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Comments on "Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act" and "Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substance Control Act."

These comments are submitted on behalf of the undersigned scientists. We declare that we have no direct or indirect financial or fiduciary interests in the subjects of these comments. The co-signers' institutional affiliations are included for identification purposes only and do imply institutional endorsement or support unless indicated otherwise.

We appreciate the opportunity to provide comments on the "Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act" and "Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act," hereafter referred to as the *CRA Principles* and *Draft Phthalates CRA Approach*, respectively. The mission of the Program on Reproductive Health and the Environment (PRHE) is to create a healthier environment for human reproduction and development through advancing scientific inquiry, clinical care and health policies that prevent exposure to harmful chemicals in our environment.[1] Our research illuminates how chemicals hurt health, and we promote evidence-based actions to prevent such harms. Through internal and external partnerships, we implement a multi-pronged strategy to transform environmental science into improved public policy by: (1) producing the best science; (2) bringing the science to decision-making through direct engagement and communications; (3) engaging scientist and health professional leaders in advocacy for better policy; and (4) developing innovative tools to harness the science to prevention-focused decisions in clinical and policy arena.

We commend the EPA on moving forward with a cumulative risk assessment approach for phthalate exposure. Evaluating the risk of multiple chemicals is consistent with both PRHE[2] and NASEM recommendations[3] and represents the "best available science" as required under the amended Toxic Substances Control Act (TSCA).[4] To that end, we also agree with the EPA's focus on applying multiple considerations for determining toxicological similarity of the six phthalates, rather than focusing solely on mechanisms of action. We agree with the EPA that use of relative potency factors is an appropriate approach for assessing anti-androgenic effects of multiple phthalates. The EPA has recognized that some individuals will have combinations of general population exposure, consumer exposure, and occupational exposure and we emphasize that careful assessment of these combinations is critical for accurate estimation of exposure and risk in the U.S. population, especially for potentially exposed or susceptible subpopulations (PESS).[5]

[1] UCSF Program on Reproductive Health and the Environment. Available: prhe.ucsf.edu/about

[2] Tracey J. Woodruff et al., "A Science-Based Agenda for Health-Protective Chemical Assessments and Decisions: Overview and Consensus Statement," *Environmental Health* 21, no. 1 (January 12, 2023): 132, https://doi.org/10.1186/s12940-022-00930-3.

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

[4] 15 USC §2625 (h)-(i) and 15 USC §2601 (b)(1)

[5] Swati D. G. Rayasam et al., "Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States," *Environmental Science & Technology* 56, no. 17 (September 6, 2022): 11969–82, https://doi.org/10.1021/acs.est.2c02079.

Our comments address the following issues:

Section 1. Comments on the *Draft Phthalates CRA Approach*

1. **EPA's review demonstrates that the evidence for toxicological similarity is abundant for each phthalate and each of the key outcomes considered**
    a. **Shared key cellular events demonstrate toxicological similarity**
    b. **Shared postnatal outcomes demonstrate toxicological similarity**
    c. **EPA presents ample evidence to support a conclusion of toxicological similarity for DINP**
    d. **The application of dose addition in the phthalates CRA is appropriate**
    e. **EPA should include other chemicals and non-chemical stressors in the phthalates CRA**
    f. **EPA should conduct cumulative risk assessments of phthalates for other health endpoints in addition to the anti-androgenic effects**
2. **EPA should model multiple outcomes, with multiple approaches, to inform its ultimate selection of relative potency factors (RPFs)**
3. **Application of RPFs is appropriate for the phthalates CRA. EPA's discussion of RPFs should incorporate additional considerations and approaches**
    a. **EPA should use the RPF approach for the phthalates cumulative risk assessment, and it should describe the advantages of the RPF approach in the *Draft Phthalates CRA Approach***
    b. **EPA should state its conceptual approach to RPF development before outlining the proposed options for deriving RPFs**
    c. **All outcomes and datasets presented are suitable for RPF development. EPA should analyze all of the data instead of pre-selecting one endpoint or a subset of endpoints for RPF development**
    d. **EPA should further develop the options for deriving RPFs, including expanded statistical approaches to combining data across studies and outcomes**
4. **EPA needs to be clearer regarding aggregate exposure, particularly the likelihood of individuals with combinations of general population exposure, consumer exposure, and occupational exposure to phthalates**
    a. **EPA's conceptual model is unclear regarding combinations of consumer, occupational and general population exposures**
    b. **EPA should fully estimate the exposure contribution of non-attributable and non-TSCA sources**
    c. **EPA should broaden its consideration of potentially exposed or susceptible subpopulations (PESS)**
    d. **EPA should evaluate the potential for an individual to use multiple phthalate-containing consumer products**
    e. **EPA should further develop its understanding of the uses and limitations of NHANES data**
5. **EPA should apply a more rigorous and informative approach to risk characterization by combining the use of RPFs with improved dose-response assessment methods. EPA's proposed use of the margin of exposure (MOE) approach is not consistent with the "best available science"**
6. **EPA must use validated systematic review methods for the CRA to have a robust evidence base and consider risks to PESS as required under TSCA**

Section 2: Comments on *CRA Principles*:

1. **EPA must conduct cumulative risk assessments to comply with the TSCA requirements to use "the best available science" and to evaluate risks to potentially exposed or susceptible subpopulations (PESS)**
2. **EPA should include non-chemical stressors in TSCA CRAs**
3. **EPA's considerations for identifying chemicals that are "toxicologically similar" should be expanded to better incorporate mechanistic evidence and to identify cumulative chemical groups when evidence is less extensive**
4. **EPA's characterization of dose addition as conservative is incorrect. Recent evidence suggests it may underestimate risk, especially for sensitive subpopulations**

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

Sincerely,

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DETAILED COMMENTS

Section 1. Comments on the *Draft Phthalates CRA Approach*

1. EPA's review demonstrates that the evidence for toxicological similarity is abundant for each phthalate and each of the key outcomes considered

EPA has not yet conducted a systematic review of the phthalates health effects evidence. The determination of toxicological similarity should follow a comprehensive search of the literature. The evidence compiled in the Draft Phthalates CRA Approach, however, provides a strong basis for preliminary conclusions and for planning the approach to conducting a cumulative risk assessment of the phthalates.

There is strong scientific evidence for EPA's proposed conclusion that a CRA should be conducted for DEHP, BBP, DBP, DIBP, DCHP, and DINP as these phthalates are toxicologically similar and share a common adverse outcome. EPA bases its conclusion on a review of evidence for seven key outcomes (reduced gene expression in the fetal testes, reduced fetal testicular testosterone, reduced anogenital distance (AGD), nipple retention (NR), hypospadias, seminiferous tubule atrophy, and multinucleated gonocytes (MNG)) that each indicate the antiandrogenic effects of phthalates and are elements of phthalate syndrome. EPA states:

> The totality of rat data indicates that gestational exposure to DEHP, BBP, DBP, DIBP, and DCHP during the critical window of development leads to a disruption of fetal testicular steroidogenesis, which results in reduced fetal testicular testosterone production, reduced AGD, nipple/areolae retention, and hypospadias. Seminiferous tubule atrophy is also consistently observed following exposure to these five phthalates. Available rat data are remarkably consistent and support temporal and dose-response concordance. For DINP, available rat data also provide consistent evidence that gestational exposure to DINP disrupts steroidogenesis in the fetal testes in a dose-related manner…available data indicate consistent, dose-related increases in incidence of MNGs following gestational exposure to DEHP, BBP, DBP, DIBP, DCHP, and DINP.[6]

EPA's review demonstrates that the evidence is robust for each phthalate and for each of the key outcomes considered. EPA's conclusion is consistent with 2008 recommendations of the NAS in *Phthalates and Cumulative Risk Assessment: The Tasks Ahead*, and with the findings of the U.S. Consumer Product Safety Commission (CPSC) and several other government agencies.
While EPA presents an extensive array of evidence across seven outcomes that strongly support a conclusion of toxicological similarity, the evidence for any one of these outcomes **alone** is sufficient to establish toxicological similarity.

a. Shared key cellular events demonstrate toxicological similarity

The seven key outcomes of phthalate syndrome reviewed by EPA include reduced expression of cholesterol transport (*Scarb1, StAR*) and steroidogenesis (*Cyp11a1, 3bHSD, Cyp17A1*) genes in the fetal testes, reduced expression of *Insl3* mRNA, and reduced fetal testicular testosterone.

[6] U.S. EPA, "Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act" (2023). P 91

For these cellular-level key events, EPA finds:

> Across available rat studies (conducted with multiple strains, including Sprague-Dawley [SD], Wistar, and Long-Evans) of DEHP, BBP, DBP, DIBP, and DCHP, consistent dose-dependent decreases in mRNA expression of cholesterol transport and steroidogenesis genes in fetal testes were observed...For DINP, dose-dependent decreases in mRNA expression of cholesterol transport and steroidogenesis genes were observed in four out of five studies.[7]
>
> Consistent, dose-dependent reductions in *Insl3* mRNA were observed for DEHP, BBP, DBP, DIBP and DCHP across the available rat studies, regardless of strain tested…For DINP, three out of four studies (all conducted with SD rats) demonstrate that DINP can reduce fetal testicular mRNA expression of *Insl3* in a dose-dependent manner at doses as low as 10 mg/kg/day.[8]
>
> Available rat studies (conducted with Wistar, SD, and Long-Evans strains) of DEHP, BBP, DBP, DIBP, and DCHP provide consistent evidence that gestational exposure during the critical window of development leads to reduced fetal testicular testosterone and/or *ex vivo* fetal testicular testosterone production. Notably, the effect on fetal testicular testosterone consistently occurred in a dose-dependent manner… In 7 out of 9 studies, gestational exposure to DINP throughout the critical window of development dose-dependently reduced fetal testicular testosterone levels and/or *ex vivo* testosterone production.[9]

The available evidence consists of studies of multiple cellular key events from multiple labs, in multiple strains. EPA should synthesize the evidence using the approach used by the Agency's Integrated Risk Information System (IRIS).[10] Using the terms for strength of evidence judgments from the IRIS Handbook, either "robust" or "moderate" evidence for any single outcome should be regarded as sufficient to establish toxicological similarity. Each category of gestational events (reduced expression of cholesterol transport genes, reduced expression of steroidogenesis genes, reduced *Insl3* mRNA, and reduced fetal testicular testosterone) on its own provides more than enough evidence to support a "robust" determination and conclude that DEHP, BBP, DBP, DIBP, DCHP and DINP are toxicologically similar. Given the general understanding of the mechanisms involved in phthalate syndrome, a strong finding of toxicological similarity could be made for any chemical with the same cellular-level evidence demonstrated for the six phthalates, even in the absence of studies showing the postnatal outcomes (e.g., reduced AGD).

As stated by the NAS:

> any agent that can produce androgen insufficiency or block androgen-receptor signaling in the developing male fetus would have effects that are included in the array of malformations known to be caused by phthalates.[11]

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[7] U.S. EPA, "Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act" (2023). p 35-36

[8] *Id.* p *37*

[9] *Id.* p 42

[10] U.S. EPA, "ORD Staff Handbook for Developing IRIS Assessments," Reports & Assessments (Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, 2022), https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=356370.

