Pew

July 26, 2026

Submitted via regulations.gov

Dr. Donald A. Prater, Acting Deputy Commissioner
U.S. Food and Drug Administration, Human Foods Program
5001 Campus Drive, HFS-009
College Park, MD 20740
Washington, DC 20460

RE: FDA Review of Select Ortho-Phthalate Food Contact Substances as Chemically or Pharmacologically Related (CPR) Substances (FDA-2026-N-5776)

Dear Deputy Commissioner Prater:

On behalf of The Pew Charitable Trusts (Pew), thank you for the opportunity to provide comments on the Food and Drug Administration (FDA)'s review of phthalates authorized as plasticizers in food contact substances (henceforth referred to as FDA's 'Phthalates CPR Review') to determine if they should be considered chemically or pharmacologically related (CPR) substances for use in a future cumulative risk assessment (CRA).[1]

Pew is a non-profit, nonpartisan research and policy organization dedicated to informing the public, improving public policy, and invigorating civic life with several initiatives related to the health and well-being of American communities, including Pew's safer chemicals project focused on reducing Americans' exposures to endocrine-disrupting chemicals (EDCs).

Overview

[1] U.S. Food and Drug Administration (FDA). "FDA Review of Select Ortho-Phthalate Food Contact Substances as Chemically or Pharmacologically Related (CPR) Substances," FDA-2026-N-5776-0001, 2026, https://www.regulations.gov/document/FDA-2026-N-5776-0001.

We appreciate FDA's attention to a CRA for the eight ortho-phthalates ((diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), di(2-ethylhexyl) phthalate (DEHP), dicyclohexyl phthalate (DCHP), butylphthalyl butyl glycolate (BPBG), diethyl phthalate (DEP), ethylphthalyl ethyl glycolate (EPEG), and diisooctyl phthalate (DIOP) that have authorized food contact uses as plasticizers in the United States. As noted in FDA's Phthalates CPR Review, while many phthalates (e.g., BBP, DBP, DMP) are no longer used as food contact substances in the U.S., the use of these eight ortho-phthalates continues.

In the case of phthalates specifically, FDA's use of a common mode of action (MOA) to determine the set of phthalates appropriate for a cumulative risk assessment has a basis given the scientific evidence that uniquely supports antiandrogenicity as a well-studied MOA relevant for the identified shared adverse outcome of concern (i.e., male reproductive toxicity). However, as discussed in FDA's Phthalates CPR Review, other authoritative scientific and regulatory bodies such as the National Research Council (NRC) of the National Academies [2] and the European Food Safety Authority (EFSA)[3] have recommended or already implemented best scientific practice for cumulative risk assessment: grouping chemicals based on a shared adverse health outcome in a particular organ or system rather than grouping by mode of action. The 2008 National Academies' National Research Council report on the health risks of phthalates noted that "…the committee finds that the focus in cumulative risk assessment should be on the health outcomes and not on the pathways that lead to them, whether defined as mechanisms of action or as modes of action," and "the committee recommends that a cumulative risk assessment be conducted for phthalates and that the assessment include other antiandrogens."[4]

Pew commends FDA on its acknowledgment throughout the Phthalates CPR Review that CRA grouping may be done at the health outcome or organ level and encourages the Agency to integrate that line of thinking more definitively to enhance transparency on its grouping approach as it conducts future scientific reviews that inform CRA approaches. Because there may be

[2] National Research Council, *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (Washington, DC: The National Academies Press, 2008), https://nap.nationalacademies.org/catalog/12528/phthalates-and-cumulative-risk-assessment-the-tasks-ahead.
[3] European Food Safety Authority (EFSA) Panel on Plant Protection Products and Residues,"Scientific Opinion on the Identification of Pesticides to Be Included in Cumulative Assessment Groups on the Basis of Their Toxicological Profile," EFSA Journal 11, no. 7 (2013): 3293, https://doi.org/10.2903/j.efsa.2013.3293.
[4] *Ibid.*

known health effects without a clear and defined MOA, Pew is concerned that FDA's focus on one specific MOA for the CRA would not only narrow groupings for phthalates and other CPR substances, but also miss opportunities to act to protect public health from potentially harmful exposures.

