Abstract

Mixture risk assessment is often hampered by the lack of dose-response information on the mixture being assessed, forcing reliance on component formulas such as dose addition. We present a **four-step** approach for evaluating chemical mixture data for consistency with dose addition for use in supporting a component based mixture risk assessment. Following the concepts in the U.S. EPA mixture risk guidance (U.S. EPA, 2000a,b), toxicological interaction for a defined mixture (all components known) is departure from a clearly articulated definition of component additivity. For the common approach of dose additivity, the EPA guidance identifies three desirable characteristics, foremost of which is that the component chemicals are toxicologically similar. The other two characteristics are empirical: the mixture components have toxic potencies that are fixed proportions of each other (throughout the dose range of interest), and the mixture dose term in the dose additive prediction formula, which we call the combined prediction model (CPM), can be represented by a linear combination of the component doses. A consequent property of the proportional toxic potencies is that the component chemicals must share a common dose-response model, where only the dose coefficients depend on the chemical components. A further consequence is that the mixture data must be described by the same mathematical function ("mixture model") as the components, but with a distinct coefficient for the total mixture dose. The mixture response is predicted from the component dose-response curves by using the dose additive CPM and the prediction is then compared with the observed mixture results. The **four** steps are to evaluate: (1) toxic proportionality by determining how well the CPM matches the single chemical models regarding mean and variance; (2) fit of the mixture model to the mixture data; (3) agreement between the mixture data and the CPM prediction; and (4) consistency between the CPM and the mixture model. Because there are **four** evaluations instead of one, some involving many parameters or dose groups, there are more opportunities to reject statistical hypotheses about dose addition, thus statistical adjustment for multiple comparisons is necessary. These **four** steps contribute different pieces of information about the consistency of the component and mixture data with the two empirical characteristics of dose additivity. We examine this **four-step** approach in how it can show empirical support for dose addition as a predictor for an untested mixture in a screening level risk assessment. The decision whether to apply dose addition should be based on all **four** of those evidentiary pieces as well as toxicological understanding of these chemicals and should include interpretations of the numerical and toxicological issues that arise during the evaluation. This approach is demonstrated with neurotoxicity data on carbamate mixtures.