



August 30, 2023

Lawrence Martin  
Environmental Protection Agency  
1200 Pennsylvania Ave, NW  
Washington, DC 20460

*Submitted via regulations.gov*

**Re: Crop Life America and RISE Comments on Guidelines for Cumulative Risk Assessment Planning and Problem Formulation. 88 Fed. Reg. 39424 (June 16, 2023).**

Dear Dr. Martin,

CropLife America (CLA) and RISE (Responsible Industry for Sound Environment) appreciate the opportunity to submit comments on the draft guidance entitled "Guidelines for Cumulative Risk Assessment Planning and Problem Formulation," which describes the planning and problem formulation of cumulative risk assessment (CRA) and offers guidelines for when CRA is appropriate.

Established in 1933, CropLife America represents the developers, manufacturers, formulators, and distributors of pesticides and plant science solutions for agriculture and pest management in the United States. CLA's member companies produce, sell, and distribute virtually all the pesticide and biotechnology products used by American farmers.

RISE is a national not-for-profit trade association representing more than 220 producers and suppliers of specialty pesticide and fertilizer products to both the professional and consumer markets. RISE member companies manufacture more than 90 percent of domestically produced specialty pesticides used in the United States, including a wide range of products used on lawns, gardens, sport fields, golf courses, and to protect public health.

CLA and RISE acknowledge the efforts of the Risk Assessment Forum and the United States Environmental Protection Agency (EPA or the Agency) have undertaken to draft the guidance per directive including Executive Order 13985 on Advancing Racial Equity and Support for Underserved Communities Through the Federal Government<sup>1</sup>. CLA and RISE appreciate EPA's ongoing commitment to scientific integrity, transparency, and use of sound science in the CRA guidance process. We support EPA involving stakeholders early in the process and look forward to working with EPA as the relevant CRA guidance is developed.

Thank you for your consideration of our comments.

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<sup>1</sup> Executive Order 13985 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."



Please contact Manojit Basu at [mbasu@croplifeamerica.org](mailto:mbasu@croplifeamerica.org) and Kristen Spatz at [kspatz@pestfacts.org](mailto:kspatz@pestfacts.org) if you have any questions or require additional information.

A handwritten signature in black ink, appearing to read "Manojit Basu".

Manojit Basu, PhD  
Vice President, Science Policy  
CropLife America

A handwritten signature in black ink, appearing to read "Kristen Spatz".

Kristen Spatz  
Senior Director, Regulatory Affairs  
RISE



## **CropLife America and RISE Comments on draft Guidelines for Cumulative Risk Assessment Planning and Problem Formulation. 88 Fed. Reg. 39424 (June 16, 2023).**

### **GENERAL COMMENTS**

The draft guidelines take a comprehensive approach to CRA by considering multiple stressors, including chemical, physical, and biological stressors. However, given the wide breadth of situations to which CRA could be applied, the resulting document is rather general in nature. The draft guidelines emphasize the need for transparency in the CRA process, including the use of clear and accessible language and the provision of detailed documentation. The development and consistent use of clear and precise terminology to identify and differentiate various risk assessment approaches that are labeled “cumulative,” (e.g., aggregate risk, chemical mixture, cumulative impact assessment) is necessary. This will help avoid confusion and misuses of the concept of CRAs. Due to the technical challenges in conducting a CRA, EPA should develop additional guidance documents, which include information on stakeholder participation, independent review, and communicating CRA results to risk managers and the public, as well as an example CRA with a tiered approach, to ensure consistency of application.

### **SPECIFIC COMMENTS**

#### **CRA Uses an Analytical Approach**

EPA [p. viii] stated that the CRA is an analytical approach. As such, it is necessary to be able to quantitate the inputs into the risk assessment. Exposure inputs including site releases, point releases, and biological and environmental monitoring are quantifiable. Receptor and illness-based hazard assessments are also quantifiable based on physiological and pharmacokinetic responses.

In the draft guidance, EPA states [p. 4] that the CRA is only feasible if “Methods are adequate to analyze the data and to integrate them into the risk characterization with an acceptable level of uncertainty.” Precautionary default assumptions when incorporated into the characterization of risk to address variability and uncertainty may lead to compounding the conservatism in the CRA, resulting in unrealistic risk characterization. Sufficient data and robust models need to be identified and available for implementation of the CRA. The use of data containing exposure information requires careful consideration for validity and reliability as some data could be outdated and/or inaccurate. Additionally, assessments that rely on multiple databases need to ensure that any combining of datasets is conducted appropriately.

