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EPN Comments on EPA's "Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act"
Docket No. EPA-HQ-OPPT-2022-0918
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Founded in 2017, the Environmental Protection Network (EPN) harnesses the expertise of more than 550 former Environmental Protection Agency (EPA) career staff and confirmation-level appointees from Democratic and Republican administrations to provide the unique perspective of former regulators and scientists with decades of historical knowledge and subject matter expertise.

I. Introduction

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

Accompanying the two draft documents was a set of charge questions designed for use by the SACC to guide the conduct of their scientific peer review. We use those charge questions to frame our comments on the two documents. The present set of comments addresses only the draft principles document. A second set of comments addressing the phthalates example will be submitted separately.

II. EPN Responses to the Charge Questions

Question 1. EPA's Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act (Draft Proposed Principles Document) provides an overview of TSCA and cumulative risk assessment (CRA) within the regulatory requirements of TSCA. In the development of this document, EPA relied substantially on existing work by EPA's Risk Assessment Forum, EPA's Office of Pesticide Programs, the Organisation for Economic Co-operation and Development, the European Commission, and the World Health Organization and International Programme on Chemical Safety (see list in Section 3 of the draft report). Please identify any additional key methodology documents that the panel is aware of that could inform EPA's approach to CRA under TSCA.

EPN Response: One additional document that may provide further insights is "Science Policy Note SPN2018-02, Cumulative Health Risk Assessment Framework" authored by the Pesticide

Management Regulatory Agency (PMRA) of Health Canada.[1]

As one might expect, the PMRA approach is quite similar to many aspects of OPP's Cumulative Risk Assessment procedures ("Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity").[2] While OPP's grouping guidance generally yields groups reflecting only strong structural similarity, the PMRA guidance appears to be open to considering the assembling of a group made up of substances that are less structurally similar. Further in-depth reading of the guidance and a search for, and examination of, PMRA case examples are in order to clarify this point.

Question 2. As described in Section 3.4 of the Draft Proposed Principles Document, EPA is proposing to establish a cumulative chemical group for purposes of CRA using a weight of evidence approach that characterizes the strengths and uncertainties of the evidence of toxicological similarity and potential co-exposure for each chemical substance in the group. Please comment on the appropriateness of this approach, including on the strengths and uncertainties. If appropriate, please provide additional considerations for existing lines of evidence that EPA may consider.

EPN Response: Section 3.4 would benefit significantly from an expansion of the discussion in the very first paragraph on determination of an appropriate "cumulative chemical group" (CCG). Before one can evaluate toxicological similarity and/or co-exposure scenarios, one has to have an initial list of candidate chemicals to which the criteria related to those two factors can be applied.

The TSCA definition of "category of chemical substances" is so broad as to be virtually useless to gain an understanding of how a CCG is created, particularly if one doesn't know how the definition has been applied in the program historically. Inclusion of specific examples from both the new and existing chemicals programs could provide a sense of where boundaries may exist. Perhaps, begin with the data-rich phthalates and explain how and why the large universe of phthalates was whittled down to the small number that constitutes the CCG for the CRA. Examples on the opposite side of the coin (that is, data-poor) could come from the new chemicals program in which often little more than molecular structure, some physical-chemical characteristics, and a "back-of-the-envelope" estimate of worker exposure constitute the premanufacture notice.

How does the proposed TSCA approach compare to the OPP approach for selecting the members of a cumulative assessment group?

This is how OPP describes its first step in the 1999 Guidance:

> "Use of structural similarity as a starting point for grouping chemicals relies on the assumption that substances that are structurally analogous could contain a common toxophore (or may yield a common toxophore upon metabolism) and may interact analogously with cellular biomolecular sites to cause a common toxic effect. To identify pesticides and other substances that are structurally similar, the agency will perform substructure searches in databases containing: registered pesticides; pesticides for which

[1] https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/policies-guidelines/science-policy-notes/2018/cumulative-health-risk-assessment-framework-spn2018-02.html

