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## **Environmental Working Group Comments for the National Academies of Sciences, Engineering, and Medicine Committee Review of the EPA's Handbook for Developing Assessments for the Integrated Risk Information System (IRIS)**

**April 15, 2021**

The Environmental Working Group, or EWG, a nonprofit research and policy organization with offices in Washington, D.C., Minneapolis, San Francisco and Sacramento, Calif., submits comments on the “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 cancer hazard identification**

EWG identified a gap among the approaches summarized in the draft handbook, specifically regarding the consideration of disease-specific information in the EPA's framework 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 prevention is the lack of inclusion of the extensive datasets and knowledge gained from decades of cancer research in the methodologies that federal and state agencies use for cancer risk assessment.

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 to dedicate resources for the methodology development necessary to meet this goal. These hallmarks 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

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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>



particularly informative for analyzing the cumulative effects of exposure to chemical mixtures, as highlighted in recent work from the Halifax Project.<sup>4</sup>

Current EPA approaches focus primarily on identifying single chemicals that can cause cancer all by themselves, but the Halifax Project's work highlights the strong possibility that "independently acting" carcinogens may be only the tip of the iceberg. New research is beginning to look at chemicals that are not carcinogenic themselves but that can affect normal cells in ways that make them more prone to becoming cancerous. EWG believes it is time to expand the definition of carcinogenesis beyond the idea of a single chemical acting alone. Federal research programs must begin to consider how combinations of chemicals working in concert and affecting a cell's functioning in disparate ways may result in cancer.

## **2. Support for the inclusion of the "key characteristics" approach in the IRIS framework with a case study on per- and polyfluoroalkyl substances**

EWG strongly supports the inclusion of the key characteristics of carcinogens approach in the draft handbook as one of the approaches that can be useful for the development of screening strategies and for the analysis and synthesis of mechanistic information. The key characteristics of carcinogens framework can facilitate the organization and characterization of data for cancer hazard identification.<sup>5</sup> Together with human and animal evidence of carcinogenicity, the key characteristics can aid in cancer hazard classification. 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>6</sup>

To illustrate the value of the key characteristics approach, we present a case study of per- and polyfluoroalkyl substances, or PFAS. These chemicals are an extremely large group of diverse, yet structurally similar, synthetic compounds. They are very persistent in the environment, and several well-studied members of the PFAS class

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<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>; 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>5</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>6</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>



have been associated with a wide range of adverse health outcomes, including increased risk of cancer, adverse birth outcomes, male and female reproductive toxicity, and harm to the immune system, such as reduced effectiveness of vaccines.

At least five PFAS are currently undergoing IRIS assessments: PFBA, PFHxA, PFHxS, PFNA and PFDA. It is essential that the IRIS handbook be updated to allow the inclusion of critical epidemiological studies in PFAS toxicity and that similarities in PFAS toxicities across the PFAS class be considered in these ongoing assessments and in future assessments of other PFAS. As the handbook stands, certain systematic review criteria may inappropriately exclude certain studies from consideration, as outlined in the public comments submitted into the docket from the research group at the University of California, San Francisco.<sup>7</sup> Importantly, published evidence shows that there are several mechanisms of shared toxicity across PFAS, and that humans are exposed to multiple PFAS simultaneously. As such, IRIS needs to be able to consider these characteristics of PFAS as a class in the EPA's assessments.

For example, an EWG assessment of long-chain and short-chain PFAS commonly detected in drinking water and/or reviewed by the Agency for Toxic Substances and Disease Registry revealed that several toxicity targets of long-chain PFAS were shared with some short-chain PFAS (Table 1). Such a comprehensive analysis can have impacts on the conclusions of toxicity assessments for individual compounds.

For instance, PFOA and PFOS cause immune suppression in animal studies, as well as reduce the effectiveness of vaccines in humans. For PFBS, a short-chain replacement chemical, comparable animal studies do not exist, yet *in vitro* studies indicate that PFBS decreases cytokine levels, and human studies indicate that PFBS is associated with certain immune outcomes, such as asthma.<sup>8</sup> Given the documented immunotoxicity of PFOA and PFOS, these data can provide additional support for the immunotoxicity data for PFBS, increasing the overall confidence in the data. Similarly, testicular cancer and male reproductive toxicity are health concerns associated with exposure to PFOA and PFOS in epidemiological studies.<sup>9</sup> A recent epidemiological study investigated changes in the reproductive hormone

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<sup>7</sup> Chartres N. et al. Comments on the ORD Staff Handbook for Developing IRIS Assessments. March 1, 2021.

[https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/IRIS%20Handbook\\_UCSF%20PRHE\\_%20EPA%20IRIS\\_Final%20%281%29.pdf](https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/IRIS%20Handbook_UCSF%20PRHE_%20EPA%20IRIS_Final%20%281%29.pdf)

<sup>8</sup> Environmental Protection Agency. Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3). Office of Research and Development. EPA/600/R-20/345F. April 2021. Washington, DC.

<sup>9</sup> Tarapore P and Ouyang B. Perfluoroalkyl Chemicals and Male Reproductive Health: Do PFOA and PFOS Increase Risk for Male Infertility? *Int. J. Environ. Res. Public Health* 2021, 18(7), 3794; <https://doi.org/10.3390/ijerph18073794>



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levels of offspring that are associated with maternal exposure to short-chain PFAS and identified similar findings previously described for PFOA and PFOS.<sup>10</sup>

**Table 1.** Health harms associated with long-chain and short-chain PFAS commonly detected in drinking water and used in consumer products. Data summarized by EWG from peer-reviewed research literature. Some toxicological endpoints had not yet been investigated for certain PFAS.

