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Attention: Docket ID Number EPA-HQ-OPPT-2022-0918
Submitted to the Federal eRulemaking Portal (www.regulations.gov)

Re: Environmental Protection Agency's "Cumulative Risk Assessment; Science Advisory Committee on Chemicals (SACC) Virtual Public Meeting; Notice of Availability and Request for Comment"

I. Introduction

The American Fuel & Petrochemical Manufacturers ("AFPM") and American Petroleum Institute ("API") respectfully submit these comments on the Environmental Protection Agency's ("EPA" or "the Agency") Federal Register notice titled "Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act."[1] AFPM and API represent the whole range of the petroleum supply chain from upstream exploration and production to midstream processing and distribution to downstream refining. In addition to fuels, many AFPM and API members manufacture base petrochemicals, such as ethylene, propylene, butylenes, benzene, toluene, and xylenes. AFPM petrochemical members take those base petrochemicals and make petrochemical derivatives that serve as building blocks for a multitude of different manufacturing supply chains.

EPA is seeking comment on its two draft documents that are being submitted to the Science Advisory Committee on Chemicals ("SACC") for peer review: "Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act" ("Draft CRA Principles Document") and "Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substance Control Act" ("Draft CRA Phthalates Document").

[1] See *88 Fed. Reg. 12354*, EPA-HQ-OPPT-2022-0918, published February 27, 2023, at https://www.govinfo.gov/content/pkg/FR-2023-02-27/pdf/2023-03974.pdf.

EPA's Office of Pollution Prevention and Toxics ("OPPT") presents a generalized overview of its plans for cumulative risk evaluations under the Toxic Substances Control Act ("TSCA"). OPPT's Draft CRA Principles Document and Draft CRA Phthalates Document will undergo SACC review during its next scheduled meeting May 8-11, 2023. AFPM and API have significant concerns with EPA using the Draft CRA principles in any type of regulatory context without first publishing a framework and robust guidance to ensure the use of the best available science in a transparent manner. In addition, AFPM and API question whether the science underpinning CRA is adequate to employ such an approach at this time. The Agency should consider and acknowledge the known deficiencies in the scientific understanding of potential synergistic effects of multiple chemicals and non-chemical stressors before attempting a CRA approach in a regulatory context. The following overview and comments are intended to help the SACC with its review and to help OPPT with subsequent revisions to the Draft CRA Principles document.

II. General Comments

The Draft CRA Principles document summarizes basic concepts and high-level CRA approaches that were developed in prior guidance documents, authored mostly by EPA. While the EPA acknowledges that TSCA does not mandate CRA as a part of chemical risk evaluations, the Agency has determined that the statute would consider CRA appropriate if "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" (EPA, 2023a).

The Draft CRA Principles Document is useful for providing a high-level review of the available CRA guidance developed by regulators up to this point; however, the Draft CRA Principles Document lacks specificity on how EPA actually plans to use and apply these principles in a chemical risk evaluation under TSCA, and it does not describe what data thresholds need to be met to justify the development of a CRA for a chemical risk evaluation. EPA states that CRAs will include a "weight of the evidence narrative," but there is no mention or description of the application of any established systematic process in the evaluation of the information used to inform the narrative, to ensure the evaluation process is sufficiently transparent. The Agency states the Draft CRA Principles Document is not a guidance document, but also indicates the draft document will be relied upon to determine if CRAs should be developed as a part of chemical risk evaluations under TSCA. These positions are contradictory and could use clarification.

Overall, the Draft CRA Principles Document raises more questions than answers because it fails to communicate the scientific and policy details necessary for stakeholders to understand when and how CRAs will be developed going forward. There are several key issues presented below that are areas where EPA should provide clarity and details regarding the application of its draft CRA principles, such that all stakeholders have a clear understanding of when and how the Offices plan to pursue a CRA in a TSCA risk evaluation. For ease of reference, these issues are presented in accordance with their order, by section, in the Draft CRA Principles Document.

III. Comments by Section

EPA should clarify if it will be drafting and releasing a CRA Framework and Process Guidance document.