Pew encourages FDA to conduct a CRA, as required by the Federal Food Drug and Cosmetic Act (FDCA),[5] to support regulatory decisions that reflect real-world exposures and potential harm that Americans experience from this set of phthalates and toxicologically similar chemicals. Moving forward, Pew recommends that FDA update its CPR approach to reflect the best available science on systematic review, evidence integration, and assessment of cumulative effects to ensure that any future CRA that FDA undertakes fully reflects the potential for harm to human health.

FDA's Should Exercise Its Authority to Evaluate Cumulative Effects of CPR Substances

FDA has authority under the FDCA to regulate substances added (food additives) or otherwise coming into contact with food (food contact substances and related materials)[6] pursuant to its statutory mandate to ensure that the nation's food supply is safe.[7] FDA defines "safe" or "safety" as "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."[8] To support FDA in reaching a conclusion based on this definition, the law includes mandatory factors that FDA must consider in its assessment. These factors include:

- "the probable consumption of the additive and of any substance formed in or on food because of the use of the additive;"
- "the cumulative effect of such additive in the diet of humans or animals, taking into account any chemically or pharmacologically related substance or substances in such diet;" and

[5] Federal Food, Drug and Cosmetic Act (FDCA), Amendments of 1958, Public L. No. 85-929, 72 Stat. 1784 (1958) §348(c)(5)
[6] Federal Food, Drug and Cosmetic Act (FDCA), Food Additive Amendment of 1958, Public L. No. 85-929 §348
[7] Federal Food, Drug and Cosmetic Act (FDCA), Food Additive Amendment of 1958, Public L. No. 85-929 §393
[8] 21 CFR §170.3 (accessed June 23, 2026)

- "safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data."[9]

Pew commends FDA for taking an important step to fulfill its statutory obligation to incorporate in a safety assessment the "cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet."[10] We encourage the agency to follow its Phthalates CPR Review with a rigorous CRA of the phthalates identified as chemically or pharmacologically related to ensure associated regulatory decisions reflect real-world exposures and are health protective.

More broadly and beyond FDA's Phthalates CPR Review, because individuals are exposed to mixtures of substances in their diets and via additional exposure routes, FDA should continue to exercise its authority to evaluate exposures to different substances that have shared adverse health outcomes (i.e., toxicologically similar substances), for example similar effects on a specific endocrine organ or tissue, to ensure that the Agency's decisions on food additives and food contact substances adequately protect public health.

Cumulative Risk Assessment is Appropriate for Phthalates Based on Multiple Shared Adverse Health Outcomes

Phthalates are long recognized as endocrine disrupting chemicals (EDCs), particularly as antiandrogenic chemicals that interfere with fetal testosterone production.[11] Substantial animal and epidemiological evidence shows the relationships between phthalate exposures and various health impacts including "phthalate syndrome," a term used to describe a cluster of male reproductive development effects, primarily in male rats, following prenatal phthalate

[9] Federal Food, Drug and Cosmetic Act (FDCA), Food Additive Amendment of 1958, Public L. No. 85-929 §348(c)(5).
[10] 21 CFR §170.3(i)(2) (accessed June 23, 2026).
[11] Elizabeth G. Radke et al., "Phthalate Exposure and Male Reproductive Outcomes: A Systematic Review of the Human Epidemiological Evidence," *Environment International* 121 (2018): 764-93, https://www.sciencedirect.com/science/article/pii/S0160412018303404.

exposure.[12] Symptoms of phthalate syndrome include shortened anogenital distance (AGD), impaired testicular development and function, reduced sperm quality and motility, and infertility.[13]