[2] https://www.epa.gov/sites/default/files/2015-07/documents/guide-2-identify-pest-chem_0.pdf

there are import tolerances; and other substances (e.g., pharmaceuticals, industrial chemicals) that are used in commerce in the United States. Search queries for identification of structurally similar substances may include, for example: toxophore (if known) or metabolic precursor of the toxophore; base structure; and accompanying functional groups or other substituents that may impact on the propensity of a substance to produce a toxicological response common with those of structurally-related chemicals."[2]

While one can understand and justify the placement of structural similarity lower on the lists of factors that are most informative/restrictive with regard to data and knowledge requirements when tackling the issues of toxicological similarity and co-occurrence, we believe it should be at the top of the list when assembling the initial list of candidates to be screened. Agency experience with the CRA process for pesticides shows us that the initial list of candidates may be substantially modified as the in-depth data review process goes forward. Chemicals could be added to or removed from the initial list, although the latter has been shown to occur more often than the former. The "survivors" of the screening for toxicological similarity and co-exposure then become the group to be subjected to the in-depth cumulative risk analysis.

EPN notes that mixture studies may provide support for cumulative chemical groupings. We question a statement on page 10 of the Draft Proposed Principles Document that EPA is "unlikely to conduct CRAs when information is limited to an effect on the same target organ as this introduces too much uncertainty to risk estimates." Does this mean that, if all EPA knows is "liver," it would not conduct a CRA, but if it knew "liver atrophy"or "liver hyperplasia" was the common outcome, then a CRA might/would be conducted? Further explanation is needed.

Determination of toxicological similarity

Implied, but not explicitly stated, is the agency's intention to use the seven categories of evidence for toxicological similarity as described in EPA's "Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures"[3] to help determine the qualification of a chemical substance to be a member of a CCG.

The seven categories, as presented in that guidance in the order deemed most to least informative, are appropriate and potentially useful as discriminators. However, we recommend reordering the list, given the agency's statement that it "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." In light of this, "effect on the same target organ" should go to the bottom of the list.

EPN generally agrees with the discussion on types of studies that would be of value in determining toxicological similarity. However, we would recommend raising the visibility and value of study types that are designed primarily to define the *toxicokinetics* of the chemicals of interest. Yes, toxicokinetics are mentioned in connection with the *in vivo* and *ex vivo* study types, but only as one of several categories of information that these studies could provide. We believe they should be given their own space. EPA should also add a discussion of the potential value of studies describing application of PBTK/PBBK models.

[3] https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533

Lastly, EPA may wish to restate its position on whether it will give greater weight to studies that have been through a credible validation process. This issue currently is a point of contention within the scientific community, particularly as it applies to some categories of new approach methods (NAMs).

Co-exposure Considerations

This section provides a useful and quite detailed discussion of the many and variable scenarios in which co-exposure can occur. We have no recommendations for revision or addition to it, other than to include acknowledgement of the necessity to incorporate exposures resulting from non-TSCA use sources.

EPN has no comments and nothing to add on Data Sources.

Question 3. Several additivity approaches can be used to evaluate multiple chemical substances for cumulative risk, including dose addition, response addition, and integrated addition (Section 3.5). Consistent with EPA guidance, the agency plans to rely upon a default assumption of dose addition when conducting CRAs for toxicologically similar chemical substances under TSCA—unless empirical evidence supports application of another approach. Please comment on this proposed approach, including associated strengths and uncertainties.

EPN Response: As noted in the question and in the draft document, EPA has stated a preference for relying on dose addition as the default approach when conducting TSCA CRAs. EPN agrees with that position but cautions the agency not to apply that choice without also having explored application of one or more of the other choices: response addition, integrated addition, as well as approaches to account for toxicological interactions. Adequate discussion of justification for choosing the default and dismissing the others must be included in all CRAs conducted and *vice versa*. If the default is not selected, justification for selection of an alternative is warranted. Documentation of the attempts to apply the other choices should be presented in an Appendix to the CRA.