[11] National Research Council, *Phthalates and Cumulative Risk Assessment*, 2008. p 7

> all chemicals that can induce some or all of the effects that make up the androgen-insufficiency syndrome should be subjected to cumulative risk assessment.[12]

EPA should use the published "key characteristics" of male reproductive toxicants when organizing and evaluating the evidence for cellular-level and organ-level effects.[13] The key characteristics represent established mechanisms and pathways of toxicity based on evidence from known male reproductive toxicants, and include: alters germ cell development, function, or death; alters somatic cell development, functions, or death; alters production and levels of reproductive hormones levels/functions; alters hormone receptor levels/functions; is genotoxic; induces epigenetic alterations; induces oxidative stress; and induces inflammation. Toxicological similarity of chemicals can be concluded based on shared key characteristics without having experimental evidence confirming the postnatal outcomes. EPA should use the key characteristics approach more generally to identify chemicals that are toxicologically similar for conducting cumulative risk assessment. Key characteristics have been published for carcinogens, cardiovascular toxicants, endocrine disrupting chemicals, female reproductive toxicants, male reproductive toxicants, hepatotoxicants, and immunotoxicants.[14,15,16,17,18,19,20]

b. Shared postnatal outcomes demonstrate toxicological similarity

The seven key outcomes of phthalate syndrome reviewed by EPA also include several postnatal outcomes, including reduced AGD, nipple retention (NR), hypospadias, seminiferous tubule atrophy, and multinucleated gonocyte formation.

For these downstream outcomes, EPA finds:

> Available experimental rat studies (conducted with Wistar, SD, and Long-Evans strains) of DEHP, BBP, DBP, DIBP, and DCHP provide consistent evidence that gestational exposure during the critical window leads to a dose-dependent reduction in male pup AGD.[21]

[12] National Research Council, *Phthalates and Cumulative Risk Assessment*. p 124
[13] Xabier Arzuaga et al., "Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments," *Environmental Health Perspectives* 127, no. 6 (2019): 065001, https://doi.org/10.1289/EHP5045.
[14] Martyn T. Smith et al., "Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis," *Environmental Health Perspectives* 124, no. 6 (June 2016): 713–21, https://doi.org/10.1289/ehp.1509912.
[15] Lars Lind et al., "Key Characteristics of Cardiovascular Toxicants," *Environmental Health Perspectives* 129, no. 9 (n.d.): 095001, https://doi.org/10.1289/EHP9321.
[16] Michele A. La Merrill et al., "Consensus on the Key Characteristics of Endocrine-Disrupting Chemicals as a Basis for Hazard Identification," *Nature Reviews Endocrinology* 16, no. 1 (January 2020): 45–57, https://doi.org/10.1038/s41574-019-0273-8.
[17] Ulrike Luderer et al., "Proposed Key Characteristics of Female Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment," *Environmental Health Perspectives* 127, no. 7 (n.d.): 075001, https://doi.org/10.1289/EHP4971.
[18] Ivan Rusyn et al., "Key Characteristics of Human Hepatotoxicants as a Basis for Identification and Characterization of the Causes of Liver Toxicity," *Hepatology* 74, no. 6 (2021): 3486–96, https://doi.org/10.1002/hep.31999.
[19] Dori R. Germolec et al., "Consensus on the Key Characteristics of Immunotoxic Agents as a Basis for Hazard Identification," *Environmental Health Perspectives* 130, no. 10 (2022): 105001, https://doi.org/10.1289/EHP10800.
[20] Arzuaga et al., "Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments."
[21] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 51

> A consistent dose-dependent increase in NR was observed for male pups gestationally exposed to DEHP, BBP, DBP, DIBP, or DCHP when evaluated between PNDs 11 to 14, which is consistent with OECD recommendations for timing of when evaluation of this outcome should occur.[22]
>
> Across the six available studies conducted with SD rats, consistent dose-related increases in hypospadias were observed starting at doses as low as 100 mg/kg/day DEHP…For DBP, consistent dose-related increases in hypospadias were observed across all available studies of SD (6 studies) and Wistar (2 studies) rats…the available studies of BBP, DIBP and DCHP report consistent dose-related increases in hypospadias.[23]
>
> Available studies consistently demonstrate that exposure to DEHP, BBP, DBP, DIBP, and DCHP lead to a dose-dependent increase in incidence of seminiferous tubule atrophy.[24]
>
> The available rat studies (conducted with both SD and Wistar rats) consistently demonstrate that gestational exposure to DEHP, DBP, DCHP, and DINP can increase MNG formation in a dose-dependent manner.[25]

The available evidence consists of studies of multiple adverse outcomes from multiple labs in multiple strains. Using the terms for strength of evidence judgments from the IRIS Handbook, either "robust" or "moderate" evidence for any single outcome should be regarded as sufficient to establish toxicological similarity. Each category of outcomes (e.g., reduced AGD) on its own provides more than enough evidence to support a "robust" determination and conclude that DEHP, BBP, DBP, DIBP, and DCHP are toxicologically similar. Effects of DINP on several downstream outcomes (AGD and NR, no hypospadias) in rat studies are described as less consistent, but, as EPA, observed this is consistent with a lower potency of DINP – that is, the difference between DINP and the other five phthalates is quantitative and not qualitative. Further, multiple studies demonstrated increased MNG formation in rats with DINP exposure.

The evidence assembled for each of these outcomes by itself would be more than sufficient to support a conclusion of toxicological similarity of the phthalates. Although there is a strong mechanistic understanding of how phthalate exposure leads to these downstream events, that understanding is not necessary to find that the phthalates are toxicologically similar. The evidence for any one of the postnatal outcomes satisfies the EPA standard of "shared apical outcome"[26] and the NAS (2009) standard of "common adverse outcome."[27]

c. EPA presents ample evidence to support a conclusion of toxicological similarity for DINP

As noted above, multiple studies have demonstrated that DINP exposure reduces expression of cholesterol transport and steroidogenesis genes, reduces expression of *Insl3*, reduces fetal testicular testosterone, and increases MNG formation. Any one of these findings is sufficient to conclude that DINP is toxicologically similar to DEHP, BBP, DBP, DIBP, and DCHP. Reduced fetal testicular testosterone

[22] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 59
[23] *Id.* p 64
[24] *Id.* p 69
[25] *Id.* p 74
[26] *Id.* p 27
[27] National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, *Science and Decisions: Advancing Risk Assessment* (Washington (DC): National Academies Press (US), 2009), http://www.ncbi.nlm.nih.gov/books/NBK214630/.

corresponds to the key characteristic for male reproductive toxicity of "alters production and levels of reproductive hormones levels/functions"[28] and thus, this outcome alone provides robust evidence of toxicological similarity and a strong basis for inclusion of DINP in the phthalates CRA.

EPA summarizes the evidence regarding DINP and some postnatal outcomes to be less consistent as compared with the other phthalates examined. EPA correctly notes that these results are "consistent with findings for steroidogenic gene expression, fetal testicular testosterone, AGD, and NR results, all of which indicate DINP is a less potent antiandrogen than other phthalates."[29] Further, EPA did identify increased MNG formation as a consistent postnatal outcome for DINP.

Findings of DINP for several postnatal outcomes, even if less consistent than for the other phthalates, is sufficient to establish toxicological similarity of DINP as they demonstrate the ability of this chemical to induce phthalate syndrome. Further, even an absence of postnatal findings for DINP would not undermine the finding of toxicological similarity, as the evidence for gestational outcomes is more than sufficient.

In addition, as observed by EPA, inclusion of DINP in the phthalates cumulative risk assessment is important because it has higher exposure levels than the other phthalates, meaning that DINP is likely to be a substantial contributor to cumulative phthalates risk.

d. The application of dose addition in the phthalates CRA is appropriate

Based on its findings of toxicological similarity, EPA proposes to apply dose addition methods for conducting the phthalates CRA. This is consistent with EPA's 2000 *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures,*[30] NAS's 2008 recommendations in *Phthalates and Cumulative Risk Assessment: The Tasks Ahead,*[31] and assessments conducted by the CPSC and other government agencies. Recent experimental evidence demonstrates that dose addition is applicable at low doses for multiple male reproductive toxicants with differing molecular-level key events.[32,33]

It is important that EPA state that dose addition is not a conservative assumption. EPA's *CRA Principles* document says that dose addition is a conservative approach, and this statement is not consistent with the best available science. The NAS said that dose addition provides good predictions of the effects of phthalate mixtures, and might underestimate the effects:

> evidence from the recent peer reviewed scientific literature shows not only that phthalates produce mixture effects but that the effects are often predicted well by using the dose-addition concept. That is also true for other classes of antiandrogens and for combinations of phthalates with such antiandrogens. Although a variety of molecular mechanisms are at play, dose addition

[28] Arzuaga et al., "Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments."
[29] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act.
[30] U.S. Environmental Protection Agency, "Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures," August 2000.
[31] National Research Council, *Phthalates and Cumulative Risk Assessment*. p 65
[32] Justin M. Conley et al., "A Mixture of 15 Phthalates and Pesticides below Individual Chemical No Observed Adverse Effect Levels (NOAELs) Produces Reproductive Tract Malformations in the Male Rat," *Environment International* 156 (November 1, 2021): 106615, https://doi.org/10.1016/j.envint.2021.106615.
[33] Justin M. Conley et al., "Mixed 'Antiandrogenic' Chemicals at Low Individual Doses Produce Reproductive Tract Malformations in the Male Rat," *Toxicological Sciences* 164, no. 1 (July 1, 2018): 166–78, https://doi.org/10.1093/toxsci/kfy069.

> provided equal or better approximations of mixture effects compared with independent action…Experimental evidence demonstrates that toxic effects of phthalates and other antiandrogens are similar despite differences in the molecular details of the mechanisms, including metabolism, distribution, and elimination…The case for using dose addition as an approximation for mixture risk assessment of phthalates and other antiandrogens is strong.[34]
>
> there are some data that indicate toxic interactions (greater than dose-additive effects) when hypospadias and other genital malformations are evaluated as the end points of concern. Rider et al. (2008) found that BBP, DBP, DEHP, vinclozolin, procymidone, linuron, and prochloraz induced more hypospadias than predicted on the basis of dose addition…it is not possible to say with certainty whether the observations represent a true synergism with respect to dose addition, but the possibility cannot be ruled out.[35]

Please see comments below (section 2, comment 4) on the *CRA Principles* document for further discussion of this issue.

e. EPA should include other chemicals and non-chemical stressors in the phthalates CRA

EPA's CRA should not be restricted to chemicals currently undergoing TSCA risk evaluation. The *Draft Phthalates CRA Approach* considers only the seven phthalates with ongoing risk evaluations for inclusion. To fully characterize the risk of phthalates on the apical and intermediate endpoints of phthalate syndrome, the CRA should incorporate other chemical stressors with shared mechanistic or apical endpoints as phthalate syndrome into the CRA. Studies have identified dipentyl phthalate (DPeP) diisopentyl phthalate (DIPP), diheptyl phthalate (DHeP), diisoheptyl phthalate (DiHeP), and others as additional phthalates that produce phthalate syndrome outcomes.[36,37] Numerous other chemicals, including several pesticides for example, are known or suspected to be endocrine disrupting compounds that can act on androgen receptors and be associated with outcomes included in phthalate syndrome.[38] The pesticides vinclozolin, procymidon, among others, have been shown to be androgen receptor agonists and associated with apical outcomes related to phthalate syndrome.[39]