Early animal studies from the 2000s show that perinatal exposure to DEHP and DINP in male rats altered sexual differentiation and induced reproductive malformations. DEHP exposure also shortened male AGD and reduced testis weight, effects often associated with impaired male fertility.[14] A study in rats also found that *in utero* exposure to DCHP affected fetal Leydig cells, which are responsible for testosterone production. The study also reported changes in steroidogenic gene expression, further supporting evidence that DCHP can disrupt pathways involved in male reproductive development.[15] A more recent study demonstrated the effects of phthalate mixtures in which exposure to DINP and DBP reduced testosterone levels and altered gene expression in fetal rat testis, both individually and additively when administered together.[16] Studies have also assessed the cumulative effects of co-exposing rats to phthalates and other

[12] Paul M. D. Foster, "Disruption of Reproductive Development in Male Rat Offspring Following in Utero Exposure to Phthalate Esters," International Journal of Andrology 29, no. 1 (2006): 140-47, https://doi.org/10.1111/j.1365-2605.2005.00563.x.
[13] National Research Council, *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (Washington, DC: The National Academies Press, 2008), https://nap.nationalacademies.org/catalog/12528/phthalates-and-cumulative-risk-assessment-the-tasks-ahead.
[14] L. Earl Gray, Jr. et al., "Perinatal Exposure to the Phthalates Dehp, Bbp, and Dinp, but Not Dep, Dmp, or Dotp, Alters Sexual Differentiation of the Male Rat," *Toxicological Sciences* 58, no. 2 (2000): 350-65, https://doi.org/10.1093/toxsci/58.2.350.
[15] Xiaoheng Li et al. "Effects of in Utero Exposure to Dicyclohexyl Phthalate on Rat Fetal Leydig Cells." In *International journal of environmental research and public health*, 246, 2016.
[16] L. Earl Gray et al., "Using Targeted Fetal Rat Testis Genomic and Endocrine Alterations to Predict the Effects of a Phthalate Mixture on the Male Reproductive Tract," *Current Research in Toxicology* 7 (2024): 100180, https://www.sciencedirect.com/science/article/pii/S2666027X24000331.

antiandrogens. Results indicate impaired male reproductive development, with certain combinations (e.g., some pesticides and phthalates) showing additive or synergistic effects.[17,18,19]

One of the earliest human epidemiological studies relevant to phthalate syndrome found that higher concentrations of phthalate metabolites in prenatal urine were associated with a shorter-than-expected anogenital index in male infants.[20] These findings were further supported in 2015 by The Infant Development and the Environment Study (TIDES) showing an inverse relationship between concentrations of DEHP metabolites in first-trimester maternal urine samples and AGD in male infants.[21] Given that humans are exposed to multiple phthalates, as evidenced by National Health and Nutrition Examination Survey (NHANES) biomonitoring data, researchers have developed potency-weighted cumulative exposure metrics based on antiandrogenicity to evaluate cumulative phthalate burden and disparities.[22]

Beyond male reproductive toxicity, recent epidemiological studies suggest an association between phthalate exposure and adverse pregnancy outcomes, including shorter gestational age

[17] Rider V.C., Wilson V.S., et. al, "Cumulative Effects of in Utero Administration of Mixtures of "Antiandrogens" on Male Rat Reproductive Development," *Toxicologic Pathology* 37, no. 1 (2009): https://doi.org/10.1177/0192623308329478.
[18] Justin M. Conley et al., "Mixed "Antiandrogenic" Chemicals at Low Individual Doses Produce Reproductive Tract Malformations in the Male Rat," *Toxicological Sciences* 164, no. 1 (2018): 166-78, https://doi.org/10.1093/toxsci/kfy069.
[19] Christiansen, Sofie, et al. "Synergistic Disruption of External Male Sex Organ Development by a Mixture of Four Antiandrogens." *Environmental Health Perspectives*, 117, no. 12 (2009): 1839–46. *JSTOR*, http://www.jstor.org/stable/30249862.
[20] S. H. Swan et al., "Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure," *Environmental Health Perspectives*, 113, no. 8: 1056-1061, https://doi.org/10.1289/ehp.8100.
[21] S. H. Swan et al., "First Trimester Phthalate Exposure and Anogenital Distance in Newborns," *Human Reproduction* 30, no. 4 (2015): 963-72, https://doi.org/10.1093/humrep/deu363.
[22] Julia R. Varshavsky, Ami R. Zota, and Tracey J. Woodruff, "A Novel Method for Calculating Potency-Weighted Cumulative Phthalates Exposure with Implications for Identifying Racial/Ethnic Disparities among U.S. Reproductive-Aged Women in Nhanes 2001–2012," *Environmental Science & Technology* 50, no. 19 (2016): 10616-24, https://doi.org/10.1021/acs.est.6b00522.

