Using *In Vivo* Toxicity Syndromes to Reduce Uncertainty in Chemical Effects
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In vivo toxicology data is subject to multiple sources of uncertainty: *observer severity bias* (a pathologist may record only more severe effects and ignore less severe ones); *dose spacing issues* (this can lead to missing data, e.g. if a severe effect has a less severe precursor, but both occur at the same tested dose); *imperfect control of key independent variables* (in databases, one can rarely control key input variables such as animal strain or dosing schedules); *effect description heterogeneity* (terminology changes over time which can lead to information loss); *statistical issues* (too few chemicals with a given phenotype, or too few animals in dose groups). These issues directly contribute to uncertainties in models built from the data. We are investigating the use of collections of endpoints (toxicity syndromes) to address these issues. These are identical in concept to medical syndromes which allow a physician to diagnose an underlying disease more accurately than can be done when relying on examination of one symptom at a time. Our test case is anemia, for several reasons: most of the phenotypes (e.g. cell counts) are quantitative; related effects are measured in an automated way; anemia is relatively common, at least at high doses (~30% of chemicals in our database show significant drops in red cell count); the causes of anemia are well understood; and, there is a standard clinical decision tree to classify anemia. Using a database of 658 chemicals, we have made several preliminary observations. Only a subset of chemicals show clear syndrome patterns that map to the standard clinical decision tree, which may reflect remaining noise in the data, or an indication that chemicals can lead to anemia through more than one route. Second, anemia often only occurs in a subset of species tested (e.g. rat, mouse, dog). This may be a reflection of the doses used, or a true cross-species effect. Finally, the majority of anemia occurs at relatively high doses, where significant weight loss and even mortality is seen. Overall though, the syndrome methodology appears to be a promising approach to classifying the toxicity of chemicals. *This abstract does not necessarily reflect U.S. EPA policy*