The EPA should account for pesticides and other chemicals that act on the same pathway (shared cellular-level or organ-level events) or have the same apical endpoints associated with phthalate syndrome, or other outcomes being considered in the risk assessment. This can be accomplished with the inclusion of adjustment factors in the risk evaluation.[40] Not accounting for these simultaneous chemical exposures will underestimate the health effects of phthalates in the CRA. Studies documenting the applicability of dose addition at low doses, described in the *Draft Phthalates CRA Approach*, further

[34] National Research Council, *Phthalates and Cumulative Risk Assessment*. p 133-134
[35] *Id.* p 123
[36] Leon Earl Gray et al., "Genomic and Hormonal Biomarkers of Phthalate-Induced Male Rat Reproductive Developmental Toxicity Part II: A Targeted RT-QPCR Array Approach That Defines a Unique Adverse Outcome Pathway," *Toxicological Sciences: An Official Journal of the Society of Toxicology* 182, no. 2 (August 3, 2021): 195–214, https://doi.org/10.1093/toxsci/kfab053.
[37] Andreas Kortenkamp, "Which Chemicals Should Be Grouped Together for Mixture Risk Assessments of Male Reproductive Disorders?," *Molecular and Cellular Endocrinology* 499 (January 1, 2020): 110581, https://doi.org/10.1016/j.mce.2019.110581.
[38] Sílvia Moreira et al., "Pesticides and Male Fertility: A Dangerous Crosstalk," *Metabolites* 11, no. 12 (November 25, 2021): 799, https://doi.org/10.3390/metabo11120799.
[39] A. Kortenkamp, "Which Chemicals Should Be Grouped Together for Mixture Risk Assessments of Male Reproductive Disorders?" Molecular and Cellular Endocrinology 499 (2020) 110581, https://doi.org/10.1016/j.mce.2019.110581
[40] Julia R. Varshavsky et al., "Current Practice and Recommendations for Advancing How Human Variability and Susceptibility Are Considered in Chemical Risk Assessment," *Environmental Health* 21, no. Suppl 1 (January 12, 2023): 133, https://doi.org/10.1186/s12940-022-00940-1.

demonstrate the importance of considering mixtures of chemicals with anti-androgen disruption and the potential of many chemicals to contribute to phthalate syndrome effects:

> Mixture studies by Conley et al. demonstrate several key points. First, they provide evidence to support the concept of "something from nothing" since effects were observed at exposure levels below the individual chemical LOAELs (i.e., LOAEL/80 in (Conley et al., 2018)) and NOAELs (i.e., NOAEL/15 in (Conley et al., 2021)). Secondly, these studies provide evidence to support the applicability of dose addition at low doses for mixtures of phthalates and other antiandrogens. Finally, these studies further demonstrate the applicability of dose addition for mixtures of antiandrogens with mixed MOAs. For example, although the tested chemicals disrupt androgen action through multiple molecular initiating events (e.g., finasteride is a 5α-reductase inhibitor, flutamide and vinclozolin are androgen receptor antagonists, linuron inhibits steroidogenic CYPs and is an androgen receptor antagonist, while the molecular initiating event for phthalates is unknown), these chemicals cause common key cellular events and lead to common adverse effects on development of the male reproductive tract in a manner consistent with dose addition.[41]

EPA should also use the proposed key characteristics of male reproductive toxicants[42] (listed above, comment 1.a) to identify additional chemicals that may act in a dose-additive manner with phthalates for inclusion in the CRA. Chemicals with "robust" or "moderate" evidence of one or more of the key characteristics should be identified as anti-androgens and accounted for in the phthalates CRA.

Non-chemical stressors can also impact the relationship between phthalate exposure and outcomes related to phthalate syndrome. Prenatal stress and phthalates may interact with effects on fetal development relevant to androgen receptors and have been shown to affect anogenital distance.[43] For example, women with low prenatal stress (a non-chemical stressor) had infant boys with larger anogenital distances on average than high prenatal stress individuals[44] (shortened anogenital distance is the adverse health outcome).

We recommend EPA use a broader and more scientifically appropriate definition of "non-chemical stressors" (see comments on *CRA Principles* Section 2, comment 2). The definition of non-chemical stressors provided by the EPA defines psychosocial factors as "poor diet, smoking, and illicit drug use." This definition is scientifically inappropriate as psychosocial stressors include extrinsic factors that are outside an individual's control. Further, this language places the blame and responsibility of these psychosocial stressors on individuals and attributes them to "lifestyle choices." The EPA should use the broader definition of social determinants of health, that encompasses psychosocial stress, and is used by the Centers for Disease Control and Prevention (CDC) and adapted from the World Health Organization (WHO):

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[41] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 100

[42] Xabier Arzuaga et al., "Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments," *Environmental Health Perspectives* 127, no. 6 (2019): 065001, https://doi.org/10.1289/EHP5045.

[43] Emily S. Barrett et al., "Prenatal Stress as a Modifier of Associations between Phthalate Exposure and Reproductive Development: Results from a Multicentre Pregnancy Cohort Study," *Paediatric and Perinatal Epidemiology* 30, no. 2 (2016): 105–14, https://doi.org/10.1111/ppe.12264.

[44] Tye E. Arbuckle et al., "Do Stressful Life Events during Pregnancy Modify Associations between Phthalates and Anogenital Distance in Newborns?," *Environmental Research* 177 (October 1, 2019): 108593, https://doi.org/10.1016/j.envres.2019.108593.

they are the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies, racism, climate change, and political systems.[45]

The inclusion of psychosocial stressors in a cumulative risk assessment, in particular naming stressors like racism, poverty and exposure to violence, would align with the Agency's goals around environmental justice and would ensure a more robust estimate of the risk from exposure to phthalates, limiting underestimation of risk.[46,47]

f. EPA should conduct cumulative risk assessments of phthalates for other health endpoints in addition to the anti-androgenic effects

In the 2008 *Phthalates and Cumulative Risk* report, the NAS identified that health effects other than phthalate syndrome could be important. More recent reviews have found phthalate exposure to be associated with liver toxicity, female reproductive toxicity, and neurodevelopmental outcomes.[48,49,50] The EPA says it will include other health outcomes in the individual phthalate risk evaluations but not in the CRA.[51] Evidence continues to grow on these adverse health outcomes and needs to be considered in the CRA through systematic review (see comments below on systematic review in comment 6). It is possible to conduct a CRA on subsets of phthalates that are associated with developmental neurotoxicity, reproductive toxicity and liver toxicity and EPA should not exclude these other health endpoints from the CRA so early in the risk assessment and decision-making process. The CRA should carry forward the available adverse health outcomes, even if not all phthalates are associated with that outcome.

2. EPA should model multiple outcomes, with multiple approaches, to inform its ultimate selection of relative potency factors (RPFs)

EPA describes its approach to addressing phthalate syndrome as "focusing on the most sensitive effect."[52] This description, however, is at odds with EPA's discussion of approaches to developing relative potency factors, which appropriately considers data from multiple effects. First, as EPA notes in its very next sentence: "One potential challenge with this approach is that no single outcome may be identified as the most sensitive across the six toxicologically similar phthalates."[53] It will take a

[45] CDC, "Social Determinants of Health," Centers for Disease Control and Prevention, December 8, 2022, https://www.cdc.gov/about/sdoh/index.html.
[46] Office of General Counsel, U.S. EPA, "EPA Legal Tools to Advance Environmental Justice: Cumulative Impacts Addendum," *360R22002*, January 2023, https://www.epa.gov/system/files/documents/2022-12/bh508-Cumulative%20Impacts%20Addendum%20Final%202022-11-28.pdf.
[47] Executive Order 14096, "Executive Order 14096. Revitalizing Our Nation's Commitment to Environmental Justice for All," April 21, 2023, https://www.govinfo.gov/content/pkg/FR-2023-04-26/pdf/2023-08955.pdf.
[48] ATSDR, "Toxicological Profile for d(2-Ethylhexyl)Phthalate (DEHP) [ATSDR Tox Profile]" (Atlanta, GA, 2022), https://www.atsdr.cdc.gov/ToxProfiles/tp9.pdf.
[49] EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) 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," *EFSA Journal* 17, no. 12 (2019): e05838, https://doi.org/10.2903/j.efsa.2019.5838.
[50] U.S. CPSC, "Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (with Appendices).," 2014, https://www.cpsc.gov/s3fs-public/CHAP-REPORT-With-Appendices.pdf.
[51] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. at pp 27
[52] *Id.* p 98
[53] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 98

substantial analysis of all outcomes to determine which is the most sensitive effect; EPA should not prematurely narrow the list of outcomes considered as this could erroneously leave out data important to RPF estimation and possibly underestimate risk. Second, determination of the most sensitive effect in a CRA is more complex than in the case of a single-chemical analysis. If there are differences in relative potencies across the phthalate syndrome effects (see further discussion below), then the most sensitive effect cannot be identified simply by comparing BMD/BMDL values. Instead, the effect posing the greatest risk will depend on the relative exposure of each phthalate combined with the relative potencies. This suggests that different sets of RPFs and different outcomes could be most sensitive for different exposure scenarios. Third, EPA's discussion of the various approaches indicates that there are other considerations besides sensitivity in determining which outcome(s) may best support development of RPFs (e.g., the number and consistency of studies for a particular effect; comparability of methods across different studies; the extent of data for each of the six phthalates for an effect; potential advantages of combining data for multiple effects).

Following a comprehensive search of the literature to identify all relevant studies, EPA should model multiple outcomes, with multiple approaches, to inform its ultimate selection of RPFs. This should be viewed as analogous to conducting hazard assessment, dose-response assessment, and risk characterization of multiple endpoints, as EPA has done in many of its completed TSCA risk evaluations. In addition, EPA should consider statistical techniques that integrate data from multiple outcomes for deriving RPFs.

EPA discusses "Addressing phthalate syndrome as a whole" as an approach that it considered but does not intend to pursue. This concept allows for combined consideration of multiple related effects in a single analysis and should be further developed by EPA. The draft CRA Approach document describes a publication by Blessinger et al. on this approach, noting its data needs and limitations.[54] While treatment of phthalate syndrome as a whole may not be feasible to apply for all studies, further exploration of the approach with a limited number of studies may be useful. Further work testing this approach should incorporate a broader set of phthalate syndrome outcomes than was applied by Blessinger et al., and use of a single outcome measure (i.e., any trait of phthalate syndrome, rather than grouping outcomes by severity) should also be considered. In addition, there are other approaches to combine data for different phthalate syndrome outcomes that should be applied in developing RPFs (see comment 3 below).

3. Application of RPFs is appropriate for the phthalates CRA. EPA's discussion of RPFs should incorporate additional considerations and approaches

EPA discusses the two methods for quantifying the risks of exposures to multiple phthalates: the hazard index (HI) approach and relative potency factor (RPF) approach. Both approaches involve weighting exposures to different chemicals in a CRA using health effects data. The HI uses reference doses (RfDs) or reference concentrations (RfCs) for weighting the exposures of each chemical by first computing the ratio of exposure to reference value for each chemical, then summing this ratio across chemicals. The HI is a unitless measure that cannot be used to estimate risk in probability-based terms, but instead is used to determine whether combined exposures represent a potential concern (typically HI $\geq$ 1) or not (HI < 1). The RfD/RfCs used for calculating an HI may or may not be for a shared effect, and they may incorporate different uncertainty factors for different chemicals.

