Dose-Response Modeling for EPA's Organophosphate Cumulative Risk Assessment: Combining Information from Several Datasets to Estimate Relative Potency Factors

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Abstract

The US EPA's Organophosphate Cumulative Risk Assessment (OPCRA) considers the effects of exposure to 33 organophosphorous pesticides (OPs) through the diet, water, and residential exposures. The OPCRA combines a relative potency factor (RPF) approach to dose-response assessment with a probabilistic exposure assessment to estimate distributions of margins of exposure in the US population. This presentation will deal with the calculation of RPFs for the oral route of exposure, as this route had by far the richest dataset. The RPFs were based on benchmark doses (BMDs) representing the expected daily dose that would result in a 10% inhibition of brain acetylcholinesterase (AChE) in rats. Multiple dose-response data sets were available for almost all of the 33 OPs considered. Typically in such a situation, one data set for each chemical would be chosen for BMD calculation. However, by combining datasets, it was possible to achieve both a more detailed view of the dose-response shape and a better estimate of the uncertainty of BMD estimates due to among-study and among-time variation. Dose-response models were fit to all the data for each OP using methods for non-linear mixed effects models to account for variation at both among major studies and among time points with major studies. By combining dose-response estimates across multiple studies, it was possible to more accurately delineate the low-dose "shoulder" that is a feature of the dose-response curves of about half the chemicals: the steepness of the response increased with increasing dose. Because this feature of the dose-response was successfully modeled, the resulting benchmark dose estimates gained both precision and credibility. However, the RPF approach applies strictly only when dose-additivity (in a narrow sense) applies, and dose-additivity applies strictly only when dose-responses can be superimposed by rescaling dose. The dose-responses for the OPs, with their variable low-dose shoulders, do not seem to satisfy this criterion. Thus, these observations call into question the quality of the approximation to risk that the RPF approach provides for these data. Some preliminary simulations based on simplified pharmacokinetic models of idealized compounds that include competition for metabolic clearance and competition for binding to acetylcholine esterase show how this sort of question might be resolved with mechanistic models. These simulations suggest that, even

when dose-responses do not scale appropriately for a pure, “exact” application of the RPF approach, such an approach can result in an excellent approximation to the true dose-response curve at environmental exposure levels. [This is an abstract of a presentation and does not necessarily reflect EPA policy.]