EPA states that the Draft CRA Principles Document "is not a framework or guidance document on the process for conducting CRAs, rather it focuses on principles for CRAs for chemical substances." This suggests that a CRA framework or guidance document is pending, since the Draft CRA Principles Document makes it clear that the development of CRA will be a consideration for TSCA risk evaluations going forward. Yet in the Draft CRA Phthalates Document EPA has proposed for assessing high-priority phthalates under TSCA (EPA, 2023b), the Agency states that the Draft CRA Principles Document "lays the foundation for EPA's proposed approach for CRA of chemical substances undergoing risk evaluation under TSCA section 6(b)." This is extremely confusing given that the Draft CRA Principles Document does not provide any detailed information as to how or when CRAs will be required or necessary in a TSCA risk evaluation.

EPA should clarify whether it plans to draft a TSCA CRA framework and guidance document and, if so, when it would be published for review and public comment. While the examples provided are helpful, the Draft CRA Principles Document lacks specificity and is therefore limited in its utility. More detailed guidance will be necessary to perform cumulative risk assessments as a part of TSCA risk evaluations.

If CRA guidance is pending, EPA should provide justification for releasing the Draft CRA Phthalates Document prior to the development of its CRA framework and process guidance. If, on the other hand, the Agency does not plan to develop a CRA framework and guidance document, it needs to correct and clarify the scope of the Draft CRA Principles Document and include a framework and guidance because it is cited as the "foundation" of the EPA's proposed CRA approach for high-priority phthalates.

The Draft CRA Principles Document should define the basics of cumulative risk assessment and the decision mechanisms EPA plans to use to justify when and how a CRA is warranted under TSCA.

The Draft CRA Principles Document appropriately distinguishes a CRA from a cumulative impacts assessment ("CIA"), noting that guidance for the latter is being developed by EPA's Office of Research and Development ("ORD"). However, half of the Draft CRA Principles Document's scope section is dedicated to CIA, while the intent of the Draft CRA Principles Document is on the development of CRAs, not CIAs, as a part of TSCA risk evaluations. Given this intent, EPA should limit the scope of the Draft CRA Principles Document to addressing CRA.

The list of reliance documents for the Draft CRA Principles Document is incomplete. The draft should clearly describe the search methods and inclusion/exclusion criteria used to identify its reliance documents.

The Draft CRA Principles Document includes a list of twelve references (i.e., reliance documents) – mostly prior EPA guidance documents – that were used to develop the

proposed CRA principles. EPA should describe the search methods and criteria used to identify these particular reliance documents. The list of resources providing the scientific foundation for the proposed TSCA CRA principles is incomplete for such a complex scientific issue. There are many more recent peer-reviewed publications that should be considered and discussed. EPA should conduct a comprehensive literature review and evaluation and include a much wider range of documents to inform its CRA principles.

The following are an example selection, not exhaustive, of more recent peer-reviewed articles recommended for consideration and discussion in the Draft CRA Principles Document:

> Goodrum et al. (2021), Boberg et al. (2021), Bopp et al. (2019), Braeuning et al. (2022), Fox et al. (2017), Kennedy et al. (2019), MacDonell et al. (2013), Park et al. (2017), Payne-Sturges et al. (2023), Pelletier et al. (2017), Socianu et al. (2022), and van der Voet et al. (2020). It is recommended that EFSA (2019a,b) be considered as well.

The Draft CRA Principles Document should clearly identify what CRA concepts were pulled from which reliance document, and which CRA concepts it considers inappropriate/insufficient.

As already noted, the Draft CRA Principles Document was developed using twelve reliance references. The dates of these reliance documents span more than three decades. The scientific evidence and thinking have evolved considerably over this time, with some concepts and ideas obsolete and others not yet validated for risk assessment purposes. EPA should elaborate on the concepts and ideas from each of the twelve references that informed the proposed CRA principles and identify those concepts it deems outdated or invalid for risk assessment purposes to provide clarity on the Agency's rationale for the CRA principles it has proposed under TSCA.

The Draft CRA Principles Document fails to address several important elements of CRA that are discussed in EPA's reliance documents.