[54] Todd D. Blessinger et al., "Ordinal Dose-Response Modeling Approach for the Phthalate Syndrome," *Environment International* 134 (January 1, 2020): 105287, https://doi.org/10.1016/j.envint.2019.105287.

The RfDs and RfCs do not represent a "safe" level of exposure for the population and it has been shown there can be substantial risks at the RfD/RfC.[55,56] Thus, using the HI and a bright line of HI < 1 to determine whether there is a risk is scientifically inappropriate as it incorporates the flawed assumption that there is a level of exposure to toxic chemicals that can be characterized as "safe" for the entire exposed population.[57]

RPFs are derived using ratios of benchmark doses (BMDs) calculated for different chemicals in the CRA to express whether each chemical is more or less potent than the others, as well as the magnitude of the difference. The BMDs used to calculate RPFs are usually for the same effect and the same benchmark response (BMR), such as a 5% or 10% effect level. RPFs are used to weight the exposures to each chemical; the weighted exposures are then summed to produce a combined mixture exposure that is expressed as the equivalent of exposure to a single chemical in the group (e.g., mg/kg/day of "index chemical equivalents"). Uncertainty factors are not applied in developing RPFs or calculating index chemical equivalents, though they may be applied in various ways in the associated dose-response analysis and/or risk characterization.

We agree with EPA's decision to use RPFs for the phthalates cumulative risk assessment. The available data are robust for development of RPFs, and index chemical equivalents are highly useful for risk characterization. Although we encourage exploration of multiple approaches to RPF development, we emphasize that the principles of including all toxicologically similar phthalates in the CRA (to avoid underestimation of risk) and use of the RPF approach (to enable a more informative approach to risk estimation; see comments in section 3.a below) are much more important than the potential uncertainties in RPF values, which may not have a large impact on the magnitude of the risk estimates and can be assessed in sensitivity analyses in the CRA.

EPA's proposed conceptual model for the phthalates CRA does not include RPF development. Development of RPFs is a critical element in conducting the CRA and should be added as Step 2 in the conceptual model.

a. EPA should use the RPF approach for the phthalates cumulative risk assessment, and it should describe the advantages of the RPF approach in the *Draft Phthalates CRA Approach*

EPA provides a useful and concise description of both the HI and RPF approaches, but it does not discuss the advantages and disadvantages of each approach. Critical advantages of the RPF approach are that it provides a useful measure of cumulative exposure to multiple phthalates that can be used in conjunction with probabilistic dose-response assessment methods to estimate risks, i.e., the proportion of the exposed population expected to experience an effect, and that (unlike the HI approach) it does not incorporate the flawed assumption of a "safe" or "no risk" level of exposure.

EPA presents its decision to use RPFs as simply a question of whether the data are sufficient, without explaining why RPFs are preferred:

[55] Weihsueh A. Chiu et al., "Beyond the RfD: Broad Application of a Probabilistic Approach to Improve Chemical Dose–Response Assessments for Noncancer Effects," *Environmental Health Perspectives* 126, no. 6 (n.d.): 067009, https://doi.org/10.1289/EHP3368.
[56] Greylin H. Nielsen et al., "Application of Probabilistic Methods to Address Variability and Uncertainty in Estimating Risks for Non-Cancer Health Effects," *Environmental Health* 21, no. 1 (January 12, 2023): 129, https://doi.org/10.1186/s12940-022-00918-z.
[57] Woodruff et al., "A Science-Based Agenda for Health-Protective Chemical Assessments and Decisions."

> Robust dose-response data are available across the toxicologically similar phthalates for multiple key outcomes associated with phthalate syndrome. Given the available data, EPA believes there is sufficient information available to support the development of RPFs for phthalates. Therefore, EPA is proposing to use an RPF approach for the phthalate CRA conducted in support of TSCA section 6 risk evaluations.[58]

In contrast, EPA has previously discussed advantages of RPFs for assessing each cumulative assessment group [CAG] in the pesticides program:

> OPP will use the RPF approach for estimating cumulative risk because it can utilize dose-response information to provide an estimate of the common toxicity, and thus allows for the quantification of exposure as it relates to the joint risk of the CAG.[59]

EPA is correct that the phthalates data are robust for RPF development, but EPA should go further to discuss the advantages of using RPFs in TSCA CRAs in general, and specifically for the case of phthalates CRA. A critical advantage is that the end result of applying RPFs is an estimate of index chemical equivalent exposures (in a relevant exposure metric such as mg/kg/day), which is much more informative and useful for risk characterization than the unitless HI.

A critical disadvantage of the HI approach is that it perpetuates the flawed notion that a "safe" level of exposure to mixtures of chemicals can be identified and that an RfD/RfC represents a safe level for an individual chemical.[60,61] The variability in characteristics affecting responses to chemical exposures across the population results in a wide range of individual thresholds and an expectation of dose–response relationships in the population that extend to low, commonly experienced doses, with probability of risk at doses below the traditional RfD and RfC. It therefore cannot be presumed that an HI < 1 is risk-free.

In *Science and Decisions* the NAS discussed problems with this concept of a "safe" level for single chemicals:

> The current formulation of the RfD is problematic because of its application as a determinant of risk vs no risk of regulatory importance, and it lacks a quantitative description of the risk at different doses. It hinders risk-risk and risk-benefit comparisons and risk management decision-making and does not make the best possible use of available scientific evidence…quantification of risk (along with the attendant uncertainty) not only at the RfD but along the dose continuum is an important advance for risk benefit analysis.[62]

Science and Decisions also explained that differences across individuals in exposures to multiple chemicals is an important variability factor that means there should not be an assumption of a population-level safe level. The concept of a "safe" level of exposure is therefore even more unjustifiable in an assessment of chemical mixtures, as exposure to multiple chemicals is one of the

[58] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 102
[59] US EPA, OPP, "Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity" (Washington, D.C., January 14, 2002), https://www.epa.gov/sites/default/files/2015-07/documents/guidance_on_common_mechanism.pdf. p 32
[60] Tracey Woodruff et al., "A Science-Based Agenda for Health-Protective Chemical Assessments and Decisions." 2023.
[61] Al McGartland et al., "Estimating the Health Benefits of Environmental Regulations | Science," *Science* 357, no. 6350 (August 4, 2017): 457–58.
[62] National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, *Science and Decisions*. p 177

factors that increases variability in response across the exposed population. In contrast to the HI, the RPF approach can be used in conjunction with more quantitative and more informative approaches to dose-response analysis and risk characterization. Please see related comments below (Comment 5 on *Draft Phthalates CRA Approach*) regarding the approach to risk characterization for the phthalates CRA.

EPA should discuss the advantages of the RPF approach in both the *Draft Phthalates CRA Approach* and the *CRA Principles* document.

b. EPA should state its conceptual approach to RPF development before outlining the proposed options for deriving RPFs

EPA presents seven datasets and six analytic options for development of RPFs for the phthalates CRA, outlining the data available and advantages and disadvantages of each option. The discussion, however, seems to embed several unstated concepts and assumptions that should be considered more carefully and discussed explicitly.

EPA's discussion of the datasets and options seems to imply that it intends to develop a single set of RPFs to use for all phthalate syndrome endpoints. This may be the best approach, but it warrants further discussion. The preliminary potency data (ED50s for each phthalate) presented for each outcome demonstrate significant variability; for example, DBP appears to have low potency (relative to the other phthalates) for fetal cholesterol transport and steroidogenesis genes, and relatively high potency for nipple retention. Perhaps the differences in relative potency will change when EPA conducts modeling at lower BMRs (e.g., 5%, 10% effect levels); however, the differences in relative potencies across outcomes suggested by the ED50s are important to consider in developing the approach to RPF development. If there is true variability in relative potencies across the various gestational and postnatal outcomes, this raises a question of whether different sets of RPFs should be developed for application to different outcomes; or, if a single set of RPFs remains a preferred approach even after considering that variability, then approaches for integrating data across all outcomes should be considered. Alternately, if the observed differences in relative potencies are believed to represent experimental variability and limitations of the available data rather than true differences in potency of phthalates across outcomes, this suggests that a single set of RPFs should be developed for application to all outcomes and raises questions regarding whether preferred outcomes for developing a single set of RPFs can be identified or whether statistical approaches that integrate data across outcomes should be applied. EPA should expand its discussion of RPF datasets and options to outline its interpretation of the differences in relative potencies suggested by the ED50s and the implications of that interpretation for RPF development. In addition, EPA should consider how much the variability in RPFs derived from different outcomes may matter to its ultimate CRA risk estimates as it plans its approach to deriving RPFs. While different approaches to RPFs may be tested, decisions on how much effort to put into RPF development should consider whether alternate RPF values will affect the ultimate decisions regarding unreasonable risks of the phthalates.

c. All outcomes and datasets presented are suitable for RPF development. EPA should analyze all of the data instead of pre-selecting one endpoint or a subset of endpoints for RPF development

EPA should retain all the presented datasets, augmented as appropriate by a comprehensive search, for RPF development. Setting aside datasets before completing the necessary systematic review steps and conducting further analysis would remove evidence informative to the ultimate selection of RPFs (see

comment 6 on systematic review). Comparisons of candidate RPFs calculated using different datasets (or combinations of datasets) will help illuminate understanding of the potential ranges of plausible RPF values. In addition, pre-selecting certain datasets for RPF development based on a notion that they represent the most sensitive outcomes could undermine the quality of the ultimate risk estimates produced in the CRA; as discussed above, identification of most sensitive outcomes requires integration of the RPFs with exposure data for each phthalate.

EPA should model multiple outcomes, with multiple approaches, to inform its ultimate selection of RPFs. This should be viewed as analogous to conducting hazard assessment, dose-response assessment and risk characterization of multiple endpoints as EPA has done in most of its completed TSCA risk evaluations. In addition, EPA should consider the possible use of statistical techniques that integrate data from multiple outcomes (discussed further below).

EPA states that various aspects of the datasets reduce its confidence in using several postnatal outcomes for RPF development. Some of these statements are poorly supported or scientifically inappropriate. Regarding use of AGD for RPF development, EPA says:

> statistically significant effects on AGD are less consistently reported for DINP across studies that test comparable doses (*i.e.,* DINP reduced AGD in two of six studies). Inconsistency in the DINP dataset reduces EPA's confidence in deriving RPFs based on this outcome.[63]

This rationale places excessive emphasis on statistical significance in studies of DINP and suggests that EPA has reduced confidence in using AGD data to develop RPFs for <u>all</u> phthalates because there are "inconsistent" data for only <u>one</u> phthalate. Elsewhere in the document EPA has appropriately observed that differences in postnatal findings for DINP reflect differences in potency and not differences in effects. Further, differences in the data for DINP should not stop EPA from developing candidate RPFs for this outcome. EPA should proceed with developing candidate RPFs using AGD data for all phthalates, including DINP. If a statistical model cannot be fit to the data for DINP, EPA should use data imputation methods or integrated modeling of multiple outcomes to fill this gap (see comment 3.d below). In Options 5 and 6, EPA proposes combining the data across postnatal outcomes, which better represents how it should proceed as compared with a statement of reduced confidence in using AGD data for RPF development.

