IN SILICO TOOLS FOR PREDICTING ACUTE ORAL TOXICITY

Acute oral systemic toxicity data serves as a cornerstone for regulatory hazard classification, labeling, and risk management across global jurisdictions. Increasingly, there are *in vitro* and *in silico* solutions that can be applied to address regulatory questions about this endpoint.

At the heart of *in silico* acute toxicity predictions are Quantitative Structure-Activity Relationship (QSAR) models. These models operate on the premise that the biological activity of a substance is a function of its chemical structure. By analyzing physicochemical properties and structural features (i.e., descriptors, such as molecular weight, water solubility, vapor pressure, octanol-water partition coefficient, and/or chemical substructure), QSAR models can predict adverse effects without biological testing.

Modern predictive toxicology involves advanced machine learning (ML) and deep learning (DL) algorithms. These approaches can handle vast datasets to capture complex, non-linear relationships between chemical structures and toxicological endpoints.

To maximise reliability, newer models are increasingly incorporating mechanistic knowledge (e.g., OTTR and AOrTA). This includes aligning predictions with molecular initiating events (MIEs), such as acetylcholinesterase inhibition or mitochondrial disruption, which are known drivers of high acute toxicity.

In practice, *in silico* models for acute toxicity are typically integrated into weight-of-evidence (WoE) frameworks. These frameworks combine computational predictions with other data sources, such as *in vitro* assays and read-across from similar chemicals, to form a comprehensive safety assessment (Zwickl et al., 2022). This integration enables the use of *in silico* tools for rapid screening, as well as satisfying regulatory requirements and classifying chemical hazards with confidence.

A non-exhaustive list of *in silico* tools for predicting acute systemic toxicity is provided below. Please contact Kyle Martin at kmartin@thepsci.eu to include additional resources on this list or with any questions.

TOOL	DEVELOPER	METHOD/APPROACH	AVAILABILITY
ACD/Percepta model for acute oral toxicity in rats	ACD/Labs	Statistical	Commercial
Acute Toxicity (LD50) model LD_{50} kNN	VEGAHub	Statistical	Open-source
ADMET Predictor	Simulations Plus	Statistical	Commercial
ATE classification tool (AOrTA; in development)	KREATiS	Statistical	Commercial
Case Ultra	MultiCase Inc.	Statistical	Commercial
Collaborative Acute Toxicity Modeling Suite (CATMoS)	US NIH	Consensus/statistical	Open-source
Derek Nexus	Lhasa Limited	Expert rule-based	Commercial
Leadscope AOT Model Suite	Instem (Leadscope Model Applier)	Statistical	Commercial
OECD QSAR Toolbox	OECD/Laboratory of Mathematical Chemistry	Statistical (read-across/QSAR)	Open-source
The Oral ToxiciTy Reporter (OTTR)	Dow, Inc.	Statistical	Open-source
Toxicity Estimation Software Tool (TEST)	US EPA	Statistical	Open-source