



## **Environmental Working Group Comments on the EPA Office of Research and Development Staff Handbook for Developing IRIS Assessments Public Comment Draft Submitted electronically to docket EPA-HQ-ORD-2018-0654**

**March 1, 2021**

The Environmental Working Group, or EWG, a nonprofit research and policy organization with offices in Washington, D.C., Minneapolis, Minn., San Francisco and Sacramento, Calif., submits comments on the Environmental Protection Agency Office of Research and Development “Staff Handbook for Developing IRIS Assessments” public comment draft released in November 2020 (hereafter “draft handbook”),<sup>1</sup> focusing on the methods and data assessment approaches for cancer hazard identification.

### **1. Recommendation for methodology development and inclusion of the Hallmarks of Cancer approach in EPA’s cancer hazard identification methods**

EWG identified an important gap in the draft handbook, specifically regarding the consideration of disease-specific information in the EPA’s approaches for cancer hazard identification. As the National Toxicology Program recently wrote, “despite enormous gains made over the past 50 years in understanding the pathobiology of human cancers, we currently lack the means to efficiently and effectively identify many agents of concern and accurately characterize the risk(s) they may pose to public health.”<sup>2</sup> In EWG’s view, one reason for this gap between cancer research and cancer prevention is the lack of inclusion of the knowledge gained from decades of cancer research in the risk assessment methodologies that federal and state agencies use for cancer hazard identification.

EWG urges the EPA IRIS program to include the Hallmarks of Cancer<sup>3</sup> approach in the agency tool kit for cancer hazard identification, and also to dedicate resources for the methodology development necessary to meet this goal. These hallmarks of cancer include distinct biological features, as well as cellular and tissue changes associated with the multistep development of tumors. The Hallmarks of Cancer framework might be particularly informative for analyzing the cumulative effects of exposure to chemical mixtures, as highlighted in the Halifax Project.<sup>4</sup>

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<sup>1</sup> U.S. EPA. ORD Staff Handbook for Developing IRIS Assessments (Public Comment Draft, Nov 2020). Regulations.gov docket EPA-HQ-ORD-2018-0654

<sup>2</sup> National Toxicology Program Board of Scientific Counselors Meeting Materials. February 2, 2021. Carcinogenicity Health Effects Innovation Program. Available at [https://ntp.niehs.nih.gov/ntp/about\\_ntp/bsc/2021/february/meeting\\_materials/carci\\_bsc\\_508.pdf](https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2021/february/meeting_materials/carci_bsc_508.pdf)

<sup>3</sup> Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5):646-74. <https://doi.org/10.1016/j.cell.2011.02.013>

<sup>4</sup> Miller MF, Goodson WH, Manjili MH, Kleinstreuer N, Bisson WH, Lowe L. Low-Dose Mixture Hypothesis of Carcinogenesis Workshop: Scientific Underpinnings and Research Recommendations. Environ Health Perspect. 2017; 125(2):163-169. <https://doi.org/10.1289/EHP411>



Current EPA approaches focus primarily on identifying “complete carcinogens” – single chemicals that can cause cancer all by themselves, but the Halifax Project’s work raises the strong possibility that complete carcinogens may be only the tip of the iceberg.<sup>5</sup> New research is beginning to look at chemicals that are not carcinogenic in and of themselves but can affect normal cells in ways that make them more prone to becoming cancerous. EWG believes that it is time to expand the definition of carcinogenesis beyond the idea of a single chemical acting alone. Our society must begin to consider how combinations of chemicals may affect cell functions in distinct ways that, jointly, may result in cancer.

Finally, although chemical hazard assessments conducted by the IRIS program typically do not focus on the topic of community exposures to those chemical pollutants, it is essential to recognize that different communities across the country face disparate burdens of environmental pollution in their air, water, soil and food. Exposures to chemicals that either initiate or promote cancer disproportionately affect socially vulnerable groups that face higher risks of environmental pollution and have fewer resources for addressing such risks.

As the EPA is working on the topic of cancer hazard assessment, EWG urges the agency to identify ways to:

- Provide resources helpful for communities dealing with the burden of pollution
- Explicitly consider and incorporate data on susceptible age groups and populations
- Ensure that risk assessment and communication materials serve to combat the historical impacts of systemic racism.

A valuable example can be found in the Centers for Disease Control and Prevention’s Social Vulnerability Index.<sup>6</sup> Risk assessment information should be combined with data on real-life exposures to prioritize research on chemicals potentially affecting the greatest number of socially vulnerable communities.

## **2. Support for the inclusion of the “key characteristics” approach in the draft handbook**

EWG supports the inclusion of the key characteristics of carcinogens approach in the draft handbook as one of the methods that can be useful for the development of screening strategies for bibliographic information (chapter four of the draft handbook), as well as for the analysis and synthesis of mechanistic information (chapter 10 of the draft handbook).

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<sup>5</sup> Goodson WH, Lowe L, Gilbertson M, Carpenter DO. Testing the low dose mixtures hypothesis from the Halifax project. *Rev Environ Health*. 2020; 35(4):333-357. <https://doi.org/10.1515/reveh-2020-0033>

<sup>6</sup> Agency for Toxic Substances and Disease Registry. CDC Social Vulnerability Index. <https://www.atsdr.cdc.gov/placeandhealth/svi/index.html>



Know your environment.  
Protect your health.

The key characteristics of carcinogens framework can facilitate the organization and characterization of mechanistic data for cancer hazard identification.<sup>7</sup> These characteristics can aid in cancer hazard classification through integrative evaluation of human and animal evidence of chemicals' carcinogenicity. The key characteristics approach is already incorporated in the International Agency for Research on Cancer procedures for the scientific review and evaluation of carcinogenic hazards.<sup>8</sup>

EWG appreciated and agreed with the draft handbook's citations of articles that established the methodology for defining the key characteristics of carcinogens. Although not mutually exclusive with other methods for the analysis and synthesis of mechanistic information, such as the mode of action and adverse outcome pathway approaches, EWG finds that the key characteristics framework is particularly robust, allowing for the inclusion of evidence from molecular epidemiology, animal toxicology and high-throughput assay screening studies. EWG recommends for the EPA to continue and to expand the work on implementation of the key characteristics approach within the Integrated Risk Information System program.

Submitted on behalf of Environmental Working Group

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<sup>7</sup> Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, Christiani DC, Beland FA, Smith MT. Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis*. 2018; 39(4): 614-622. <https://doi.org/10.1093/carcin/bgy031>

<sup>8</sup> Samet JM, Chiu WA, Coglianò V, et al. The IARC Monographs: Updated Procedures for Modern and Transparent Evidence Synthesis in Cancer Hazard Identification. *J Natl Cancer Inst*. 2020;112(1):30-37. <https://doi.org/10.1093/jnci/djz169>