Regarding use of nipple retention data for RPF development, EPA says:

> although male pup nipple/areolae retention is a biomarker of disrupted androgen action in rodents, it is not directly a human relevant effect. This uncertainty reduces EPA's confidence in deriving RPFs based on nipple/areolae retention in male pups.[64]

It is scientifically inappropriate for EPA to dismiss nipple retention as not indicative of human harm, as nipple retention in rodents is widely accepted as an indication of disrupted fetal androgen activity and relevant to human health risk assessment; as stated in Table 3-1, this endpoint has been used as a critical outcome in assessments by the CPSC, Health Canada, and the Danish EPA. The fact that this

[63] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 104

[64] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 104

effect is not observed in humans should have no bearing on the confidence in use of this outcome for RPF development.

EPA has not considered *Insl3* data for RPF derivation. After presenting relative potency data (ED50s) for *Insl3* in Table 3-21, no mention is made of this outcome in the discussion of RPF datasets and options in Section 4.4; it is not clear why. The ED50s for *Insl3* indicate a different pattern of relative potencies, with higher relative potency for DEHP, DBP, and DIBP than for other gene expression endpoints.

d. EPA should further develop the options for deriving RPFs, including expanded statistical approaches to combining data across studies and outcomes

EPA presents six options under consideration for deriving RPFs. Options 1-4 describe various approaches to use of data on reduced fetal testicular steroidogenic gene expression and reduced fetal testicular testosterone production. Options 5-6 describe approaches to use of data on postnatal outcomes, including reduced AGD, NR, seminiferous tubule atrophy, and hypospadias.

The options represent use of multiple datasets for multiple outcomes that are all relevant to estimating relative potencies of the six phthalates. The options represent different approaches to combining data across studies and outcomes for deriving RPFs. For example, for any specified outcome RPFs might be calculated using data from individual studies (Option 1), or from multiple studies combined in a meta-regression (Option 2). Data from different outcomes (e.g., reduced gene expression and reduced fetal testosterone) might be combined using the output of individual study models (Option 3) or meta-regression (Option 4) – though no particular approach to combining RPFs across the outcomes under these options is mentioned. For postnatal effects, EPA suggests two options that each involve modeling each postnatal effect separately and then combining RPFs across outcomes – though again no particular approach to combining BMDs across outcomes is mentioned.

We agree that combining data across outcomes for the postnatal effects is likely to be a helpful approach for addressing the challenges presented by the datasets for these outcomes, and these options are far preferable to excluding any of the identified postnatal outcomes from modeling to develop candidate RPFs. However, EPA should go further in considering approaches for combining data. First, EPA should describe statistical methods for combining RPFs across outcomes (Options 3, 4, 5 and 6). As written, it is unclear whether EPA is thinking of computing simple averages of RPFs or employing more complex statistical techniques. Second, EPA should consider broader combinations of datasets for deriving RPFs. The best approach to RPF development may be one that integrates all of the identified datasets for all outcomes (gestational and postnatal) in a single model or modeling construct. Techniques such as nested or multi-level models (e.g., Bayesian hierarchical modeling[65]) or structural equation models[66] may be applicable and useful for computing RPFs. In a nested model, BMDs may be computed for individual studies, then composited at the level of outcomes and combined across outcomes in a single model. A structural equation model would apply the concept that there is a single "true" set of latent (or unobserved) RPFs that can be estimated by using all the relevant observed data. EPA should explore the possible application of these and other techniques that may provide a formal statistical construct to the concept of combining the identified datasets, particularly if they resolve other challenges in modeling the outcomes separately or in choosing from RPFs produced by different

[65] Daniel A. Axelrad et al., "Dose–Response Relationship of Prenatal Mercury Exposure and IQ: An Integrative Analysis of Epidemiologic Data," *Environmental Health Perspectives* 115, no. 4 (April 2007): 609–15, https://doi.org/10.1289/ehp.9303.
[66] Esben Budtz-Jørgensen et al., "Structural Equation Models for Meta-Analysis in Environmental Risk Assessment," *Environmetrics* 21, no. 5 (2010): 510–27, https://doi.org/10.1002/env.1000.

options/outcomes. If applicable and tractable, these approaches may enable EPA to make optimal use of all the available data and reduce the need for selecting particular datasets, outcomes and models for RPFs.

4. EPA needs to be clearer regarding aggregate exposure, particularly the likelihood of individuals with combinations of general population exposure, consumer exposure, and occupational exposure to phthalates

The *Draft Phthalates CRA Approach* states that EPA will combine non-attributable and non-TSCA sources with general population, occupational, and fenceline exposures, yet further detail and justification in how these sources will be combined is needed. The EPA states:

> EPA recognizes that some individuals may be part of multiple populations and may require additional combinations of exposures. For example, combining occupational exposures with consumer exposures and fenceline exposures for workers who use consumer products at home and who live near the fenceline of a facility with phthalate releases.[67]
>
> EPA is proposing to use environmental monitoring data and modeling to build scenarios for estimating non-attributable and non-TSCA human exposure to phthalates through relevant pathways of exposure using a scenario-based approach. Under this approach, non-attributable and non-TSCA phthalate exposure will be estimated for the susceptible subpopulations identified in section 5 by applying exposure factors specific to each lifestage.[68]

However, the exposure assessments for each phthalate will be completed separately for general population, occupational exposures and fenceline exposures. Details on how the EPA will combine these exposures, and under what circumstances are lacking and need to be clarified.

a. EPA's conceptual model is unclear regarding combinations of consumer, occupational and general population exposures

Individuals are often a part of multiple exposure populations, and although separation of exposure assessment into categories of occupational, general population, and consumer exposures is a practical approach, it involves a risk of underestimating aggregate exposure. Fully characterizing exposure to phthalates in the CRA requires anticipating that many in the population will have combinations of exposures across exposure assessment categories:

> A complete aggregate exposure assessment would account for individuals who experience combinations of inhalation and dermal exposure at work, contact with multiple consumer products at work or home and are exposed to contamination air or drinking water in their communities.[69]

[67] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 15

[68] *Id.* 128

[69] Rayasam et al., "Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States." *Environmental Science & Technology, 2022 September 6; 56* (17):11969-11982. doi:10.1021/acs.est.2c02079

For example, a worker with occupational exposures is also part of the general population, possibly also be part of a fenceline community, and may also be a user of phthalate-containing consumer products. It has been demonstrated (based on evidence from NHANES) that almost everyone in the U.S. has daily general population exposures to the phthalates and the NHANES median can be used to establish the minimum background level of exposure. Consumer product exposures to these phthalates should be added on top of the general population levels, as consumer product use can add any combination of the six phthalates, on top of the general population exposure. Similarly, occupational exposures should be added on top of both the general population and consumer product exposures. Workers may be exposed to fewer phthalates attributable directly to work but there could still be exposure to more than one phthalate.

Regarding workplace exposures, the EPA says it will combine non-attributable, non-TSCA sources with cumulative exposure from the workplace to determine a cumulative exposure for workers. But there are insufficient details on the assumptions to be applied when data is missing, or how the exposures will be combined.

The EPA states:

> For fenceline and general population exposures, the EPA has not identified a proposed methodology, data sources, or lines of evidence to fully develop the cumulative fenceline assessment. In the absence of data or evidence, assumptions may be necessary to determine reasonable combinations of exposure for identified populations, which involve considering the likelihood of co-exposure, the possibility of double counting and of over- or under-estimating exposures.[70]

We agree that soliciting comments from the SACC and public is important on this issue. However, there are things the EPA can do now based on previous public comments and SACC recommendations on the "Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0."[71] For example, the EPA could define who they consider fenceline communities, describe how they will consider aggregate exposure within and across fenceline communities, and apply the recommendations from comments submitted to the EPA in March, 2022.[72] Additionally, the EPA should consider what data sources can contribute to the identification of fenceline exposures including data from the Superfund program since both DEHP and DINP are listed as superfund chemicals.[73]

b. EPA should fully estimate the exposure contribution of non-attributable and non-TSCA sources

The EPA has proposed to use a scenario-based approach to estimate cumulative phthalate exposure. However, deciding on one exposure assessment method now, prior to conducting the literature review is premature. The EPA needs to complete both the scenario-based approach and the reverse dosimetry

[70] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 148

[71] U.S. EPA, "SACC Meeting Minutes and Final Report No. 2022-01. Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposure to Fenceline Communities Ion 1.0" (Virtual Meeting via Zoom.gov: U.S. EPA, March 15, 2022), https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0415-0095.

[72] Program on Reproductive Health and the Environment, "Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0," Submitted via regulations.gov to docket EPA-HQ-OPPT-2021-0415, March 22, 2022.

[73] 4/28/23 1:33:00 PM

approach in the *Draft Phthalates CRA Approach*. Both methods have data gaps and the exposure estimate for each will depend on the assumptions that the EPA will apply when using these approaches. For example, reverse dosimetry with NHANES data can miss higher level of exposures. However, completing both approaches is necessary to evaluate the success of the exposure estimate. A risk assessment conducted by U.S. CPSC (2014) found that the scenario-based approach estimated a higher risk than the biomonitoring approach:

> U.S. CPSC found their estimates of scenario-based modeled daily intake values to be higher than those estimated using reverse dosimetry and 2005/2006 NHANES biomonitoring data for several phthalates (i.e., BBP and DINP)… *indicating that their scenario-based approach included potentially worst-case scenarios.* Yet, U.S. CPSC concluded that their results were within an order of magnitude of those from biomonitoring data and were useful in determining contributions of certain products or phthalates within the combined risk.[74] (emphasis ours)

Although U.S. CPSC concluded their results "were within an order of magnitude" of the biomonitoring data, it was only possible to determine the proximity of their approach because both approaches were completed and compared. Additionally, U.S. CPSC stated that their results were likely due to using a "worst case" scenario, while the EPA has stated in this draft CRA that it will apply adjustments to avoid double counting, implying that their approach will be more likely to underestimate and not consider worst case exposures. This underestimation will be exacerbated in PESS groups (see comment 2.c. below).

In addition to completing the risk assessment with both the reverse dosimetry and scenario-based approach, we also recommend the EPA do following when considering and completing the exposure assessment approach for the phthalate CRA:

- Specify the assumptions being applied in their exposure assessment for each approach and how it will treat the data gaps in each approach, particularly where source apportionment is not possible (e.g., air, water, dust, breast milk, or urinary measurements).
- Define "reasonable combinations" used when estimating TSCA, non-attributable, and non-TSCA exposures to determine cumulative risk.[75]
- Identify areas where the scenario based and reverse dosimetry approach could underestimate exposure and how to overcome those underestimations, rather than focusing on the risk for "double counting" or overestimation.
- Ensure that the parameter values in the reverse dosimetry approach sufficiently account for human variability. Studies supporting estimation of these parameters frequently have very small sample sizes. For any parameters based on a data from a small number of individuals and/or a study population that does not reflect the diversity of the U.S. population, extrapolation beyond the data or application of adjustment factors will be necessary to avoid underestimation of exposure.
- Clearly describe how the different exposure scenarios will be combined to identify the cumulative risk for TSCA COUs and for each population such as consumers, workers, and general population.
- Account for the likelihood that some proportion of people with general population exposure will also have consumer exposure and worker exposure.

