August 30, 2023

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Comments on Draft Guidelines for Cumulative Risk Assessment Planning and Problem Formulation.

These comments are submitted on behalf of the undersigned scientists, community members, and advocates. 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 Guidelines for Cumulative Risk Assessment Planning and Problem Formulation" hereafter referred to as the "Draft CRA Guidelines."

Every day, people living in the United States are exposed to dozens of chemicals, and certain subpopulations are more susceptible to harm from these exposures due to either intrinsic (e.g., pre-existing disease, life stage, reproductive status, age, sex, genetic traits) or extrinsic (e.g., food insecurity, geography, poverty, socioeconomic status, racism, discrimination, culture, workplace) factors.[1] EPA's traditional approach of conducting single-chemical risk evaluations does not fully capture these real-world chemical exposures and risks, particularly for susceptible subpopulations.[2] Cumulative risk assessment ("CRA"), which EPA has previously defined as the "analysis, characterization, and possible quantification of the combined risks to health or the environment posed by multiple agents or stressors"[3] is required to adequately characterize risks to protect public health from the harms of real-world chemical exposures and risks, particularly for communities disproportionately burdened by multiple chemical exposures and/or nonchemical stressors, including racial injustice, food insecurity, and poverty.

In 2021, President Biden signed Executive Orders ("EOs") 13985 and 14008 to advance racial equity, increase resources for underserved communities, and address the climate crisis. EO 14008 specifically calls on all federal agencies to "make achieving environmental justice part of their missions by developing programs, policies, and activities to address the disproportionately high and adverse human health, environmental, . . . and other cumulative impacts on disadvantaged communities."[4] In response to this requirement, EPA appropriately released the

[1] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., Bennett, D. H., Birnbaum, L. S., Brown, P., Carignan, C. C., Cooper, C., Cranor, C. F., Diamond, M. L., Franjevic, S., Gartner, E. C., Hattis, D., Hauser, R., Heiger-Bernays, W., Joglekar, R., Lam, J., … Zeise, L. (2023). A science-based agenda for health-protective chemical assessments and decisions: Overview and consensus statement. *Environmental Health*, *21*(1), 132. https://doi.org/10.1186/s12940-022-00930-3

[2] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). 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*(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079

[3] U.S. EPA Framework for Cumulative Risk Assessment (2003). EPA/600/P-02/001F. National Center for Environmental Assessment, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC: [online]. Available: https://www.epa.gov/risk/framework-cumulative-risk-assessment

[4] Exec. Order No. 14,008, 86 Fed. Reg. 7619, 7629 (Jan. 27, 2021).

"Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act", the "Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act", for which we submitted comments to regulations.gov, [5] and most recently, the Draft CRA Guidelines.

We support EPA's continued effort to establish frameworks for evaluating cumulative chemical risk. Unlike previous CRA guidance documents, the Draft CRA Guidelines correctly proposes an expanded definition of "non-chemical stressors," the quantitative and qualitative inclusion of social determinants of health, and a requirement to involve stakeholders "early in the process" of CRA—recommendations that would make CRA more equitable and holistic.

However, the Draft CRA Guidelines overall does not sufficiently advance or improve upon past CRA guidelines and does not adequately evaluate or consider the best available scientific methods for conducting CRA. Instead, the Draft CRA Guidelines recommends flawed approaches to evaluating scientific evidence, and a "tiered" approach to CRA scoping that does not adequately account for cumulative risk and would likely result in exclusion of nonchemical stressors from CRAs. This proposed "tiered" approach could also result in a failure to consider CRA when it is scientifically appropriate. EPA also relies on flawed descriptions of "toxicological similarity" and "non-chemical stressors" and fails to consider several critical "initiating factors" for conducting CRA, including the need to initiate a CRA based on evidence of environmental releases of multiple chemicals, production of multiple chemicals, and biomonitoring evidence of widespread exposure in the human population. A failure to consider these as potential "initiating factors" could result in an underestimation of risk to communities facing disproportionate chemical exposures. EPA should also revise the Draft CRA Guidelines section on "Risk Management Considerations" to ensure that it does not create inappropriate obstacles to the inclusion of non-chemical stressors in CRA.

It appears that EPA's intent in developing this document is to promote application of CRA. However, if EPA does not correct the significant problems in the Draft CRA Guidelines, it will make it more difficult to conduct scientifically appropriate CRAs and entrench bad practices into any future CRAs that are conducted. The Draft CRA Guidelines also has important implications for EPA's implementation of environmental statutes, including the Toxic Substances Control Act ("TSCA"). It is critical, therefore, that the Draft CRA Guidelines are useful for these programs. As written, the Draft CRA guidelines does not incorporate "the best available science."[6] Our comments recommend specific improvements to the Draft CRA Guidelines that will result in CRA that is scientifically supported, legally compliant, and reflective of real-world chemical exposures and risks.

[5] Comments submitted by the Program on Reproductive Health and the Environment (PRHE) at the University of California, San Francisco can be downloaded at: https://www.regulations.gov/comment/EPA-HQ-OPPT-2022-0918-0014

[6] 15 U.S.C. §2625(h).

Our comments focus on the following main points:

1. **The Draft CRA Guidelines is inconsistent with the best available scientific methods in several key areas.**
    a. **EPA relies on a flawed "tiered" approach to CRA scoping.**
    b. **EPA does not consider all relevant "initiating factors."**
    c. **EPA does not rely on best available methods for evaluating scientific evidence.**
        i. **The Draft CRA Guidelines presents a flawed "weight of evidence" approach.**
        ii. **A requirement to establish causality in stressor-response relationships would be a barrier to conducting CRA.**
    d. **EPA relies on flawed, inconsistent, and incomplete descriptions of key terms for CRA**
        i. **The Draft CRA Guidelines presents inconsistent and incomplete definitions of "nonchemical stressors" and "populations of interest."**
        ii. **The Draft CRA Guidelines presents a flawed and inconsistent characterization of "toxicological similarity."**
    e. **EPA's proposed "fit for purpose" model is inconsistent with expert recommendations.**

2. **The Draft CRA Guidelines proposes risk management considerations that unduly narrow the scope of CRA and pose obstacles to conducting CRA.**
    a. **CRA planning does not need detailed identification and analysis of risk management interventions.**
    b. **EPA's proposed risk management considerations would likely result in the exclusion of nonchemical stressors from CRAs.**

Sincerely,

Jessica Trowbridge, PhD
Associate Research Scientist, Science and Policy
Program on Reproductive Health and the Environment
University of California, San Francisco

Rashmi Joglekar, PhD
Associate Director, Science and Policy
Program on Reproductive Health and the Environment
University of California, San Francisco

Daniel Axelrad, MPP
Independent Consultant
Washington, DC

Swati Rayasam, MSc
Science Associate
Program on Reproductive Health and the Environment
University of California, San Francisco

Courtney Cooper, MPH
Science Associate
Program on Reproductive Health and the Environment
University of California, San Francisco

Tracey Woodruff, PhD, MPH
Director
Program on Reproductive Health and the Environment
University of California, San Francisco

Lisa Bero, PhD
Professor of Medicine and Public Health
University of Colorado Anschutz Medical Campus

Linda S. Birnbaum, PhD
Scientist Emeritus and Former Director; Scholar in Residence
NIEHS and NTP; Duke University