There is no mention of other considerations integral to CRA that are addressed in various CRA guidance documents. For example, the Draft CRA Principles Document does not address how CRA should inform data quality objectives, problem formulations, fate and transport, and conceptual site-model development. EPA should include specific sections on these and other key CRA topic areas in its Draft CRA Principles Document.

The Draft CRA Principles document should list the criteria it will use to define potentially exposed or susceptible subpopulations (PESS) considered under a CRA.

PESS are subsets of people who are either more likely to be exposed to a particular chemical substance or are more susceptible to a substance than the general population. The Draft CRA Principles Document states that since TSCA does not define "greater susceptibility" or "greater exposure," EPA has the discretion to consider both chemical

and non-chemical stressors when identifying PESS. EPA chemical risk evaluations already define sensitive subpopulations by particular life stages (e.g., pregnant women, infants and children, the elderly, etc.), genetic susceptibility, and state of health, and account for them through an intraspecies uncertainty factor when deriving chemical-specific toxicity values or deriving a margin of exposure ("MOE").

If EPA plans to expand the definition of sensitive populations based on additional non-chemical stressors for CRAs under TSCA, the Agency needs to clarify how they plan to do this and if and how it plans to mitigate compounding uncertainties that are an inevitable result of combining hazards and risks across chemicals and chemical groups. Further, the Draft CRA Principles Document states "As OPPT continues to develop its approaches for CRA, OPPT will take into consideration PESS in hazard, exposure, and risk methods and results." To this end, EPA should discuss what the PESS identification and characterization process will entail at each of these stages and how the Agency will define PESS and quantitatively incorporate these considerations into a CRA process. As part of this discussion, EPA should also delineate which non-chemical stressors it will consider appropriate when characterizing PESS for a CRA; otherwise, it is inevitable that the distinction between a CRA and a CIA will be blurred.

EPA should clearly delineate which non-chemical stressors will be considered and differentiate how these will be considered differently than in a CIA.

The Draft CRA Principles document states:

> *"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."*

This language is extremely confusing and blurs the lines between a CRA and a CIA and, as such, contradicts the stated scope of the document. Despite distinguishing between CRA and CIA in the scope of the Draft CRA Principles Document, the discussion of stressors adds substantial confusion by equivocating on whether or not CRAs under TSCA will account for non-chemical stressors and prompts several questions:

- What is the principle by which EPA will consider non-chemical stressors as part of a CRA under TSCA?
- Given the diversity of potential non-chemical stressors in the daily lives of people, are there limitations to what EPA considers to be non-chemical stressors relevant to CRA conducted under TSCA?
- How will the qualitative information be incorporated?

Given the ambiguity of non-chemical stressors, EPA should include a comprehensive list of potential non-chemical stressors that it foresees addressing as a part of a CRA under

TSCA. More generally, the Agency needs to revisit the scope of the draft proposed CRA principles and revise or clarify the stressors section to ensure it is consistent with the scope and distinct from EPA's other efforts to develop CIA guidance.

EPA should clarify if and how non-TSCA exposures will impact CRA and risk management decisions.

The Draft CRA Principles document states CRAs will account for non-TSCA exposures (e.g., food, cosmetics, pesticides):

> *"'[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)' 82 FR at 33735. 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."*

Since chemical substances covered under other laws are excluded from the definition of "chemical substance" [see TSCA section 3(2)(A)], it is difficult to understand which exposures are proposed to be included in the CRA and how the various exposures will be considered for risk management under TSCA. Does EPA plan to use these excluded exposures as part of risk management decisions? For example, if the majority of exposure to a certain chemical or chemical group occurs through routes and pathways not regulated under TSCA (e.g., food or pesticides) but EPA determines that the total exposures (including small exposures due to TSCA conditions of use) represent an unacceptable risk or hazard, will the Agency automatically deem the TSCA condition of use (COU) an unreasonable risk regardless of how small the overall exposure from the TSCA condition of use?

EPA should describe a clear methodology for establishing Cumulative Chemical Groups.

