University of California
San Francisco
UCSF
Obstetrics, Gynecology
& Reproductive Sciences

Program on Reproductive Health and the Environment
Department of OB/GYN & RS
Mailstop 0132
550 16th Street, 7th Floor
San Francisco, CA 94143
prhe@obgyn.ucsf.edu

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Comments on DIDP and DINP: Manufacturer Requests for Risk Evaluation Under the Toxic Substances Control Act (TSCA)

Submitted online via Regulations.gov to dockets EPA-HQ-OPPT-2018-0435 and EPA-HQ-OPPT-2018-0436

The following comments are being submitted by the University of California, San Francisco (UCSF) Program on Reproductive Health and the Environment (PRHE). We have no direct or indirect financial or fiduciary interest in the manufacture or sale of any chemical or product that is the subject of these comments.

We appreciate the opportunity to provide written comments on the manufacturer requests for EPA to conduct risk evaluations on the phthalates diisodecyl phthalate (DIDP) and diisononyl phthalate (DINP), pursuant to the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act.[1,2]

Phthalates are chemicals widely found in food, everyday products, and air and dust in the indoor environment. The U.S. population, including pregnant women and children, is "co-exposed to many phthalates simultaneously," and these phthalates can "cause a wide range of toxicities."[3] TSCA mandates that EPA use the "best available science"[4] to inform its decisions on chemicals, and that EPA apply the same standards to manufacturer-requested risk evaluations as required for all other evaluations.[5]

[1] Exxon Mobil Chemical Company and American Chemistry Council High Phthalates Panel (2019) Manufacturer Request for Risk Evaluation of Diisodecyl Phthalate (DIDP). Available: https://www.epa.gov/sites/production/files/2019-06/documents/didp_main_submission_epa_05_23_19.pdf

[2] Exxon Mobil Chemical Company and American Chemistry Council High Phthalates Panel (2019) Manufacturer Request for Risk Evaluation of Diisononyl Phthalate (DINP). Available: https://www.epa.gov/sites/production/files/2019-06/documents/dinp_main_submission_epa_05_23_19.pdf

[3] Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Retrieved from U.S. Consumer Product Safety Commission website: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf pg. 1; pg. 3

[4] 15 USC §2625(h)

[5] 15 USC §2605(b)(4)(C) and 15 USC §2605(b)(4)(E)(ii) "…the Administrator shall not expedite or otherwise provide special treatment to such risk evaluations."

EPA recently proposed to list five phthalates as high-priority substances under TSCA and if these listings are finalized, the five phthalates would be subject to TSCA risk evaluations.[6] Should EPA decide to proceed with the manufacturer-requested risk evaluations for DIDP and DINP, EPA should treat all seven phthalates as a "category" under TSCA and conduct a single cumulative risk evaluation for this group of chemicals. EPA must apply the best available science, and robust evidence indicates that a cumulative assessment is required.

More than a decade ago, the National Research Council (NRC) reviewed the evidence on phthalates and found that because people are exposed to multiple phthalates at the same time, and phthalates contribute to one or more common adverse health outcomes, "a cumulative risk assessment should be conducted that evaluates the combined effects of exposure."[7] The NRC further found that "Cumulative risk assessment based on common adverse outcomes is a feasible and physiologically relevant approach to the evaluation of the multiplicity of human exposures and directly reflects EPA's mission to protect human health."[8]

TSCA explicitly envisions that EPA will conduct risk evaluations on categories of chemicals, as the statute states: "Any action authorized or required to be taken by the Administrator under any provision of this chapter with respect to a chemical substance or mixture may be taken by the Administrator in accordance with that provision with respect to a category of chemical substances or mixtures."[9] Further, the statute defines 'category of chemical substances' as: "a group of chemical substances the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or into the environment, or the members of which are in some other way suitable for classification as such for purposes of this chapter…"[10]

The evidence indicates a cumulative evaluation of phthalates as a category is required to appropriately assess risks, and the law supports such an approach.

Our comments address the following main issues:

1. **Should EPA proceed with the risk evaluation of DIDP and DINP, it should conduct a cumulative assessment together with the five phthalates on its high priority list and assess all common adverse health outcomes for the seven phthalates.**
2. **Should EPA proceed with the risk evaluation of DIDP and DINP, it should include all intended, known or reasonably foreseen conditions of use and the associated exposures. Failure to do so will underestimate risk, especially to potentially exposed or susceptible sub-populations.**
3. **To make a risk determination, EPA must have adequate data. EPA needs to determine the completeness of the database on the phthalates for assessment and exercise its full authorities to fill data gaps under TSCA sections 4 and 8 and make information public under section 14.**
4. **The reference lists presented in the manufacturer requests do not include all relevant information.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

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[6] 84 FR 44300. The five are butyl benzyl phthalate (BBP), dibutyl phthalate (DBP), dicyclohexyl phthalate (DCHP), di-ethylhexyl phthalate (DEHP), and di-isobutyl phthalate (DIBP).

