Purchased in New York State. *Environmental Health Perspectives*, 121(4): 473-494. At: http://ehp.niehs.nih.gov/wp-content/uploads/121/4/ehp.1206367.pdf

[10] 21 U.S.C. 348(c)(5)(B).

[11] 21 CFR 170.18(a).

[12] Federal Register Vol. 81, No. 1. January 4, 2016. Food and Drug Administration 21 CFR Part 176 [Docket No. FDA–2015–F–0714] Indirect Food Additives: Paper and Paperboard Components. Final Rule. At: https://www.gpo.gov/fdsys/pkg/FR-2016-01-04/pdf/2015-33026.pdf

[13] OECD. 2014. Guidance on Grouping of Chemicals, second edition. Organization for Economic Co-operation and Development. April 14, 2014. At: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en

[14] *Id*. at 12.

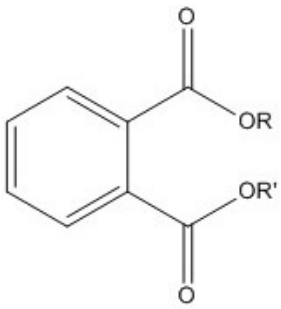

Figure 1. Chemical structure of ortho-phthalates[15]

In terms of the rationale of likelihood of common precursors and/or breakdown products, ortho-phthalates metabolism can be summarized as occurring in three steps: Step 1: Diesters are cleaved into monoesters; Step 2: Phase I oxication of the alkyl side-chain of the monoester and modification with functional groups (e.g., hydroxyl, keto or carboxy groups) or shortened by beta oxidation; and Step 3: hydrolytic monoesters and oxidized secondary metabolites can be conjugated with glucuronic acid.[16] Clearly, ortho-phthalates meet the rationale of likelihood of common precursors and/or breakdown products.

In conclusion, the 30 ortho-phthalates are a class of chemically-related substances.

Ortho-phthalates are pharmacologically related and linked to adverse health effects

Although "pharmacologically-related" is not defined in the statute, the approach FDA recently took when it revoked the approval of three PFCs was to state, for a defined class, "data for subsets of long-chain PFCs (demonstrating biopersistence and reproductive and developmental toxicity) are applicable to long-chain PFCs on a general basis and that this data raises significant questions as to the safety of the authorized uses of the three FCSs subject to the petition."[17] Thus, FDA concludes that chemically-related substances of a class are assumed to have similar pharamacological effects, e.g., biopersistence and reproductive and developmental toxicity.

As the CHAP noted in its 2014 report on phthalates and phthalate alternatives to the CPSC, when ortho-phthalates have been studied, similar or related pharmacological effects, such as reproductive, developmental and endocrine toxicity effects, have been identified affecting children's health.[18]

A number of studies have found that exposures to ortho-phthalates during pregnancy are associated with adverse neurodevelopment in children. Prenatal exposure to DEHP, as well as

[15] http://biomonitoring.ca.gov/sites/default/files/downloads/PotenDesig_orthoPhthalates_071615_0.pdf
[16] German Federal Environment Agency. 2011. Substance monograph: Phthalates—New and updated reference values for monoesters and oxidized metabolites in urine for adults and children. At: http://www.umweltbundesamt.de/sites/default/files/medien/pdfs/substance_monograph_on_phthalates.pdf
[17] P. 7 in Federal Register Vol. 81, No. 1. *Op cit.*
[18] CPSC. 2014. *Op cit.*

BBzP, has been associated with impaired cognitive development among girls.[19] Home dust levels of DEHP were found to be higher among children with developmental delays relative to typically developing children.[20] The review done by the CHAP concluded that poorer neurodevelopment test scores are associated with higher prenatal urinary concentrations of DEHP, DiBP, di-*n*-butyl phthalate (DnBP), and diethyl phthalate (DEP) and recommended reducing human exposure to these phthalates.[21] Another systematic review, published in 2015, concluded that prenatal exposure to BBzP, DEHP, DEP, DiBP and DnBP are associated with adverse cognitive and behavioral outcomes in children, including lower IQ and problems with attention, hyperactivity, and poorer social communication.[22]

In terms of reproductive and endocrine effects, many phthalates are anti-androgenic and maternal phthalate is linked to anti-androgenic effects in the fetus.[23] A 2014 review of human and animal experimental studies found that ortho-phthalates interfere with thyroid hormone during development leading to various neurotoxic effects.[24] The fact that many studies have found differential effects on neurobehavioral outcomes by sex in epidemiological studies could be due to disruption of testosterone production, which may explain the "phthalate syndrome" seen in experimental animals that includes malformations in the male epididymis, vas derens, seminal vesicles, prostate, as well as shortening of the anogenital distance (AGD).[25] Perinatal exposure to DEHP at a low dose has been shown to suppress aromatase activity in the hypothalamic/preoptic area in rat pups.[26]