The Draft CRA Principles Document states that EPA plans to establish "cumulative chemical groups" based on the "principle considerations" of both toxicological similarity and the potential for co-exposures, and that the establishment of cumulative chemical groups will be through "a narrative that clearly characterizes strengths and uncertainties of the evidence" in each case. The Draft CRA Principles Document provides some key toxicology and exposure factors that will be considered in making this determination, but it is far from clear <u>*how*</u> these elements will be used to determine whether there is sufficient evidence for establishing a cumulative chemical group.

The process by which a cumulative chemical group is established by EPA needs to be transparent and consistent. Reference to a "weight of the evidence narrative" is made, but a systematic and detailed process for the transparent and consistent development of such narratives is not described in the draft document. Considering the potential impact that such chemical groupings can have on a chemical risk evaluation under TSCA, it is imperative that clarity and transparency are brought to this decision-making process

through a detailed systematic approach that is either included in this draft document or a subsequent CRA framework and guidance document.

EPA should include a section on how the proposed CRA principles will incorporate systematic review methods in the Draft CRA Principles Document.

Surprisingly, systematic review is not mentioned among the proposed principles in the draft document, despite systematic review being a mandatory element of TSCA risk evaluations. The only mention of systematic review is in the TSCA definition of "weight-of-the-evidence" in the document glossary, which is quoted from 40 CFR § 702.33. EPA must clearly state how systematic review will be implemented in the determination of cumulative chemical groups, and in what aspects it will be similar or different from the systematic review methodology it has been applying to chemical risk evaluations up to this point. Per the TSCA statute, EPA must identify the systematic review method it plans to utilize for CRAs and include details on:

i) how it plans to structure key research and objectives questions relevant to CRAs

ii) the pre-establishment of protocols for identifying and evaluating evidence streams

iii) integrating the available evidence in support of group determinations

EPA should indicate how the various toxicodynamic information will be weighted to inform chemical toxicological similarity.

The Draft CRA Principles Document lists four general categories of toxicology study types that the Agency could use to assess toxicological similarity. (as noted below, epidemiology studies should be categorized separately) These range in utility from animal bioassays to *in silico* models and are not equivalent in their generalizability or applicability for predicting risk and hazard endpoints relevant to human health risk evaluation. EPA should describe the relative importance of these various data categories and provide general insight into how the Agency plans to weight the outcomes of these study types. For example, the document should explain how EPA plans to deal with variable and conflicting data across study types (e.g., if chemicals or a chemical mixture elicits a key response in an *in vitro* model but fails to elicit toxicological responses *in vivo*) and include a general tiered system that illustrates which study types should be considered more reliable for informing CRA. This is an example of a weight-of-the-evidence approach required under TSCA.

Human epidemiological studies should have their own entry in the Draft CRA Principles Document.

The Draft CRA Principles Document lists specific types of toxicodynamic information that would be considered as a part of the process for determining toxicological similarity between chemicals. It is notable that human epidemiology studies do not have their own listing but instead are included under "*in vivo* studies." Human epidemiology and controlled laboratory animal studies and databases are considered as separate evidence

streams in risk assessment due to their fundamentally different study designs. To be consistent with the TSCA risk evaluation process (and risk assessment practices in general), the Draft CRA Principles Document should include a separate entry for human epidemiology studies.

EPA should describe a clear decision-based methodology for determining co-exposures to chemicals.

The Draft CRA Principles document lists various indicators that may be used to determine co-exposure to chemicals; however, no details are provided regarding the indicators. For example, EPA states "… inclusion and grouping of two or more chemical substances into a CRA requires consideration of whether exposure to multiple chemical substances occur at toxicologically significant concentrations…" The term "toxicologically significant concentrations," however, has not been defined. Similarly, EPA states "if a chemical is biologically persistent, co-exposure will be assumed to occur;" however, the Agency does not describe how it will differentiate between the endogenous presence of a chemical or its metabolite and that which may result from exogenous exposure (e.g. ethylene oxide, phenol, acetone, acetaldehyde).

Cumulative risk estimates based solely on common target organ or system effects represent a screening-level approach that should not be used to make CRA decisions.