[7] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Retrieved from http://site.ebrary.com/id/10274055

[8] Id. pg. 11-12

[9] 15 USC §2625(c)

[10] Id.

Sincerely,

Veena Singla, PhD
Associate Director of Science and Policy
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Nicholas Chartres, PhD
Associate Research Scientist
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Swati Rayasam, MSc
Science Associate
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Tracey Woodruff, PhD, MPH
Professor and Director
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

DETAILED COMMENTS

1. **Should EPA proceed with the risk evaluation of DIDP and DINP, it should conduct a cumulative assessment together with the five phthalates on its high priority list and assess all common adverse health outcomes for the seven phthalates.**

The NRC found that because people are exposed simultaneously to multiple phthalates, and phthalates can contribute to common adverse health outcomes, the scientifically appropriate approach is a cumulative risk assessment.[11] Should EPA decide to proceed with risk evaluation of DIDP and DINP, it should conduct a cumulative assessment of these together with the five phthalates it has proposed to designate as high priority: DIBP, DCHP, DEHP, BBP, and DBP.[12]

Previous cumulative assessments of phthalates by the NRC and the Consumer Product Safety Commission Chronic Hazard Advisory Panel (CHAP) focused on one particular health outcome- effects on the development of the male reproductive system due to anti-androgenicity- but the NRC cautioned that while this is the most extensively studied endpoint, "The committee's suggestions should not be interpreted to

[11] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Retrieved from http://site.ebrary.com/id/10274055

[12] 84 FR 44300

imply that other health effects are not important or that nonchemical stressors should be ignored."[13] Likewise, the CHAP acknowledged concerns for other health effects, including cancer and neurodevelopmental toxicity, but did not quantify cumulative risks for these endpoints due to lack of data.[14]

Therefore, the NRC and CHAP risk findings on particular phthalates are not comprehensive; no cumulative assessment was conducted for other relevant health endpoints. In particular, since the NRC and CHAP reports, additional evidence on phthalates' neurodevelopmental toxicity has emerged indicating that prenatal and early life exposures are associated with a variety of adverse outcomes including lower IQ and problems with attention, hyperactivity and poorer social communication (see comments from Project TENDR to the European Food Safety Authority attached as Appendix A for a brief review of these data).

Regarding what health endpoints should be included in a cumulative assessment, the NRC committee found "…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. Multiple pathways can lead to a common outcome, and a focus on only a specific pathway can lead to too narrow an approach in conducting a cumulative risk assessment. Accordingly, the chemicals that should be considered for cumulative risk assessment should be ones that cause the same health outcomes or the same types of health outcomes…"[15] This indicates that the focus should not be limited to phthalates with an anti-androgenic mechanism of action, and instead any phthalates that can contribute to an adverse health outcome (such as neurodevelopmental toxicity) should be grouped together.

To identify the relevant health endpoints for cumulative assessment, EPA should conduct a systematic literature review using an established, peer-reviewed method such as the National Toxicology Program's OHAT or the Navigation Guide. [16,17] The TSCA systematic review method should not be used, as it is not peer-reviewed or validated, and EPA's Science Advisory Committee on Chemicals has raised serious concerns about it.[18]

At a minimum the health endpoints in the cumulative evaluation should include those already identified by the NRC and the CHAP, as well as those raising concern in recent studies:

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[13] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Retrieved from http://site.ebrary.com/id/10274055. Pg. 4

[14] Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Retrieved from U.S. Consumer Product Safety Commission website: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf pg. 13; pg. 29-33

[15] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Retrieved from http://site.ebrary.com/id/10274055. Pg. 4

[16] National Toxicology Program (2015) Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences.

[17] Woodruff TJ, Sutton P (2014) The Navigation Guide sytematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environmental Health Perspectives. 122(10):A283.

[18] SACC (2019) A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Peer Review for EPA Draft Risk Evaluation of C.I. Pigment Violet 29

- Developmental toxicity
    - Male reproductive system
    - Neurodevelopmental toxicity
    - Other developmental toxicity (ie, skeletal malformations,[19] immune toxicity, fertility)
- Cancer
- Systemic toxicity (ie, liver, kidney effects)[20]

2. Should EPA proceed with the risk evaluation of DIDP and DINP, it should include all intended, known or reasonably foreseen conditions of use and the associated exposures. Failure to do so will underestimate risk, especially to potentially exposed or susceptible sub-populations.