Phil Brown, PhD
University Distinguished Professor of Sociology and Health Sciences
Northeastern University

Timothy H Ciesielski, ScD, MD, MPH
Senior Research Associate
Case Western Reserve University, School of Medicine,
Department of Population Quantitative Health Sciences

Kathleen A. Curtis, LPN
Founding Director
Moms for a Nontoxic New York

Sibyl Diver, PhD
Lecturer
Stanford University, Earth Systems Program & Environmental Justice Working Group

Kaley Dodson, MESM
Environmental Scientist

Susan Fisher, PhD
Professor
University of California, San Francisco

Stanton A. Glantz, PhD
Professor of Medicine (Retired)
University of California San Francisco

Robert Gould, MD
Adjunct Assistant Professor
Program on Reproductive Health and the Environment
University of California, San Francisco*

Donna Hunter, PhD
Retired Advanced Lecturer
Stanford University, Program in Writing and Rhetoric

Carly Hyland, PhD, MS
Assistant Professor
University of California Berkeley/UC Cooperative Extension

Jean-Marie Kauth, PhD, MPH
Professor
Benedictine University

Erica Koustas, PhD
Scientific Consultant

Juleen Lam, PhD MHS MS
Associate Professor
California State University, East Bay

Christopher Leboa, MS
PhD Candidate
University of California Berkeley

Rainer Lohmann, PhD
Professor of Oceanography, Director, URI STEEP Superfund Research Center
University of Rhode Island

Rachel Massey, ScD
Senior Science and Policy Advisor
Collaborative for Health and Environment*

Maricel V. Maffini, PhD
Independent Consultant,
Frederick, Maryland

Pamela Miller, M.E.S
Executive Director and Principal Investigator

Alaska Community Action on Toxics *

Joshua O'Floinn, MS, RN
Staff Nurse, Pediatric ICU
Kaiser Permanente Oakland Medical Center

Kristina Sinclair
Associate Attorney
Center for Food Safety*

Patrice Sutton, MPH
Research Collaborator
Program on Reproductive Health and the Environment
University of California, San Francisco

Lisette van Vliet
Senior Policy Manager
Breast Cancer Prevention Partners *

Ronald H. White, M.S.T.
Principal
RHWhite Consulting

Marya Zlatnik, MD
Professor of Obstetrics and Gynecology
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

*denotes sign-on on behalf of their institution

Detailed Comments:

1. **The Draft CRA Guidelines is inconsistent with the best available scientific methods in several key areas.**

CRA is the best available tool to evaluate the risks associated with real-world chemical exposures. A robust CRA considers the full extent of chemical and nonchemical stressors that contribute to adverse health outcomes, including both intrinsic and extrinsic[7] nonchemical stressors that make individuals more susceptible to harm from chemical exposures. Previously published CRA frameworks provide specific recommendations on how to group chemicals into CRA, consider and identify relevant nonchemical stressors and other sources of human variability and vulnerability, and identify all relevant exposure sources. While the Draft CRA Guidelines cites several of these frameworks,[8,9,10] EPA fails to provide recommendations for conducting CRA that are aligned with these frameworks, and instead offers vague guidelines that either contradict or fall short of these best available practices.

These shortcomings are likely to result in an underestimation of health impacts on people across the country, including groups who face disproportionately high exposures to multiple chemical and nonchemical stressors; if EPA does not fully estimate combined exposures and cumulative risks, then EPA will not be able to ensure that its chemical regulations eliminate unreasonable risk to those communities. Below, we provide examples of how the decisions made in the Draft CRA Guidelines preclude EPA from conducting a scientifically supported cumulative risk assessment.

a. **EPA relies on a flawed "tiered" approach to CRA scoping.**

EPA's proposed "tiered" approach to implementing CRA is inconsistent with the best available science. EPA claims that this "tiered" approach will result in a more "tractable CRA design" and aims to use the tiers to "balance resources against the desire to reduce uncertainty in the assessment."[11] However, this approach does not adequately account for cumulative risk and would likely result in exclusion of nonchemical stressors from CRAs. This proposed "tiered" approach could also result in failure to consider CRA when it is scientifically appropriate. Additionally, the emphasis on using fewer resources could lead to the under inclusion of studies, factors, and stressors.

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[7] Intrinsic factors (e.g., pre-existing disease, life stage, reproductive status, age, sex, genetics) and extrinsic factors (e.g., food insecurity, geography, socioeconomic status, racism/discrimination, cultural factors, workplace/occupation) impact susceptibility to or likelihood of environmental chemical exposures, leading to differential risks

[8] National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. (2009). *Science and Decisions: Advancing Risk Assessment*. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK214630/

[9] U.S. EPA. (2014). *Framework for Human Health Risk Assessment to Inform Decision Making* (EPA/100/R-14/001 April 2014; EPA Risk Assessment Forum). U.S. EPA.

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

[11] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 13

EPA should delete the tiered approach from the Draft CRA Guidelines and instead require that following CRA "initiation", either 1) the CRA is conducted in entirety using all reasonably available information and appropriate application of uncertainty factors to account for any data gaps, or 2) if sufficient information is not available to conduct a CRA, EPA uses its authority under various statues, including TSCA, to obtain or generate data that fill critical data gaps and support an accurate and robust CRA. In both cases, EPA should recommend the use of uncertainty factors to account for inherent variability and uncertainty associated with multiple chemical exposures, human variability in the response to chemical exposures, and human vulnerability due to nonchemical stressors.

EPA defined the tiered approach as follows:

> Tiering is focused on a stepwise process to evaluate the adequacy of data to meet the purpose of the CRA [12]

and

> the objective of tiering is to optimize the efficiency of the analysis by first assessing apparent margins of low hazard or exposure based on conservative scenarios. Subsequent tiers incorporate more rigorous analysis with additional data, based on initial indications of possible hazard and risk from exposure.[13]

Each increasing "tier" within EPA's proposed approach involves a more rigorous analysis requiring additional data based on the indicators for possible hazard and exposure risk. Since any tier can result in risk management and more resources are required with each increasing tier, there is little motivation to continue up the tiers and conduct a rigorous CRA, especially given EPA's stated "objective of tiering is to optimize the efficiency of the analysis." EPA even recommends that if the initial "Tier 0" analysis, which requires the least amount of supporting hazard and exposure data, "does not reveal cause for concern, further analysis is not indicated." Further, the Draft CRA Guidelines recommend considering cost, time and resources needed to conduct CRA. By using a tiered system that can be stopped at any stage, including following a preliminary "Tier 0" analysis with limited available data, the risk assessor is provided with too many opportunities to leave the CRA process and potentially move to risk management (or decide against risk management activities) using an incomplete or inadequate CRA or not conduct a CRA at all. In other words, the tiering system allows the risk assessor to stop advancing the CRA process for almost any reason, including resources, cost, or overly strict data quality requirements.

b. EPA does not consider all relevant "initiating factors."

The Draft CRA Guidelines outline possible stakeholders who can request a CRA and other "initiating factors" that can begin the CRA planning and scoping and "provide the rationale for CRA."[14] However, its list of proposed initiating factors is missing important considerations that

[12] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 13
[13] *Id.* p 13
[14] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 7

could result in fewer and less health protective CRAs, particularly for communities experiencing disproportionate exposures to chemical and nonchemical stressors.

