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EPN Comments on EPA's "Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act"

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Founded in 2017, the Environmental Protection Network (EPN) harnesses the expertise of more than 550 former Environmental Protection Agency (EPA) career staff and confirmation-level appointees from Democratic and Republican administrations to provide the unique perspective of former regulators and scientists with decades of historical knowledge and subject matter expertise.

I. Introduction

On February 24, 2023, EPA issued two documents for public comment and peer review by the TSCA Science Advisory Committee on Chemicals (SACC). The first, entitled "Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act," describes a set of proposed principles for evaluating cumulative risks under the Toxic Substances Control Act (TSCA). The second document, entitled "Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act, " describes the proposed approach for application of the principles to a cumulative assessment of a group of phthalates currently undergoing risk evaluation under Section 6 of TSCA.

Accompanying the two draft documents was a set of charge questions designed for use by the SACC to guide the conduct of their scientific peer review. We plan to use those charge questions to frame our comments on the two documents. The present set of comments addresses the phthalates example. Comments addressing the draft principles document have been prepared separately.

II. EPN Response to the Charge Questions on Draft Proposed Approach for CRA of High-Priority Phthalates and Two Manufacturer-Requested Phthalates under TSCA

EPN Comment: Change the title of the document to reflect the fact that there were manufacturers' requests for two phthalates (DIDP and DINP), not just one.

Question 5: As described in Section 1.1, EPA has identified evaluations conducted by multiple other regulatory agencies and authoritative bodies, including the U.S. CPSC, Health Canada, Australia NICNAS, and the European Food Safety Authority. Please identify any additional notable phthalate CRAs that the panel is aware of that may inform EPA's proposed approach.

EPN Response: Some additional citations are provided below. While ATSDR and CPSC are government entities, the other papers are from non-government sources. CRA is a complex process and EPA should not summarily dismiss these other sources, as they also may provide interesting and useful insights.

1. ATSDR 2017 Interaction Profile for: Chlorinated Dibenzo-p-Dioxins, Polybrominated

Diphenyl Ethers and Phthalates. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA. https://www.atsdr.cdc.gov/interactionprofiles/ip14.html

2. Patton, L.E. 2010. CPSC Staff Toxicity Review of 17 Phthalates for Consideration by the Chronic Hazard Advisory Panel – 2010. Consumer Product Safety Commission. Bethesda, MD. https://www.cpsc.gov/s3fs-public/CPSCStaffToxicity17Phthalates.pdf

3. Dewalque L. , Charlier C., Pirard, C. 2014. Estimated daily intake and cumulative risk assessment of phthalate diesters in a Belgian general population. *Toxicol Letters* Volume 231, Issue 2, 1 December 2014, Pages 161-168. https://www.sciencedirect.com/science/article/abs/pii/S0378427414002781

4. T. Søeborg, H. Frederiksen, A. M. Andersson 2012. Cumulative risk assessment of phthalate exposure of Danish children and adolescents using the hazard index approach. *Int. J. Andrology* 33(3): 245-252. https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2605.2011.01240.x

5. Wei-Hsiang Chang, Wei-Chun Chou, Alexander Waits, Kai-Wei Liao, Pao-Lin Kuo, Po-Chin Huang 2021 Cumulative risk assessment of phthalates exposure for recurrent pregnancy loss in reproductive-aged women population using multiple hazard indices approaches. *Environment International* 154 (2021) 106657.

6. Christensen KL, Makris SL, Lorber M 2014. Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment. *Regul Toxicol Pharmacol.* 2014 Aug; 69(3):380-9. doi: 10.1016/j.yrtph.2014.04.019.

7. Ji H, Wu Z, Chen D, Miao M, Chen H, Shuai W, Liang H, Yuan W. 2023 Individual and joint effects of phthalates exposure on the risk of early miscarriage. *J Expo Sci Environ Epidemiol.* 2023 Mar 23. doi: 10.1038/s41370-023-00533-1.