Ortho-phthalates have additive effects

As noted previously, the regulations on tolerances for related food additives state that "[f]ood additives that cause **similar or related pharmacological effects will be regarded as a class**, and in the absence of evidence to the contrary, as **having additive toxic effects** and will be considered as related food additives," **bold** added.[27] The National Academy of Sciences report, "Phthalates and Cumulative Risk Assessment: The Task Ahead," published in 2008,

[19] Tellez-Tojo MM, Cantoral A, Cantonwine DE, Schnaas L, Peterson K et al. 2013. Prenatal urinary phthalate metabolite levels and neurodevelopment in children at two and three years of age. *Science of the Total Environment*, 461-462: 386-390. At: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3735862/pdf/nihms482462.pdf
[20] Philippat C, Bennett DH, Krakowiak P, Rose M, Hwang HM and I Hertz-Picciotto. 2015. Phthalate concentrations in house dust in relation to autism spectrum disorder and developmental delay in CHildhood Autism Risks from Genetics and the Environment (CHARGE) study. *Environmental Health*, 14: 56. At: https://ehjournal.biomedcentral.com/articles/10.1186/s12940-015-0024-9
[21] *Id.*
[22] Ejaredar M, Nyanza EC, Ten Eycke K and D Dewey. 2015. Phthalate exposure and children's neurodevelopment: A systematic review. *Environmental Research*, 142: 51-60.
[23] Swan SH. 2008. Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. *Environmental Research*, 108(2): 177-184. At: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2775531/pdf/nihms74898.pdf
[24] Miodovnik A, Edwards A, Bellinger DC and R Hauser. 2014. Developmental neurotoxicity of ortho-phthalates diesters: review of human and experimental evidence. *NeuroToxicology*, 41: 112-122.
[25] CPSC. 2014. *Op cit.*
[26] Holahan MR and CA Smith. 2015. Phthalates and neurotoxic effects on hippocampal network plasticity. *NeuroToxicology*, 48: 21-34.
[27] 21 CFR 170.18(a).

recommends that effects of ortho-phthalates should be considered additive.[28] Studies since then have found that mixtures of four[29] and five[30] ortho-phthalates have effects on testosterone production, gene expression and/or alterations of the reproductive tract. Other studies have found that some phthalates could have additive effects with cholesterol-lowering medication on fetal testicular development[31] as well as synergistic effect in a mixture with other anti-androgenic chemicals.[32]

Majority of ortho-phthalates lack safety studies and/or exposure studies

As the food additive petition points out, 17 of the 30 ortho-phthalates have not been studied for reproductive, developmental, or endocrine toxicity.[33] In addition, there are no exposure assessments for 21 of the 30 ortho-phthalates.[34] Back in 1973, when only 8 of the 24 then approved ortho-phthalates had chronic safety studies, FDA scientists proposed that, given the paucity of safety data on the large majority of approved ortho-phthalates, all ortho-phthalates should be presumed to have the hazards of the most toxic one, which they indicated was DEHP.[35] We agree with this approach.

Furthermore, to set an appropriate ADI, one must calculate a no-observed-adverse-effect level (NOAEL) and then multiply by an appropriate safety factor. We believe that a total safety factor of 1,000 should be used: 10 for inter-species variability X 10 for intra-species variability X 10 for adverse effects on fetuses and children, since ortho-phthalates clearly have been shown to have adverse effects on fetuses and children; the 2014 CHAP report also recommends a 1,000 safety factor. As noted in the 2014 CHAP report, the NOAEL for DEHP (which is the lowest NOAEL for 10 phthalates for which there are sufficient data to calculate a NOAEL) is 3-5 mg/kg bw/day, which gives an ADI of 3 μg/kg bw/day.

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[28] National Academy of Sciences, National Research Council Committee on the Health Risks of Phthalates, "Phthalates and Cumulative Risk Assessment: The Tasks Ahead," 2008.

[29] Hannes BR, Lambright CS, Furr J, Howdeshell KL, Wilson VS and LE Gray, Jr. 2011. Dose response assessment of fetal testosterone production and gene expression levels in rate testes following *in utero* exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate and diisononyl phthalate. *Toxicological Sciences*, 123: 206-216. At: http://toxsci.oxfordjournals.org/content/123/1/206.full.pdf

[30] Howdeshell KL, Wilson VS, Furr J, Lambright CS, Rider CV et al. 2008. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. *Toxicological Sciences*, 105: 153-165. At: http://toxsci.oxfordjournals.org/content/105/1/153.full.pdf

[31] Beverly BEJ, Lambright CS, Furr J, Sampson H, Wilson VS et al. 2014. Simvastatin and dipentyl phthalate lower *ex vivo* testicular testosterone production and exhibit additive effects on testicular testosterone and gene expression via distinct mechanistic pathways in the fetal rat. *Toxicological Sciences*, 141(2): 524-537. At: http://toxsci.oxfordjournals.org/content/141/2/524.full.pdf

