January 26, 2021

Comments submitted for the National Toxicology Program February 2, 2021, Board of Scientific Counselors meeting

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., urges the Board of Scientific Counselors of the National Toxicology Program (NTP) to strengthen and broaden the NTP efforts to identify and characterize environmental cancer hazards and to prioritize the goal of environmental justice.

EWG recommends that the NTP's Combined Exposures and Mixtures Program focus on real-life exposures to chemical mixtures, documented by biomonitoring and environmental media and food testing, in order to select chemical combinations for thorough analysis. EWG also urges the NTP to emphasize the Key Characteristics approach within the NTP's Carcinogenicity Health Effects Innovation Program.

As the NTP summarized in the materials published prior to the Board of Scientific Counselors meeting, "*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*." The lack of effective risk identification for potential cancer-initiating and cancer-promoting substances and exposure conditions has hampered the progress of cancer prevention efforts. To address the existing limitations in translating cancer research to public health protection measures, EWG makes the following recommendations.

1. Recommendations for the Carcinogenicity Health Effects Innovation Program

Based on the materials published ahead of the meeting, EWG identified two key shortcomings that we request the Board of Scientific Counselors to review and address:

- Lack of discussion about how the Carcinogenicity Health Effects Program incorporates data on exposures and risks for susceptible and vulnerable populations and communities.

- Disproportionate focus on mutations as a path toward cancer. This focus on mutagenicity, reflected in the meeting materials for the Carcinogenicity Health Effects Program, limits the research on other characteristics of carcinogens.

To address these shortcomings, EWG makes the following recommendations:

1.1. Ensure that NTP research programs explicitly consider and incorporate data on susceptible and vulnerable populations and communities.

Environmental 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. The pre-meeting materials mention that the NTP is looking for ways of "*developing and implementing a modern education and communication strategy to effectively convey and contextualize information generated*." However, the materials that discuss the communication plans for the Carcinogenicity Health Effects Innovation Program make no reference to socially vulnerable populations and communities.

EWG urges the Board of Scientific Counselors to guide the NTP toward identifying ways for:

- Explicitly considering and incorporating data on susceptible age groups and populations;
- Providing resources helpful for communities that are dealing with the burden of pollution;
- Ensuring 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.[1] 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.

1.2. Ensure a balanced research portfolio that addresses all 10 Key Characteristics of Carcinogens.

EWG recommends that the research portfolio under the Carcinogenicity Health Effects Program be broadened to include all 10 Key Characteristics of Carcinogens that have been identified,[2] instead of focusing on just one characteristic, namely mutagenesis. Genotoxicity is a well-established pathway to cancer development. However, the goal of an *innovative* program is to conduct investigations that go beyond the current paradigm. Besides genotoxicity and epigenetic alterations, carcinogens can exhibit some of the following cancer-relevant activities and characteristics (from Smith et al. 2016)[3]:

[1] https://www.atsdr.cdc.gov/placeandhealth/svi/index.html
[2] Guyton KZ, Rieswijk L, Wang A, Chiu WA, Smith MT. Key Characteristics Approach to Carcinogenic Hazard Identification. Chem Res Toxicol. 2018; 31(12): 1290-1292. 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.
[3] Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K. Key Characteristics of

- Act as an electrophile either directly or after metabolic activation
- Induce oxidative stress
- Induce chronic inflammation
- Suppress the immune system
- Modulate hormonal receptor-mediated effects
- Cause immortalization
- Alter cell proliferation, cell death or nutrient supply

As an example of the importance of considering a wide variety of carcinogenic features and pathways,[4] EWG recently published a study presenting the application of the key characteristics of carcinogens framework to per- and polyfluoroalkyl substances, or PFAS.[5] The most well-studied member of the PFAS class, perfluorooctanoic acid, or PFOA, induces tumors in animal bioassays and has been associated with an elevated risk of cancer in humans. GenX, a PFOA replacement chemical, induces tumors in animal bioassays as well. Using the Key Characteristics of Carcinogens framework for cancer hazard identification, EWG study considered the existing epidemiological, toxicological and mechanistic data for 26 different PFAS. The study found strong evidence that multiple PFAS induce oxidative stress, suppress the immune system and modulate receptor-mediated effects. The study also found suggestive evidence indicating that some PFAS can induce epigenetic alterations and influence cell proliferation. Experimental data indicate that PFAS are not genotoxic and generally do not undergo metabolic activation. Under the restricted framework focusing on mutagenicity and genotoxicity, PFAS carcinogenic activities would be missed. This study offers just one of many possible illustrations for the reasons why a multipronged approach is essential for carcinogenicity assessment.

Further, the evaluation of Key Characteristics of Carcinogens should be expanded to include *in vivo* data. Research on the carcinogenetic activity of endocrine disruptors[6] supports the importance of dedicating more research to non-genotoxic mechanisms of cancer. EWG urges the NTP to identify what improvements can be made in ongoing and future carcinogenicity testing to enable the collection of animal toxicity data to further elucidate the role of the Key Characteristics in cancer development.

Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. Environ Health Perspect. 2016; 124(6): 713-21.

[4] Smith MT, Guyton KZ, Kleinstreuer N, Borrel A, Cardenas A, Chiu WA, Felsher DW, Gibbons CF, Goodson WH 3rd, Houck KA, Kane AB, La Merrill MA, Lebrec H, Lowe L, McHale CM, Minocherhomji S, Rieswijk L, Sandy MS, Sone H, Wang A, Zhang L, Zeise L, Fielden M. The Key Characteristics of Carcinogens: Relationship to the Hallmarks of Cancer, Relevant Biomarkers, and Assays to Measure Them. Cancer Epidemiol Biomarkers Prev. 2020; 29(10):1887-1903.

[5] Temkin AM, Hocevar BA, Andrews DQ, Naidenko OV, Kamendulis LM. Application of the Key Characteristics of Carcinogens to Per and Polyfluoroalkyl Substances. Int J Environ Res Public Health. 2020; 17(5):1668

[6] Del Pup L, Mantovani A, Cavaliere C, Facchini G, Luce A, Sperlongano P, Caraglia M and Berretta M: Carcinogenetic mechanisms of endocrine disruptors in female cancers (Review). Oncol Rep 36: 603-612, 2016.

EWG also urges the Board of Scientific Counselors to provide guidance to the NTP, emphasizing the use of epidemiological data for a comprehensive risk assessment. EWG brings to the EPA's attention a study published by our team on the "Analysis of Cumulative Cancer Risk Associated with Disinfection Byproducts in United States Drinking Water."[7] This study conducted the first side-by-side comparison of cancer risk assessments based on toxicological and epidemiological studies of disinfection byproducts, using a comprehensive contaminant occurrence dataset for haloacetic acids and trihalomethanes, two groups of disinfection byproducts in tap water. This analysis highlights the value of using human data in health risk assessments to the greatest extent possible in order to evaluate health impacts accurately and better protect human health.

To date, there are ongoing debates about best practices for the use of epidemiological and toxicological data for chemical risk assessments, as illustrated by the January 2021 WHO webinar, "Promoting transdisciplinary approaches for identifying and assessing chemical hazards and risks to protect public health."[8] Similarly, many questions remain about the appropriate use of New Approach Methodologies for public health protection. EWG recognizes that, as the NTP meeting materials stated, "*questions regarding processes for establishing confidence in these new approaches, including the choice of reference data (rodent or human) … cannot be universally addressed*." In EWG's perspective, the number one priority should be public health protection. If scientific uncertainty exists, decisions should be made with a precautionary principle in mind.[9]

As an illustration of the importance of including epidemiological data wherever possible, we bring to the Board of Scientific Counselors' attention EWG's recent study (Temkin et al., 2019) on the health impacts of nitrate in drinking water.[10] As reviewed by Temkin et al., multiple epidemiological studies demonstrated that exposure to nitrate from drinking increases the risk of colorectal cancer. The NTP meeting materials stated that the program plans to "*prioritize resources for projects related to early-onset colorectal cancer*." EWG supports the focus on colorectal cancer as a disease that causes a tremendous social and medical burden and loss of life. We urge the NTP to develop specific programs to identify the environmental contributions to colorectal cancer rather than focus on the very narrow approach listed in the meeting materials of "*analyzing previously published sequencing data*" and "*comparing mutation signatures*."

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[7] Evans S, Campbell C, Naidenko OV. Analysis of Cumulative Cancer Risk Associated with Disinfection Byproducts in United States Drinking Water. Int J Environ Res Public Health. 2020;17(6):2149.
[8] https://www.who.int/news-room/events/detail/2021/01/20/default-calendar/webinar-on-promoting-transdisciplinary-approaches-for-identifying-and-assessing-chemical-hazards-and-risks-to-protect-public-health
[9] Gee D, Krayer von Krauss MP. Late lessons from early warnings: towards precaution and realism in research and policy. Water Sci Technol. 2005; 52(6):25-34. Grandjean P, Bailar JC, Gee D, Needleman HL, Ozonoff DM, Richter E, Sofritti M, Soskolne CL. Implications of the Precautionary Principle in research and policy-making. Am J Ind Med. 2004; 45(4):382-5
[10] Temkin A, Evans S, Manidis T, Campbell C, Naidenko OV. Exposure-based assessment and economic valuation of adverse birth outcomes and cancer risk due to nitrate in United States drinking water. Environ Res. 2019; 176:108442.

2. Recommendations for the Combined Exposures and Mixtures Program

In EWG's assessment, extensive datasets already exist to identify common and prevalent chemical mixtures that are relevant for real-life exposures of the American public.

Examples of such mixtures include:

- Contaminants in drinking water, such as disinfection byproduct mixtures, as documented by community water system testing data and the EPA Unregulated Contaminant Monitoring Program;
- Mixtures of PFAS in drinking water and other environmental media;
- The pesticides most frequently detected in fruits and vegetables, identified through the USDA Pesticide Data Program;[11]
- Chemicals identified by biomonitoring in people, such as the CDC's National Report on Human Exposure to Environmental Chemicals.