EPA has proposed to assess a subset of conditions of use for DIDP and DINP, which include the conditions of use identified by the manufacturers and others identified by EPA.[21, 22] However, TSCA requires EPA to determine whether "the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, or that any combination of such activities, presents an unreasonable risk of injury to health or the environment," including to potentially exposed or susceptible sub-populations.[23]

To meet this mandate, the law requires that EPA comprehensively assess all intended, known or reasonably foreseen conditions of use for phthalates, and the associated exposures. This scope is necessary both for chemicals selected for risk evaluations based on manufacturer requests and those designated high-priority by the Agency. Otherwise, risk will be underestimated, including for potentially exposed and susceptible subpopulations such as children. For example, the CHAP found that "DINP had the maximum potential for exposure to infants, toddlers, and older children…exposures were primarily from food, but also from mouthing teethers and toys, and from dermal contact with child care articles and home furnishings."[24] If EPA does not include these known exposures in its assessment, it will be missing the majority of DINP exposures for children.

To accurately account for real-life exposures, EPA needs to aggregate exposures across exposure pathways. EPA has described the concept of assessing aggregate exposures as "the risk cup," where every use of a chemical contributes to filling the cup.[25] The Agency can only determine if risks exceed levels of concern, that is whether the risk cup is full or overflowing, by adding together all contributing exposures. However, if known chemical uses and exposures are ignored, the cup levels will be an underestimate of the true risk posed, suggesting that risks are below levels of concern when in reality the cup might be full or overflowing,

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[19] Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Retrieved from U.S. Consumer Product Safety Commission website: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf pg. 8

[20] Id. pg 8

[21] EPA (2019) Possible Conditions of Use (COU) Tables for Di-isononyl Phthalate (DINP)

[22] EPA (2019) Possible Conditions of Use (COU) Tables for Di-isodecyl Phthalate (DIDP)

[23] 15 USC §2605(b)

[24] Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Retrieved from U.S. Consumer Product Safety Commission website: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf pg. 3

[25] US EPA (January 31, 1997) PRN 97-1: Agency Actions under the Requirements of the Food Quality Protection Act. Available: https://www.epa.gov/pesticide-registration/prn-97-1-agency-actions-under-requirements-food-quality-protection-act#risk

indicating an unreasonable risk that warrants action. We have previously submitted detailed comments to EPA on this topic.[26]

3. To make a risk determination, EPA must have adequate data. EPA needs to determine the completeness of the database on the phthalates for assessment and exercise its full authorities to fill data gaps under TSCA sections 4 and 8 and make information public under section 14.

TSCA statute[27] and regulation[28] require that EPA has adequate data on chemicals to inform its risk evaluations. Regulation also requires the evaluation of "relevant" potential human and environmental hazards.[29]

Certain health hazards are specifically designated in TSCA, indicating that Congress expressly recognized these types of health effects could present an unreasonable risk, and envisioned that EPA should assess them: "cancer/ carcinogenesis, mutagenesis/ gene mutation, teratogenesis, behavioral disorders, and birth defects."[30] To assess the sufficiency/ adequacy of the data on the phthalates for assessment, EPA should compare the completeness of the database on each chemical to existing lists of traits deemed important to assess for chemical safety. Additionally, EPA must assess the completeness of the database regarding information needed to conduct a cumulative assessment.

For the existing list of traits deemed important to assess for chemical safety, we recommend as a starting point the health hazard dataset needed for EPA's Design for the Environment (DfE) program to conduct an alternatives assessment, which is similar to the widely used chemical assessment protocol GreenScreen. [31,32] The dataset includes the following health endpoints:

1. Acute mammalian toxicity
    a. Oral
    b. Dermal
    c. Inhalation
2. Respiratory sensitization
3. Skin sensitization
4. Eye irritation/ corrosivity
5. Skin irritation/ corrosivity
6. Carcinogenicity
7. Mutagenicity/ genotoxicity
8. Reproductive and developmental toxicity
9. Developmental neurotoxicity
10. Neurotoxicity

[26] US EPA. (2016). Asbestos; TSCA Review and Risk Evaluation. Comment submitted by Veena Singla, PhD, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco et al. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0736-0479

[27] 15 USC §2601 (b)(1)

[28] 40 CFR § 702.41 (b)

[29] 40 CFR § 702.41 (d)(3)