While EPA states that "[i]nitiating factors can relate to concerns of environmental justice, specific stressors (sources) or population exposures (receptors)," only one proposed initiating factor entitled "Community Concern" partially captures these aspects. [15] This initiating factor also wrongly places the burden of identifying sufficient data to initiate CRA on the community members. Because residents of communities facing high levels of chemical exposures and nonchemical stressors are more likely to be people of color,[16,17,18,19] this burden also raises concerns around racial injustice. The community may not know about chemical exposures that may be occurring, limiting opportunities for identifying concerns and initiating CRA; and even when the community is aware, it may lack the resources to raise concern to EPA's attention.

Importantly, none of the proposed initiating factors expressly consider the prevalence of non-chemical stressors alone as rationale for initiating CRA. These stressors include both intrinsic (e.g., pre-existing disease, life stage, reproductive status, age, sex, genetic traits) and extrinsic (e.g., food insecurity, geography, poverty, socioeconomic status, racism, discrimination, culture, workplace) factors that make individuals more susceptible to harm from chemical exposures. Multiple scientific authoritative bodies recommend that these factors must be accounted for in cumulative risk assessment.[20,21] EPA should expressly consider the prevalence of multiple nonchemical stressors as additional justification to initiate CRA, at minimum under the "Community Concern" or "Elevated Stressor Levels" initiating factors.

EPA should also expand the current initiating factor entitled "Elevated Stressor Levels" to expressly include evidence of high-volume chemical production and high-volume chemical releases, including releases from chemical facility accidents, spills, or unintended releases that can result in acute risks to nearby communities. These events are known consequences of chemical manufacturing, transport, use, and disposal, and are not adequately reflected in the Draft CRA Guidelines. Both high-volume chemical releases and high chemical production volume are strongly associated with human exposures, particularly in communities neighboring

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[15] *Id.* p 7

[16] Robert D. Bullard et al., United Church of Christ, *Toxic Wastes and Race at Twenty 1987—2007,* at 54 (2007), https://www.ucc.org/wp-content/uploads/2021/03/toxic-wastes-and-race-at-twenty-1987-2007.pdf

[17] Jill E. Johnston et al., *Wastewater Disposal Wells, Fracking, and Environmental Injustice in Southern Texas*, 106 Am. J. Pub. Health 550 (2016), https://pubmed.ncbi.nlm.nih.gov/26794166/

[18] Jane Kay & Cheryl Katz, *Pollution, Poverty and People of Color: Living with Industry*, Sci. Am. (June 4, 2012), https://www.scientificamerican.com/article/pollution-poverty-people-color-living-industry/

[19] Ronald White et al., Env't Just. Health All. for Chem. Pol'y Reform et al., *Life at the Fenceline: Understanding Cumulative Health Hazards in Environmental Justice Communities* (2018), https://ej4all.org/assets/media/documents/Life%20at%20the%20Fenceline%20-%20English%20-%20Public.pdf

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

[21] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. *Environmental Health*, *21*(Suppl 1), 133. https://doi.org/10.1186/s12940-022-00940-1

high-production volume facilities.[22] In most cases, evidence of chemical environmental concentrations or human exposures are not needed to demonstrate potential human health risk. Scientists agree that "where chemical production volumes are so high (i.e., they are produced or imported into the US in quantities of 500 tons per year or greater) that human exposures should be expected", and that high-production volume chemicals alone should "trigger additional scrutiny and potential interventions."[23] Accordingly, EPA should expand the "Elevated Stressor Levels" initiating factor to expressly include evidence of high chemical production volumes and, at minimum, high-volume chemical releases.

EPA can utilize its own publicly-available data sources to generate evidence to support this expanded initiating factor without placing the burden of evidence on communities. For example, EPA can rely on chemical manufacturing and import data reported to the Chemical Data Reporting database to identify facilities with high production volume of multiple chemicals. As another example, chemical release data reported to the Toxics Release Inventory ("TRI") and National Emissions Inventory ("NEI") indicated that over 3 million pounds of three TSCA High Priority Chemicals (1,3-butadiene, formaldehyde, and phthalic anhydride) were released in the Greater Houston Area between 2010-2022. In addition, at facilities subject to EPA's Risk Management Plan Rule,[24] which covers only a small fraction of the facilities that are subject to TSCA, there were more than 1,175 harmful chemical incidents between 2011 and 2020—an average of 117 per year.[25] Many of these incidents involved large releases of TSCA risk evaluation chemicals, such as a 2019 explosion at a Port Neches chemical manufacturing facility that released as much as 30,000 pounds of 1,3-butadiene (as well as untold amounts of asbestos) into the surrounding community.[26,27] Using these data as an example, EPA could initiate a CRA evaluating cumulative exposures to TSCA chemicals for communities in the Greater Houston Area, some of which are predominantly communities of color who experience food insecurity, healthcare inequity, higher incidence of cardiovascular disease, and other nonchemical stressors.[28]

EPA should also expand its list of possible initiating factors to include evidence of widespread exposure in the human population. While scientists caution against waiting for biomonitoring data to take action and protect public health, in cases where these data are available, EPA should initiate CRA. For example, it should "be sufficient to show that a chemical (or its metabolite) is

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[22] Vandenberg, L. N., Rayasam, S. D. G., Axelrad, D. A., Bennett, D. H., Brown, P., Carignan, C. C., Chartres, N., Diamond, M. L., Joglekar, R., Shamasunder, B., Shrader-Frechette, K., Subra, W. A., Zarker, K., Woodruff, T. J. (2023). Addressing systemic problems with exposure assessments to protect the public's health. Environmental health : a global access science source, 21(Suppl 1), 121. https://doi.org/10.1186/s12940-022-00917-0

[23] *Id.*

[24] 40 C.F.R. §§ 68.1–68.220.

[25] Community In-Power & Develop Association et al., (July 29, 2021) *Comments on Accidental Release Prevention Requirements: Risk Management Programs Under the Clean Air Act*, Docket No. EPA-HQ-OLEM-2021-0312-0170, at 13, https://www.regulations.gov/comment/EPA-HQ-OLEM-2021-0312-0170 (click "Download").

[26] U.S. Chemical Safety & Hazard Investigation Board, (2020), *Fire and Explosions at TPC Group Port Neches Operations Facility*, https://www.csb.gov/assets/1/17/tpc_factual_update_10-29-2020.pdf?16614

[27] Melissa Alonso & Jason Hanna, (Nov. 29, 2019), *Evacuation Order Lifted After Texas Chemical Plant Explosions, but Officials Warn About Asbestos Debris*, CNN, https://www.cnn.com/2019/11/29/us/texas-plant-explosions-friday/index.html.

[28] Bethel, H.L., (ND), A Closer Look at Air Pollution in Houston: Identifying Priority Health Risks, Report available: https://www3.epa.gov/ttn/chief/conference/ei16/session6/bethel.pdf

detected in human urine [or blood] to acknowledge the reality of human exposures" [29] and that "we should assume universal system/organ exposure based on measurements in urine/blood." [30] The National Research Council ("NRC"), an advisory body made up of scientific experts from the National Academies of Sciences, Engineering, and Medicine ("NASEM"), recommends conducting a CRA when there is substantial evidence supporting multiple chemical exposures in the human population, including biomonitoring data. [31] In the case of *ortho*-phthalates, EPA appropriately chose to conduct a CRA under TSCA for a subset of *ortho*-phthalates where large-scale biomonitoring data indicated widespread phthalate exposures in the human population, including in people from diverse racial and ethnic backgrounds. [32] Consistent with the best available science and previous proposed CRAs within the Agency, EPA should expressly consider evidence of widespread human exposure as an initiating factor for CRA. [33] [34]

c. EPA does not rely on best available methods for evaluating scientific evidence.

i. The Draft CRA Guidelines presents a flawed "weight of evidence" approach.

