RISK DIFFERENCE ADDITIVITY IS AN INAPPROPRIATE TEST OF BIOLOGICAL INTERACTION FOR MANY COMBINATION EXPOSURES

Gregory J. Howard, *Dickinson College, United States*
Thomas F. Webster, *Boston University School of Public Health, United States*

Background and Aims: Epidemiologists and toxicologists are faced with similar problems in assessing interactions between exposures, yet they approach the question very differently. Epidemiologic analysis of interactions has been categorized into several "contexts" (statistical, biological, public health, and individual). While statistical "interactions" are said to carry no biological meaning, it is often asserted that additivity of the risk differences (RDA) is the fundamental criterion for causal inference about biological interactions. Here, we contrast the theoretical frameworks for interaction in these fields, elucidating the different cases in which risk difference additivity is or is not a biologically appropriate criterion.
Methods: We analyze a simple thought experiment that has been used in both fields to develop the definition of non-interaction, with nearly opposite interpretations. In epidemiology, the "sham combination" leads to a requirement that non-interactive dose-response curves be linear. In toxicology, the same thought experiment results in the model of "concentration addition" (CA), a definition of non-interaction generally accepted by toxicologists as appropriate for similarly-acting chemicals. We apply epidemiologic tools for interaction analysis to mathematical models of concentration-additive combination exposures in order to evaluate the usefulness of these tools.
Results: The RDA model is equivalent to CA only when dose-response curves are linear, an uncommon situation. Simple models demonstrate that concentration-additive combinations can result in strong synergy or antagonism in the epidemiologic framework at even the lowest exposure levels. For these types of combination exposures, RDA is an inappropriate tool for the assessment of biological interactivity. In addition, for combinations which act through non-similar pathways, RDA is appropriate only at low effect levels.
Conclusions: RDA is not a biologically appropriate test of interaction for many exposures of interest. We suggest more appropriate methods for analysis of concentration-additive epidemiologic data. The two fields can learn a great deal about interaction from each other.