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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Request for Information (RFI) on Assays and Approaches for Evaluating Chemical Effects on Cancer Pathways

AGENCY: National Institutes of Health, HHS.

ACTION: Request for Information.

SUMMARY: The National Toxicology Program (NTP) at the National Institute of Environmental Health Sciences is seeking input on assays and approaches for evaluating chemical effects on cancer pathways, specifically, pathways that map to the hallmarks of cancer and key characteristics of carcinogens.

DATES: The National Toxicology Program's Request for Information is open for public comment for a period of 60 days. Comments must be received by [FEDERAL REGISTER INSERT THE DATE 60 DAYS FOLLOWING THE DATE OF PUBLICATION] to ensure consideration. After the public comment period has closed, the comments received by the NTP will be used to inform the April 29-30th Workshop Converging on Cancer

(https://ntp.niehs.nih.gov/go/coc). All responses to information requested in this RFI are voluntary.

ADDRESSES: Submissions may be electronically to https://ntp.niehs.nih.gov/go/COC_RFI or by mail to Cynthia Rider, PhD, National Institute of Environmental Health Sciences, 111 TW Alexander Drive, PO Box 12233, MD:K2-12, Research Triangle Park, NC 27709.

FOR FURTHER INFORMATION CONTACT: Questions about this request for information should be directed to FOR FURTHER INFORMATION CONTACT: Questions about this request for information should be directed to Cynthia Rider, PhD, National Institute of Environmental Health Sciences, 111 TW Alexander Drive, PO Box 12233, MD:K2-12, Research Triangle Park, NC 27709, cynthia.rider@nih.gov, 984-287-3175.

SUPPLEMENTARY INFORMATION: Cancer is a leading cause of mortality worldwide. While the defining feature of cancer is uncontrolled division of abnormal cells, it is a complex disease with varied presentations (i.e., different etiologies and target tissues) that involves dysregulation of multiple interconnected signaling pathways. Diverse environmental factors have been associated with the development and progression of various cancer types. A critical question in the field of environmental health is how to harness what is known about cancer biology and associated environmental exposures to improve public health outcomes. This Request for Information is in support of the Converging on Cancer Workshop, which is aimed at providing a clear path forward for evaluating the interactions between environmental exposures and cancer biology using the latest tools in toxicology and identifying knowledge gaps that

require research attention. Potential applications of this understanding include building a framework for incorporating mechanistic data into cancer risk assessment, developing efficient and reliable screening tools to detect the carcinogenic potential of environmental chemicals (including mixtures), engineering safer products, and designing more effective multi-target therapeutics.

The hallmarks of cancer (1) and key characteristics of carcinogens (2) offer two paradigms for organizing information to better understand the interactions between environmental exposures and biological systems that lead to cancer. The hallmarks of cancer represent the biological traits of tumors that allow for the unchecked growth of cancer, while the key characteristics framework begins with known human carcinogens and identifies their defining properties. It is clear from biomonitoring studies that we are constantly exposed to numerous structurally-diverse chemicals. A recent nomination to NTP was for development of a testing strategy to better understand how environmental chemicals might interact with multiple cancer-relevant biological pathways to elicit mixture effects that would not be expected based on single chemical considerations. This RFI is intended to generate input that will facilitate new testing approaches designed to evaluate these hypotheses in a cancer context. Responses to the RFI should provide information on technologies targeting cancer-specific pathways and mechanisms, including organotypic and/or mechanistically insightful tools, preferred animal models, and in silico/computational approaches to link relevant pathways, as well as cancer types for use in evaluating hypotheses regarding the joint action of chemicals that target cancer pathways.

INFORMATION REQUESTED: The NTP requests information regarding assays and approaches to measure the key biological mechanisms/pathways associated with chemical carcinogenesis. Responses to any or all of the questions below are invited from interested individuals/groups, including, but not limited to, the environmental health research community, health professionals, educators, policy makers, industry, and the public.

- Systematic review approaches to transparently identify and evaluate mechanistic information on the carcinogenic properties of chemicals and chemical mixtures.

- Assays associated with the biological mechanisms/pathways described by the hallmarks of cancer and the key characteristics of carcinogens.

- Assays that integrate across multiple cancer-related pathways (e.g., organotypic microphysiological systems, mechanistic animal models).

- Modeling approaches to assess the joint effects of multiple chemicals on carcinogenic potential.

- Feedback on critical pathways and mechanisms to target when developing novel carcinogenicity testing strategies.

- Feedback on cancer types conducive to exploring chemical interaction hypotheses.

- Environmental chemicals known to affect key biological mechanisms/pathways leading to cancer and which key biological mechanisms/pathways are affected by these chemicals.

- Types of scientific data (e.g., mechanistic, epidemiological) needed to address underlying knowledge gaps of chemical exposures leading to carcinogenesis.

- New technologies and innovative research approaches that could be leveraged to address these underlying knowledge gaps.

REFERENCES:

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74. doi: 10.1016/j.cell.2011.02.013. PubMed PMID: 21376230.

2. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. Environmental health perspectives. 2016;124(6):713-21. doi: 10.1289/ehp.1509912. PubMed PMID: 26600562; PubMed Central PMCID: PMC4892922.

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