[30] 15 USC §2603 (b)(2)(A); 15 USC §2603 (e); 15 USC §2605 (b)(2)(D)

[31] US EPA (2011) Design for the Environment Alternatives Assessment Criteria for Hazard Evaluation. Available: https://www.epa.gov/sites/production/files/2014-01/documents/aa_criteria_v2.pdf

[32] Clean Production Action (2018) GreenScreen for Safer Chemicals. Available: https://www.greenscreenchemicals.org/images/ee_images/uploads/resources/GS_TwoPager_July2018.pdf

11. Repeated dose toxicity
12. Endocrine activity

For phthalates, the CHAP already identified carcinogenicity and neurodevelopmental toxicity as endpoints of concern where data is lacking for individual phthalates, and for mixture effects. In general, the CHAP notes that aside from male reproductive toxicity, "Unfortunately, phthalate mixtures have not generally been studied with respect to other health effects."[33]

To determine the methodological approaches to the cumulative risk assessment (ie dose addition, independent action, or some other method) the NRC stated, "The committee concludes that the answer should be based on empirical data that directly test any proposed method."[34] Therefore, data needed by EPA to complete an appropriate cumulative assessment should include testing with chemical mixtures at environmentally relevant dose levels and ratios of chemicals.

If EPA proceeds, it should describe the key areas (hazard and exposure) where data is lacking for each chemical and for mixtures, and issue orders or rules pursuant to TSCA Section 4 and/ or Section 8 to require manufacturers to develop or submit these data. Section 4 test orders should be focused on the most relevant test models, exposure pathways, health outcomes, and target populations (including any vulnerable or sensitive populations) anticipated to support the generation of high-quality and relevant evidence to support timely decision-making.

EPA should make the data developed or submitted under these rules or orders publicly available. TSCA section 14 clearly states that health and safety studies are not confidential business information (CBI) and thus are not protected from disclosure. EPA should also provide a public summary characterizing the data and its completeness for each chemical and relevant mixtures.

4. The reference lists presented in the manufacturer requests do not include all relevant information.

The reference lists presented in the Manufacturer Requests do not capture all information relevant for the risk evaluations, as the requests state these lists are limited to information relevant to the conditions of use identified in the requests. [35, 36] EPA is required to evaluate all conditions of use under TSCA and thus the manufacturers should be including all information on these phthalates that is reasonably available to them, including previously unpublished or unsubmitted studies and data in the manufacturers' possession.

Based on established best practices that have been peer-reviewed and validated for existing systematic review methods, we present recommendations on ways to improve the level of detail presented for how the

[33] Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Retrieved from U.S. Consumer Product Safety Commission website: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf pg. 2

[34] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Retrieved from http://site.ebrary.com/id/10274055. Pg. 9

[35] Exxon Mobil Chemical Company and American Chemistry Council High Phthalates Panel (2019) Manufacturer Request for Risk Evaluation of Diisodecyl Phthalate (DIDP).

[36] Exxon Mobil Chemical Company and American Chemistry Council High Phthalates Panel (2019) Manufacturer Request for Risk Evaluation of Diisononyl Phthalate (DINP).

search was conducted and additional steps needed in the literature search to ensure that all relevant literature is captured for the risk evaluation.[37, 38]

- An independent information specialist should review the search terms and strategy to ensure the search is as sensitive as it can be. For example, all terms used could have been fully truncated, which will return more potentially relevant results. Searching the term DIDP in Pub Med, across "All Fields" reported 149 results. But use of the truncated term DIDP* across "All Fields" reported 159 results.
- In addition to the search terms being listed, the field/s the terms have been searched across should also be stated, as it is not clear whether the terms were searched across all fields or limited in some way. Further, there is no information on if the search was restricted by publication date or language.
- Due to the limited number of studies found in this search, we recommend:
    - that the number of databases searched are extended to include Embase, Scopus, Toxline, TSCATS, PRISM and IHAD;
    - hand searching of the reference lists of the included studies;
    - searching databases for reports published in languages other than English and for the gray literature;
    - searching additional data sources including PubChem and Toxnet.

[37] National Research Council. 2014. *Review of EPA's Integrated Risk Information System (IRIS) Process*. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764.

[38] National Toxicology Program (2015) Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences.

Appendix A: Comments on the European Food Safety Administration (EFSA) Food Ingredients and Packaging draft scientific opinion on 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 plastic food contact materials, from members of the Project TENDR collaboration

Comments on the European Food Safety Administration (EFSA) Food Ingredients and Packaging draft scientific opinion on 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 plastic food contact materials, from members of the Project TENDR collaboration.

