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Evaluating Morphological, Behavioral & Transcriptomic Responses in the Zebrafish Developmental Toxicity Assay to Chemical Mixtures Commonly Associated with Environmental and Human Biomonitoring Studies

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For several decades, the topic of joint toxicity from combined chemical exposures has been subject to scrutiny, with multiple organizations tackling the topic of mixture risk assessment. However, little effort to date has been made to investigate if dose addition, independent action, synergism, or antagonism are the primary drivers for chemicals found in biomonitoring samples where arguably, these chemicals are unintentionally co-occurring.

This project aims to address the mechanism of action and mixture behavior of individual chemicals (that are common to both human and environmental biomonitoring) within and eventually across chemical subclasses on development, behavior and transcriptome using embryonic zebrafish. Thereby investigating if dose addition, independent action, synergism or antagonism are the drivers for mixture risk. This will be addressed in this research project via three specific aims:

- Aim 1 – Investigate the developmental toxicity and behavioral response via a photomotor assay of individual compounds in the zebrafish model
- Aim 2 – Evaluate the developmental toxicity and behavioral response via a photomotor assay of defined mixtures in zebrafish model of the individual compounds evaluated in Aim 1
- Aim 3 – Identify transcriptomic and biological pathway alterations induced by individual compounds and defined mixtures

Implications: These studies will expand knowledge of methods to improve risk evaluations of unintended environmental co-exposures by systematically evaluating responses in experiments using defined mixtures. The results will provide data that can be analyzed to distinguish dose addition from response addition. Additionally, the project will pilot an evaluation of transcriptomics to compare individual compound-induced perturbations to defined mixture-induced gene perturbations. Overall, these studies will advance the development and application of data-driven approaches for evaluating combined exposures to co-occurring environmental chemicals.

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