In the Draft CRA Guidelines, EPA states that the evaluation of evidence that may be used in a CRA should be based on the "Weight of Evidence," an approach that is poorly defined and could unnecessarily narrow the body of scientific evidence needed to conduct a health protective CRA. The entire Draft CRA Guidelines section on "Integration of Data for Examining Stressor-Response Relationship(s)" presents a general discussion of using a "weight of evidence" (WoE) process in conducting a CRA.

For example, EPA states:

> "Evidence evaluation to assess whether causal relationships exist is an essential consideration in CRAs because of their scope and complexity. Because sources of

[29] Vandenberg, L. N., Rayasam, S. D. G., Axelrad, D. A., Bennett, D. H., Brown, P., Carignan, C. C., Chartres, N., Diamond, M. L., Joglekar, R., Shamasunder, B., Shrader-Frechette, K., Subra, W. A., Zarker, K., Woodruff, T. J. (2023). Addressing systemic problems with exposure assessments to protect the public's health. *Environmental Health*, *21*(1), 121. https://doi.org/10.1186/s12940-022-00917-0

[30] *Id.*

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

[32] Centers for Disease Control, (Feb. 2015), *Fourth National Report on Human Exposure to Environmental Chemicals* at 354– 433,https://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf

[33] Buckley, J. P., Kuiper, J. R., Bennett, D. H., Barrett, E. S., Bastain, T., Breton, C. V., Chinthakindi, S., Dunlop, A. L., Farzan, S. F., Herbstman, J. B., Karagas, M. R., Marsit, C. J., Meeker, J. D., Morello-Frosch, R., O'Connor, T. G., Romano, M. E., Schantz, S., Schmidt, R. J., Watkins, D. J., … Woodruff, T. J. (2022). Exposure to Contemporary and Emerging Chemicals in Commerce among Pregnant Women in the United States: The Environmental influences on Child Health Outcome (ECHO) Program. *Environmental Science & Technology*, *56*(10), 6560–6573. https://doi.org/10.1021/acs.est.1c08942

[34] Woodruff, T. J., Zota, A. R., & Schwartz, J. M. (2011). Environmental chemicals in pregnant women in the United States: NHANES 2003-2004. *Environmental Health Perspectives*, *119*(6), 878–885. https://doi.org/10.1289/ehp.1002727

> evidence might be available from multiple disciplines, the evaluation of the data required for a CRA should consider WoE both within and across evidence streams. E.g. Epidemiology, toxicology, and mechanistic studies." [35]

Scientific authoritative bodies have determined that the "Weight of Evidence" approach lacks consistent definitions. For example, the 2014 NRC review of EPA's Integrated Risk Information System (IRIS) process found:

> *Systematic review* and *weight-of-evidence analysis* have historically been described in various ways, and the terms are sometimes used interchangeably; this vagueness in use of terminology results in some confusion as to what the terms mean in practice…The committee views weight-of-evidence analysis as a judgment-based process for evaluating the strength of evidence to infer causation. However, it found that the phrase as used in practice has become too vague and is of little scientific use.[36]

Based in part on NASEM advice, as well as developmental work at the National Toxicology Program, the University of California, San Francisco ("UCSF") and elsewhere, multiple EPA programs have adopted systematic review procedures to structure the identification, evaluation and integration of scientific evidence and to provide a robust foundation for drawing conclusions. To adhere to the best available scientific methods, EPA should replace the discussion of weight of evidence in the Draft CRA Guidelines with specific recommendations to use systematic review for identifying, evaluating and integrating evidence as a necessary process for conducting a CRA. Both the 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 have been used or recommended by the NASEM,[37,38,39] and have been demonstrated in case-studies in peer reviewed

[35] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum).
[36] National Research Council (2014) Review of EPA's Integrated Risk Information System (IRIS) Process National Academies Press (US), Washington (DC) p 4
[37] National Academies of Science, Engineering, and Medicine (NASEM). (2017). *Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active chemicals* [Report]. The National Academies Press. https://www.nap.edu/catalog/24758/application-of-systematic-review-methods-in-an-overall-strategy-for-evaluating-low-dose-toxicity-from-endocrine-active-chemicals
[38] National Academies Press. (2014). *Review of EPA's Integrated Risk Information System (IRIS) Process*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK230074/
[39] National Academies of Science, Engineering, and Medicine (NASEM). (2018). *Progress toward transforming the Integrated Risk Information System (IRIS) program: A 2018 evaluation* (Report 9780309474917). The National Academies Press. https://doi.org/10.17226/25086

literature.[40,41,42,43,44,45,46,47] Further, EPA's Office of Research and Development has adopted a systematic review methodology as part of its Integrated Risk Information System (IRIS) program.[48] While we have provided comments regarding some inadequacies in the current IRIS method, it provides a basis for a revision to this section of the Draft CRA Guidelines.

ii. A requirement to establish causality in stressor-response relationships would be a barrier to conducting CRA.

The Draft CRA Guidelines also include inappropriate statements regarding causal determinations. EPA incorrectly emphasizes the need for establishing causality in the stressor-response relationship for conducting a CRA. EPA states that:

> Evidence evaluation to assess whether causal relationships exist is an essential consideration in CRAs because of their scope and complexity. Because sources of evidence might be available from multiple disciplines, the evaluation of the data required for a CRA should consider WoE both within and across evidence streams—e.g., epidemiology, toxicology, and mechanistic studies.[49]

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[40] Johnson, P. I., Sutton, P., Atchley, D. S., Koustas, E., Lam, J., Sen, S., Robinson, K. A., Axelrad, D. A., & Woodruff, T. J. (2014). The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth. *Environmental Health Perspectives*, *122*(10), 1028–1039. https://doi.org/10.1289/ehp.1307893

[41] Koustas, E., Lam, J., Sutton, P., Johnson, P. I., Atchley, D. S., Sen, S., Robinson, K. A., Axelrad, D. A., Woodruff, T. J. (2014). The Navigation Guide—Evidence-based medicine meets environmental health: Systematic review of nonhuman evidence for PFOA effects on fetal growth. In *Environmental Health Perspectives*. https://doi.org/10.1289/ehp.1307177

[42] Lam, J., Koustas, E., Sutton, P., Johnson Paula, I., Atchley D., S., Sen, S., Robinson K. A., Axelrad D. A., Woodruff T. J. (2014). The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth. In *Environmental Health Perspectives* (Vol. 122, Issue 10, pp. 1040–1051). https://doi.org/10.1289/ehp.1307923

[43] Vesterinen, H. M., Johnson, P. I., Atchley, D. S., Sutton, P., Lam, J., Zlatnik, M. G., Sen, S., Woodruff, T. J. (2015). Fetal growth and maternal glomerular filtration rate: A systematic review. In *J Matern Fetal Neonatal Med* (Vol. 28, Issue 18, pp. 2176–2181). https://doi.org/10.3109/14767058.2014.980809

