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RE: EPA's Current Risk Evaluations of Phthalates Under TSCA

Dear Drs. Freedhoff and Orme-Zavaleta:

We are environmental health scientists and public health professionals concerned about the impacts of phthalate exposure on public health. Collectively, we have published extensively on the hazards and risks of phthalates to human health as well as on the practice of cumulative risk assessment—of relevance to the evaluation of health risks resulting from exposures to phthalates. We write to strongly recommend that the EPA Office of Pollution Prevention and Toxics (OPPT) take a cumulative risk approach to the seven ortho-phthalates currently undergoing risk evaluation under the Toxic Substances Control Act (TSCA)[1] and to work collaboratively and closely with the EPA Office of Research and Development (ORD) to implement such an approach.

We are also affiliated with Project TENDR, a collaboration of leading scientists, health professionals, and children's health and environmental advocates who have come together out of concern over the substantial evidence linking toxic chemicals to neurodevelopmental disorders, such as autism spectrum disorder, attention deficits, hyperactivity, intellectual disability, and

[1] The seven phthalates currently undergoing risk evaluation under TSCA are assigned as "Phthalates" under the "Chemical Group" column of the table provided by EPA here: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/chemicals-undergoing-risk-evaluation-under-tsca.

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learning disorders.[2] Recently, members of Project TENDR published an article documenting the scientific evidence of neurodevelopmental toxicity for several members of the phthalate chemical class—raising concern for the potential for *any* phthalate to induce neurodevelopmental harm—and recommending that assessments of phthalates be done as a class.[3] In evaluating the risks of phthalates undergoing review under TSCA we strongly urge the agency to quantitatively assess risks for neurodevelopmental toxicity for each phthalate and for combined exposures to them.

TSCA plainly authorizes, and potentially mandates, that the agency take a cumulative approach to evaluating the risks of the seven phthalates under review. The law requires that the agency use the "best available science" in developing chemical risk evaluations.[4] In 2008, the preeminent National Research Council published a report, *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (NRC 2008 Report), recommending that a cumulative risk assessment approach be taken to evaluate the health risks of phthalate exposures.[5] Since that time, a number of government authorities and researchers, including the U.S. Consumer Product Safety Commission's (CPSC) Chronic Hazard Advisory Panel (CHAP) (which included Dr. Russ Hauser, a co-signer of this letter and an author of the NRC 2008 report), have similarly concluded that phthalates should be evaluated using a cumulative risk assessment approach.[6] The recommendations in the CHAP's *Final Report on Phthalates and Phthalate Alternatives* were generally followed by the CPSC when it adopted a rule regulating eight phthalates in children's

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[2] Deborah Bennett et al., *Project TENDR: Targeting Environmental Neuro-Developmental Risks The TENDR Consensus Statement*, 124 Environ. Health Perspect. A118 (2016), https://doi.org/10.1289/EHP358.

[3] 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 (2021), https://doi.org/10.2105/AJPH.2020.306014.

[4] 15 U.S.C. § 2625(h).

[5] National Research Council. *Phthalates and Cumulative Risk Assessment: The Tasks Ahead.* Washington, DC: The National Academies Press (2008), https://doi.org/10.17226/12528.

[6] Chris Gennings et al., *Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives, Final Report* (2014), https://www.cpsc.gov/s3fs-public/CHAP-REPORT-FINAL%20(1).pdf; EFSA Panel on Food Contact Materials et al., *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*, 17 EFSA J. e05838 (2019), https://doi.org/10.2903/j.efsa.2019.5838.; Kembra L. Howdeshell et al., *Cumulative Effects of Antiandrogenic Chemical Mixtures and Their Relevance to Human Health Risk Assessment*, 220 Int. J. Hyg. Environ. Health 179 (2017), https://doi:10.1016/j.ijheh.2016.11.007.; Andreas Kortenkamp & Holger M. Koch, *Refined Reference Doses and New Procedures for Phthalate Mixture Risk Assessment Focused on Male Developmental Toxicity*, 224 Int. J. Hyg. Environ. Health 113428 (2020), https://doi.org/10.1016/j.ijheh.2019.113428.

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toys and child care articles.[7] Indeed, EPA itself recommended a cumulative approach to the assessment of phthalates in its 2012 Phthalates Action Plan, stating that these substances "should be assessed together to appropriately characterize exposures and avoid underestimating risk," and that "[t]he assessment of combined exposure is important to determine the potential impacts of these chemicals."[8] The consistent and long-standing recommendation to assess phthalates using a cumulative approach reflects the clear evidence that such an approach represents the "best available science."

