Extending the Derek-Meteor Workflow to Predict Chemical-Toxicity Space Impacted by Metabolism: Application to ToxCast and Tox21 Chemical Inventories

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A central aim of EPA's ToxCast project is to use *in vitro* high-throughput screening (HTS) profiles to build predictive models of *in vivo* toxicity. Where assays lack metabolic capability, such efforts may need to anticipate the role of metabolic activation (or deactivation). A workflow combining two structure-based expert systems – Meteor (predicts bio-transformations) and Derek (predicts in vivo toxicity) – was previously developed and applied to identify ToxCast Phase I chemicals likely to require metabolic activation for rat carcinogenicity (Rat Carc). Positive and negative Derek predictions for the parent structures [P+, P-] and for the Meteor-generated metabolites [M+, M-] were compared and validated using rat chronic study results from ToxRefDB. In cases where Derek has implicit knowledge of metabolic activation requirements associated with a structural alert (SA), the parent chemicals and associated metabolites are both predicted as rat carcinogens [P+/M+]. However, because the Derek knowledge-base is incomplete, some compounds trigger a positive Derek prediction only after the parent compound is metabolically transformed by Meteor, i.e., [P-/M+]. We extended the workflow to combine metabolic activation-related knowledge implicitly contained in Derek SAs (through review of SA narratives) with that implied by the [P-, M+] outcomes of the Meteor-Derek workflow. In principle, the extended workflow enables the extraction of a set of metabolic-activation (or deactivation) structural features in association with any Derek toxicity endpoint. This cheminformatics workflow is being applied to the full ToxCast Phase I&II (1060 unique chemicals) and Tox21 (>8600 chemicals) inventories to identify regions of chemical HTS space where *in vitro* to *in vivo* Rat Carc associations are more likely to be impacted by metabolism. These results will be used to enhance future predictive modeling efforts.

This abstract does not necessarily represent U.S. EPA policy.