Question 6. In Section 2.1, EPA defines some key concepts relevant to the CRA. Please comment on the clarity and appropriateness of EPA's definition for these terms with respect to the phthalate proposed cumulative approach.

EPN Response: No comments.

Question 7: In Section 3.1.3, EPA summarizes available data for seven key outcomes associated with the development of phthalate syndrome for the five high-priority and two manufacturer-requested phthalates. Please comment on the key outcomes associated with the "phthalate syndrome" identified by EPA for focusing its phthalate CRA.

EPN Response: In the introductory paragraphs of Section 3.1 Evidence of Toxicologic Similarity, EPA summarizes its argument that the male reproductive effects are the most appropriate to serve as the focus of the hazard assessment in the CRA. EPA should provide more detailed justification for selecting phthalate syndrome for this purpose. EPN will reserve judgment on this point until it has had the opportunity to review the chemical-specific risk evaluations and draft CRA. Questions

to consider: Is/are the endpoint(s) which make up the syndrome occurring at dose levels equivalent to or lower than those affecting female reproductive function, carcinogenic potential, neurodevelopment, or any other non-syndrome related effect? If so, no problem. If not, how does the agency plan to adjust for this circumstance? Extra uncertainty factors when deriving margins of exposures?

As an aside, EPA occasionally refers to "the mode of action" (MOA) in the singular for the phthalate syndrome but also alludes to the possibility/likelihood that both androgen-dependent and androgen-independent phenomena may be at play. This suggests the possibility that more than one MOA may be involved in this spectrum of adverse outcomes. There is not enough information in this document to resolve this question. EPN reserves judgment until such time as it has had the opportunity to review the draft chemical-specific risk evaluations and draft CRA. Clarifying whether there is just one or more than one MOA will be of greater or lesser importance depending upon whether the agency chooses to apply the data on the adverse outcome at the end of the MOA/adverse outcome pathway or a molecular initiating event or key event within the pathway(s) to support the relative potency comparisons.

It is unclear to EPN what exactly EPA is asking for in this question when simply saying, "Please comment on the key outcomes….." We will just say that, given the robustness of the databases on each, all seven key outcomes are relevant for inclusion in the hazard analysis and development of relative potencies, where appropriate.

Question 8: Sections 3.1.6 and 3.1.7 describe EPA's weight of evidence analysis and proposed conclusions regarding toxicologic similarity for the five high-priority and two manufacturer-requested phthalates. EPA has preliminarily concluded that DEHP, BBP, DBP, DIBP, DCHP, and DINP (but not DIDP) are toxicologically similar and can induce effects consistent with phthalate syndrome in rats. However, EPA acknowledges that DINP is less potent than the other evaluated phthalates. Please comment on the strengths and uncertainties of this preliminary conclusion.

EPN Response: We commend EPA for acknowledging the need for incorporating non-attributable and non-TSCA related exposures with TSCA exposures into the exposure assessments. This is something that EPN has advocated for in earlier risk evaluations. However, we would posit that another step needs to be incorporated into the process, well before the exposure assessment is begun. That step comes at the very beginning when assembling the initial candidate cumulative chemical group (CCG) pool and should be integrated into Step 1 of the draft conceptual model introduced in Figure 2-1. First, EPA needs to answer the question as to whether or not there are other phthalates that are assigned to the same chemical subclass as the seven highlighted in this Draft Proposed Approach document. Patton[1] may help to shed light on this. Furthermore, the footnote on page 31 ("The TSCA Work Plan includes one additional phthalate (i.e., di-n-octyl phthalate) that is not currently prioritized for risk evaluation. However, Environment Canada/Health Canada (EC/HC, 2015e) concluded that di-n-octyl phthalate does not induce effects on the developing male reproductive system consistent with phthalate syndrome. Di-n-octyl phthalate is not further discussed in this document.") does not provide adequate justification for

[1] Patton, L.E. 2010. CPSC Staff Toxicity Review of 17 Phthalates for Consideration by the Chronic Hazard Advisory Panel – 2010. Consumer Product Safety Commission. Bethesda, MD. https://www.cpsc.gov/s3fs-public/CPSCStaffToxicity17Phthalates.pdf

excluding Di-n-octyl phthalate from the CCG. Expanded discussion of this issue is warranted in its chemical-specific risk evaluation and the subsequent CRA document.