Earlier in the document EPA states it is generally "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." The general instinct here is reasonable, as such approaches are considered highly conservative for estimating cumulative risk, especially for noncancer endpoints. This approach to estimating cumulative risk is typically described using a hazard index ("HI") calculation that assumes target organ or system additivity, and its use is mostly limited to the screening-level stage of the risk assessment process. This is because HI estimates represent compounded uncertainties, wherein the uncertainties inherent to multiple parameters (in this case multiple chemical toxicity values) are added together, making the total HI estimate more uncertain than the hazard quotient ("HQ") estimate for any single chemical. As EPA acknowledges in its 2008 Cumulative Risk Assessment guidance, there are three critical uncertainties inherent to the HI calculation:

- "The assumption of common MOA might not apply because only commonality of the target organ is considered."
- "The use of a safe level, such as a lower bound on the toxicity threshold, might not be an accurate measure of toxic potency. Weak toxicity data usually result in a lower safe level because of larger uncertainty factors or use of lower confidence bounds on dose."
- "The use of RfDs [or RfCs] as safe levels may result in an overestimate of the degree of concern because the RfD [or RfC] is based on one critical or most sensitive effect.

Thus, when a chemical causes multiple effects and is to be included in more than one HI calculation, the general use of its RfD [and/or RfC] is problematic." [2]

Another uncertainty is that HI assumes the chemicals accounted for in the cumulative risk estimate do not interact or impact each other's fate and transport in the environment.

While it is encouraging that EPA states it is "unlikely" to use what amounts to a screening-level approach to estimating cumulative risk in TSCA risk evaluations, the Draft CRA Principles Document does not rule out this approach. Given the considerable uncertainties associated with the HI estimates, EPA should:

1) revise the language to be more explicit about whether the Agency would consider using this method in CRA under TSCA

2) explain the circumstance(s) when EPA would consider it appropriate to apply this approach to a CRA, enumerating the criteria that would need to be satisfied to justify the approach in a CRA

Given the numerous assumptions and underlying uncertainties in additivity approaches, EPA should provide additional details that justify why additivity represents the best available science as a default approach to CRA.

EPA states that dose addition will be the default approach for CRAs under TSCA, though they acknowledge that other approaches may be used if supported by empirical evidence. To support this decision, the Agency cites prior EPA guidance from more than 20 years ago (EPA, 1986, 2000). In addition to providing additional details justifying dose and response additivity as the default CRA approach, EPA should expand the discussions to include other methods that may be applicable based on toxicological evidence (e.g., the human-relevant potency threshold and maximum cumulative ratio).

EPA should explain how the various tiered CRAs would impact the decision-making process and ultimately their respective chemical risk evaluations.

EPA describes the potential utility of a tiered approach to performing CRAs depending on the amount of information available. For example, they state:

> *"Tier 0 hazard assessments [as defined in the WHO/IPCS framework2] may group chemical substances based on a conservative assumption of dose addition with limited evidence of toxicological similarity (e.g., predictive hazard tools might be used to group chemical substances based on similar target organ), while higher tier hazard assessments may incorporate more refined information on MOA or utilize physiologically-based pharmacokinetic or biologically-based*

[2] MOA is mechanism or mode of action, which describes the way in which a chemical substance interacts with the body to cause a functional or anatomical change. RfD is a reference dose at which there are no adverse effects over a lifetime of exposure. RfC is a reference concentration at which there are no adverse effects over a lifetime of exposure.

dose response models that may allow for probabilistic estimates of hazard."

Theoretically, a tiered approach could be a very useful way to handle groups of chemicals with highly variable databases. Assuming EPA plans to develop and apply a tiered system of applying CRA methods, it will be imperative that the Agency provides clear definitions of each tier methodology and of the data thresholds that would justify Agency decision-making in a transparent and consistent manner across CRAs.

EPA should clarify if it will prioritize less rigorous, more conservative CRA methods over more refined CRA methods that reflect the state of the science if the latter, more certain methods lead to less conservative CRA estimate.