and increased risk of preterm birth.[23,24,25,26] A robust body of epidemiological literature as well as rodent toxicological studies also indicate that a number of phthalates, including DEHP, BBzP, DBP and DEP, may cause harm to the developing brain, increasing the risk of neurodevelopmental impacts on behavior and cognition from prenatal exposure.[27,28,29,30] Adverse impacts on the female reproductive system from exposure to certain phthalates have also been described in the scientific literature.[31]

Additionally, researchers have recommended class-based approaches for policies aimed at reducing human exposure to phthalates given their widespread exposures and multiple shared

[23] Elizabeth G. Radke et al., "Phthalate Exposure and Female Reproductive and Developmental Outcomes: A Systematic Review of the Human Epidemiological Evidence," *Environment International* 130 (2019): 104580, https://www.sciencedirect.com/science/article/pii/S0160412018316453.

[24] Barrett M. Welch et al., "Associations between Prenatal Urinary Biomarkers of Phthalate Exposure and Preterm Birth: A Pooled Study of 16 Us Cohorts," *JAMA Pediatrics* 176, no. 9 (2022): 895-905, https://doi.org/10.1001/jamapediatrics.2022.2252.

[25] Leonardo Trasande et al., "Prenatal Phthalate Exposure and Adverse Birth Outcomes in the USA: A Prospective Analysis of Births and Estimates of Attributable Burden and Costs," *The Lancet Planetary Health* 8, no. 2 (2024): e74-e85, https://doi.org/10.1016/S2542-5196(23)00270-X.

[26] Buckley JP, Pacyga DC, Xun X, et al., "Gestational Exposure to 10 Classes of Priority Chemicals and Birth Outcomes in the ECHO Cohort," *JAMA Netw Open*. 2026;9(6):e2618883, https://doi.org/10.1001/jamanetworkopen.2026.18883

[27]Qi Zhang et al, "The association between prenatal exposure to phthalates and cognition and neurobehavior of children-evidence from birth cohorts," *Neurotoxicology,* 2019 Jul;73:199-212, https://doi.org/10.1016/j.neuro.2019.04.007. Epub 2019 Apr 17. PMID: 31004626.

[28] Seonyoung Park et al."Prenatal phthalate exposure and emotional–behavioral problems in children aged 1.5 to 3 years from the PROTECT birth cohort," *J Expo Sci Environ Epidemiol* (2026). https://doi.org/10.1038/s41370-026-00931-1

[29] Jiwon Oh et al.m, "Early childhood exposures to phthalates in association with attention-deficit/hyperactivity disorder behaviors in middle childhood and adolescence in the ReCHARGE study," Int J Hyg Environ Health. 2024 Jun;259:114377, https://Doi.org/10.1016/j.ijheh.2024.114377..

[30] Suzanne Ducroq, Valerie Grange-Messent, and Sakina Mhayouty Kodja,"Exposure to Low Doses of Phthalates in Male Rodents: Effects on Reproductive and Cognitive Behaviors," *Neuroendocrinology* 2023;113(12):1215-1231, https://doi.org/10.1159/000534836.