If additional TSCA or non-TSCA chemicals are identified as potential candidates for inclusion in the CCG, they, too, should be subjected to the toxicologic similarity screen. If any of these meet the criteria, they should be carried forward, along with the already-identified seven, into the exposure assessment phase. If any of the seven-plus-X are identified as meeting the co-exposure criteria, they then should become component(s) of the final CCG and included in the CRA because they all meet the toxicological similarity and co-exposure criteria. This process was applied to di-n-octyl phthalate and DIDP. In this case, these chemicals were removed from further analysis or inclusion in the final CCG. However, simply because DINP is less potent than the other evaluated phthalates shouldn't make it a candidate for removal from the CCG.

Question 9: Section 3.2 provides a qualitative evaluation of the available evidence of human co-exposure to the five high-priority and two manufacturer-requested phthalates. Based on available human biomonitoring data (i.e., NHANES) and evidence of exposure through manufacturing and/or industrial, commercial, or consumer use, EPA has preliminarily concluded that there is evidence that humans are co-exposed to or have the potential to become co-exposed to DEHP, BBP, DBP, DIBP, DCHP, DINP, and DIDP. EPA acknowledges that there is less robust evidence to support co-exposure to DCHP. Please comment on the strengths and uncertainties of EPA's preliminary conclusion.

EPN Response: The agency's conclusions about co-exposure are incomplete and premature. As addressed in earlier comments above, EPN believes that additional phthalates (additional TSCA chemicals, but, more importantly, some non-TSCA chemicals) should be added to the initial CCG candidate list and screened first for toxicologic similarity and, depending upon the outcome of that analysis, for co-exposure potential. CDC[2] reports on its analysis of NHANES data showing 15 metabolites of phthalate diesters in urinary samples. It utilized data on 12 of the reported metabolites to determine exposure of pregnant women in the population to *nine* phthalate diesters which is more than the total currently in EPA's CCG candidate pool. Since this analysis shows the general population and at least one potentially exposed and subpopulation (PESS) are exposed to more than EPA's current CCG candidate list, these other chemicals should be subjected to screening for toxicological similarity and added to EPA's candidate CCG list until EPA determines whether or not these additional phthalate esters meet the co-exposure criteria.

Question 10: EPA's proposed phthalate cumulative chemical group for CRA, based on the weight of evidence supporting toxicologic similarity and human co-exposure, is described in Section 3.3. Please comment on EPA's preliminary proposal to include DEHP, BBP, DBP, DIBP, DCHP, and DINP in the cumulative chemical group under TSCA. In your response, and in light of comments on charge questions 8 and 9, please include a discussion of the strengths and uncertainties of this preliminary conclusion.

EPN Response: EPN agrees that DEHP, BBP, DBP, DIBP, DCHP, and DINP should be included in the final CCG to be assessed in the CRA. The evidence is strong that these chemicals meet the

[2] ATSDR 2017 Interaction Profile for: Chlorinated Dibenzo-p-Dioxins, Polybrominated Diphenyl Ethers and Phthalates. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, GA. https://www.atsdr.cdc.gov/interactionprofiles/ip14.html

two criteria for inclusion. The uncertainty, or rather the inadequacy, of the currently-proposed decision, is addressed in the EPN responses to Questions 8 and 9 and can be summed up in one sentence: EPA has not done sufficient background investigation to ferret out and screen for toxicologic similarity and co-exposure of ALL of the phthalates (TSCA and non-TSCA) that could be included in the final CCG, leading to the conduct of a scientifically-sound and credible CRA.

