Qeios

Peer Review

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

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Review of Qeios - doi.org/10.32388/P2EDQF – “Mixture Toxicity: Evidence from Experimental Studies on Concurrent Chemical Exposures. Jose L. Domingo.

This concise article is a timely contribution in an important area – i.e., how to assess risks from exposures to multiple chemicals and to mixed exposures to chemicals and other stressors. The author clearly outlines the tools used for the literature review to ensure broad coverage of the topic and then organizes the paper to cover multiple issues in assessing and regulating mixture exposures. One challenge in such a short article with broad coverage is achieving adequate coverage of all the diverse topics in the text. To accomplish this goal, the article provides a good range of references that direct the reader to more detailed information if interested. Overall, it is a well-written, timely contribution on an important topic that should be of broad interest.

Below are some specific comments for the author to consider.

Last sentence in the abstract: “calls for abandoning the outdated single-agent paradigm in favor of holistic, ….”. How would this change be implemented for chemicals that are not well studied even as single agents? It seems a better argument would be to “call for expanding the inadequate single-agent paradigm in favor of ….”

Introduction first line “saturated”. Saturated seems to me (as a chemist) to mean it contains the maximum amount possible. The point is that there is an ever-increasing number of anthropogenic chemicals being introduced into commerce and thereby increasing the diversity of complex mixture exposures to humans and other species.

Bottom of page 2: Statement that chemicals can interact in additive, synergistic, or antagonistic ways. Do the words synergistic and antagonistic carry any mechanistic information, or do they just mean more than additive (synergistic) or less than additive (antagonistic) without any mechanistic definition?

Pages 5-6: Leeman et al. suggested that at low doses below NOAELs, mixtures could elicit cumulative effects and called this "something from nothing". Wouldn't the same behavior be expected for compounds with common MOAs that are just showing additive interactions?

Page 7: Co-exposures of lead, methylmercury, and arsenic in pregnant mice altered the toxicokinetics. Were any of the other mixture exposures in Table 1 assessed to see if there were changes in kinetics? The metal example is called out as a special case, but mightn't some of the other examples in Table 1 have a TK component to altered toxicity if studied with appropriate methods?

Page 11: "present unique methodological challenges." This reader was left wondering what challenges in these human mixture studies were considered unique by the author. Explain.

Page 15: End of the first paragraph – "the authors highlighted the potential of mechanistically-based models that consider uptake and toxicity as time-dependent processes." Has there been much progress in developing PBTK models that consider the interactions between and among various classes of compounds for induction of binding/metabolic processes, competition for metabolic clearance, etc.? If there are discrete papers on these topics in relation to interactions with mixtures, they would be good additions to this review.

Page 15 towards the bottom discusses interactions of mercury and aluminum, noting that thimerosal-containing vaccines represent the most widespread binary mixture exposure to these metals in developing countries. How does the human dose of the metals in these vaccines compare to doses used in animal studies, and how might suitable endpoints from the animal studies be used to begin a thimerosal-containing vaccine risk assessment for children? I raise this question based on renewed discussions in the United States about the safety of vaccines and their possible linkage to increased autism risks. This question may lie outside the scope of the review, although some comment in this review about the potential of mixture risk assessment approaches in addressing this issue would be welcome.

Page 16: Carcinogenicity and low-dose effects. The first line suggests that this mixture study examined the likely role of compounds in increasing the risks of carcinogenesis. However, this study looked at "cancer phenotypes," i.e., responses of key pathways/mechanisms related to cancer without

consideration of the dose responses for the relationship of changes in these pathways to cancer. It deserves mention that the dose response of pathway perturbations and cancer is not well-developed.

Page 17 middle: “collectively precipitate”. would just “collectively cause” work just as well.

Page 18 bottom and Page 19 top talk about developing comprehensive mixture risk assessment frameworks that better reflect the multifaceted nature of real work exposures. This new focus is a laudable goal but raises two questions. First, should regulatory bodies initiate activities to develop new mixture guidance documents, and secondly, how would these new initiatives be funded, e.g., by research grants or by requiring companies to submit improved mixture-based studies for registration. Does the author have any ideas or suggestions about funding mechanisms for new mixture risk-assessment initiatives?

One final comment: All references start with various letter or symbol superscripts. What do these superscripts signify?

In reading through the paper, I frequently accessed cited references and found them to align closely with the text and provide important information illuminating the text. Overall, a very useful, well-organized review on an important topic.

Declarations

Potential competing interests: No potential competing interests to declare.