October 3, 2019

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

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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. 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.” 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.”

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.” 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...”

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).
8 Id. pg. 11-12
9 15 USC §2625(c)
10 Id.
Sincerely,

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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. 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.

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

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imply that other health effects are not important or that nonchemical stressors should be ignored.”

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.

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...” 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. 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.

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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- Developmental toxicity
  - Male reproductive system
  - Neurodevelopmental toxicity
  - Other developmental toxicity (i.e., skeletal malformations, immune toxicity, fertility)
- Cancer
- Systemic toxicity (i.e., liver, kidney effects)

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. 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.

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 teether and toys, and from dermal contact with child care articles and home furnishings.” 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. 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.
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 statute27 and regulation28 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

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)
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.”

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.” 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. 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

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

\begin{itemize}
  \item 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\textsuperscript{*} across “All Fields” reported 159 results.
  \item 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.
  \item Due to the limited number of studies found in this search, we recommend:
    \begin{itemize}
      \item that the number of databases searched are extended to include Embase, Scopus, Toxline, TSCATS, PRISM and IHAD;
      \item hand searching of the reference lists of the included studies;
      \item searching databases for reports published in languages other than English and for the gray literature;
      \item searching additional data sources including PubChem and Toxnet.
    \end{itemize}
\end{itemize}


\textsuperscript{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-isonymylphthalate (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.

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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,

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