Question 11: In Section 4.1, EPA describes two options for addressing phthalate syndrome—assessing the syndrome as a whole and focusing on the most sensitive effect. Please comment on the strengths and uncertainties of EPA's preliminary proposal to address phthalate syndrome under TSCA by focusing on the most sensitive effect(s).

EPN Response: This question requires more deliberation and time than we have available, given the near-term deadline for submission of comments. The two options for addressing phthalate syndrome are actionable and complex. The agency proposals of six suboptions for focusing on the most sensitive effect all have merits and downsides. So we offer a recommendation that will probably do little to clarify the agency's decision-making roadmap at this moment. The recommendation is "Do all of the above." This is the first opportunity the agency has had to conduct a CRA under TSCA. It is particularly complex and challenging because of the decision to focus on integration of assessments of multiple components of a syndrome, dependent upon data generated in studies ranging widely in study design. This is in stark contrast to OPP's luxury of being able to use data from studies required by regulation and conducted according to a predetermined standardized design.

Question 12: In Section 4.2, EPA describes the applicability of dose addition for evaluating phthalates for cumulative risk to human health. Please comment on the appropriateness of EPA's proposal to evaluate phthalates under an assumption of dose addition.

EPN Response: EPA has a 20+-year history of using dose addition as the default in assessing mixtures. And, it is reasonable to try to do so in this instance as well. However, we would once again recommend a Do –it-all approach for the same reasons we recommended DO-it-all above. It's the first example of a CRA to be conducted under TSCA. We believe EPA is obligated to try out all possibilities and then provide robust justification for selection of the approach to be used and exclusion of the other(s).

Question 13: In the National Research Council's 2008 report Phthalates and Cumulative Risk Assessment: The Tasks Ahead, the NRC recommended against the use of a relative potency factor (RPF) approach for phthalates because phthalates exhibit dose-response curves with differing slopes and shapes. However, based on scientific analysis developed since the publication of the 2008 report (described in Section 4.3.3), EPA considers the RPF approach to be scientifically supportable for phthalates. Please comment on the strengths and uncertainties of using a RPF approach for phthalates.

EPA Response: We are likely to be supportive of the selection of the RPF approach as most appropriate in this case, but do not have the time available to adequately evaluate the details to confirm the scientific integrity.of the choice. But,once again, we encourage EPA to also apply the Hazard Index approach and compare the outcomes as a step in building its justification for using the RPF approach in the end.

Question 14: Section 4.4 describes six options EPA is considering for deriving RPFs for phthalates. Please comment on the strengths and uncertainties of the proposed options. Please describe any additional options EPA may consider for deriving RPFs for phthalates.

EPN Response: We have no comments beyond those to be found in the response to Question 11.

Question 15: In Section 5.0, EPA proposes that the potentially exposed and susceptible subpopulations (PESS) that may be more susceptible to phthalate syndrome, include
• pregnant women/women of reproductive age, and
• male infants, male toddlers, and male children.
EPA proposes to focus its CRA for phthalates on these susceptible subpopulations and add others through the risk evaluation process as applicable. Please comment on the strengths and uncertainties of this proposal.

EPN Response: The draft Proposed Conceptual Model (Figure 2-1) highlights fenceline communities as an example of a PESS. *The Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act* also note fenceline communities, and includes tribal populations as a PESS as well. Should not tribal populations also be included in the Conceptual Model? And, if so, where?