[74] U.S. CPSC, "Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives (with Appendices)." p 124 – 125
[75] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 110

- Clearly describe how the EPA will consider and incorporate non-attributable and non-TSCA sources; as the *Draft Phthalates CRA Approach* states, "certain non-TSCA sources may be major pathways of human exposure, and their exclusion from a CRA may lead to an underestimation of risk." [76]

The EPA's concern for double counting and overestimating throughout the Draft CRA is not scientifically supported. Rather the EPA should focus on assumptions and methods that are less likely to underestimate risk, in particular for PESS. EPA says:

> exposure estimates for non-attributable and non-TSCA pathways can be varied for different populations and combined differently for an aggregated daily exposure profile for specific populations to limit the possibility of "double counting."[77]

The EPA needs to clarify its approach by clearly defining the criteria through which they will consider combining the different sources and citing evidence for not combining exposures. In other words, exposures should be fully characterized including multiple exposure routes and sources and excluded only if there is sufficient evidence to support their exclusion. Failure to combine attributable and non-attributable sources will result in under-estimation of the exposure and risk.

c. EPA should broaden its consideration of potentially exposed or susceptible subpopulations (PESS)

The EPA has identified pregnant women, women of reproductive age, male infants, male toddlers, and male children as PESS for the phthalates CRA. However, other groups should also be considered as PESS particularly related to socio-economic status, race/ethnicity, or certain occupations with high potential for exposure, not likely to be monitored by OSHA. EPA states:

> Additional PESS based factors that may include but are not limited to race, ethnicity, or socioeconomic status who have higher exposure to phthalates may also be identified throughout the risk evaluation process and incorporated into the CRA as appropriate.[78]

We agree with the inclusion of the groups mentioned in the *Draft Phthalates CRA Approach* and emphasize the importance of considering individuals with chronic conditions, people who live or work near manufacturing, processing, use, or disposal sites. Additionally, phthalates are used in consumer products and recommend that the EPA consider difference in use by race/ethnicity given that previous research finds certain populations have higher exposures via personal care products.[79] Income level could be another important PESS group, since income can impact social stress, availability of fresh food, consumer product use and type of occupation. Food is an important exposure source for phthalates and NHANES data indicate that individuals who eat fast food or take-out food are more highly exposed to phthalates than those who eat at home.[80] Other PESS considerations should include occupational

[76] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 114
[77] *Id.* p 117
[78] *Id.* p 108
[79] Ami R. Zota and Bhavna Shamasunder, "The Environmental Injustice of Beauty: Framing Chemical Exposures from Beauty Products as a Health Disparities Concern," *American Journal of Obstetrics and Gynecology* 217, no. 4 (October 2017): 418.e1-418.e6, https://doi.org/10.1016/j.ajog.2017.07.020.
[80] Julia R. Varshavsky et al., "Dietary Sources of Cumulative Phthalates Exposure among the U.S. General Population in NHANES 2005–2014," *Environment International* 115 (June 1, 2018): 417–29, https://doi.org/10.1016/j.envint.2018.02.029.

groups, such as nail-salon workers, who have a high occupational exposure to phthalates and who may also have co-exposures from consumer products. Additionally, they may live in or near their stores thus face co-exposures from the store in their homes. Other occupations outside of manufacturing and industry that could also be considered in the evaluation of occupational exposures, and considered under PESS include: painters, house cleaners, medical personnel, among others.

d. EPA should evaluate the potential for an individual to use multiple phthalate-containing consumer products

Phthalate-containing consumer products should be considered an important source of exposure and co-exposures to multiple such products needs to be fully characterized. Where data are not available, co-exposures and co-use should be assumed. The EPA *Draft Phthalates CRA Approach* document states:

> As described above in Section 6.4.1.2, there is currently a lack of evidence that multiple consumer products are used concurrently by consumers. Therefore, EPA is not proposing to combine risk for co-use of multiple consumer products for consumers, unless new information is identified to support doing so.[81]

However, this argument scientifically inappropriate: 1. No systematic review was completed to identify studies evaluating co-exposure to phthalates in multiple consumer products, so it has not been established that there is no evidence (though EPA cites one study). 2. The results of the study cited (Han *et al*) were misinterpreted as the measure of association (correlation) is not appropriate for determining co-use. The correlation statistic does not inform the relevant question, which is whether there are some individuals in the population who use more than one product. Indeed, Han *et al* found several instances of co-use of consumer products (e.g., shampoo and conditioner) and among the most highly exposed participants, authors identified co-exposure of multiple different chemicals, coming from multiple consumer products. Likewise, a study by Stanfield et al. (2021) combined consumer product ingredient data with purchasing data and identified many potential chemical co-exposures from consumer products.[82] While the EPA says that "the presence of consumer products in the home is insufficient to paint a realistic picture of daily exposure for customers" it does provide evidence for the possibility of co-exposure that needs to be further investigated and quantified to fully evaluate the aggregate exposure. Unless there is a strong basis to indicate otherwise, EPA should assume that some proportion of users of one consumer product will also be users of a second consumer product – not that there is zero overlap among the users of the two products. Based on the study presented in the *Draft Phthalates CRA Approach* and the 2021 study by Stanfield et al. there is not sufficient evidence to exclude consumer products as a source of exposure to multiple phthalate chemicals, and some consumer products, themselves, may have multiple phthalates.

In Section 6.4.1.2, EPA used manufacturer websites or Safety Data Sheets (SDS) for preliminary analysis to determine if consumer products may have more than one phthalate and found little evidence. However, this relies on industry reported data which may be incomplete. Also, as stated above, multiple consumer products may be used, or may be used with other non-TSCA sources, or co-occur with non-attributable exposures. Data identifying co-use of consumer products is limited and product

[81] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 134

[82] Zachary Stanfield et al., "Mining of Consumer Product Ingredient and Purchasing Data to Identify Potential Chemical Coexposures," *Environmental Health Perspectives* 129, no. 6 (n.d.): 067006, https://doi.org/10.1289/EHP8610.

formulations may not report all ingredients in the product, including phthalates. Therefore, the EPA must identify and specify other data sources and assumptions to be in the exposure assessments.

e. EPA should further develop its understanding of the uses and limitations of NHANES data

NHANES data represent levels measured in a representative sample of the U.S. population and are useful for identifying background exposures and identifying chemicals that have concurrent exposures in the general population. Phthalates have a short half-life and levels measured in NHANES represent recent exposures, however the high detection frequency in NHANES (i.e., that most phthalate metabolites here are detected in almost 100% of people measured) indicates chronic daily exposure throughout the U.S. population. While extremely useful, NHANES data are unlikely to capture higher end exposures such as occupational or other sources of high levels of exposure (e.g., fenceline communities, nail salon workers), due to the survey's sample size and sampling strategy. The risk for underestimating exposure could be significant. As stated in the *Draft Phthalates CRA Approach* document:

> Based on the assumption that the median exposure represented by NHANES data may not include individuals exposed to TSCA sources, EPA could combine the median exposures with exposure from TSCA COUs to estimate a cumulative exposure where a portion of the exposure was attributable to TSCA and could be used to inform individual phthalate risk determinations.[83]

EPA should further explore improved exposure estimates by combining the entire NHANES distribution including upper percentiles (not just the median) with additional data sources identified in the *Draft Phthalates CRA Approach* to evaluate occupational exposure, fenceline exposures and unusual consumer product use scenarios that would not be represented in NHANES.

5. EPA should apply a more rigorous and informative approach to risk characterization by combining the use of RPFs with improved dose-response assessment methods. EPA's proposed use of the margin of exposure (MOE) approach is not consistent with the "best available science."

EPA goes further in the *Draft Phthalates CRA Approach* than it has previously in committing to the margin of exposure (MOE) approach as the sole method it will apply for characterization of non-cancer risks. The preamble to the final risk evaluation framework rule recognizes that there are other approaches:

> the proposed rule included the specific mention of margin of exposure (MOE), which is just one approach for risk characterization. EPA acknowledges that MOE is just one of several approaches to risk characterization and agrees that it does not make sense to single out this one particular approach. There will be risk scenarios where one approach may be better than another and, as commenters correctly pointed out, the science of risk characterization is still evolving, particularly for non-cancer hazards.[84]

In contrast, the Draft Phthalates CRA Approach says that EPA will use the MOE approach and does not mention any alternative approaches that might be applied:

[83] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act. p 121

[84] U.S. EPA, "Procedures for Chemicals Risk Evaluation Under the Amended Toxic Substances Control Act," 40 CFR Part 702 §, Preamble, accessed April 12, 2023, https://www.regulations.gov/document/EPA-HQ-OPPT-2016-0654-0108.

> To estimate cumulative risk for each specific exposure scenario, an MOE (ratio of index chemical point of departure [POD] to cumulative exposure estimate expressed in index chemical equivalents [Step 9]) is calculated for comparison to the benchmark MOE (*i.e.,* the total uncertainty factor associated with the assessment) (Section 4.3.2). The lower the MOE (margin between the toxicity effect level and the exposure dose), the more likely a chemical is to pose a risk.[85]

The MOE approach is a scientifically inappropriate approach for characterizing risk and is inconsistent with amended TSCA's requirements to use the "best available science" and to ensure protection of "potentially exposed and susceptible subpopulations" (PESS). Use of the MOE, which relies only on a point of departure (POD) with no extrapolation to lower doses, is a simplistic approach that only compares the POD to the exposure level to determine whether this ratio "indicates the potential for risk to human health" or not.[86] The MOE does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals affected and perpetuates the scientifically flawed notion that a "safe" or "no risk" level of chemical exposure can be identified for a diverse exposed population (see discussion for comment 3 above).[87,88] The NAS[89] and WHO[90] have outlined superior methods for risk estimation that have been demonstrated in published case studies.[91,92,93,94,95] EPA should use the WHO approach and combine its outputs with index chemical equivalent exposures (calculated with an appropriate approach to RPF development; see comment 3 above) to estimate the proportion of the exposed population projected to experience phthalate syndrome outcomes. This would provide greater information for decision-makers and outputs that can be used to quantify health benefits in benefit-cost analysis. This improved approach to risk characterization should be incorporated in both the *Draft Phthalates CRA Approach* document and the *CRA Principles* document.

