

Correlation of Tox21 and ToxCast *In Vitro* and Small Model Organism Outcomes to Rat Oral Toxicity

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At present, many national and international regulatory authorities use data from rat acute oral toxicity test methods for hazard classification and labeling. The Tox21 and ToxCast programs have tested over 2000 and 8000 chemicals, respectively, in *in vitro* and zebrafish (ZF) assays. We evaluated data from Tox21 and ToxCast to determine the potential of the more than 800 measures collected thus far to reduce animal use in toxicity testing for hazard identification. Rat oral LD50 data were obtained for 3582 Tox21 and 670 ToxCast Phase I and II chemicals. An ongoing analysis identified high-quality LD50 data for 76 chemicals that have been tested in ZF toxicity assays. The Tox21 and ToxCast data were analyzed for correlation and model fit to the LD50 data in order to determine which tests (and combinations thereof) best characterized the rat oral toxicity data. Correlation analyses were performed on binary outcomes of response for chemicals classified by LD50 as “toxic” (LD50 < 5000 mg/kg-bw). In this assessment of fit to the up-and-down protocol, some models returned a sensitivity >0.80, which was modestly improved by including measures identified through random forest assessment. In parallel with the *in vitro* assessment, ZF toxicity assays were found to be more sensitive than rat oral toxicity for 75 of 76 chemicals, which was confirmed with a Mann–Whitney U test ($p < 1e-15$). Correlating the combined *in vitro* assays to rat oral LD50s suggests that combinations of *in vitro* assays and small model organisms offer promise for predicting outcomes of rat acute LD50 limit tests. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No.HHSN27320140003C.*