Strategies for Studying Combined Exposures and Mixtures

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Background Materials

2011 NIEHS Mixtures Workshop

- Website: "Advancing Research on Mixtures: New Perspectives and Approaches for Predicting Adverse Human Health Effects" https://www.niehs.nih.gov/about/events/pastmtg/2011/mixtures/
- Manuscripts:
    - Unraveling the health effects of environmental mixtures: An NIEHS priority. Carlin DJ, Rider CV, Woychik R, Birnbaum LS. Environ Health Perspect. 2013 Jan;121(1):A6-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3553446/
    - Mixtures research at NIEHS: an evolving program. Rider CV, Carlin DJ, Devito MJ, Thompson CL, Walker NJ. Toxicology. 2013 Nov 16;313(2-3):94-102. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4232209/

Polycyclic Aromatic Compound Mixtures Assessment Program

- Website: https://ntp.niehs.nih.gov/results/areas/pacs/index.html
- Concept document: https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2012/december/pahresearchconcept_508be.pdf

Sufficient Similarity and Botanical Dietary Supplements

- Website: "Addressing Challenges in the Assessment of Botanical Dietary Supplement Safety" https://ntp.niehs.nih.gov/about/presscenter/events/2016/index.html

Overview

People are exposed daily to complex and dynamic mixtures, and determining the risk associated with these exposures presents significant challenges. In 2011, the National Institute of Environmental Health Sciences (NIEHS) held a workshop titled "Advancing Research on Mixtures: New Perspectives and Approaches for Predicting Adverse Human Health Effects," which brought together experts from toxicology, epidemiology, statistics, exposure science, and risk analysis to identify and discuss major knowledge gaps in mixtures research. Subsequently, the NIEHS Strategic Plan (2012-2017) included addressing "how combined environmental exposures affect disease pathogenesis" as a priority area for research (Goal 4). Based on conclusions from the 2011 workshop and in response to Goal 4 of the Strategic Plan, NTP has developed multiple mixtures-based projects to advance our understanding of mixtures and their effects on human health.

Currently, human health risk from exposure to mixtures can be assessed based on either the whole mixture or the components of the mixture. The whole mixture approach requires data on

the mixture of interest or a "sufficiently similar" reference mixture, while component-based approaches rely on individual chemical data and models of additivity to estimate cumulative risk. While the whole mixture approach is preferred by risk analysts because fewer assumptions are required, whole mixture data are rarely available, and methods for determining sufficient similarity of complex mixtures are still in development. Component-based approaches represent the overwhelming majority of cumulative risk assessments; however, there continues to be a great deal of uncertainty in application of these approaches, which are often considered to be overly simplistic and reductionist. A whole mixtures research program with botanical dietary supplements (e.g., *Ginkgo biloba* extract) is aimed at developing and refining methods for comparing complex mixtures to determine sufficient similarity, identifying active constituents, and investigating absorption, distribution, metabolism, and excretion (ADME) profiles of whole mixtures. The polycyclic aromatic compound (PAC) mixtures assessment program was developed to address uncertainty in application of currently existing component-based approaches.

Both the component-based and whole mixture risk assessment approaches begin with an exposure and end with a risk estimate for a given health effect. More recently, attention has focused on starting with a disease and identifying exposures that could potentially contribute to disease development. Also referred to as a "systems-based" mixtures approach, adverse outcome pathways are used as a framework for predicting chemicals that may converge at the pathway or tissue level to cumulatively contribute to disease development. NTP has several ongoing projects that will contribute to the knowledge base in applying this systems-based approach to mixtures. For example, the Cancer Network and enVironmental Exposure Research Agenda (CNVERGE) begins with the Hallmarks of Cancer pathways (Hanahan and Weinberg, 2000 and 2011) and identifies environmental exposures that target each pathway in order to develop and test hypotheses about mixtures of chemicals that are not complete carcinogens but could contribute to cancer development.