

Peer Review

Review of: "Mixture Toxicity: Evidence from Experimental Studies on Concurrent Chemical Exposures"

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It is potentially an important paper, but as currently written, it is hard to follow. The individual sections are not arranged for smooth reading, and grasping the important concepts in the paper may be missed.

General Comment:

This review discusses the limitations of traditional single-chemical risk assessment models in understanding the toxicological effects of concurrent chemical exposures. It highlights how organisms in natural environments are often subjected to complex chemical mixtures that can lead to non-additive effects. The review emphasizes the need for more sophisticated methodologies, such as mechanistically informed frameworks and tiered risk-assessment strategies, to better reflect real-world exposure scenarios and protect public and environmental health. The document discusses the complexities of concurrent chemical exposures and their biological and toxicological effects, emphasizing that these interactions often deviate from simple additive models. It highlights the significance of understanding chemicals' modes of action (MoA) and the potential for synergistic or antagonistic interactions, particularly during vulnerable developmental stages.

Specific Comments

INTRODUCTION

“to synthesize and critically evaluate the current body of experimental studies on the toxicological effects of chemical exposure”: Most studies were reported but not “critically” evaluated.

METHODS

A systematic search—insufficient details are given to support a systematic search; # found, # number accepted; limited to English language or not; etc.

What is the “initial list” (page 4, paragraph 2 from the bottom of the page)?

The rest of the paper is divided into sections dealing with

- **Complex interactions of chemical exposures:** The effects of concurrent chemical exposures are often more complicated than previously assumed, with many interactions being synergistic or antagonistic rather than additive. This complexity is particularly evident in cases with dissimilar modes of action.
- **Importance of methodological advancements:** Advances in modeling and technology are crucial for understanding the impacts of low-dose chemical mixtures and developing effective testing strategies that account for the interactions and relative proportions of various components.

Experimental evidence reveals that concurrent chemical exposures create a complex mixture of toxicity that simple additive models cannot accurately represent. While dose addition is often a reasonable assumption, deviations occur based on various factors, including chemical composition and biological endpoints. Mechanistically based models that consider toxicokinetic and toxicodynamic interactions are essential for enhancing risk assessment accuracy.

- **Cumulative effects of chemical mixtures:** Studies indicate that exposure to multiple chemical toxicants leads to cumulative biological effects that differ from predictions based on individual toxicities. Factors such as chemical identities, concentrations, and organism characteristics, particularly vulnerability during early life stages, influence these interactions.

Declarations

Potential competing interests: No potential competing interests to declare.