6. EPA must use validated systematic review methods for the CRA to have a robust evidence base and consider risks to PESS as required under TSCA

We have made numerous statements regarding EPA's current TSCA Systematic Review Method (TSCA Method)'s scientific flaws and inconsistencies with current, established, best available empirical

[85] U.S. EPA, Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act, 23. p
[86] U.S. EPA, "Toxic Substances Control Act Risk Determiniation: Tricholoroehtylene," accessed April 12, 2023, https://www.regulations.gov/document/EPA-HQ-OPPT-2016-0737-0147. Risk Evaluation for Trichloroethylene, 2020.
[87] Woodruff et al., "A Science-Based Agenda for Health-Protective Chemical Assessments and Decisions." 2023.
[88] McGartland et al., "Estimating the Health Benefits of Environmental Regulations" *Science*, 2017.
[89] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academies Press; 2009. Ch 5
[90] WHO. Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11. WHO; 2014. Available from: http://www.inchem.org/documents/harmproj/harmproj/harmproj11.pdf
[91] Nielsen et al., "Application of Probabilistic Methods to Address Variability and Uncertainty in Estimating Risks for Non-Cancer Health Effects."
[92] Blessinger T, Davis A, Chiu WA, et al. Application of a unified probabilistic framework to the dose-response assessment of acrolein. *Environment international.* 2020;143:105953. doi: 10.1016/j.envint.2020.105953
[93] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi: 10.1289/EHP3368
[94] Ginsberg GL. Cadmium risk assessment in relation to background risk of chronic kidney disease. Toxicol Environ Health A. 2012;75(7):374-90. doi: 10.1080/15287394.2012.670895.
[95] Nielsen et al., "Application of Probabilistic Methods to Address Variability and Uncertainty in Estimating Risks for Non-Cancer Health Effects."

methods for systematic review.[96] Additionally, the TSCA Method has undergone review by authoritative bodies such as the NASEM and EPA's own Scientific Advisory Committee on Chemicals (SACC). The NASEM indicated there was a "strong consensus" the TSCA Method "did not meet the standards of systematic review methodology"[97] after which EPA retooled the method, claiming it had incorporated the NASEM's comments. However, in a subsequent review by the SACC, the peer-review body issued over 200 recommendations for improvement, identifying numerous NASEM recommendations that had gone unaddressed by EPA.[98]

EPA used this scientifically flawed systematic review method to underpin the first ten risk evaluations conducted under amended TSCA leading to an underestimation of the true risk of exposure to human and environmental health. Furthermore, this method is more time intensive to apply compared to other, more rigorous systematic review methods.[99,100]

EPA's failure to establish a scientifically defensible, efficient systematic review methodology for its TSCA risk evaluations has led the Agency to systematically underestimate risks to human health, further delaying necessary action to protect the public, especially historically marginalized communities that are more highly exposed to toxic chemicals and experience disproportionate burdens of disease and all PESS. Furthermore, this methodology will provide any CRA conducted with a potentially incomplete evidence base.[101] Thus, **EPA's inability to abandon this scientifically flawed method is a direct threat to its goals to advance environmental justice.**

Both PRHE's Navigation Guide and the National Toxicology Program's Office of Health Assessment and Translation *OHAT Approach for Systematic Review and Evidence Integration for Health Effects Evaluations* (OHAT) method have been used or recommended by the NASEM[102, 103,104] and demonstrated

[96] Program on Reproductive Health and the Environment, "Comment Submitted by University of California, San Francisco Program on Reproductive Health and the Environment (UCSF PRHE)," accessed April 14, 2023, https://www.regulations.gov/comment/EPA-HQ-OPPT-2021-0414-0015.

[97] NASEM. (2021). The use of systematic review in EPA's Toxic Substances Control Act Risk Evaluations. https://www.nap.edu/catalog/25952/the-use-of-systematic-review-in-epas-toxic-substances-control-act-risk-evaluations

[98] US EPA. (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2 DOCKET ID NUMBER: EPA–HQ–OPPT–2021–0414

[99] US EPA. (2021). Draft systematic review protocol supporting TSCA risk evaluations for chemical substances version 1.0: A generic TSCA systematic review protocol with chemical-specific methodologies. https://www.epa.gov/system/files/documents/2021-12/draft-systematic-review-protocol-supporting-tsca-risk-evaluations-for-chemical-substances_0.pdf

[100] Eick, S.M., Goin, D.E., Chartres, N. et al. Assessing risk of bias in human environmental epidemiology studies using three tools: different conclusions from different tools. Syst Rev 9, 249 (2020). https://doi.org/10.1186/s13643-020-01490-8

[101] Rayasam et al., "Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States."

[102] National Academy of Sciences Engineering and Medicine (NASEM), "Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals," Report (The National Academies Press, 2017), https://www.nap.edu/catalog/24758/application-of-systematic-review-methods-in-an-overall-strategy-for-evaluating-low-dose-toxicity-from-endocrine-active-chemicals.

[103] National Research Council (NRC), "Review of EPA's Integrated Risk Information System (IRIS) Process," Report (The National Academies Press, 2014), https://doi.org/10.17226/18764.

[104] National Academy of Sciences Engineering and Medicine (NASEM), "Progress toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation," Report (The National Academies Press, 2018), https://doi.org/10.17226/25086.

in case studies in the peer-reviewed literature.[105,106,107,108,109,110,111,112] Further, EPA's Office of Research and Development has adopted a systematic review methodology as part of its Integrated Risk Information System (IRIS) program.[113] While we have provided comments regarding some inadequacies in the current IRIS method, it is a fundamentally stronger method than the current TSCA Method.

Section 2: Comments on *CRA Principles*

1. **EPA must conduct cumulative risk assessments to comply with the TSCA requirements to use "the best available science" and to evaluate risks to potentially exposed or susceptible subpopulations (PESS)**

In explaining the rationale for preparing the *CRA Principles* document, EPA says:

> TSCA does not explicitly require EPA to conduct CRAs. However, TSCA does require that EPA, when conducting TSCA risk evaluations in 3 to 3.5 years [15 U.S.C. § 2605(b)(4)(G)], consider the reasonably available information, consistent with the best available science, and make decisions based on the weight of the scientific evidence [15 U.S.C. § 2625(h), (i), (k)]. EPA recognizes that for some chemical substances undergoing risk evaluation, the best available science may indicate that the development of a CRA is appropriate to ensure that any risks to human health and the environment are adequately characterized…Because individuals are co-exposed to many chemicals in their daily lives, some of which may have the same health effects, EPA believes that in some cases the best approach to assess risk to human health may be to look at the combined risk to health from exposure to multiple chemicals.[114]

EPA has taken a critical step in recognizing that consideration of whether to conduct cumulative risk assessment in TSCA risk evaluations must take into account the TSCA requirement to use the "best available science." Unfortunately, EPA equivocates by saying "for some chemical substances undergoing risk evaluation, the best available science may indicate that the development of a CRA is appropriate" and "in some cases the best approach to assess risk to human health may be to look at the combined risk to health from exposure to multiple chemicals." However, the hazards of chemicals undergoing TSCA risk evaluation are also the hazards posed by many other chemicals and non-chemical stressors. In

[105] Paula I. Johnson et al., "The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth," *Environmental Health Perspectives* 122, no. 10 (October 2014): 1028–39, https://doi.org/10.1289/ehp.1307893.
[106] Erica Koustas et al., "The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth," *Environmental Health Perspectives*, 2014, https://doi.org/10.1289/ehp.1307177.
[107] Juleen Lam et al., "The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth," *Environmental Health Perspectives*, 2014, https://doi.org/10.1289/ehp.1307923.
[108] H. M. Vesterinen et al., "Fetal Growth and Maternal Glomerular Filtration Rate: A Systematic Review," *J Matern Fetal Neonatal Med*, 2015, https://doi.org/10.3109/14767058.2014.980809.
[109] P. I. Johnson et al., "Application of the Navigation Guide Systematic Review Methodology to the Evidence for Developmental and Reproductive Toxicity of Triclosan," *Environ Int*, 2016, https://doi.org/10.1016/j.envint.2016.03.009.
[110] Juleen Lam et al., "A Systematic Review and Meta-Analysis of Multiple Airborne Pollutants and Autism Spectrum Disorder," *PLoS ONE*, 2016, https://doi.org/10.1371/journal.pone.0161851.
[111] J. Lam et al., "Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-Analysis," *Environ Health Perspect*, 2017, https://doi.org/10.1289/EHP1632.
[112] J. Lam et al., "Exposure to Formaldehyde and Asthma Outcomes: A Systematic Review, Meta-Analysis, and Economic Assessment," *PLoS One*, 2021, https://doi.org/10.1371/journal.pone.0248258.
[113] Engineering and Medicine (NASEM), "Progress toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation."
[114] U.S. EPA, "Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act" (2023). p 5

other words, every chemical being evaluated under TSCA is toxicologically similar to other chemicals for at least one hazard. EPA should significantly strengthen the document by modifying the language quoted above to:

> EPA recognizes that for all chemical substances undergoing risk evaluation, the best available science indicates that the development of a CRA is appropriate to ensure that any risks to human health and the environment are adequately characterized…Because individuals are co-exposed to many chemicals in their daily lives, some of which may have the same health effects, EPA believes that the best approach to assess risk to human health is to look at the combined risk to health from exposure to multiple chemicals, along with non-chemical stressors that can also contribute to or exacerbate the health effects identified for a given chemical.

Amended TSCA also requires EPA to:

> determine whether a chemical substance presents an unreasonable risk to a potentially exposed or susceptible subpopulation. §2605(b)(4)(A)

Amended TSCA defines potentially exposed or susceptible populations (PESS) as:

> a group of individuals within the general population identified by the Administrator who, 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. §2602(12*)*

In order to meet TSCA's mandates to identify unreasonable risks to PESS for each chemical undergoing risk evaluation, EPA must consider the susceptibility factors that make a group of individuals more susceptible. Among these factors are co-exposures to other chemicals with similar health consequences, including chemicals that are not currently undergoing risk evaluation, and non-chemical stressors that can contribute to or exacerbate the health consequences of the chemical being evaluated. EPA cannot fully identify PESS and assess risks to PESS without conducting CRAs incorporating those other chemicals and non-chemical stressors. The *CRA Principles* document must acknowledge that assessment of risks to PESS will require CRA in all cases.

2. EPA should include non-chemical stressors in TSCA CRAs

Under "Stressors for Consideration" the *CRA Principles* document says:

> The term "stressors" refers to both chemical and non-chemical stressors. Non-Chemical stressors may include radiological, biological and other physical stressors; lifestyle conditions; and socioeconomic stressors. Non-chemical stressors may directly or indirectly affect health adversely, increase vulnerability to chemical stressors or have exposure-response modifying effects on other chemical stressors.[115]
>
> Until Agency-wide guidance and established methodologies have been developed, EPA does not expect to quantitatively evaluate non-chemical stressors when conducting CRAs under TSCA.[116]

[115] U.S. EPA, Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act. p 6
[116] *Id.* p 8

As noted above (section 1, comment 1.e) the inclusion of non-chemical stressors is necessary to identify and assess risks to PESS; specifically, exclusion of non-chemical stressors is likely to result in underestimation of risks. In many instances, high quality studies enabling quantification of the impacts of selected non-chemical stressors may be available that can be applied in the near-term while EPA continues to develop Agency-wide CRA guidance. For example, a systematic review of the combined effect of chemical exposures and psychosocial stress on fetal growth found that smoking (not a psychosocial stressor) was associated with higher odds of low birthweight, particularly when combined with high stress (determined by low socioeconomic status(SES)) versus low stress (high SES).[117] Additionally, a recent study of fine particulate matter quantified differences in mortality risks by race and income level.[118] Although this last example is from the air pollution literature, similar findings may be available for chemicals subject to TSCA CRA and would be suitable for use in a CRA.

In addition, EPA's discussion of non-chemical stressors in the *CRA Principles* document misrepresents the nature of these stressors and their impacts. Under the definition of non-chemical stressor in the *CRA Principles* document the EPA includes problematic examples of psychosocial factors: "poor diet, smoking, and illicit drug use"[119] which places the blame on individual choices, rather than extrinsic factors. This shortcoming can be overcome by using a more updated definition of non-chemical stressor. The EPA should use the definition of non-chemical stressor that include social determinants of health cited by the Centers for Disease Control and Prevention (CDC) and adapted from the World Health Organization[120] where nonchemical stressors "are the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include *economic policies and systems, development agendas, social norms, social policies, racism, climate change, and political systems*" (emphasis ours), or the one cited in EPA Legal Tools to Advance Environmental Justice: Cumulative Impacts addendum that includes the definition of nonchemical stressors as: "'factors found in the built, natural, and social environments,' including factors such as the economy, community, home, school, demographics, safety, and welfare."[121] It is important to accurately define and evaluate non-chemical stressors and psychosocial stressors since "poorer communities are vulnerable both because they carry a disproportionate amount of the environmental burden and, by virtue of their social environments, are uniquely sensitive to environmental pollutant exposures."[122]

Animal studies can also help inform the impact of non-chemical stressors on adverse health outcomes. A 2023 article summarizing evidence in vulnerability factors and the interaction of phthalates with psychosocial stress identified studies in animal models that social stress increased anogenital distance in rats, that the developing male was more sensitive to maternal stress and may be analogous to the stress of growing up in a low socioeconomic status (SES) household in human populations.[123]

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[117] Hanna M. Vesterinen et al., "Cumulative Effects of Prenatal-Exposure to Exogenous Chemicals and Psychosocial Stress on Fetal Growth: Systematic-Review of the Human and Animal Evidence," *PLOS ONE* 12, no. 7 (July 12, 2017): e0176331, https://doi.org/10.1371/journal.pone.0176331.