[44] Johnson, P. I., Koustas, E., Vesterinen, H. M., Sutton, P., Atchley, D. S., Kim, A. N., Campbell, M., Donald, J. M., Sen, S., Bero, L., Zeise, L., Woodruff, T. J. (2016). Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. In *Environ Int* (Vols. 92–93, pp. 716–728). https://doi.org/10.1016/j.envint.2016.03.009

[45] Lam, J., Sutton, P., Kalkbrenner, A., Windham, G., Halladay, A., Koustas, E., Lawler, C., Davidson, L., Daniels, N., Newschaffer, C., & Woodruff, T. (2016). A systematic review and meta-analysis of multiple airborne pollutants and autism spectrum disorder. In *PLoS ONE*. https://doi.org/10.1371/journal.pone.0161851

[46] Lam, J., Lanphear, B. P., Bellinger, D., Axelrad, D. A., McPartland, J., Sutton, P., Davidson, L., Daniels, N., Sen, S., Woodruff, T. J. (2017). Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis. In *Environ Health Perspect* (Vol. 125, Issue 8, p. 086001). https://doi.org/10.1289/EHP1632

[47] Lam, J., Koustas, E., Sutton, P., Padula, A. M., Cabana, M. D., Vesterinen, H., Griffiths, C., Dickie, M., Daniels, N., Whitaker, E., Woodruff, T. J. (2021). Exposure to formaldehyde and asthma outcomes: A systematic review, meta-analysis, and economic assessment. In *PLoS One* (Vol. 16, Issue 3, p. e0248258). https://doi.org/10.1371/journal.pone.0248258

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

[49] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 28

This emphasis on establishing causality would unnecessarily narrow the body of available scientific evidence by potentially excluding stressors with uncertain evidence (e.g. stressors with "probable" or "suggestive" evidence of an association; or stressors without an assigned hazard descriptor), creating a significant and inappropriate barrier to conducting health protective CRAs. EPA does not require a causal relationship for risk characterization, and therefore evidence of a causal relationship should not be required for any aspect of CRA. EPA practices across multiple programs establish that *associations* between chemical exposures and adverse health outcomes are sufficient for risk characterization and risk management, and EPA has routinely regulated toxic chemicals for non-cancer effects without a causal determination. In most cases, EPA evaluates risks for chemicals with probable or suggestive evidence of an association with one or more adverse outcomes. 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 for inclusion of a chemical for any aspect of CRA.[50] EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* provides additional alternative data and approaches that can be implemented when causal data are not available, including approaches like extrapolation. [51]

Text in the Draft CRA Guidelines suggesting that only chemicals with "known" causal relationships to adverse health outcomes would be included in a CRA should be removed, as such an approach would inappropriately exclude chemicals from a CRA and result in an underestimation of risk to human health, particularly for vulnerable and historically marginalized communities. [52]

d. EPA relies on flawed, inconsistent, and incomplete descriptions of key terms for CRA.

i. The Draft CRA Guidelines presents inconsistent and incomplete definitions of "nonchemical stressors" and "populations of interest."

EPA relies on inconsistent definitions of "nonchemical stressors" and left out key aspects for the consideration of "populations of interest." More specifically, EPA's characterization of both terms fails to encompass the full range of scientifically supported factors that contribute to human susceptibility to harm from chemical exposures. This omission is inconsistent with the best available science and the requirements of Executive Order 13985, and could result in CRAs that underestimate risk to susceptible populations, including groups that EPA has committed to protecting using CRA:

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

[51] Office of Research and Development -NCEA. (2000). *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (EPA/630/R-00/002). p 15

[52] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., & Chartres, N. (2022). 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*(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079

> CRA is responsive to national policy, such as Executive Order 13985 on Advancing Racial Equity and Support for Underserved Communities Through the Federal Government, which directs all agencies of the federal government to "pursue a comprehensive approach to advancing equity for all, including people of color and others who have been historically underserved, marginalized, and adversely affected by persistent poverty and inequality." [53]

In the Draft CRA Guidelines, EPA defines nonchemical stressors as:

> A stressor that is not based on chemical exposure. This could include biological or physical factors and activities that directly or indirectly adversely affect health or increase vulnerability to chemical stressors. The term is often used to refer to psychological or social stressors that might also act as an exposure-response modifier to other stressors.[54]

yet later states:

> The second area of advancement in CRA methods is in evaluating the combined effects of chemical and nonchemical stressors (*e.g., radiation, biological, nutritional, economic, psychological, habitat alteration, land-use change, global climate change, natural disaster)* (NRC, 2009; U.S. EPA, 2003b, 1997b). Some methods for evaluating the combined effects of chemical and nonchemical stressors have been suggested, and other approaches are being developed.[55]

These differences in definition of nonchemical stressors, calling them "biological or physical factors and activities" in one place and referring to them as "radiation, biological, nutritional, economic, psychological, habitat alteration, land-use change, global climate change, natural disaster" in another, creates confusion on the definition that should be applied. Furthermore, the definitions discussed in the Draft CRA Guidelines are incomplete. We recommend that EPA adopt one consistent definition of "nonchemical stressors" that incorporates the following additional language (indicated in bold) and is consistent with recommendations from dozens of scientific experts in risk assessment and public health:[56]

> A stressor that is not based on chemical exposure. This could **include either intrinsic (e.g., pre-existing disease, life stage, reproductive status, age, sex, genetic traits) or extrinsic (e.g., food insecurity, geography, poverty, socioeconomic status, racism, discrimination, culture, workplace) factors that** directly or indirectly adversely affect health or increase **susceptibility to harm from chemical exposures.** The term is often used to refer to psychological or social stressors that might also act as an exposure-

[53] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 1
[54] *Id.* pp *iv*
[55] *Id.* p A-6
[56] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., Bennett, D. H., Birnbaum, L. S., Brown, P., Carignan, C. C., Cooper, C., Cranor, C. F., Diamond, M. L., Franjevic, S., Gartner, E. C., Hattis, D., Hauser, R., Heiger-Bernays, W., Joglekar, R., Lam, J., … Zeise, L. (2023). A science-based agenda for health-protective chemical assessments and decisions: Overview and consensus statement. *Environmental Health*, *21*(1), 132. https://doi.org/10.1186/s12940-022-00930-3

response modifier to other stressors.

Finally, EPA states that "considering the vulnerability of children, gender-related differences, and exposure to other environmental stressors are important elements of CRA." [57] In alignment with the revised definition of "nonchemical stressors" stated above, we urge EPA to expand this statement to include all highly exposed or susceptible populations. We also urge EPA to expand its current description of "individuals with increased (or decreased) exposures or vulnerabilities" under "Populations of Interest" to better reflect the robust and scientifically supported definitions of human susceptibility. EPA presents the TSCA definition of "potentially exposed or susceptible subpopulations" as "one example;" we recommend that EPA expand this definition as shown below:

> Susceptible population means a group of individuals or communities within the general population identified by the Agency who, due to greater susceptibility may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, including but not limited to infants, children, pregnant people, workers, or the elderly. **Susceptibility can be due to either intrinsic (e.g., pre-existing disease, life stage, reproductive status, age, sex, genetic traits) or extrinsic (e.g., food insecurity, geography, poverty, socioeconomic status, racism, discrimination, culture, workplace) factors when identifying this population.**

ii. The Draft CRA Guidelines presents a flawed and inconsistent characterization of "toxicological similarity."