14 April 2019

Project TENDR (*Targeting Environmental Neuro-Development Risks)* is a collaboration of leading scientists, health professionals and children's and environmental advocates in the United States. The project came together in 2015 out of concern over the now substantial scientific evidence linking toxic chemicals and pollutants to neurodevelopmental disorders such as autism spectrum disorder, attention deficits, hyperactivity, intellectual disability and learning disorders.

In these comments, we specifically address the EFSA statement: "*effects on other endpoints such as metabolism and neurodevelopment have not been elucidated yet*" and recommend that EFSA revise its assessment to include neurodevelopmental risks.

In fact, accumulating epidemiologic evidence has shown links between prenatal exposures to phthalates and adverse child neurodevelopment. Of 24 longitudinal birth cohort studies [1-24], all but four [15, 21-23] found associations between phthalate metabolites in maternal urine during pregnancy and adverse child cognitive, motor and/or behavioral development. In addition, concentrations of di-2-ethylhexyl phthalates (DEHP) in home dust has been shown to be higher among children with developmental delays relative to typically developing children [25]. Similarly, the presence of PVC flooring in the parents' bedroom during pregnancy (a source of both DEHP and butyl benzyl phthalate [BBzP]) [26-28] has also been significantly associated with the occurrence of autism at child ages 6-8 years [29]. Results from mechanistic and experimental studies in laboratory animals provide support for these epidemiologic findings [30].

A recent analysis conducted by the Chronic Hazard Advisory Panel for the U.S. Consumer Products Safety Commission (CPSC) concluded that poorer neurodevelopment test scores are generally associated with higher maternal prenatal urinary concentration of DEHP, di-butyl phthalate (DBP) and diethyl phthalate (DEP), and that human exposure to these phthalates should be reduced [31]. Another recent review similarly concluded that prenatal exposures to specific phthalates, including to DEP, BBzP, DEHP, Di-*n*-butyl phthalate (DnBP) and Di-iso-butyl phthalate (DiBP), are associated with adverse cognitive and behavioral outcomes in children, including lower IQ and problems with attention, hyperactivity and poorer social communication [32].

Studies of gestational and early life exposure in rats and mice are consistent with the observations from epidemiologic studies. Effects include hyperactivity [33, 34], anxiety [35-39], fear [40], depressive-like behaviors [41] and impacts on learning and memory [35, 37, 42-47]. Consistent with the epidemiologic findings, results are frequently sexually dimorphic. A recent review of the phthalate literature discusses several possible mechanisms to explain the epidemiological and animal toxicity literature [30], including effects on the thyroid function, calcium signaling, nuclear receptor activation, and lipid metabolism.

Multiple human observational studies have found that prenatal exposures to DEHP, DnBP, DiBP, BBzP, and DEP have adverse impacts on child neurodevelopment. These findings are of concern especially in light of the supporting evidence from experimental studies and a growing understanding of the mechanisms whereby phthalates can adversely affect fetal brain development.

In light of the mounting scientific evidence on phthalates and neurodevelopment, we urge EFSA to reconsider and revise its draft scientific opinion on the risk evaluation of the five phthalates listed above to include neurodevelopmental risks. Thank you for this opportunity to comment.

Sincerely,

Charlotte Brody, RN
National Director, Healthy Babies Bright Futures

Russ Hauser, MD, ScD, MPH
Frederick Lee Hisaw Professor of Reproductive Physiology; Professor, Environmental and Occupational Epidemiology, Harvard University; Professor of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School

Robin M. Whyatt, DrPH
Professor Emeritus, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University

Ami Zota, ScD, MS
Assistant Professor, Dept. of Environmental and Occupational Health, Milken Institute School of Public Health, The George Washington University