Regarding non-chemical stressors, EPA states [p. 12]:

The lack of available methods for assessing and quantifying these stressors may limit their incorporation into an analysis plan. When such constraints exist, the conceptual model should flag them for further study or note that any relevant qualitative information be included in the risk characterization for consideration by risk managers. Methods to incorporate such information qualitatively or quantitatively (when possible) should be fully considered during CRA scoping.

There is limited guidance on quantitative methods to integrate some non-chemical stressors into the CRA. The draft guideline provides limited guidance on quantitative methods for integrating multiple



stressors, especially non-chemical stressors like psychological and societal factors. Non-chemical stressors<sup>2</sup> can impact health and responses to xenobiotic exposure and we commend EPA for evaluating ways to incorporate these into the CRA. We agree with the statement in the draft guidance, that quantitative risk assessments may not be the most appropriate approach when there may be unacceptable uncertainty in the system. The Cumulative Impact Assessment (CIA<sup>3</sup>) may be a more appropriate framework to evaluate the impact of non-chemical stressors. The CIA is a process of evaluating both quantitative and qualitative data representing cumulative impacts to inform a decision. It is unclear how the CRA conducted in accordance with the framework suggested in this draft guidance and the CIA would work together. We request EPA to clarify this.

This guidance suggests encompassing many disparate applications and non-chemical stressors that are hard to quantify and incorporate in a CRA. Furthermore, these parameters would need to be quantified with valid and reliable methodology. CLA and RISE have some concerns about how incorporation of these parameters would impact the CRA for pesticides, which are already highly regulated and thoroughly assessed. A robust and rigorous risk assessment process already exists and should be considered when weighing the need for a CRA.

### **Exposure-Response Modifiers**

For highly regulated chemicals like pesticides, many exposure-response modifiers are already incorporated into the existing health-protective risk assessments. On page 12 of the draft guidance EPA states “A goal of the Agency is to address age- and gender-specific issues, using age- and gender-differentiated data in Agency risk assessments and risk management decisions, whenever appropriate, and when relevant information is available (U.S. EPA, 2021<sup>4</sup>, 1997b<sup>5</sup>, 1995b<sup>6</sup>).” As a part of the pesticide risk assessment, aggregate risk assessments for consumers consider risk to the general population and various subpopulations such as infants, children, adolescents, and women of childbearing age, from dietary and non-dietary residential exposure. This is also extended to CRAs conducted for pesticides. On page 25 of the draft guidance, EPA states:

Examples of human health exposure-response modifiers include genetics, gender, disease states, altered physiological functions, psychosocial stress, and life stages (Sexton and Linder, 2011<sup>7</sup>). Behavioral variability such as occupation or hand-to-mouth activity, can modify exposure. An example of an environmental exposure-response modifier is pH, which can affect metal bioavailability.

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<sup>2</sup> Non-chemical stressors are factors found in the built, natural, and social environments including physical factors such as noise, temperature, and humidity and psychosocial factors (e.g., poor diet, smoking, and illicit drug use) Tulve, N., Ruiz, J. D. C., Lichtveld, K., Darney, S. P., & Quackenbos, J. J. (2016). Development of a Conceptual Framework Depicting a Child's Total (Built, Natural, Social) Environment in Order to Optimize Health and Well-Being. *Journal of Environment and Health Science*, 2(2), 1-8. doi:10.15436/2378-6841.16.1121 F

<sup>3</sup> <https://www.epa.gov/system/files/documents/2023-05/CUMULATIVE%20IMPACTS%20RESEARCH-FINAL%20REPORT-EPA%20600-R-22-014A%20%2812%29.PDF>

<sup>4</sup> U.S. EPA. (2021). Policy on Children's Health. Memorandum, October 5. Washington, D.C.: U.S. Environmental Protection Agency, Office of the Administrator.

<sup>5</sup> U.S. EPA. (1997b). Guidance on Cumulative Risk Assessment. Part 1. Planning and Scoping. Washington, D.C.: Science Policy Council, U.S. EPA. [http://www2.epa.gov/sites/production/files/2015-01/documents/cumrisk2\\_0.pdf](http://www2.epa.gov/sites/production/files/2015-01/documents/cumrisk2_0.pdf)

<sup>6</sup> U.S. EPA. (1995b). Policy on Children's Health. Washington, DC: U.S. Environmental Protection Agency, <https://www.epa.gov/children/epas-policy-childrens-health>

<sup>7</sup> Sexton, K; Linder, SH. (2011). Cumulative risk assessment for combined health effects from chemical and nonchemical stressors. *Am J Public Health* 101 Suppl 1: S81-88.