[32] Christiansen S, Scholze M, Dalgaard M, Vinggaard AM, Axelstad M, Kortenkamp A and U Haas. 2009. Synergistic disruption of external male sex organ development by a mixture of four antiandrogens. *Environmental Health Perspectives*, 117(12): 1839-1846. At: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2799456/pdf/ehp-117-1839.pdf

[33] See Table 1, pp. 7, 8 in Federal Register Vol. 81, No. 98. May 20, 2016. *Op cit.*

[34] See Table 3, pp. 12, 13 in *Id.*

[35] Shibko SI and H Blumenthal. 1973. Toxicology of phthalic acid esters used in food packaging material. *Environmental Health Perspectives*, January, pp. 131-137. At: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1474904/pdf/envhper00500-0127.pdf

Given that toxicity of ortho-phthalates is considered to be additive and that the class of ortho-phthalates should be presumed to have the hazards of the most toxic one, this would mean that the ADI for the total ortho-phthalates should be 3 μg/kg bw/day, which is the same as that for DEHP, which is considered the most toxic phthalate in the class. As 21 CFR 170.18 clearly states, "[w]here food additives from two or more chemicals in the same class are present in or on a food, the tolerance for the total of such additives shall be the same for the additive having the lowest numerical tolerance in the class."

In sum, the ADI for the total ortho-phthalates in the class is 3 μg/kg bw/day.

Estimated Daily Intake (EDI) for ortho-phthalates significantly exceeds the ADI

According to the CHAP report[36] there are biomonitoring estimates for eight of the 30 ortho-phthalates: DEP, BBzP, DiBP, DnBP, DEHP, DnOP, DiNP, DiDP, and the mean women's exposure, based on biomonitoring, to these eight ortho-phthalates are 0.093, 0.16, 0.13, 0.078, 1.4, 0.13, 4.8, and 3.2 μg/kg bw/day, respectively. The total average daily exposure just for these eight ortho-phthalates is 10.0 μg/kg bw/day or over three times the ADI for the entire class of ortho-phthalates. Exposure to either DiNP (4.8 μg/kg bw/day) or DiDP (3.2 μg/kg bw/day) exceeds the total ADI for the ortho-phthalate class of 3 μg/kg bw/day. If we look at the CHAP women 95th percentile for exposure, the figures for the eight ortho-phthalates are 0.36, 0.25, 0.46, 0.23, 4.9, 0.36, 15.0 and 9.3, respectively. The total average daily exposure for the women 95th percentile fo9r 8 ortho-phthalates is 30.86 μg/kg bw/day or more than ten times higher than the ADI for the entire class. Clearly, the EDI for just the eight ortho-phthalates for which there are biomonitoring data significantly exceeds the ADI for the entire class, with the figure being more than 3 times higher for the average women's daily exposure or more than 10 times for the 95th percentile of women's daily exposure. This is without even factoring in the exposure to the 22 other ortho-phthalates.

In sum, the EDI for the eight ortho-phthalates for which there are biomonitoring data clearly and dramatically exceeds the ADI. Consequently, the FDA can no longer maintain that, for the class as a whole, there is a reasonable certainty of no harm. Therefore, FDA is obligated to withdraw approvals for the 30 ortho-phthalates in the class, and we strongly support the food additive petition referenced above.

Conclusion

All 30 ortho-phthalates presently approved as indirect food additives in food contact articles are chemically related and pharmacologically related and therefore they should be considered as a class. In addition, the toxicity of these ortho-phthalates should be considered to be additive. Data show that exposure to phthalates is ubiquitous in the U.S. and the major route of exposure is through the diet. Of the 30 orthophthalates, 13 have been found to have adverse reproductive, developmental, and/or endocrine effects, while the other 17 have enough data gaps for reproductive, developmental, and/or endocrine effects such that their safety cannot adequately be determined. In addition, there is a lack of exposure information for 21 of the 30 ortho-phthalates. Given the lack of safety data for 17 of 30 ortho-phthalates, we agree with the

[36] See Table E1-S1 Appendix E1-49 in CHAP 2014. *Op cit.*

petitioners that it should be presumed that all the ortho-phthalates have the hazard of the most toxic one, which is di-2-ethyhexyl phthalate (DEHP) and that an additional 10-fold safety factor, on top of the normal 100-fold safety factor (for interspecies differences and intraspecies differences), should be used when calculating and acceptable daily intake (ADI) to take into account risk to developing fetuses and children. The resulting ADI for DEHP is 3 μg/kg bw/day. Thus, the ADI for the total amount of the 30 ortho-phthalates should be 3 μg/kg bw/day. We also agree with petitioners that the estimated daily exposure (EDI) for all ortho-phthalates significantly exceeds the ADI, so that there is no longer a reasonable certainty of no harm for the food contact use of the 30 ortho-phthalates, which means that the indirect food additive uses of all of them should be revoked.

Thank you for your consideration of our comments.

Respectfully submitted,

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