Chemical	Harm to the immune system	Harm to development and reproduction	Harm to the endocrine system	Metabolic changes	Changes in the liver	Increased risk of cancer
	Weaker immune response; lower antibody production in response to vaccination; increased allergic response; increased risk of asthma; changes in spleen and thymus	Reduced birth weight; pregnancy-induced hypertension; preeclampsia; reduced fertility; reduced duration of breastfeeding; altered mammary gland development; harm to the male reproductive system	Changes in hormone levels, including thyroid and reproductive hormones; thyroid disease; hormone receptor activation	Increased cholesterol and lipids; weight gain; diabetes	Increased liver weight; changes in liver enzymes	Increased risk of testicular, kidney or breast cancer; increased tumors in laboratory animals; evidence for one or more of the key characteristics of carcinogens
PFOA*#	■	■	■	■	■	■
PFOS*#	■	■	■	■	■	■
PFNA*#	■	■	■	■	■	●
PFHxS*#	■	■	■	●	■	●
PFDA*#	■	■	■	■	■	●
PFDoA#	●	●	●	▲	■	●
PFUA#	●	■	●	▲	■	●
PFHxA*#	■	■	■	▲	■	●
GenX*	■	■	■	▲	■	■
PFBS*#	●	■	■	●	■	●
PFBA*#	●	■	●	▲	■	●
PFHpA*#	▲	▲	●	▲	■	●

\* PFAS chemicals detected by EWG in U.S. public drinking water supplies (<https://www.ewg.org/research/national-pfas-testing/>)

# PFAS included in the ATSDR toxicological profile

- Strong evidence of health effect documented in people or in laboratory animal studies
- Moderate evidence of health effect documented in people or in laboratory animal studies
- ▲ Not studied or no reported association in available studies

<sup>10</sup> Nian M, Luo K, Luo F, Aimuzi R, Huo X, Chen Q, Tian Y, Zhnag J. Association between prenatal exposure to PFAS and fetal sex hormones: Are the short-chain PFAS safer? *Environmental Science & Technology*. 2020, 54, 8291-8299. <https://dx.doi.org/10.1021/acs.est.0c02444>



Additionally, using the key characteristics of carcinogens approach, our team evaluated 26 different PFAS, including the five currently undergoing IRIS assessments, and determined that every substance displayed at least one of the key characteristics, predominantly “mediates receptor-mediated effects,” and up to five different key characteristics of carcinogens for the well-studied long-chain PFAS (Table 2).<sup>11</sup>

**Table 2.** Summary of findings assessing 26 PFAS using the key characteristics of carcinogens approach.

Key characteristic	Evidence strength		
	PFOA	Long-chain PFAS	Short-chain PFAS
KC 1 – Is electrophilic or can be metabolically activated	N/A	N/A	N/A
KC 2 – Is genotoxic	N/A	N/A	N/A
KC 3 – Alters DNA repair or causes genomic instability	Insufficient	Insufficient	Insufficient
KC 4 – Induces epigenetic alterations	Suggestive	Suggestive	Insufficient
KC 5 – Induces oxidative stress	Strong	Strong	Insufficient
KC 6 – Induces chronic inflammation	Insufficient	Insufficient	Insufficient
KC 7 – Is immunosuppressive	Strong	Strong	Suggestive
KC 8 – Modulates receptor-mediated effects	Strong	Strong	Strong
KC 9 – Causes immortalization	Insufficient	Insufficient	Insufficient
KC 10 – Alters cell proliferation, cell death or nutrient supply	Suggestive	Suggestive	Suggestive

*Source: Adapted from Temkin et al., 2020.<sup>11</sup>*

Considering the evidence together, it is likely that PFAS as a class can affect multiple key characteristics of carcinogens. For PFAS with only one key characteristic, the finding likely resulted from a lack of data rather than data supporting no association. If PFAS assessment were done one chemical at a time, without comparing the findings with other PFAS, important mechanisms of potential

<sup>11</sup> Temkin AM, Hocevar BA, Andrews DQ, Naidenko OV, Kamendulis LM. Application of the key characteristics of carcinogens to per and polyfluoroalkyl substances. *International Journal of Environmental Research and Public Health*. 2020 Mar 4;17(5):1668. doi: 10.3390/ijerph17051668.



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carcinogenicity might be overlooked. Although more research is needed to generate sufficient data for assessing potential carcinogenicity of various PFAS currently in commerce, the key characteristics approach provides an assessment tool that may inform regulatory and policy decisions toward risk mitigation and standard setting.

Overall, EWG agreed with the draft handbook's citation of the key characteristics approach. Although it is not mutually exclusive with other methods for analyzing and synthesizing mechanistic information, such as the mode of action and adverse outcome pathway approaches, EWG finds that the key characteristics methodology is robust, allowing for the inclusion of evidence from molecular epidemiology, animal toxicity and high-throughput assay screening studies.

**In summary**, we urge the EPA to develop a framework that would combine the Hallmarks of Cancer and the key characteristics approaches within the IRIS assessment methods.

Submitted on behalf of Environmental Working Group,

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