Most of these exposure-response modifiers are quantifiable and directly considered in pesticide risk assessments. In addition, individual risks from both chemical and non-chemical stressors need to be quantified in terms of a “common metric” (contributory versus protective) and the common metric needs to be comparable so that the “addition” of risks from each stressor is consistent and scientifically supportable.

### *Life Stage Modifiers*

Various life stage modifiers are considered in the pesticide aggregate risk assessment for dietary and non-dietary exposure. The dietary consumption data from the National Health and Nutrition Examination Survey (NHANES<sup>8</sup>) includes sampling from all life stages. The non-dietary residential exposure assessment includes toddlers, children, and adult post-application exposure, including accounting for behavioral variability such as increased hand-to-mouth activity in toddlers. Exposure to consumers that apply pesticides inside and/or outside of their homes is also included in the aggregate risk assessment.

### *Environmental Exposure-Response Modifiers*

The key environmental fate parameters for pesticides are measured in multiple soils and environmental conditions (aerobic, anaerobic, etc.). While the average of the measured soil adsorption parameters ( $K_{oc}$  or  $K_d$ ) is used, the upper 90<sup>th</sup> percentile confidence bound on the mean soil half-life is used in regulatory assessments. Health-protective higher-end values for other environmental fate parameters are used in pesticide aquatic and drinking water exposure assessments. While the use of conservative default assumptions may be appropriate in single chemical assessments, their use in cumulative assessments could result in overly conservative conclusions, i.e., compounded conservatism. It is critical that sufficient data and robust models are identified and available to inform a CRA to prevent the compounding of conservative assumptions, which leads to inaccurate characterization of risk.

## **Community Involvement**

The draft guideline emphasizes the importance of community involvement and stakeholder engagement in the CRA process. This is in line with the recommendation by Solomon et al., 2016<sup>9</sup> and Moretto et al., 2016<sup>10</sup>. CLA and RISE support robust community involvement, but risk assessments must be data driven and based on sound science. Additionally, multidisciplinary venues, including community involvement and committees like the Children’s Health Protection Advisory Committee should be well informed on the robust risk assessment process that already exists for pesticides.

## **Use of New Data and Methods**

The draft guideline encourages the use of new data and methods, including new exposure assessment methods and new toxicity testing methods. CRAs must consider exposures and exposure-modifying factors prior to hazard assessment. Exposure assessments must quantitatively evaluate the potential of chemical co-exposures and it is not appropriate to assume that chemicals in a class with a similar mode of action will co-occur in an individual. Additionally, methods for quantifying exposure, and thus co-

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<sup>8</sup> <https://www.cdc.gov/nchs/nhanes/index.htm>

<sup>9</sup> Solomon, KR; Wilks, MF; Bachman, A; Boobis, A; Moretto, A; Pastoor, TP; Phillips, R; Embry, MR. (2016). Problem formulation for risk assessment of combined exposures to chemicals and other stressors in humans. *Crit Rev Toxicol* 46: 835-844.

<sup>10</sup> Moretto, A; Bachman, A; Boobis, A; Solomon, KR; Pastoor, TP; Wilks, MF; Embry, MR. (2017). A framework for cumulative risk assessment in the 21st century. *Crit Rev Toxicol* 47: 85-97.



exposure, must be accurate and reproducible (e.g., well defined), and the limitations of biomonitoring and epidemiological data must be considered.

We look forward to more specific guidance on the development and incorporation of these methods into the CRA by the Agency.

### **Tiered and Phased Approach**

Tiered and phased approaches can help in identifying the important factors in a complex system involving multiple stressors and interactions. While the tiering approach would help prioritize the generation of data, the phasing would help prioritize the complex interactions of specific stressors and quantifying those impacts (e.g., modifying exposure or response).

### **Limited Guidance on Risk Management**

The draft guideline provides limited guidance on risk management strategies for addressing cumulative risks, which may limit the usefulness of the risk assessment for decision-making. We look forward to additional comment opportunities to provide feedback on risk management guidance.

### **Next Steps and Outstanding Questions**

Below are some outstanding questions we would like answered via a response to comments or other dialogue with EPA.

- Will the regulated industry be requested to provide new data to estimate and characterize cumulative risks? How will missing data be addressed?
- Is it possible that a cumulative assessment could yield results with sufficient (unacceptable) uncertainty as to be meaningless or would the planning phase be expected to foresee that?
- How will EPA resourcing influence prioritization of CRAs?
- How is this approach different from a cumulative impact assessment?
- Have considerations been made on how to communicate complex methods and outcomes to the community?
- The definition of stakeholder is broad. How is stakeholder defined? How will stakeholder expectations be managed?