

Collaboration to Develop Predictive Models for Acute Oral Systemic Toxicity

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Acute oral systemic toxicity testing is required by regulatory agencies world-wide with acute toxicity tests representing the highest cumulative animal use across chemical sectors. One of ICCVAM's priorities is to develop alternative methods for acute toxicity tests, beginning with the acute oral systemic toxicity assay. To support this goal, NICEATM organized an international collaborative effort to develop in silico models for the acute oral systemic toxicity assay that would address ICCVAM agency regulatory needs. NICEATM and EPA's NCCT compiled rat acute oral lethality data (LD50 values) and associated structure information for 11,992 chemicals to facilitate developing predictive in silico models of acute oral systemic toxicity. This data set was used by collaborators for predictive modeling with varying approaches, applicability domains, strengths, and limitations. In total, the consortium of 35 groups delivered 139 models. These models were combined to establish consensus predictions for five different endpoints covering binary, categorical, and continuous values. The consensus predictions leverage each model's strengths and overcome the limitations of any individual approach. A summary of the compiled LD50 dataset as well as details regarding the predictive modeling will be presented. This unique approach to developing alternatives to animal testing involved initiating work with a definition of needs set forth by regulatory agencies, involving diverse stakeholders at every step, and integrating collective expertise from the international modeling community. US federal funds from NIEHS/NIH/HHS Contract HHSN273201500010C supported this work; *the views expressed are those of the authors and do not necessarily reflect US EPA views or policy.*