# Informatics approach using metabolic reactivity classifiers to link *in vitro* to *in vivo* data in application to the ToxCast Phase I dataset

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Strategic combinations and tiered application of alternative testing methods to replace or minimize the use of animal models is attracting much attention. With the advancement of high throughput screening (HTS) assays and legacy databases providing *in vivo* testing results, sufficiently large data sets are now available for evaluation and potential development of new analysis methods. Correlations of *in vitro* to *in vivo* results may be the initial goal of these attempts; however, finding signatures representing class relationships between biological-assays and *in vivo* effects by navigating through the relevant classes in the chemical domain may improve the prospects of discovering such associations. When relating *in vitro* observations to *in vivo* effects, *in vitro* assay data must be interpreted within a context that also considers the metabolic fate of the chemicals, whereas species-specific metabolism is intrinsically represented in *in vivo* experiments. In this paper, an informatics approach is applied to a large dataset from the ToxCast™ Phase I project. We expand the chemical classifiers by including metabolic reactivity indicators to help elucidate in vivo to in vitro relationships at both compound and chemical feature levels. The chemical feature hyperspace can be further characterized by P450 isoform activities and physicochemical properties to augment metabolic reactivity classifiers. This work is a collaborative effort involving regulatory agency, industry, software provider, and academic research groups to establish methods to incorporate metabolic knowledge into new *in vitro* HTS approaches. ***This abstract has been reviewed by FDA and EPA, but does not necessarily represent policies of either Agency, nor is an endorsement of products implied.***