1. Engel, S.M., A. Miodovnik, R.L. Canfield, C. Zhu, M.J. Silva, A.M. Calafat, and M.S. Wolff, 2010. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. Environ Health Perspect. 118(4): p. 565-71.
2. Factor-Litvak, P., B. Insel, A.M. Calafat, X. Liu, F. Perera, V.A. Rauh, and R.M. Whyatt, 2014. Persistent Associations between Maternal Prenatal Exposure to Phthalates on Child IQ at Age 7 Years. PLoS One. 9(12): p. e114003.
3. Kim, Y., E.H. Ha, E.J. Kim, H. Park, M. Ha, J.H. Kim, Y.C. Hong, N. Chang, and B.N. Kim, 2011. Prenatal exposure to phthalates and infant development at 6 months: prospective Mothers and Children's Environmental Health (MOCEH) study. Environ Health Perspect. 119(10): p. 1495-500.
4. Lien, Y.J., H.Y. Ku, P.H. Su, S.J. Chen, H.Y. Chen, P.C. Liao, W.J. Chen, and S.L. Wang, 2015. Prenatal exposure to phthalate esters and behavioral syndromes in children at 8 years of age: Taiwan Maternal and Infant Cohort Study. Environ Health Perspect. 123(1): p. 95-100.
5. Miodovnik, A., S.M. Engel, C. Zhu, X. Ye, L.V. Soorya, M.J. Silva, A.M. Calafat, and M.S. Wolff, 2011. Endocrine disruptors and childhood social impairment. Neurotoxicology. 32(2): p. 261-7.
6. Polanska, K., D. Ligocka, W. Sobala, and W. Hanke, 2014. Phthalate exposure and child development: the Polish Mother and Child Cohort Study. Early Hum Dev. 90(9): p. 477-85.

7. Swan, S.H., F. Liu, M. Hines, R.L. Kruse, C. Wang, J.B. Redmon, A. Sparks, and B. Weiss, 2010. Prenatal phthalate exposure and reduced masculine play in boys. Int J Androl. 33(2): p. 259-69.
8. Tellez-Rojo, M.M., A. Cantoral, D.E. Cantonwine, L. Schnaas, K. Peterson, H. Hu, and J.D. Meeker, 2013. Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. Sci Total Environ. 461-462: p. 386-90.
9. Whyatt, R.M., X. Liu, V.A. Rauh, A.M. Calafat, A.C. Just, L. Hoepner, D. Diaz, J. Quinn, J. Adibi, F.P. Perera, and P. Factor-Litvak, 2012. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. Environ Health Perspect. 120(2): p. 290-5.
10. Doherty, B.T., S.M. Engel, J.P. Buckley, M.J. Silva, A.M. Calafat, and M.S. Wolff, 2017. Prenatal phthalate biomarker concentrations and performance on the Bayley Scales of Infant Development-II in a population of young urban children. Environ Res. 152: p. 51-58.
11. Percy, Z., Y. Xu, H. Sucharew, J.C. Khoury, A.M. Calafat, J.M. Braun, B.P. Lanphear, A. Chen, and K. Yolton, 2016. Gestational exposure to phthalates and gender-related play behaviors in 8-year-old children: an observational study. Environ Health. 15(1): p. 87.
12. Singer, A.B., M.S. Wolff, M.J. Silva, A.M. Calafat, and S.M. Engel, 2017. Prenatal phthalate exposures and child temperament at 12 and 24 months. Neurotoxicology. 62: p. 248-257.
13. Engel, S.M., G.D. Villanger, R.C. Nethery, C. Thomsen, A.K. Sakhi, S.S.M. Drover, J.A. Hoppin, P. Zeiner, G.P. Knudsen, T. Reichborn-Kjennerud, A.H. Herring, and H. Aase, 2018. Prenatal Phthalates, Maternal Thyroid Function, and Risk of Attention-Deficit Hyperactivity Disorder in the Norwegian Mother and Child Cohort. Environ Health Perspect. 126(5): p. 057004.
14. Kim, S., S. Eom, H.J. Kim, J.J. Lee, G. Choi, S. Choi, S.Y. Kim, G. Cho, Y.D. Kim, E. Suh, S.K. Kim, G.H. Kim, H.B. Moon, J. Park, K. Choi, and S.H. Eun, 2018. Association between maternal exposure to major phthalates, heavy metals, and persistent organic pollutants, and the neurodevelopmental performances of their children at 1 to 2years of age-CHECK cohort study. Sci Total Environ. 624: p. 377-384.
15. Braun, J.M., A.E. Kalkbrenner, A.C. Just, K. Yolton, A.M. Calafat, A. Sjodin, R. Hauser, G.M. Webster, A. Chen, and B.P. Lanphear, 2014. Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: the HOME study. Environ Health Perspect. 122(5): p. 513-20.
16. Bornehag, C.G., C. Lindh, A. Reichenberg, S. Wikstrom, M. Unenge Hallerback, S.F. Evans, S. Sathyanarayana, E.S. Barrett, R.H.N. Nguyen, N.R. Bush, and S.H. Swan, 2018. Association of Prenatal Phthalate Exposure With Language Development in Early Childhood. JAMA Pediatr. 172(12): p. 1169-1176.
17. Ipapo, K.N., P. Factor-Litvak, R.M. Whyatt, A.M. Calafat, D. Diaz, F. Perera, V. Rauh, and J.B. Herbstman, 2017. Maternal prenatal urinary phthalate metabolite concentrations and visual recognition memory among infants at 27 weeks. Environ Res. 155: p. 7-14.
18. Minatoya, M., S. Itoh, K. Yamazaki, A. Araki, C. Miyashita, N. Tamura, J. Yamamoto, Y. Onoda, K. Ogasawara, T. Matsumura, and R. Kishi, 2018. Prenatal exposure to bisphenol