The law also requires that EPA explicitly consider and protect "potentially exposed or susceptible subpopulations," groups that "due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly."[9] While large-scale biomonitoring studies from the CDC National Health and Nutrition Examination Survey (NHANES) have detected metabolites of multiple phthalates in the urine of most Americans,[10] certain populations experience greater exposure to phthalates than the general population. For example, Black and Latino communities are disproportionately exposed to phthalates,[11] and studies examining phthalate exposures in women of reproductive age found higher concentrations of phthalate metabolites in Black and Latina women.[12] Available biomonitoring data provides ample evidence that exposures to multiple phthalates also occur across susceptible subpopulations like developing fetuses and children. Data from the State of

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[7] *See* Prohibition of Children's Toys and Child Care Articles Containing Specified Phthalates, 82 Fed. Reg. 49,938 (Oct. 27, 2017).

[8] EPA, *Phthalates Action Plan*, at 10 (Mar. 14, 2012), https://www.epa.gov/sites/production/files/2015-09/documents/phthalates_actionplan_revised_2012-03-14.pdf.

[9] 15 U.S.C. § 2602(12).

[10] CDC, *Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables,* at 321– 361 (Mar. 2021), https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume2_Mar2021-508.pdf.

[10] Daniel Ruiz et al., *Disparities in Environmental Exposures to Endocrine-Disrupting Chemicals and Diabetes Risk in Vulnerable Populations*, 41 Diabetes Care 193 (2018), https://doi.org/10.2337/dc16-2765.

[11] *Id.*

[12] Tamarra M. James-Todd et al., *Racial and Ethnic Variations in Phthalate Metabolite Concentration Changes Across Full-Term Pregnancies*, 27 J. Expo. Sci. Environ. Epidemiol. 160 (2017), https://doi.org/10.1038/jes.2016.2; Julia R. Varshavsky et al., *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*, 50 Environ. Sci. Technol. 10616 (2016), https://doi.org/10.1021/acs.est.6b00522; Francesca Branch et al., *Vaginal Douching and Racial/Ethnic Disparities in Phthalates Exposures Among Reproductive-Aged Women: National Health and Nutrition Examination Survey 2001–2004*, 14 Environ. Health 57 (2015), https://doi.org/10.1186/s12940-015-0043-6.

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California's biomonitoring program[13] also reveal extensive exposure to phthalates across the population, including among pregnant women and children.[14] Other research reveals the presence of phthalate metabolites in amniotic fluid[15] and evidence that phthalates can cross the human placental barrier.[16] And, given that adverse health outcomes are frequently shared across various phthalates—as is true for the seven phthalates undergoing risk evaluation—exposure to one phthalate can be expected to increase an individual's susceptibility to health effects resulting from exposure to other phthalates. Therefore, the agency must account for increased susceptibility resulting from phthalate co-exposures when adopting a cumulative risk assessment approach.

We similarly recommend that the agency consider and integrate information about co-exposures to other chemicals and non-chemical stressors that present similar hazards when evaluating the risks of the phthalates currently under review. For example, co-exposure to other neurodevelopmental[17] and reproductive toxicants may have an important influence on risks posed by phthalates. If the agency does not account for these co-exposures, EPA could be seriously underestimating risks resulting from exposure to the phthalates under review, and consequently not protecting human health, including that of potentially exposed or susceptible subpopulations. To the extent that formal integration and quantification of these relevant co-exposures presents challenges in evaluating risks to the phthalates, EPA should still account for them through other means, such as applying an additional uncertainty factor during risk characterization or using a Relative Source Contribution (RSC) approach as is done by the Office of Water under the Safe Drinking Water Act.[18]

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[13] *See* Cal. Dep't of Pub. Health & Cal. Dep't of Toxic Substances Control, *Results for Phthalates*, Biomonitoring Cal. (last updated Mar. 1, 2018), https://biomonitoring.ca.gov/results/chemical/284.

[14] Five of the seven phthalates undergoing review under TSCA are represented across various Biomonitoring California efforts: DEHP, DIBP, BBP, DBP, and DCHP. Except for DCHP, where levels fell below the limit of detection, metabolites for these phthalates were detected through these efforts.

[15] M.J. Silva et al., *Detection of Phthalate Metabolites in Human Amniotic Fluid*, 72 Bull Environ. Contam. Toxicol. 1226 (2004), https://doi.org/10.1007/s00128-004-0374-4; Ioanna Katsikantami et al., *Phthalate Metabolites Concentrations in Amniotic Fluid and Maternal Urine: Cumulative Exposure and Risk Assessment*, 7 Toxicol. Rep. 529 (2020), https://doi.org/10.1016/j.toxrep.2020.04.008.