[31] Hlisníková H, Petrovičová I, Kolena B, Šidlovská M, Sirotkin A. Effects and Mechanisms of Phthalates' Action on Reproductive Processes and Reproductive Health: A Literature Review. *Int J Environ Res Public Health.* 2020 Sep 18;17(18):6811, https://doi.org/10.3390/ijerph17186811.

health outcomes.[32,33] Taken together, the scientific literature underscores the importance of considering cumulative effects related to exposure to phthalates.

Recommendations on FDA's Approach to Select Phthalates Considered CPR to Inform Future Cumulative Risk Assessments

In its Phthalates CPR Review, FDA proposes an approach to determine which of eight ortho-phthalates that remain for use as food contact substances, can be considered chemically or pharmacologically related, or "CPR." FDA notes that chemical similarity involves both comparing chemical structures and physicochemical similarity. FDA interprets "pharmacologically related," a term typically applied to drugs, in this context to mean toxicologically similar, using the phrase "toxicodynamic" to describe "the adverse effects and undesirable interactions of a substance (i.e., a toxicant) on a biological system."[34] As FDA notes, guidance for conducting CRAs, as well as CRAs specifically for ortho-phthalates has been the subject of multiple other scientific and regulatory body publications including OECD,[35] Chronic

[32] Devon Payne-Sturges, Sulakkhana De Saram, and Deborah A. Cory-Slechta, "Cumulative Risk Evaluation of Phthalates Under TSCA," *Environ Sci Technol*," 2023 Apr 25;57(16):6403-6414, https://doi.org10.1021/acs.est.2c08364.
[33] Stephanie M. Engel et al. "Neurotoxicity of Ortho-Phthalates: Recommendations for Critical Policy Reforms to Protect Brain Development in Children," *American Journal of Public Health*, 111, 687_695, https://doi.org/10.2105/AJPH.2020.306014
[34] U.S. FDA. "FDA Review of Select Ortho-Phthalate Food Contact Substances as Chemically or Pharmacologically Related (CPR) Substances," FDA-2026-N-5776-0001, 2026, https://www.regulations.gov/document/FDA-2026-N-5776-0001.
[35] Organization for Economic Co-operation and Development (OECD), "Considerations for Assessing the Risks of Combined Exposure to Multiple Chemicals," OECD Publishing, 2018, https://doi.org/10.1787/ceca15a9-en.

Hazard Advisory Panel to the Consumer Product Safety Commission,[36] EPA,[37] NRC,[38] Health Canada,[39] and EFSA.[40,41]

Briefly, FDA's proposed approach to determining pharmacological relatedness involved a literature search to identify toxicological studies of the eight ortho-phthalates. Studies meeting specified inclusion criteria were reviewed to identify adverse effects observed across studies for each of the eight phthalates. Based on this analysis, FDA determined male reproductive toxicity to be a common endpoint across multiple phthalates and further examined the literature to identify if a shared mode of action, or MOA, could be assigned to the observed male reproductive effects. Considering previously published cumulative risk assessments of phthalates, and the agency's own determination of male reproductive toxicity as a common endpoint, FDA examined antiandrogenicity as a potential shared MOA across the eight phthalates.

To assess antiandrogenicity as a potential shared MOA, FDA created the following criteria:

1. "reported decreases in at least two androgen-responsive tissues in adult males (i.e., decrease in testes, epididymus, prostate, and/or seminal vesicle weight(s)), ideally reported in more than one study;" and