A and phthalates and behavioral problems in children at preschool age: the Hokkaido Study on Environment and Children's Health. Environ Health Prev Med. 23(1): p. 43.
19. Philippat, C., D. Nakiwala, A.M. Calafat, J. Botton, M. De Agostini, B. Heude, and R. Slama, 2017. Prenatal Exposure to Nonpersistent Endocrine Disruptors and Behavior in Boys at 3 and 5 Years. Environ Health Perspect. 125(9): p. 097014.
20. Balalian, A.A., R.M. Whyatt, X. Liu, B.J. Insel, V.A. Rauh, J. Herbstman, and P. Factor-Litvak, 2019. Prenatal and childhood exposure to phthalates and motor skills at age 11 years. Environ Res. 171: p. 416-427.
21. Kim, J.I., Y.C. Hong, C.H. Shin, Y.A. Lee, Y.H. Lim, and B.N. Kim, 2017. The effects of maternal and children phthalate exposure on the neurocognitive function of 6-year-old children. Environ Res. 156: p. 519-525.
22. Gascon, M., D. Valvi, J. Forns, M. Casas, D. Martinez, J. Julvez, N. Monfort, R. Ventura, J. Sunyer, and M. Vrijheid, 2015. Prenatal exposure to phthalates and neuropsychological development during childhood. Int J Hyg Environ Health. 218(6): p. 550-8.
23. Huang, H.B., H.Y. Chen, P.H. Su, P.C. Huang, C.W. Sun, C.J. Wang, C.A. Hsiung, and S.L. Wang, 2015. Fetal and Childhood Exposure to Phthalate Diesters and Cognitive Function in Children Up to 12 Years of Age: Taiwanese Maternal and Infant Cohort Study. PLoS One. 10(6): p. e0131910.
24. Braun, J.M., D.C. Bellinger, R. Hauser, R.O. Wright, A. Chen, A.M. Calafat, K. Yolton, and B.P. Lanphear, 2017. Prenatal phthalate, triclosan, and bisphenol A exposures and child visual-spatial abilities. Neurotoxicology. 58: p. 75-83.
25. Philippat, C., D. Bennett, A.M. Calafat, and I.H. Picciotto, 2015. Exposure to select phthalates and phenols through use of personal care products among Californian adults and their children. Environ Res. 140: p. 369-76.
26. Bornehag, C.G., B. Lundgren, C.J. Weschler, T. Sigsgaard, L. Hagerhed-Engman, and J. Sundell, 2005. Phthalates in indoor dust and their association with building characteristics. Environ Health Perspect. 113(10): p. 1399-404.
27. Carlstedt, F., B.A. Jonsson, and C.G. Bornehag, 2013. PVC flooring is related to human uptake of phthalates in infants. Indoor Air. 23(1): p. 32-9.
28. Just, A.C., R.L. Miller, M.S. Perzanowski, A.G. Rundle, Q. Chen, K.H. Jung, L. Hoepner, D.E. Camann, A.M. Calafat, F.P. Perera, and R.M. Whyatt, 2015. Vinyl flooring in the home is associated with children's airborne butylbenzyl phthalate and urinary metabolite concentrations. J Expo Sci Environ Epidemiol. 25(6): p. 574-9.
29. Larsson, M., B. Weiss, S. Janson, J. Sundell, and C.G. Bornehag, 2009. Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6-8 years of age. Neurotoxicology. 30(5): p. 822-31.
30. Miodovnik, A., A. Edwards, D.C. Bellinger, and R. Hauser, 2014. Developmental neurotoxicity of ortho-phthalate diesters: review of human and experimental evidence. Neurotoxicology. 41: p. 112-22.
31. CPSC, 2014. Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives. U.S. Consumer Product Safety Commision, Bethesda MD.
32. Ejaredar, M., E.C. Nyanza, K. Ten Eycke, and D. Dewey, 2015. Phthalate exposure and childrens neurodevelopment: A systematic review. Environ Res. 142: p. 51-60.