Grouping chemical exposures in CRA is an important consideration, and a failure to accurately group chemicals for consideration in CRA can result in an underestimation of exposure and risk. Existing EPA guidelines establish "toxicological similarity" as a key concept underpinning methods for assessing risks of multiple chemicals in combination. Dose addition methods (e.g. relative potency factors) can be applied to chemicals determined to be toxicologically similar. [58] However, the description of "toxicological similarity" in the Draft CRA Guidelines is vague and inappropriately limits the evidence that can support a chemical grouping for CRA and applicability of scientifically-supported dose addition methods. "Toxicological similarity" is defined once in the document, but then referred to inaccurately as shared mechanism of action, which is overly narrow and could result in an underinclusive grouping of chemicals for CRA.

The Draft CRA Guidelines describe "toxicological similarity" in a footnote as:

> Toxicological similarity infers [*sic*] a general knowledge about the action of a chemical or a mixture and is used as an overarching term with a wide range of reference, including mechanism of action, target organ (e.g., enzyme changes in the liver), adverse outcome

[57] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 12
[58] U.S. EPA. (2000). *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (EPA/630/R-00/002). Risk Assessment Forum Technical Panel. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533

> pathways, and in silico tools such as structure-activity or read-across analyses (Williams et al., 2021). Similarity judgments can be tailored to both the specific goals of the risk assessment and the availability of information (U.S. EPA, 2000d).[59]

Although this description of toxicological similarity is overly brief and unclear, it does acknowledge that a wide range of evidence may support a conclusion of toxicological similarity, consistent with EPA's 2000 mixtures guidance.

The NRC report *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* emphasized a broad consideration of toxicological similarity, moving beyond chemical structure and mechanism and instead grouping chemicals for CRA based on common adverse outcomes:

> Phthalates may not all act by the same mechanisms, and they do not have parallel dose-response curves. However, those facts do not negate the appropriateness of using general dose-addition methods in a cumulative risk assessment…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. [60]

EPA inappropriately disregards this recommendation throughout the Draft CRA Guidelines, and instead states that chemicals with a common outcome may not be considered "toxicologically similar:"

> There is less familiarity with conducting CRAs that incorporate nonchemical stressors or **chemicals that are not toxicologically similar but act on a common outcome**. [61] (emphasis added)

and

> EPA typically assumes the chemicals are toxicologically similar if the chemicals have a common mode of action, or if they affect a common target organ. Such mixtures are typically evaluated using dose addition. For exposures to chemicals **that elicit a common outcome but are not toxicologically similar**, EPA has employed methods that are not based on dose addition, such as response addition. [62] (emphasis added)

This explanation of "*a common outcome but are not toxicologically similar"* is inconsistent with the best available science and should be removed.

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[59] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 16
[60] National Research Council. (2008). *Phthalates and Cumulative Risk Assessment: The Task Ahead*. National Academies Press. https://doi.org/10.17226/12528 p 9
[61] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 16
[62] *Id.* p 24

We recommend that EPA adopt a single, consistent description of the types of evidence that establish "toxicological similarity" that is adapted from the draft TSCA CRA Principles document and incorporates the NRC recommendations:[63,64]

> Evidence of "Toxicological similarity" may be determined by one or more of the following criteria:
>
> - identical toxicodynamics (i.e., same molecular initiating event [MIE], downstream key events, and apical outcome; an example of this is a group of chemical substances that have a common toxic metabolite);
> - similar toxicodynamics (e.g., different MIE, convergent toxicodynamic pathways leading to a common downstream effect, and same apical outcome);
> - shared syndrome (e.g., phthalate syndrome (NRC, 2008), T (tremor)-syndrome or CS (choreoathetosis and salivation)-syndrome elicited by Type I and II pyrethroids, respectively (U.S. EPA, 2011)); [65]
> - common adverse outcome;
> - common key cellular-level or organ-level events;

[63] U.S. EPA. (2023). *Draft Proposed Principles of Cumulative Risk Assessment under the Toxic Substances Control Act* (EPA Document #EPA-740-P-23-001). p 9

[64] National Research Council. (2008). *Phthalates and Cumulative Risk Assessment: The Task Ahead*. National Academies Press.

[65] *id.*

- common key characteristics;[66,67,68,69,70,71,72,73]
- effect on the same target organ;
- structural similarity;
- similarly shaped dose-response curves in comparable toxicity studies.

Furthermore, scientifically-supported systematic review methods rather than "weight of evidence" should be required to assemble evidence to support "toxicological similarity" [74] (discussed in detail in Section 1.d.ii). EPA should adopt NRC's recommended systematic review methods and expressly require the use of these methods to establish "toxicological similarity" among groups of chemicals being considered for CRA.

Finally, when describing areas of advancement for CRA methodologies, EPA also incorrectly mentions a causal relationship:

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[66] 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. Key characteristics have already been established for carcinogens, cardiovascular toxicants, endocrine disrupting chemicals, female reproductive toxicants, male reproductive toxicants, hepatotoxicants, and immunotoxicants

[67] Smith, M. T., Guyton, K. Z., Gibbons, C. F., Fritz, J. M., Portier, C. J., Rusyn, I., DeMarini, D. M., Caldwell, J. C., Kavlock, R. J., Lambert, P. F., Hecht, S. S., Bucher, J. R., Stewart, B. W., Baan, R. A., Cogliano, V. J., & Straif, K. (2016). Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. *Environmental Health Perspectives*, *124*(6), 713–721. https://doi.org/10.1289/ehp.1509912

[68] Lind, L., Araujo, J. A., Barchowsky, A., Belcher, S., Berridge, B. R., Chiamvimonvat, N., Chiu, W. A., Cogliano, V. J., Elmore, S., Farraj, A. K., Gomes, A. V., McHale, C. M., Meyer, -Tamaki Kathleen B., Posnack, N. G., Vargas, H. M., Yang, X., Zeise, L., Zhou, C., & Smith, M. T. (n.d.). Key Characteristics of Cardiovascular Toxicants. *Environmental Health Perspectives*, *129*(9), 095001. https://doi.org/10.1289/EHP9321

[69] La Merrill, M. A., Vandenberg, L. N., Smith, M. T., Goodson, W., Browne, P., Patisaul, H. B., Guyton, K. Z., Kortenkamp, A., Cogliano, V. J., Woodruff, T. J., Rieswijk, L., Sone, H., Korach, K. S., Gore, A. C., Zeise, L., & Zoeller, R. T. (2020). Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nature Reviews Endocrinology*, *16*(1), Article 1. https://doi.org/10.1038/s41574-019-0273-8

[70] Luderer, U., Eskenazi, B., Hauser, R., Korach, K. S., McHale, C. M., Moran, F., Rieswijk, L., Solomon, G., Udagawa, O., Zhang, L., Zlatnik, M., Zeise, L., & Smith, M. T. (n.d.). Proposed Key Characteristics of Female Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment. *Environmental Health Perspectives*, *127*(7), 075001. https://doi.org/10.1289/EHP4971