EPA indicates that it may consider the applicability of a variety of dose addition approaches when conducting a CRA, such as hazard index, relative potency factor, and margin of exposure. Other approaches may be based on response addition or integrated addition if they "are more appropriate and are similarly or more health protective." This statement is ambiguous and suggests the potential for conducting CRAs that contradict the TSCA statutory requirement that EPA conduct risk evaluations using the "best available science." That the Agency would only consider other science-based approaches if they are "similarly or more health protective" than the standard approach(es) turns the risk paradigm on its head. That is, the initial step in a risk assessment is typically conducted according to screening-level methodologies that are overly conservative and require relatively less effort to perform, while with more refined scientific methods result in more accurate estimates of risk and hazard. Similarly, species-specific effects and mechanistic studies can shed light on the relevance of adverse effects observed in laboratory animals to humans. Excluding data that would result in a less conservative but more accurate CRA simply because it results in a less "health protective" outcome as compared with a less informed CRA based on conservative default assumptions would not reflect best science approaches.

IV. Comments on EPA's Draft CRA Phthalates Document

The Draft CRA Phthalates Document presents a proposed approach to conduct a CRA on the phthalates currently undergoing risk assessment under TSCA (DEHP, BBP, DBP, DIBP, and DCHP), as well as consideration of two additional phthalates subject to manufacturer-requested risk evaluation (i.e., DINP and DIDP). The following overview and comments are intended to help the SACC with its review, as well as to help EPA with subsequent revisions to the Draft CRA Phthalates Document.

It is unclear how EPA plans to use the findings presented in the Draft CRA Phthalates Document. In the executive summary, EPA initially says that the results of the individual phthalate risk evaluations that are currently ongoing will be used as important inputs into the phthalate CRA. Then in the following paragraph, the Agency states that "the phthalate CRA will not contain a risk determination. Instead, results from the CRA are anticipated to inform EPA's individual phthalate risk determinations, pending completion of the CRA in parallel with individual phthalate risk evaluations." It is unclear how the "results from the CRA" will inform individual phthalate risk determinations if a cumulative risk determination is not made (EPA, 2023b).

Upon evaluation of the five high-priority and two manufacturer-requested phthalates, the cumulative chemical group was identified based on a shared ability to elicit key markers of phthalate syndrome and evidence of human co-exposure. EPA's proposed cumulative chemical group includes DEHP, BBP, DBP, DIBP, DCHP, and DINP but not DIDP. The Draft CRA Phthalates Document provides explanations as to why some of the various approaches were selected for consideration (e.g., hazard index, relative potency factor, and margin of exposure approaches), but the selection of other approaches for consideration (e.g., estimating exposure from other sources) were not explained. Prior to the evaluation of various approaches to assess cumulative risk of a chemical group, it is important that EPA provide justification as to how and why each approach was identified and selected for consideration.

EPA should clarify if it intends for the CRA to depend on the individual risk evaluations or if the individual risk evaluations will depend on the CRA.

In the Executive Summary of the Draft CRA Phthalates Document, EPA states that "the results of the individual phthalate risk evaluations are important inputs into the CRA…" Conversely, in the Background section of the same document, EPA proposes "that a subset of the phthalates undergoing risk evaluation represent a cumulative chemical group, and that a *cumulative risk assessment is necessary to ensure that individual risk evaluations on the phthalates in the cumulative chemical group have considered the reasonably available information, are consistent with the best available science, and based on the weight of the scientific evidence* [emphasis added]" (EPA, 2023b). In addition to the uncertainty of which evaluation will influence the other, the latter quote from EPA suggests that the CRA for phthalates is going to be used to check on the adequacy and conclusions of the individual risk evaluations. This is confusing considering those same individual risk evaluations are also "important inputs into the CRA." EPA should clarify its intention for how these risk assessments will inform one another.

EPA should provide more information on what constitutes a chemical with a "low hazard potential."