Selection of the default dose addition approach offers more than one choice of component method: the Hazard Index (HI) approach, the Toxicity Equivalency Factor (TEF) approach, or the Relative Potency Factor (RPF) approach. EPA defines the HI approach as the calculation of the potential for non-cancer health effects as a result of exposure to one or more substances with the same or similar modes of toxic action or toxic endpoints. The TEF approach is applied to all health endpoints, exposure routes, and exposure durations exhibited by the group members (Example: EPA's Dioxins assessment). The RPF approach is more constraining. It is used to assess risks posed by chemical assessment group members that exhibit the same or common mode of action. Similar modes of action (MOAs) do not qualify. The potency of each group member is compared to that of an index chemical generating a measure of potency for each component that is relative to the toxicity of the index chemical. For application, the shapes of the individual component dose-response functions must be similar over the region of the mixture exposure which is not a requirement in the HI approach (Examples: EPA's PAH assessment and all OPP pesticide CRAs). Detailed discussion of the three methods can be found in EPA's 2000 Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures.[4]

[4] https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533

As we stated earlier with regard to selection of the default dose addition approach, selection and application of a specific approach requires justification for that choice. In cases where the MOA is the same for all group members, application of both the HI and RPF models should be attempted and compared before the preferred model is selected.

Question 4. Please comment on the overall clarity of EPA's Draft Proposed Principles Document, including additional areas that EPA may consider for inclusion.

EPN Response: The charge questions do not include any that specifically address the proposed Scope of the document or the specific principles related to Sections 3.1 Populations for Consideration, 3.2 Stressors for Consideration, or 3.3 Sources, Pathways, and Routes of Exposure Considered. Nonetheless, EPN offers its perspective on each of these.

Scope:

Cumulative Impact Assessment: The agency states that "This draft principles document primarily relies on the definition in EPA's *Framework for Cumulative Risk Assessment* that defines CRA as "an analysis, characterization, and possible quantification of the combined risks to health and/or the environment from multiple agents and/or stressors" (U.S. EPA, 2003)." EPA goes on to say that "this draft CRA principles document does not address cumulative impacts, which refer to the total burden—positive, neutral, or negative—from chemical and non-chemical stressors and their interactions that affect the health, well-being, and quality of life of an individual, community, or population at a given point in time or over a period of time (U.S. EPA, 2022)." The document adds that OPPT will wait until ORD completes its work to "strengthen the scientific underpinning for assessing cumulative impacts" and only then *may* consider "cumulative impacts in the future and as appropriate data, methods, and guidance are available."

EPN considers this to be too passive a stance to take. While we are not recommending that OPPT attempt, in the near term, to conduct cumulative (human health) impact assessments *de novo* for every cumulative chemical group it identifies, it should not exclude integration of assessments of other chemical or non-chemical stressors if data are available to show that one or more of these stressors interact in ways "that affect the health, well-being, and quality of life of an individual, community, or population." Screening for such information should be an integral component of the literature searches for any identified CCGs. If not already done, it should be implemented for the phthalates. Helpful clues also may be found in the cumulative assessments conducted by other parties which are referenced in the "Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act."

Section 3.1 Populations for Consideration

Ecological taxa: In the draft document, EPA reminds the reader that

> "Pursuant to TSCA section 6(b) and the Risk Evaluation Rule, (single chemical) risk evaluations must include both hazard and exposure assessments for the chemical substance in order to characterize any risk that the substance may pose under its COUs to *ecological* (emphasis added) and human populations. At this time, EPA proposes to focus its CRA efforts on human health, not on ecological taxa. This is because established Agency

> cumulative risk guidance documents are available to support human health, but not yet ecological CRA. The Agency may, in the future, develop an approach for conducting CRA under TSCA for ecological taxa."

EPN finds this exclusion of CRA for ecological taxa quite disappointing, especially given that the language of the law and the rule states an obligation to conduct such an assessment. EPA's 2002 *Framework for Cumulative Risk Assessment* [5] contains extensive discussion of ecological analysis and, while there are a few necessary differences in the processes for human health and ecological targets, there was no inference that the challenge was too daunting to do an ecological CRA at that time. The Framework also describes several examples of CRA activities underway when the Framework was issued in 2002 (see box on page xix). We would expect that more examples have accumulated in the intervening years. Furthermore, EPA's 1998 *Guidelines for Ecological Risk Assessment* provides some guidance on cumulative assessment. So while there may be no stand-alone CRA guidance solely focused on ecological scenarios, it's hardly at zero, as the agency's draft document suggests.