[36] U.S. Consumer Product Safety Commission (CPSC) Directorate for Health Sciences, "Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives," 2014, https://www.cpsc.gov/s3fs-public/CHAP-REPORT-FINAL%20(1).pdf.
[37] Draft Phthalate CRA Approach, EPA-HQ-OPPT-2022-0918-0009, Environmental Protection Agency, 2023, https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0918-0009.
[38] National Research Council, *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (Washington, DC: The National Academies Press, 2008), https://nap.nationalacademies.org/catalog/12528/phthalates-and-cumulative-risk-assessment-the-tasks-ahead.
[39] Health Canada Environment and Climate Change Canada, "Screening Assessment Phthalate Substance Grouping" Government of Canada 2020, https://www.canada.ca/content/dam/eccc/documents/pdf/pded/phthalates/FSAR-Phthalates-EN.pdf.
[40]EFSA, "Draft Update of the Risk Assessment of Di-Butylphthalate (Dbp), Butyl-Benzyl-Phthalate (Bbp), Bis(2-Ethylhexyl)Phthalate (Dehp), Di-Isononylphthalate (Dinp) and Di-Isodecylphthalate (Didp) for Use in Food Contact Materials " *EFSA Journal* (2019): 95, https://www.efsa.europa.eu/sites/default/files/consultation/consultation/Phthalates_in_plastic_FCM_draft_opinion_for_public_consultation.pdf.
[41] Elsa Nielsen et al., "Identification of Cumulative Assessment Groups of Pesticides," *EFSA Supporting Publications* 9, no. 4 (2012): 269E, https://doi.org/10.2903/sp.efsa.2012.EN-269.

2. "reported decrease in AGD following gestational phthalate exposure, or a positive Hershberger bioassay."[42]

Finally, FDA assessed chemical relatedness based on structural and physiochemical similarity and shared toxicokinetics.

FDA identified DEHP, DCHP, and DINP as sharing a common MOA, antiandrogenicity, and DIOP as physicochemically and toxicokinetically similar to these three antiandrogenic compounds. As such, FDA considers these four ortho-phthalates as relevant to group together for a cumulative risk assessment. While this resultant grouping is generally consistent—though limited to only phthalates with approved food contact uses—with grouping decisions in other scientific and regulatory CRAs of phthalates based on antiandrogenicity, Pew offers the following recommendations for how FDA can improve its approach and future cumulative risk assessments:

- FDA should follow best available practices in evidence mapping, systematic review, and evidence integration such as those developed by Integrated Risk Information System (IRIS) [43] of the EPA and the Navigation Guide.[44] For example, FDA's current approach offers no discussion of study quality or risk of bias assessments and narrowly searches only one database without a clear search strategy. Additionally, the criteria for study inclusion regarding number of animals and number of dose levels may ignore relevant studies for hazard identification and potential dose-response characterization that could be integrated into evidence evaluation using established methods.[45] FDA should consider epidemiological or mechanistic studies, both of which are critically important evidence

[42] U.S. FDA. "FDA Review of Select Ortho-Phthalate Food Contact Substances as Chemically or Pharmacologically Related (CPR) Substances," FDA-2026-N-5776-0001, 2026, http://www.regulations.gov/document/FDA-2026-N-5776-0001.
[43] U.S. EPA. "ORD Staff Handbook for Developing IRIS Assessments," EPA 600/R-22/268, 2022, https://iris.epa.gov/Document/&deid%3D356370#downloads.
[44] T. J. Woodruff and P. Sutton, "The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes," no. 1552-9924 (Electronic).
[45] *Ibid.*

streams for supporting hazard identification, potential shared adverse health outcomes, and dose-response assessment. [46]

- While FDA mentions throughout the Phthalates CPR Review that chemical grouping may be done at the health outcome or organ level, the agency pursues a narrow MOA approach, antiandrogenicity, for phthalate grouping after identifying a shared adverse health outcome, male reproductive effects. Pew recommends that FDA align its approach with the NRC recommendation to organize a cumulative risk assessment of phthalates around a shared health outcome.[47] EFSA models this approach in the grouping of pesticides for cumulative assessment (cumulative assessment groups), where the agency groups pesticides that have similar effects in a specific organ or system even if a MOA is unknown or uncertain.[48]

- Should FDA pursue grouping based on antiandrogenicity, it should update and provide robust rationale for the criteria used to assess antiandrogenicity. FDA should expand beyond changes in AGD following gestational exposure to include an additional, scientifically supported set of male reproductive effects associated with antiandrogenicity and other pathways such as reductions in fetal testosterone levels, nipple retention, hypospadias, sex organ weights, among others.[49,50] This approach also aligns with the recommendation to organize the CRA around shared health outcome (i.e., male reproductive effects) rather than MOA. It is unclear whether FDA's current criteria