These sources of data can help the NTP's Combined Exposures and Mixtures Program to identify and select chemical combinations for in-depth analysis. It is both intuitive and documented in peer-reviewed publications[12] that testing all mathematically possible combinations of all substances, whether synthetic, natural or formed as degradation byproducts, is neither feasible nor reasonable. Real-world datasets should be prioritized for testing of mixtures effects, starting with small groups of the most common substances identified by biomonitoring studies, such as those detected most commonly in the National Health and Nutrition Examination Survey testing.[13]

Concurrent studies of the Key Characteristics of Carcinogens *and* the impacts of combined exposures to mixtures can serve as a basis for the innovative approach for cancer prevention. Given that different chemical stressors can affect different Adverse Outcome Pathways and Hallmarks of Cancer,[14] research on carcinogenic effects of mixtures is urgently needed.

3. Need for greater transparency regarding the "Rethinking Carcinogenicity Assessment for Agrochemicals Project"

Finally, EWG noted with concern one project listed in the NTP meeting materials, "Rethinking Carcinogenicity Assessment for Agrochemicals Project," which has a group of partners that does

[11] https://www.ams.usda.gov/datasets/pdp
[12] Taylor KW, Joubert BR, Braun JM, Dilworth C, Gennings C, Hauser R, Heindel JJ, Rider CV, Webster TF, Carlin DJ. Statistical Approaches for Assessing Health Effects of Environmental Chemical Mixtures in Epidemiology: Lessons from an Innovative Workshop. Environ Health Perspect. 2016; 124(12):A227-A229.
[13] Kapraun DF, Wambaugh JF, Ring CL, Tornero-Velez R, Setzer RW. A Method for Identifying Prevalent Chemical Combinations in the U.S. Population. Environ Health Perspect. 2017; 125(8):087017.
[14] Goodson WH, Lowe L, Gilbertson M, Carpenter DO. Testing the low dose mixtures hypothesis from the Halifax project. Rev Environ Health. 2020. https://doi.org/10.1515/reveh-2020-0033

not represent a wide variety of stakeholder viewpoints on the topic of carcinogenicity assessment of agricultural chemicals. The listed partners include four major companies that manufacture pesticides (BASF, Bayer Crop Science, Corteva Agriscience, and Syngenta), the EPA, and just one nonprofit organization, PETA International Science Consortium. Although the pre-meeting materials also list an academic institution, the University of South Florida, the partner list does not include any organizations focused on public health or children's health. Further, the materials do not disclose the exact nature of individual partner involvement.

Pesticide exposures especially impact the farmworker communities, including farmworkers themselves, their families and their young children. Latinx farmworker communities are disproportionately affected by such exposures.[15] As the NTP and the Board of Scientific Counselors well know, the Agricultural Health Study has identified a number of associations between the use of specific pesticides and an elevated risk of cancer. Although a full review of the Agricultural Health Study's findings is beyond the scope of these comments and the NTP meeting, we provide several references for the most recent publications that made this finding.[16]

Given that decisions on pesticide risk assessment have a significant effect on public health and children's health, a broad range of stakeholders should be included in the "Rethinking Carcinogenicity Assessment for Agrochemicals Project," and all materials for this project should become a part of the public record. EWG urges the Division of the National Toxicology Program to fully disclose how the current group of partners for this project was selected and how the work of this project may influence EPA decision-making for pesticide product registrations.

Submitted on behalf of the Environmental Working Group,

Olga V. Naidenko, Ph.D.
VP Science Investigations, Environmental Working Group

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[15] Harley KG, Parra KL, Camacho J, Bradman A, Nolan JES, Lessard C, Anderson KA, Poutasse CM, Scott RP, Lazaro G, Cardoso E, Gallardo D, Gunier RB. Determinants of pesticide concentrations in silicone wristbands worn by Latina adolescent girls in a California farmworker community: The COSECHA youth participatory action study. Sci Total Environ. 2019; 652:1022-1029

[16] Andreotti G, Beane Freeman LE, Shearer JJ, Lerro CC, Koutros S, Parks CG, Blair A, Lynch CF, Lubin JH, Sandler DP, Hofmann JN. Occupational Pesticide Use and Risk of Renal Cell Carcinoma in the Agricultural Health Study. Environ Health Perspect. 2020; 128(6):67011.
Lerro CC, Beane Freeman LE, DellaValle CT, Andreotti G, Hofmann JN, Koutros S, Parks CG, Shrestha S, Alavanja MCR, Blair A, Lubin JH, Sandler DP, Ward MH. Pesticide exposure and incident thyroid cancer among male pesticide applicators in agricultural health study. Environ Int. 2021; 146:106187.
Lerro CC, Hofmann JN, Andreotti G, Koutros S, Parks CG, Blair A, Albert PS, Lubin JH, Sandler DP, Beane Freeman LE. Dicamba use and cancer incidence in the agricultural health study: an updated analysis. Int J Epidemiol. 2020; 49(4):1326-1337.