Question 16: In Section 6.3.2, EPA describes two approaches (scenario-based and reverse dosimetry) for estimating non-attributable and non-TSCA exposure (Step 5 in the Conceptual Model [Figure 2-1]). In Section 6.3.2.5, EPA proposes to primarily utilize the scenario-based approach (described inSection 6.3.2.1) to estimate non-attributable and non-TSCA exposures for combining with TSCA exposures. The Agency proposes to use the reverse dosimetry approach (described in Section 6.3.2.2) as a comparator for scenario-based daily intake estimates (i.e., help contextualize whether scenario-based estimates are an over or underestimation of total exposure) and to analyze temporal trends to better understand changes in phthalate exposure over time.
a) Please comment on the strengths and uncertainties of EPA's proposed approach to primarily assess the non-attributable and non-TSCA exposure using a scenario-based method.
b) EPA recognizes there are limitations and uncertainties with the proposed reverse dosimetry approach outlined in Section 6.3.2.2, which relies on Equation 6-1. Given these uncertainties and limitations, please comment on EPA's proposal to use reverse dosimetry as a supplementary approach to help characterize exposure and use it as a comparator for exposure estimates from the scenario-based approach.
c) EPA recognizes that intake estimates using scenario-based approach may not be directly comparable to estimates from a reverse dosimetry approach. Please comment on how these estimates can or cannot be calibrated to each other based on the uncertainties of each approach.

EPN Response: Our recommendation is to apply both approaches (scenario-based and reverse dosimetry) when available information allows; compare the results; then select and justify the choice.

Question 17: In Section 6.3.2.1, EPA briefly discusses a tiered approach to exposure assessment based on data availability, where different tiers may utilize deterministic or probabilistic models. Exposures from different exposure scenarios may be estimated using different tiers of models based on data availability and combined to determine cumulative exposure. Section 6.3.2.4 discusses the uncertainties of combining exposures estimated using different tiers of assessment. Please comment on the challenges associated with combining exposure estimated across different tiers of exposure

assessment and potential solutions.

EPN Response: We don't have the resources to comment at this time.

Question 18: As shown in Step 4–5 of EPA's conceptual model (Figure 2-1), and subsequently described in detail in Section 6.4.1 and 6.4.2 for consumers and workers, EPA proposes to consider non-attributable and non-TSCA exposure for combining with TSCA exposures for consumer and occupational conditions of use (COUs) in Step 9 that are identified as major exposure pathways and are anticipated to lead to co-exposure. Please comment on strengths and uncertainties of this approach. If appropriate, please provide alternative approaches that the EPA may consider for determining cumulative exposure.

EPN Response: We don't have the resources to comment at this time.

Question 19: In Section 6.4.1.2, EPA proposes an approach to determine co-exposure to multiple phthalates from consumer TSCA COUs for consumers as part of Step 7 of EPA's conceptual model (Figure 2-1). EPA discusses the limited data to support co-exposure to multiple phthalates across different consumer TSCA COUs as well as the limited data to support the co-occurrence of multiple phthalates within a single product. Please comment on strengths and uncertainties of this approach. If appropriate, please provide information on additional existing data that EPA may consider for determining co-exposure to consumer products.

EPN Response: We don't have the resources to comment at this time.

Question 20. In Section 6.4.2.2, EPA proposes an approach to determine co-exposure to multiple phthalates from occupational TSCA COUs for workers as part of Step 7 of EPA's conceptual model (Figure 2-1). In the absence of workplace monitoring data, EPA proposes to utilize release estimates to determine the potential for co-exposure to workers in a workplace setting. Please comment on strengths and uncertainties of this approach. If appropriate, please provide information on additional existing data that EPA may consider for determining co-exposure for workers.

EPN Response: We don't have the resources to comment at this time.

Question 21:. In Sections 6.4.3.2 and 6.4.3.3, EPA proposes a step-wise approach to determine co-exposure to individuals who may be part of a fenceline community and who are also consumers and/or workers. However, EPA has not identified a proposed methodology, data sources, or lines of evidence to fully develop the cumulative fenceline assessment. Please provide information on existing data sources that EPA may consider for developing the cumulative fenceline assessment.

EPN Response: We do not have the resources to comment at this time. However, we would recommend that EPA also propose an approach to determine co-exposure to individuals who may be part of a tribal population. The agency has been virtually silent in this document on how it might address concerns related to this PESS. That is unacceptable.