Development of Framework for Characterizing Risks Posed by Mixtures

Paul Price, Ph.D. *Risk Sciences International, Ontario, Canada*

This project will develop a framework for characterizing mixture risks. The framework will be documented in a Discussion Draft White Paper that is suitable for public release. The framework will be based on two established concepts. The first concept is the use of the Aggregate Exposure Pathway (AEP), the Adverse Outcome Pathway (AOP), and AOP Networks as a framework for defining the exposure and dose response for both individual chemicals and mixtures. The second concept is the use of the statistical characteristics of data on interindividual variation in both toxicity and combined exposures to predict the potential for mixture risks. Prior findings related to these concepts that will be examined in the White Paper include:

1. The concept of perturbation of biological systems as a basis for defining toxicity and the extension of this concept to mixture risks.
2. The implications of AEP and AOP networks for determining the dose dependency of toxicological interactions and mixture toxicity.
3. The tendency of complex mixtures to have a combined toxicity that is dominated by one or two chemicals.

The document will address the following issues.

1. Whether the ability to characterize mixture risks will benefit from an improved understanding of chemicals' AEP and AOPs and in particular, the development of quantitative estimates of the doses that trigger MIEs.
2. Whether *in vivo* dose-response data can discriminate between dose addition, response addition, or supra-dose addition (synergy).
3. Whether high levels of inter-individual variation in doses of chemicals for an exposed population impact the potential for mixture risk.
4. Whether propagation of uncertainty in the toxicity of individual chemicals in the estimates of the hazard index and other measures of mixture risk indicates a potential for overestimating risk.
5. Whether studies of the mechanisms of release and transport of chemicals can be used to identify human and ecological populations that are at greater risk of combined effects (concurrent exposures to large numbers of chemicals) than other populations.

As part of this effort, limited quantitative analyses of mixture risks may be performed to illustrate key aspects of the framework. In addition, the implications of the framework for the characterization and management of mixture risk will be explored and recommendations for future research will be presented

Upon completion of the Discussion Draft White Paper, the document will be circulated to a selected set of regulatory science experts from academe, government, and industry. In addition, three webinars will be held to solicit reviews, comments, and discussion from the greater regulatory scientific community. The feedback from the reviews and webinars will be considered and the White Paper will be converted to a manuscript that will be submitted to a peer-review journal.

Implications: It is the norm that humans are simultaneously exposed to multiple chemicals (both natural and synthetic) from foods, beverages, household and personal care products, and environmental sources. However, exposures to chemical mixtures where the dose of each chemical is small do not necessarily result in health risks because of, 1) the thresholds in both toxicity and the biological perturbations that precede toxicity, and 2) the patterns of inter- and intra-individual variation in concurrent exposures of multiple chemicals. As a result, there is a need for a coherent framework that explicitly addresses how scientific findings of toxicity and exposure determine when simultaneous exposures to multiple chemicals are likely or unlikely to pose risk to humans. In the absence of such a framework, the uncertainty in the magnitude and the origin of mixture risk may result in regulatory actions that do not improve public health.

Project start and end dates: September 2025 – July 2026

Abstract revision date: October, 31 2025