Collaborative Modeling Project for Predicting Acute Oral Toxicity

K. Mansouri[1], A. Karmaus[1], J. Fitzpatrick[2,3], G. Patlewicz[2], P. Pradeep[2,3], D. Allen[1], W. Casey[4], N. Kleinstreuer[4]

[1]ILS, Research Triangle Park, NC, USA: [2]CCTE/EPA, Research Triangle Park, NC, USA: [3]ORISE, Oak Ridge, TN, USA; [4]NIH/NIEHS/DNTP/NICEATM, Research Triangle Park, NC, USA

Regulatory agencies have a pressing need to accurately assess an increasing number of chemicals for acute oral systemic toxicity potential (LD50). With the lack of in vitro approaches and the availability of existing LD50 data for a broad range of chemicals, in silico models provide an alternative to predict acute oral toxicity and bridge data gaps. NICEATM and the ICCVAM Acute Toxicity Workgroup organized an international collaborative project to develop in silico models for predicting acute oral toxicity. In total, 35 groups participated, submitting 139 predictive models built using a dataset of 11,992 chemicals split into training (75%) and evaluation sets (25%). Crowdsourced models were developed for five endpoints: LD50 value, EPA hazard categories, GHS hazard categories, very toxic (LD50 < 50 mg/kg), and non-toxic (LD50 > 2000 mg/kg). Predictions within the applicability domains of the submitted models were evaluated using external validation sets, then combined into consistent consensus predictions based on a weight-of-evidence approach, forming the Collaborative Acute Toxicity Modeling Suite (CATMoS). The resulting consensus model leverages the strengths and overcomes the limitations of individual modeling approaches. The consensus predictions are fully reproduceable and performed as well as the in vivo acute oral toxicity assay with evaluation set balanced accuracy ranging from 0.74 to 0.84 for the four categorical endpoints predictions and an R^2 of 0.65 for LD50. The CATMoS consensus model is available via the free and open-source tool OPERA (Open Structure-activity/property Relationship App). OPERA also provides predictions for physicochemical and pharmacokinetic properties, and other toxicological endpoints with applicability domain assessments and accuracy estimates (https://github.com/NIEHS/OPERA). CATMoS predictions for the ~850k chemical structures in DSSTox are being made publicly accessible via NTP's Integrated Chemical Environment (ice.ntp.niehs.nih.gov) and the EPA's CompTox Chemicals Dashboard (comptox.epa.gov/dashboard). This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C. This abstract does not necessarily reflect EPA policy.

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