33. Ishido, M., Y. Masuo, J. Sayato-Suzuki, S. Oka, E. Niki, and M. Morita, 2004. Dicyclohexylphthalate causes hyperactivity in the rat concomitantly with impairment of tyrosine hydroxylase immunoreactivity. J Neurochem. 91(1): p. 69-76.
34. Masuo, Y., M. Morita, S. Oka, and M. Ishido, 2004. Motor hyperactivity caused by a deficit in dopaminergic neurons and the effects of endocrine disruptors: a study inspired by the physiological roles of PACAP in the brain. Regul Pept. 123(1-3): p. 225-34.
35. Barakat, R., P.C. Lin, C.J. Park, C. Best-Popescu, H.H. Bakry, M.E. Abosalem, N.M. Abdelaleem, J.A. Flaws, and C. Ko, 2018. Prenatal Exposure to DEHP Induces Neuronal Degeneration and Neurobehavioral Abnormalities in Adult Male Mice. Toxicol Sci. 164(2): p. 439-452.
36. Carbone, S., O.J. Ponzo, N. Gobetto, Y.A. Samaniego, R. Reynoso, P. Scacchi, J.A. Moguilevsky, and R. Cutrera, 2013. Antiandrogenic effect of perinatal exposure to the endocrine disruptor di-(2-ethylhexyl) phthalate increases anxiety-like behavior in male rats during sexual maturation. Horm Behav. 63(5): p. 692-9.
37. Ma, P., X. Liu, J. Wu, B. Yan, Y. Zhang, Y. Lu, Y. Wu, C. Liu, J. Guo, E. Nanberg, C.G. Bornehag, and X. Yang, 2015. Cognitive deficits and anxiety induced by diisononyl phthalate in mice and the neuroprotective effects of melatonin. Sci Rep. 5: p. 14676.
38. Quinnies, K.M., E.P. Harris, R.W. Snyder, S.S. Sumner, and E.F. Rissman, 2017. Direct and transgenerational effects of low doses of perinatal di-(2-ethylhexyl) phthalate (DEHP) on social behaviors in mice. PLoS One. 12(2): p. e0171977.
39. Yan, B., J. Guo, X. Liu, J. Li, X. Yang, P. Ma, and Y. Wu, 2016. Oxidative stress mediates dibutyl phthalateinduced anxiety-like behavior in Kunming mice. Environ Toxicol Pharmacol. 45: p. 45-51.
40. DeBartolo, D., S. Jayatilaka, N. Yan Siu, M. Rose, R.L. Ramos, and A.J. Betz, 2016. Perinatal exposure to benzyl butyl phthalate induces alterations in neuronal development/maturation protein expression, estrogen responses, and fear conditioning in rodents. Behav Pharmacol. 27(1): p. 77-82.
41. Xu, X., Y. Yang, R. Wang, Y. Wang, Q. Ruan, and Y. Lu, 2015. Perinatal exposure to di-(2-ethylhexyl) phthalate affects anxiety- and depression-like behaviors in mice. Chemosphere. 124: p. 22-31.
42. Boberg, J., S. Christiansen, M. Axelstad, T.S. Kledal, A.M. Vinggaard, M. Dalgaard, C. Nellemann, and U. Hass, 2011. Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats. Reprod Toxicol. 31(2): p. 200-9.
43. Dai, Y., Y. Yang, X. Xu, and Y. Hu, 2015. Effects of uterine and lactational exposure to di-(2-ethylhexyl) phthalate on spatial memory and NMDA receptor of hippocampus in mice. Horm Behav. 71: p. 41-8.
44. Kougias, D.G., E.P. Sellinger, J. Willing, and J.M. Juraska, 2018. Perinatal exposure to an environmentally relevant mixture of phthalates results in a lower number of neurons and synapses in the medial prefrontal cortex and decreased cognitive flexibility in adult male and female rats. J Neurosci.
45. Li, X.J., L. Jiang, L. Chen, H.S. Chen, and X. Li, 2013. Neurotoxicity of dibutyl phthalate in brain development following perinatal exposure: a study in rats. Environ Toxicol Pharmacol. 36(2): p. 392-402.

46. Li, Y., M. Zhuang, T. Li, and N. Shi, 2009. Neurobehavioral toxicity study of dibutyl phthalate on rats following in utero and lactational exposure. J Appl Toxicol. 29(7): p. 603-11.
47. Lin, H., K. Yuan, L. Li, S. Liu, S. Li, G. Hu, Q.Q. Lian, and R.S. Ge, 2015. In Utero Exposure to Diethylhexyl Phthalate Affects Rat Brain Development: A Behavioral and Genomic Approach. Int J Environ Res Public Health. 12(11): p. 13696-710.