Due to the relatively higher exposure of DINP to subpopulations susceptible to phthalate syndrome, EPA includes DINP in the cumulative chemical group despite its lower potency, compared to the other high-priority phthalates also included in the cumulative chemical group. Despite including DINP in the phthalate CRA, the Agency acknowledges that "not all chemicals identified as part of common mechanism group need to be carried forward for quantitative CRA. For example, a chemical with low hazard potential may be excluded" (EPA, 2023b). No further details are provided on what criteria qualify a chemical as a "low hazard potential" in the context of CRA. EPA should clarify what criteria it applied here and plans to apply to future CRA risk evaluations under TSCA to determine whether chemicals of low hazard will be included in CRAs. As a general observation, the lack of transparency on how this decision was made illustrates why the Draft CRA Principles Document is inadequate as a foundational reference for describing CRA approaches under TSCA. It is critical for EPA to develop a framework and guidance that clearly describes the systematic method and process by which CRA decision criteria are developed and applied by the Agency for all chemical risk evaluations under TSCA to ensure consistency and transparency.

Due to the lack of mode of action data presented by EPA for phthalates, it is unclear from the current draft CRA approach whether the Agency will utilize mode of action data (when available) for other cumulative chemical groups to refine risk estimates and lower uncertainty.

Although EPA used the default dose additive approach for phthalates in the Draft CRA Phthalates Document, the Agency also acknowledged the National Research Council's ("NRC") support for the use of mechanism of action data "for defining critical pathways, determining human relevance of observed effects, and reducing uncertainty in risk estimates" (EPA, 2023b). This suggests that if empirical mode of action data were available, EPA may consider alternate approaches to help reduce uncertainty in risk estimates. However, in the Draft CRA Principles Document it appears the Agency will only consider other approaches if they "are more appropriate *and are similarly or more health protective* [emphasis added]." Yet in the same document, EPA affirms that when conducting TSCA risk evaluations, TSCA requires EPA to "consider the reasonably available information, consistent with the best available science and make decisions based on the weight of scientific evidence [15 U.S.C. § 2625(h), (i), (k)]" (EPA, 2023a). It is important that EPA adheres to TSCA's requirements and uses the best available science and weight-of-evidence based on systematic methods to inform risk and hazard calculations even if it results in less conservative human health risk estimates.

EPA should define what criteria need to be met to conduct a cumulative exposure evaluation and be transparent in its selection of cumulative exposure approaches for consideration.

EPA proposed "to combine non-attributable and non-TSCA exposures with exposures from TSCA COUs when appropriate to determine cumulative exposure" in the Draft CRA Principles Document (EPA, 2023a). Although the Agency adequately explains why accounting for other sources is necessary for the CRA of phthalates, EPA should provide explicit guidance to help determine when it is "appropriate to determine cumulative exposure" for other cumulative chemical groups. Additionally, in the Draft CRA Phthalates Document, EPA considered two approaches for estimating non-attributable and non-TSCA exposures, scenario-based and reverse dosimetry. Although EPA provided a thorough comparison of each exposure estimate approach, the rationale for how they arrived at these two options is not clear.

As a relatively "data rich" chemical set, the high-priority phthalates are not an ideal "test" group for applying EPA's Draft CRA Principles.

The Draft CRA Principles Document presents a number of challenges that risk assessors will need to contend with while determining if a chemical risk evaluation warrants a CRA. The high-priority phthalates at the center of EPA's Draft CRA Phthalates Document are well-studied compounds that have already been evaluated as a chemical group by the National Academy of Sciences in the past (NRC, 2008; NASEM, 2017). Very few chemical groups evaluated under TSCA are going to be data rich. The Agency should develop case study examples of data-poor chemicals it would consider designating as "cumulative chemical groups" per the Draft CRA Principles Document to better illustrate when and how EPA plans to pursue CRA for a chemical risk evaluation under TSCA.

V. Conclusion

AFPM and API generally support the pursuit of cumulative risk assessment approaches. The current draft CRA principles proposed by EPA are high-level and a useful outline for further work. AFPM and API are concerned, however, by the lack of guidance and clarity as to how, when, where, and why EPA intends to use a CRA approach. The draft documents need more work to answer key questions raised by these comments. AFPM and API are willing to work with the Agency as it continues its CRA work.

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VI. References

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