[71] Rusyn, I., Arzuaga, X., Cattley, R. C., Corton, J. C., Ferguson, S. S., Godoy, P., Guyton, K. Z., Kaplowitz, N., Khetani, S. R., Roberts, R. A., Roth, R. A., & Smith, M. T. (2021). Key Characteristics of Human Hepatotoxicants as a Basis for Identification and Characterization of the Causes of Liver Toxicity. *Hepatology*, *74*(6), 3486–3496. https://doi.org/10.1002/hep.31999

[72] Germolec, D. R., Lebrec, H., Anderson, S. E., Burleson, G. R., Cardenas, A., Corsini, E., Elmore, S. E., Kaplan, B. L. F., Lawrence, B. P., Lehmann, G. M., Maier, C. C., McHale, C. M., Myers, L. P., Pallardy, M., Rooney, A. A., Zeise, L., Zhang, L., & Smith, M. T. (2022). Consensus on the Key Characteristics of Immunotoxic Agents as a Basis for Hazard Identification. *Environmental Health Perspectives*, *130*(10), 105001. https://doi.org/10.1289/EHP10800

[73] Arzuaga, X., Smith, M. T., Gibbons, C. F., Skakkeb, æk N. E., Yost, E. E., Beverly, B. E. J., Hotchkiss, A. K., Hauser, R., Pagani, R. L., Schrader, S. M., Zeise, L., & Prins, G. S. (2019). 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*(6), 065001. https://doi.org/10.1289/EHP5045

[74] National Academies Press. (2014). *Review of EPA's Integrated Risk Information System (IRIS) Process*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK230074/

> The first area of advancement is in assessing the effects of chemical mixtures that share common modes of action or that *cause common adverse outcomes*. [75]

As mentioned above (Section 1.c.ii), the best available science demonstrates that determination of causal relationships is not required for CRA. [76] Accordingly, EPA should remove this language from the Draft CRA Guidelines.

e. EPA's proposed "fit for purpose" model is inconsistent with expert recommendations.

Appropriately targeting a risk assessment to meet the needs of risk managers is an important part of planning a risk assessment and was recommended by the NRC in *Science and Decisions.* EPA has increasingly adopted the term "fit for purpose" as a shorthand representation of this concept in recent years. While the meaning of this term and its use in practice are frequently unclear, EPA often uses it to justify decisions that inappropriately narrow the scope of risk assessment, contrary to stakeholder requests. EPA states:

> Clarity on the management decision context, and what information (and data quality) is necessary to support it, is the first step in determining if a CRA may be suitable, and if so, determining an assessment design. This step is described as 'fit for purpose' in the EPA framework for Human Health Risk assessment to inform decision making and is an important step in the CRA planning process. This step is common to all assessment processes because the assessor should understand the strengths and limitations of the assessment framework potentially being used to address the risk management decisions. 'Assessments are most useful when they are designed to answer specific questions, with a level of technical evaluation that is appropriate for the decision context' [77]

NASEM in their 2023 report *Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests* emphasized that "the term 'fit for purpose' is not clearly and consistently defined, so there is little guidance as to how to specify the intended use…The committee therefore uses the term 'intended purpose and context of use' to encompass these ideas, and this is further elaborated." [78] In line with this NASEM recommendation, EPA should stop using the term "fit for purpose" and instead use "intended purpose and context of use", while also elaborating on the details of the proposed methodology and justification for its use.

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[75] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p A-6

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

[77] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 2

[78] National Academies of Sciences, Engineering, and Medicine. 2023. *Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26906. p 74

2. The Draft CRA Guidelines proposes risk management considerations that unduly narrow the scope of CRA and pose obstacles to conducting CRA.

The Draft CRA Guidelines section on "Project and Risk Management Considerations" outlines an excessively detailed consideration of regulatory alternatives as a distinct step in the process of planning a CRA. As described in the Draft CRA Guidelines, the process of considering risk management is transformed from a step that is helpful to ensuring that a risk assessment is well-targeted to an unnecessarily burdensome exercise that would be a significant obstacle to conducting a CRA. The section particularly discourages the inclusion of nonchemical stressors in a CRA – which is counter to recommendations of the NASEM and to other sections of the Draft CRA Guidelines that encourage consideration of nonchemical stressors.

If the Draft CRA Guidelines envision the exclusion of nonchemical stressors from CRAs, then it serves little purpose, as EPA's existing chemical mixtures guidance is already available to EPA risk assessors conducting assessments of multiple chemicals. [79]

a. CRA planning does not need detailed identification and analysis of risk management interventions.

The Draft CRA Guidelines describes risk management issues to be considered as part of CRA planning as follows:

> Some risk management issues that might be included in planning a CRA include:
> • Relevant regulatory considerations (e.g., program-specific guidance influencing CRA scope); and
> • **Technical feasibility and cost of alternative interventions** that might reduce stressor levels to different extents, introduce new stressors or buffers, or be completed more quickly than other intervention(s). [80] (emphasis added)

This is not a useful portrayal of how risk management considerations can inform CRA planning because it would be extremely unusual for feasibility and cost of interventions to been assessed before a risk assessment is conducted. Further, no such step is recommended in *Science and Decisions* or in EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* ("HHRA Framework").[81]

Science and Decisions notes the need for planning analyses of costs and technical feasibility, but does not draw a connection between those analyses and planning a risk assessment:

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[79] Office of Research and Development -NCEA. (2000). *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (EPA/630/R-00/002).
[80] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). pp 17-18
[81] U.S. EPA (2014). *Framework for Human Health Risk Assessment to Inform Decision Making.* Office of the Science Advisor, Risk Assessment Forum. https://www.epa.gov/risk/framework-human-health-risk-assessment-inform-decision-making

> The questions to be posed for risk assessment arise from early consideration of the types of assessments needed to judge the relative merits of the options considered…Risk management involves choosing among the options after the appropriate assessments have been undertaken and evaluated. Assessments of relevant risk-management factors other than risk—such as costs, technical feasibility, and other possible benefits—also require early planning.[82]

Similarly, EPA's *HHRA Framework* mentions cost and feasibility analyses only as inputs to risk management, alongside risk assessment, and not as inputs to risk assessment planning. The suggestion in the Draft CRA Guidelines that feasibility and cost of interventions might need to be considered up-front would unnecessarily prolong or even preclude the CRA planning process—turning the planning process into a multi-year exercise that significantly delays actually conducting a CRA.

The Draft CRA Guidelines then elaborate on consideration of risk management in the CRA planning process, saying that

> The goal is to **identify all the interventions that might be implemented** to reduce the cumulative human health risk(s) associated with a scenario.[83] (emphasis added).