[46] Arzuaga X, Smith et al. "Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments," *Environ Health Perspect.* 2019 Jun;127(6):65001, https://doi.org/10.1289/EHP5045.
[47] National Research Council, *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (Washington, DC: The National Academies Press, 2008), https://nap.nationalacademies.org/catalog/12528/phthalates-and-cumulative-risk-assessment-the-tasks-ahead.
[48] European Food Safety Authority (EFSA) Panel on Plant Protection Products and Residues, "Scientific Opinion on the Identification of Pesticides to Be Included in Cumulative Assessment Groups on the Basis of Their Toxicological Profile," *EFSA Journal* 11, no. 7 (2013): 3293, https://doi.org/10.2903/j.efsa.2013.3293.
[49] National Research Council, *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (Washington, DC: The National Academies Press, 2008), https://nap.nationalacademies.org/catalog/12528/phthalates-and-cumulative-risk-assessment-the-tasks-ahead.
[50] Kortenkamp, Andreas. "Which Chemicals Should Be Grouped Together for Mixture Risk Assessments of Male Reproductive Disorders?" *Molecular and Cellular Endocrinology*, 499, no. 110581 (2020):1-9, https://doi.org/10.1016/j.mce.2019.110581.

require that antiandrogenicity must occur following adult *and* gestational exposures. Pew recommends that the criteria allow for antiandrogenicity associated with either. FDA should support its final set of criteria for antiandrogenicity with strong justification, as the criteria currently appear arbitrary in the absence of such rationale.

- To the extent FDA pursues a CRA of phthalates based on male reproductive toxicity and antiandrogenicity, the agency should consider including other substances that cause similar male reproductive harm as phthalates, including but not limited to, those present in the diet, like other phthalates, Bisphenol A (BPA) and butylparaben as recommended by NRC and other peer-reviewed publications.[51,52]

- While the NRC offers male reproductive harm as one way to group phthalates, it also notes that other health effects may be important.[53] For instance, in FDA's review, the agency identified additional shared health impacts across multiple phthalates, including female reproductive toxicity.[54] FDA should expand its assessment to consider these other adverse effects and ensure that its CRA is based on the most sensitive endpoint, and protective of other effects.

Importantly, future classes of chemicals that will be the subject of CPR assessments may not have the benefit of decades of research identifying a common health outcome *and* a shared MOA (antiandrogenicity) as is the case for phthalates, though other health effects and MOAs also may occur. Using a rigidly defined MOA for CRA may not sufficiently protect public health.

Conclusion

[51] Kortenkamp, Andreas. "Which Chemicals Should Be Grouped Together for Mixture Risk Assessments of Male Reproductive Disorders?" *Molecular and Cellular Endocrinology*, 499, no. 110581 (2020):1-9, https://doi.org/10.1016/j.mce.2019.110581.
[52] National Research Council, *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (Washington, DC: The National Academies Press, 2008), https://nap.nationalacademies.org/catalog/12528/phthalates-and-cumulative-risk-assessment-the-tasks-ahead.
[53] *Ibid.*

Pew supports FDA's progress, represented in the Phthalates CPR Review, to group a subset of phthalates for a future CRA. We recommend that the agency conduct a CRA that takes a broader approach to determine 'chemically or pharmacologically related' substances, and at a minimum organize the current Phthalate CPR review around a common adverse effect rather than a shared MOA, antiandrogenicity. Moving forward, FDA has an important opportunity to apply best practices in chemical grouping, evidence mapping, systematic review, and evidence integration for CPR substances.

We appreciate the opportunity to comment. Please contact Kyle Kinner, Director, Government Relations (kkinner@pewtrusts.org) for additional information or questions.

Sincerely,

Jennifer McPartland
Director, Safer Chemicals
The Pew Charitable Trusts