[118] Kevin P. Josey et al., "Air Pollution and Mortality at the Intersection of Race and Social Class," *The New England Journal of Medicine* 388, no. 15 (April 13, 2023): 1396–1404, https://doi.org/10.1056/NEJMsa2300523.

[119] U.S. EPA, Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act. p 21

[120] CDC, "Social Determinants of Health"; WHO, "Social Determinants of Health," accessed April 27, 2023, https://www.who.int/health-topics/social-determinants-of-health.

[121] Office of General Counsel, U.S. EPA, "EPA Legal Tools to Advance Environmental Justice: Cumulative Impacts Addendum."

[122] NEJAC, "Ensuring Risk Reduction in Communities with Multiple Stressors: Environmental Justice and Cumulative Risks/Impacts," December 2004, https://www.epa.gov/sites/default/files/2015-02/documents/nejac-cum-risk-rpt-122104.pdf.

[123] Devon Payne-Sturges, Sulakkhana De Saram, and Deborah A. Cory-Slechta, "Cumulative Risk Evaluation of Phthalates Under TSCA," *Environmental Science & Technology*, April 12, 2023, https://doi.org/10.1021/acs.est.2c08364.

At minimum the EPA needs to accurately describe the intrinsic and extrinsic factors that should be taken into account and the potential impact on the risk assessment based on the available data. Additionally, the EPA should apply adjustment factors (see Section 1, comment 1.e) to account for the intra-species and inter human variability in humans[124]

3. EPA's considerations for identifying chemicals that are "toxicologically similar" should be expanded to better incorporate mechanistic evidence and to identify cumulative chemical groups when evidence is less extensive

To guide the determination of chemicals that are "toxicologically similar" for purposes of TSCA CRAs, the *CRA Principles* document provides a list of several considerations such as "identical toxicodynamics" (a very narrow definition of toxicologically similar), "shared syndrome" and "shared apical outcome."[125] Several items in this list are consistent with the NAS recommendation that chemicals with a "common adverse outcome" should be considered for CRA:

> For cumulative risk assessment, the committee strongly recommends that EPA group chemicals that cause common adverse outcomes and not focus exclusively on structural similarity or on similar mechanisms of action.[126]

EPA should add a clarifying statement that evidence of <u>any</u> item in the bullet point list is sufficient to establish toxicological similarity, and that it is not necessary to establish more than one of these concepts to conclude that chemicals are toxicologically similar. In addition, EPA should clarify that when chemicals are determined to share a key cellular-level events (e.g., reduced gene expression, reduced testosterone synthesis, reduced Leydig cell function, reduced Sertoli cell function) or mechanistic events associated with a given apical outcome, evidence of the apical outcome itself is not needed for each chemical included in a cumulative assessment group. The list of considerations should be expanded to include "shared key markers" and "common key cellular-level or organ-level events" that are established as leading to common outcomes. These common key events are sufficient to establish toxicological similarity, regardless of differences in molecular-level events and independent of confirmatory studies of apical outcomes. In addition, "shared key characteristics" should be added to the list of considerations for determining toxicological similarity. Identified key characteristics are mechanistic properties or biological pathways of chemicals that are known to be linked to health endpoints commonly considered in chemical risk assessments. Sets of key characteristics have been published for carcinogens, cardiovascular toxicants, endocrine disrupting chemicals, female reproductive toxicants, male reproductive toxicants, hepatotoxicants, and immunotoxicants.[127,128,129,130,131,132,133]

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[124] Varshavsky et al., "Current Practice and Recommendations for Advancing How Human Variability and Susceptibility Are Considered in Chemical Risk Assessment."
[125] U.S. EPA, Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act. p 9-10
[126] National Research Council, *Phthalates and Cumulative Risk Assessment*, 9.
[127] Smith et al., "Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis."
[128] Lind et al., "Key Characteristics of Cardiovascular Toxicants."
[129] La Merrill et al., "Consensus on the Key Characteristics of Endocrine-Disrupting Chemicals as a Basis for Hazard Identification."
[130] Luderer et al., "Proposed Key Characteristics of Female Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment."
[131] Rusyn et al., "Key Characteristics of Human Hepatotoxicants as a Basis for Identification and Characterization of the Causes of Liver Toxicity."
[132] Germolec et al., "Consensus on the Key Characteristics of Immunotoxic Agents as a Basis for Hazard Identification."
[133] Arzuaga et al., "Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments."

EPA states that one item in its list of considerations, "effect on the same target organ" will not be considered as a basis for conducting CRAs:

> Generally, EPA is unlikely to conduct CRAs under TSCA when the reasonably available information is limited to an effect on the same target organ as this approach may introduce too much uncertainty to risk estimates.[134]

EPA does not present any explanation of why this approach would be too uncertain, and EPA does not need to make such a broad statement in this document. The same target organ is a reasonable indicator of potential for cumulative risk, and (as noted in the *CRA Principles* document) has been routinely used in other EPA programs. Excluding this consideration overemphasizes concern about uncertainty and disregards the importance of potential underestimation of risk by possibly precluding inclusion in CRAs of chemicals that actually are toxicologically similar. It may be useful to couple findings of effects on the same target organ with the key characteristics or inference methods like read-across to better inform a decision regarding toxicological similarity. Sensitivity analysis (inclusion or exclusion of a chemical with the same target organ in a CRA) may also be informative to determination of chemicals with more limited evidence to include in a CRA group. Judgments of whether chemicals with evidence of same target organ should be included in a CRA should be left to a case-by-case determination in individual CRA, rather than precluding their inclusion with this broad statement in the *CRA Principles* document.

4. EPA's characterization of dose addition as conservative is incorrect. Recent evidence suggests it may underestimate risk, especially for sensitive subpopulations

Dose addition is a well-established and useful approach. Empirical evidence has continued to accumulate supporting dose addition as a good predictor of outcomes, yet EPA inappropriately characterizes it as a conservative approach (in the sense of being more likely to overestimate risk rather than underestimate risk). The *CRA Principles* document says:

> EPA's default assumption when evaluating toxicologically similar chemical substances for cumulative risk is dose addition…This default assumption is based on previous analyses of empirical data demonstrating that dose addition is broadly applicable and is a more conservative, health protective approach than response addition.[135]

While it is correct that dose addition provides estimates that are superior to those from response addition, this statement reflects an outdated view of dose addition and must be corrected. The extensive literature on anti-androgens indicates that even at low doses for chemicals with different molecular initiating events, dose addition provides an accurate prediction of outcomes.[136,137] In addition, the NAS *Phthalates and Cumulative Risk* report repeatedly described dose addition as a "predictive" method and noted instances where it was found to underestimate effects:

> Mixture studies in laboratory animals have been conducted with phthalates, with other antiandrogens, and with phthalates and other antiandrogens; the results all indicate that the mixture effects in each case are predicted well with dose addition methods. Although a variety

[134] U.S. EPA, Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act. p 10
[135] Id. p 13
[136] Conley et al., "Mixed 'Antiandrogenic' Chemicals at Low Individual Doses Produce Reproductive Tract Malformations in the Male Rat."
[137] Conley et al., "A Mixture of 15 Phthalates and Pesticides below Individual Chemical No Observed Adverse Effect Levels (NOAELs) Produces Reproductive Tract Malformations in the Male Rat."

> of mechanisms clearly are involved, dose addition proved adequately predictive when the committee evaluated the available data. More important, when the model predictions differed significantly, no case could be found in which independent action predicted mixture effects better than dose addition. Thus, the evidence supports the use of dose addition as an approximation in estimating cumulative risk posed by phthalates and other antiandrogens.[138]
>
> there are some data that indicate toxic interactions (greater than dose-additive effects) when hypospadias and other genital malformations are evaluated as the end points of concern. Rider et al. (2008) found that BBP, DBP, DEHP, vinclozolin, procymidone, linuron, and prochloraz induced more hypospadias than predicted on the basis of dose addition…it is not possible to say with certainty whether the observations represent a true synergism with respect to dose addition, but the possibility cannot be ruled out.[139]
>
> there is strong empirical evidence of dose addition as an accurate predictor of mixture effects.[140]
>
> evidence from the recent peer reviewed scientific literature shows not only that phthalates produce mixture effects but that the effects are often predicted well by using the dose-addition concept. That is also true for other classes of antiandrogens and for combinations of phthalates with such antiandrogens. Although a variety of molecular mechanisms are at play, dose addition provided equal or better approximations of mixture effects compared with independent action (when such comparisons were performed). In no example in the literature did independent action produce a mixture-effect prediction that proved to be correct and differed substantially from that produced with dose addition. The evidence that supports adoption of a physiologic approach is strong. Experimental evidence demonstrates that toxic effects of phthalates and other antiandrogens are similar despite differences in the molecular details of the mechanisms, including metabolism, distribution, and elimination…The case for using dose addition as an approximation for mixture risk assessment of phthalates and other antiandrogens is strong.[141]

An important recent addition to the literature by Jang et al. applies new approach methods (NAMs) to inform mixtures risk assessment, including consideration of human variability. This study measured cytotoxicity in human lymphoblastoid cell lines from 146 individuals exposed to eight different diverse chemical mixtures. The study finds that dose addition typically underestimates mixture effects for the median individual, and "under-predicted the sensitive tail of the distribution by up to an order of magnitude."[142] The authors proposed that an adjustment factor be routinely applied to dose-addition calculations to account for the underestimation:

> our results support the need for cumulative risk assessment conducted using default additivity assumptions to implement more stringent benchmarks by up to 10-fold in order to ensure public health protection of mixture effects.[143]

This study provides a strong model of human variability by testing in diverse cell lines, but 146 individuals (representing four distinct populations originating in Europe and Africa, but none from Asia

[138] National Research Council, *Phthalates and Cumulative Risk Assessment*. p 9-10
[139] *Id.* p 123
[140] *Id.* p 125
[141] *Id.* p 133- 134
[142] Suji Jang et al., "Cumulative Risk Meets Inter-Individual Variability: Probabilistic Concentration Addition of Complex Mixture Exposures in a Population-Based Human In Vitro Model," *Toxics* 10, no. 10 (October 2022): 549, https://doi.org/10.3390/toxics10100549.
[143] Jang et al., "Cumulative Risk Meets Inter-Individual Variability."

or Latin America) are not likely to represent the full diversity of responses in the U.S. general population; thus, an adjustment factor greater than 10 is warranted.

The experimental literature examining dose additivity provides strong evidence that the method is not conservative, i.e. it is not expected to overestimate effects. There is now substantial evidence to indicate that dose addition is expected to underestimate effects, warranting application of an adjustment factor to improve risk estimates.