Bottom line: EPN recommends that EPA conduct CRA for ecological taxa for each identified CCG to the extent that the available data allow, beginning with the phthalates. This is a data-rich group and should lend itself well to such an analysis.

Human Populations

As the draft document notes, "Under TSCA, the key human populations considered include the general population and [potentially exposed or susceptible sub-populations (PESS)] such as workers and occupational non-users (ONUs), consumers and consumer bystanders, fenceline communities, and tribal populations." For those who have followed the development of the risk evaluations for the first ten chemicals, the first five categories (general population, workers, occupational non-users, consumers, consumer bystanders) should be very familiar. EPN is pleased to see the addition of fenceline communities and tribal populations to the PESS. Both of these subpopulations are likely to meet one or both of the criteria for inclusion (greater susceptibility or greater exposure). Also, evaluating the PESS primarily by life stage (infants, children, pregnant women, workers, the elderly) continues—appropriately so.

3.2 Stressors for Consideration

The draft document states that "EPA is proposing to focus its quantitative CRA efforts on the evaluation of chemical substances. *However, if EPA identifies potential non-chemical stressors that may be reasonably anticipated to impact cumulative risk estimates from chemical substance exposure, then EPA may include a qualitative discussion of the non-chemical stressors and their potential impact on a case-by-case basis* until such time that peer-reviewed, Agency-wide guidance for quantitative evaluation of non-chemical stressors is available." Yes, EPN heartily agrees with the italicized quote but wishes to reemphasize that the agency must actively screen for such information in every case now, beginning with the phthalates.

Section 3.3 Sources, Pathways, and Routes of Exposure Considered

The draft document reminds the reader that TSCA explicitly prohibits EPA from promulgating a risk management rule under section 6(a) that directly regulates non-TSCA uses. Chemical substances

[5] https://www.epa.gov/sites/default/files/2014-11/documents/frmwrk_cum_risk_assmnt.pdf

introduced into commerce for use as a food, food additive, drug, cosmetic, medical device, or pesticide fall into the prohibition category. However, and more importantly, "incidental effects of 6(a) regulation on non-TSCA uses are not prohibited by TSCA's chemical substance definition." It goes on to say:

> "[t]he potential risks of non-TSCA uses may help inform the Agency's risk determination for the exposures from uses that are covered under TSCA (e.g., as background exposures that would be accounted for, should EPA decide to evaluate aggregate exposures). For example, EPA may take into account exposure to multiple chemical substances resulting from non-TSCA uses and/or naturally occurring sources, should the Agency decide to conduct a CRA."

When commenting on the first ten risk evaluations, EPN strenuously argued that EPA should take into account exposures to the chemical under review that were outside the regulatory purview of TSCA and that risk determinations for the whole chemical and its COUs should include consideration of, and an accounting for, these contributions. We adamantly support the position that if a non-TSCA regulated chemical substance meets the criteria for inclusion in a TSCA CCG, it should be placed there and assessed along with the others. This should begin with the phthalate CRA. If there are any phthalates not already in the group selected for the phthalates CRA because it is not a TSCA chemical substance, relevant information should be assembled and evaluated to determine if it meets the criteria for inclusion.

With regard to routes and pathways of exposure, EPA states that:

> "Relevant pathways and routes of exposure to a person from various sources will be considered for a CRA conducted under TSCA. Potentially relevant routes of exposure include inhalation, oral, and dermal routes. Possible pathways of exposure to a chemical substance may include, but are not limited to, ingestion of contaminated groundwater, inhalation of volatile compounds emitted in an indoor environment, or dermal exposure to products during use."

EPN agrees with the position that inhalation, oral, and dermal are potentially relevant routes. EPN agrees with the position on possible pathways of exposure only if it also includes qualifying exposures unrelated to TSCA COUs. See EPN comment above on Sources.

3.6 Addressing Data Gaps

EPN Response: We urge EPA to issue test rules or orders before chemicals are prioritized for risk evaluation in order to get industry to generate critical missing exposure or hazard data as soon as possible. We note that validated NAMs should be utilized to fill in data gaps. Computational tools such as (Q)SAR and read-across have long been a feature in the evaluation of chemicals submitted in the New Chemicals program and can be of value in the Existing Chemicals setting as well.