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Biotransformation and ToxCast™

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A major focus in current toxicology research is developing methods for predicting in vivo chemical toxicity from in vitro data. Within the EPA ToxCast program, a broad range of in vitro biochemical and cellular assays are being used to profile the biological activity of the 309 ToxCast Phase I chemicals. However, only a limited number of these assays have metabolic capacity, and it is not feasible to test all potential metabolites in the over 500 assays of ToxCast. In order to assess the magnitude of this issue and explore practical solutions, ToxCast Phase I includes 12 parent-metabolite chemical pairs, allowing comparisons of in vitro assay results between parents and metabolites. Clear differences in cytotoxicity and other endpoints across several cell lines were observed when comparing these parent-metabolite results. Biochemical assay results also yielded distinct activities for certain metabolites, relative to the parent chemical, emphasizing the need for development of biochemical assays with biotransformation capacity or to account for biotransformation through other approaches. A practical solution may include metabolic simulation or prediction, along with targeted testing of prioritized metabolites. Results from the wide range of assays in ToxCast, with and without metabolic capacity, are being incorporated into the data mining and interpretive process. The bioactivity profiles of parent-metabolite pairs allowed us to identify assays with the potential to characterize chemical-specific biotransformation. This will be evaluated further by the selection of additional assays, and parent and metabolite chemicals for future phases of ToxCast. *This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.*