[16] Lu-Xi Li et al., *Exposure Levels of Environmental Endocrine Disruptors in Mother-Newborn Pairs in China and Their Placental Transfer Characteristics*, 8 PLoS ONE e62526 (2013), https://doi.org/10.1371/journal.pone.0062526.

[17] The NRC 2008 Report more broadly suggested evaluating combined exposures to substances that contribute to the same or similar effects, citing as another example cognitive deficits linked to exposures to lead, mercury, and polychlorinated biphenyls.

[18] *How EPA Regulates Drinking Water Contaminants*, EPA (last updated Jan. 27, 2020), https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants.

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Additionally, in assessing the seven phthalates under review, we strongly recommend that EPA take into consideration background exposures from their so-called "non-TSCA uses." EPA previously stated that "[t]he potential risks of non-TSCA uses may help inform the Agency's risk determination for the exposures from uses that are covered under TSCA (e.g., as background exposures that would be accounted for . . . .)."[19] Given the extensive exposure of children and adults to phthalates from non-TSCA uses (e.g., food and food packaging, personal care products, and medical devices),[20] failure to consider exposures from those uses would be arbitrary, capricious, inconsistent with the "best available science," and would underestimate actual risks. While EPA may not be able to directly regulate non-TSCA uses, EPA cannot adequately evaluate the conditions of use that are subject to TSCA regulation, or control their unreasonable risks, if the agency ignores relevant background sources of exposure.

As recommended by the NRC and others, we strongly urge the agency to base its evaluation of cumulative risks on common adverse outcomes rather than adopting the unduly and unscientifically narrow approach used by EPA's Office of Pesticide Programs under the Federal Food, Drug, and Cosmetic Act, which limits assessments to chemicals that share a specific mechanism of toxicity.[21] TSCA does not contain any such limitation, and ignoring the cumulative effects of chemicals that do not share a common mechanism of toxicity is neither supported by the science for conducting cumulative risk assessments nor protective of public health. The authors of the NRC 2008 Report noted:

> [t]he current practice of restricting cumulative risk assessment to structurally or mechanistically related chemicals ignores the important fact that different

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[19] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, 82 Fed. Reg. 33,726, 33,735 (July 20, 2017).

[20] KG Harley et al., *Reducing Phthalate, Paraben, and Phenol Exposure from Personal Care Products in Adolescent Girls: Findings from the HERMOSA Intervention Study*. Environ Health Perspect., 124(10):1600-1607 (2016), https://doi.org/10.1289/ehp.1510514; Stephanie C. Hammel et al., *Children's Exposure to Phthalates and Non-Phthalate Plasticizers in the Home: The TESIE Study*, 132 Environ. Int. 105061 (2019), https://doi.org/10.1016/j.envint.2019.105061; Joe M. Braun et al., *Personal Care Product Use and Urinary Phthalate Metabolite and Paraben Concentrations During Pregnancy Among Women from a Fertility Clinic*, 24 J. Expo. Sci. Environ. Epidemiol. 459 (2014), https://doi.org/10.1038/jes.2013.69; Ruthann A. Rudel et al., *Food Packaging and Bisphenol A and Bis(2-Ethyhexyl) Phthalate Exposure: Findings from a Dietary Intervention*, 119 Environ. Health Perspect. 914 (2011), https://doi.org/10.1289/ehp.1003170.

[21] *Cumulative Assessment of Risk from Pesticides*, EPA (last updated Feb. 19, 2021), https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides; EFSA Panel on Food Contact Materials et al., *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*, 17 EFSA J. e05838 (2019), https://doi.org/10.2903/j.efsa.2019.5838; Andreas Kortenkamp, *Which Chemicals Should Be Grouped Together for Mixture Risk Assessments of Male Reproductive Disorders?*, 499 Mol. Cell Endocrinol. 110581 (2020), https://doi.org/10.1016/j.mce.2019.110581.

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> chemical exposures may result in the same common adverse outcomes. Focusing primarily on physiologic consequences rather than structural or mechanistic similarity is a critical and achievable step in cumulative risk assessment and is more directly relevant to relating chemical exposures to human diseases and disorders.[22]

Finally, EPA must also ensure that the most sensitive subpopulation is evaluated against the most sensitive endpoint when calculating the risks of phthalates under review, in order to meet requirements under TSCA to use the best available science and protect potentially exposed or susceptible subpopulations.

Taking a cumulative approach to the evaluation of risks of the seven phthalates undergoing TSCA review provides a key opportunity for EPA to demonstrate its commitment to basing decisions on the best available science. We strongly recommend that OPPT work with ORD to develop and implement a cumulative risk approach to the phthalates under review. We thank the agency for considering the recommendations made in this letter and will be reaching out to both of your offices to discuss them further.

Sincerely,

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[22] NRC 2008 Report at 10.

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