Assuming that a CRA includes consideration of nonchemical stressors, as encouraged by the NASEM and as recommended in other sections of the Draft CRA Guidelines, the term "all the interventions" can be interpreted as extremely broad and would likely encompass interventions that are outside of EPA's authorities, or beyond the scope of interventions that the EPA risk manager may consider. There is no utility to the CRA planning process to identify interventions to address, for example, the nonchemical stressors of lack of access to good nutrition or psychosocial stress. Even if the identification of interventions is more reasonably targeted to chemical stressors, it is not necessary to identify all possible interventions EPA could apply during the planning process. The CRA planning process should be guided by the perspectives of risk managers regarding the interventions under consideration, which may be a subset of "all the interventions that might be implemented." However, analysis of intervention considerations like cost or technical feasibility should not be required to initiate or plan a CRA and should instead be implemented alongside risk assessment. As the CRA is conducted, the risk assessors and risk managers can meet periodically to ensure that the assessment will meet any evolving risk management needs—including any updates regarding interventions under consideration—as recommended in EPA's *HHRA Framework*:

> The informational needs, identified as part of planning and scoping, and are updated and refined throughout the assessment process.[84]

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[82] National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. (2009). *Science and Decisions: Advancing Risk Assessment*. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK214630/ p 242

[83] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 18

[84] U.S. EPA. (2014). *Framework for Human Health Risk Assessment to Inform Decision Making* (EPA/100/R-14/001 April 2014; EPA Risk Assessment Forum). U.S. EPA. p 47

With this type of an iterative process, the proper targeting of a risk assessment to meet risk management needs is not reliant on excessively detailed consideration of risk management during the CRA planning process. The highly detailed consideration of risk management in CRA planning envisioned by the Draft CRA Guidelines is not needed, and assessors can proceed with conducting the assessment informed by an early view of the interventions under consideration, and without risk management analyses such as evaluations of intervention costs and technical feasibility. The Draft CRA Guidelines should be revised accordingly to remove language concerning risk management that could pose a significant obstacle to initiating a CRA.

b. EPA's proposed risk management considerations would likely result in the exclusion of nonchemical stressors from CRAs.

Consideration of nonchemical stressors is of central importance to the development of the Draft CRA Guidelines. Without inclusion of nonchemical stressors, an assessment of multiple stressors is simply a chemical mixtures assessment – and EPA's 2000 *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* is available to inform the planning of such an assessment.[85]

In *Science and Decisions*, the NRC highlighted the importance of considering nonchemical stressors in CRA:

> **An analysis that does not consider nonchemical stressors**, that considers only a subset of routes and pathways of exposure, or that does not consider vulnerability **should not be termed a cumulative risk assessment**.[86] (emphasis added)

Consideration and inclusion of nonchemical stressors is critical for CRA because these stressors can be critical drivers of human variability in response to chemical exposures, and can particularly amplify the health risks from chemical exposures in environmental justice communities.

The statements in the Draft CRA Guidelines encouraging consideration of nonchemical stressors are, however, undermined by the Risk Management Considerations section, which proposes to exclude from a CRA any stressors that would not be addressed by the identified interventions:

> There are two goals of this process:
> 1. To identify a subset of stressor(s) or health outcome(s) on which the CRA would potentially focus in a systematic and transparent manner. Other **stressors or health outcomes that would presumably not be affected through implementation of any of the interventions under consideration could be <u>eliminated</u> from the CRA.**

[85] Office of Research and Development -NCEA. (2000). *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (EPA/630/R-00/002).
[86] National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. (2009). *Science and Decisions: Advancing Risk Assessment*. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK214630/ p 225

2. To compare the secondary conceptual model(s) to the initial conceptual model. A key question is whether the interventions under consideration would address the stressors or health outcomes that likely contribute significantly to the population's disease burden? If the answer is yes, the **other stressors** and health outcomes identified in the initial conceptual model **could be screened out**. If the answer is no, additional interventions may need to be identified or the utility of conducting a CRA may be re-evaluated.[87] (emphasis added)

The Risk Management Considerations section thus proposes that the scope of stressors included in a CRA can be limited to the stressors that can be addressed by the available risk management interventions. Assuming that the identification of interventions is more practically targeted (as suggested in comments above) to those that the EPA risk manager may consider, this exclusion of stressors could substantially narrow the scope of the CRA. In particular, these recommendations would serve to completely exclude nonchemical stressors from a CRA, contrary to the other sections of the draft that encourage inclusion of nonchemical stressors.

These two stated goals also seem to completely misunderstand some key points regarding CRA that are supported by the best available science. A CRA that excludes relevant non-chemical stressors can result in mistaken conclusions that there is not a risk warranting regulatory attention. A CRA that excludes nonchemical stressors entirely will not represent the state of the science regarding effect modification and will not address community concerns regarding how the combination of chemical and nonchemical stressors has resulted in a disproportionate burden of disease for their residents. These points are made by the NRC in *Science and Decisions*:

> risk-assessment applications in the Environmental Protection Agency (EPA) and elsewhere…are often centered on evaluating risks associated with individual chemicals in the context of regulatory requirements or isolated actions, such as the issuance of an air permit for an industrial facility. However, there is increasing concern among stakeholder groups (especially communities affected by environmental exposure) that such a narrow focus does not accurately capture the risks associated with exposure, given simultaneous exposure to multiple chemical and nonchemical stressors and other factors that could influence vulnerability. More generally, a primary aim of risk assessment should be to inform decision-makers about the public-health implications of various strategies for reducing environmental exposure, and omission of the above factors may not provide the information needed to discriminate among competing options accurately. Without additional modifications, risk assessment might become irrelevant in many decision contexts, and its application might exacerbate the credibility and communication gaps between risk assessors and stakeholders. [88]

[87] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p 18

[88] National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. (2009). *Science and Decisions: Advancing Risk Assessment*. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK214630/ p 123

A portion of this passage is quoted on page 1 of the Draft CRA Guidelines, in the context of explaining the need for CRA guidelines. EPA should revise the Risk Management Considerations section of the Draft CRA Guidelines to incorporate these considerations.

Science and Decisions also observes that inclusion of nonchemical stressors is important to addressing environmental justice concerns in risk assessment, saying that it:

> will also provide information that can be used in environmental-justice analyses focused on inequality in outcomes and help to bring risk assessment and environmental justice into a single analytic framework. [89]

As discussed elsewhere in the Draft CRA Guidelines, the contribution of nonchemical stressors in estimating risk will frequently be as effect modifiers:

> Because of EPA's regulatory function to protect human health and the environment from toxic chemicals and chemical pollution, nonchemical stressors are most likely to be considered for their role as potential exposure-response modifiers to chemical stressors. [90]

Further, the Draft CRA Guidelines recognizes the critical role of effect modifiers in assessing risks to vulnerable populations in a CRA:

> if a CRA is initiated to address the needs of a vulnerable population(s), it should identify pertinent exposure-response modifiers to incorporate vulnerability into the conceptual model and identify whether and how to include this information in analysis and decision-making stages. [91]

The Risk Management Considerations section of the Draft CRA Guidelines makes a critical error by recommending only the inclusion of stressors directly affected by risk management interventions (presumably only chemical stressors) but excluding the nonchemical stressors that can influence the magnitude of risk reduction by effect modification without being subject to control by EPA interventions.

Science and Decisions states specifically that nonchemical stressors should be included in CRA and that an assessment that excludes nonchemical stressors should not be considered a CRA but instead would be a chemical mixtures assessment. EPA should revise the "Risk Management Considerations" section to incorporate these NRC recommendations.

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[89] National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. (2009). *Science and Decisions: Advancing Risk Assessment*. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK214630/ p 221

[90] U.S. EPA. (2023). *Cumulative Risk Assessment (CRA) Guidelines for Planning and Problem Formulation (public comment draft)* (U.S. Environmental Protection Agency, Risk Assessment Forum). p12

[91] *Id.* p 25