Collaborative Modeling Project for Predicting Acute Oral Toxicity

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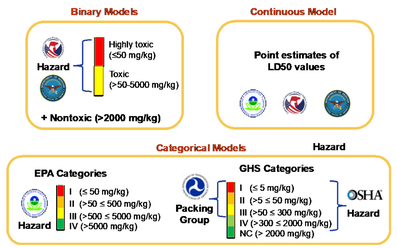
Abstract

With an increasing number of chemicals to assess for acute systemic toxicity potential and a lack of sufficiently predictive in vitro approaches, in silico models provide an alternative to predict acute oral toxicity and bridge data gaps. NICEATM and the ICCVAM Acute Toxicity Workgroup (ATWG) organized an international collaborative project to develop in silico models for predicting acute oral toxicity [1]. In total, 35 groups participated, submitting 139 predictive models built using a dataset of 11,992 chemicals. 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) [2]. Predictions within the applicability domains of the submitted models were evaluated using external validation sets, then combined into consensus predictions for each endpoint, forming the Collaborative Acute Toxicity Modeling Suite (CATMoS) [3]. The resulting consensus predictions leverage the strengths and overcome the limitations of individual modeling approaches. The consensus predictions performed at least as well as the in vivo acute oral toxicity assay in terms of accuracy and reproducibility. CATMoS consensus predictions can be generated for new chemical structures and are made available as free and open-source models via the OPERA predictive tool, which provides applicability domain assessments and accuracy estimates [4-5]. CATMoS predictions for the ~850k chemical structures in DSSTox will ultimately be publicly accessible via NTP's Integrated Chemical Environment and the EPA's CompTox Chemicals Dashboard [6-7].

Project Data

- Endpoints: five endpoints were selected by the ICCVAM ATWG member agencies to serve as endpoints for predictive modeling within the CATMoS project.
- Collected data: 34,508 rat oral LD50 values for 16,297 chemicals total.

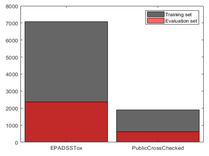


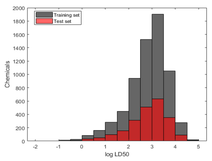
15,688 chemical structures
21,200 LD50 values

QSAR-ready standardization

Desalted, stereochemistry stripped, tautomers and nitro groups standardized, valence corrected, structures neutralized

11992 chemicals with standardized structures



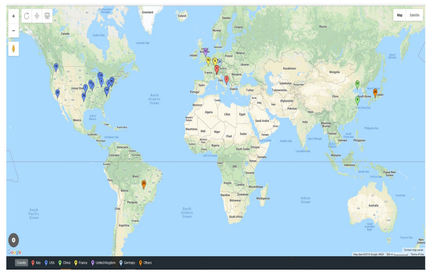


Available data split into:
- 75% training set: 8,994 chemicals
- 25% evaluation set: 2,998 chemicals

- Training data for all endpoints included in same structure file
- Similar distributions and variability for values and categories
- Similar distribution of chemical structure sources

Collaborators

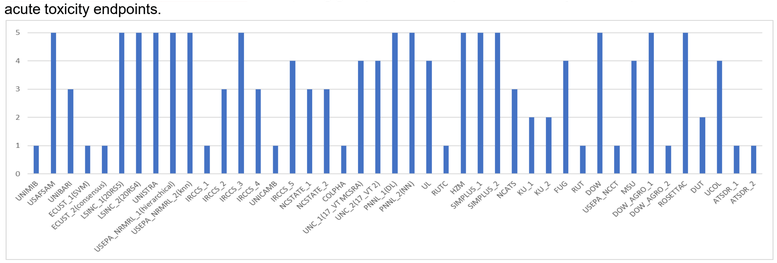
A consortium of **35 participants/groups** from around the globe representing academia, industry, and government



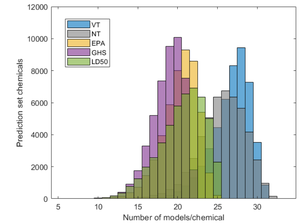
Group ID	Institution	Country
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods	USA
UNIBARI	Università degli Studi di Bari	Italy
LOREAL	L'Oréal R&I	France
UNICAMB	University of Cambridge	UK
UNC	UNC Eshelman School of Pharmacy	USA
FUG	Federal University of Goias	Brazil
UNIMIB	University of Milano-Bicocca	Italy
DOW	The Dow Chemical Company	USA
IRCCS (5 groups)	Istituto di Ricerche Farmacologiche Mario Negri	Italy
MSU	Michigan State University	USA
SIMPLUS	Simulations Plus, Inc.	USA
KU	Kyoto University Graduate School of Medicine	Japan
ECUST	East China University of Science and Technology, China	China
USAFSAM	Henry M Jackson Foundation for the Advancement of Military Medicine	USA
RUT (2 groups)	Rutgers University	USA
COLPHA	Collaborations Pharmaceuticals, Inc.	USA
UL	Underwriters Laboratories	USA
NCSTATE	North Carolina State University	USA
PNNL	Pacific Northwest National Laboratory	USA
NCCT	National Center for Computational Toxicology, USEPA	USA
HZM	Helmholtz Zentrum München, Germany	Germany
UNISTRA	Universite de Strasbourg	France
NRMRL	National Risk Management Research Laboratory, USEPA	USA
LSINC	Leadscope Inc.	USA
NCATS	National Center for Advancing Translational Sciences, NIH	USA
ATSDR	Agency for Toxic Substances and Disease Registry, CDC	USA
ROSETTAC	Rosettastein Consulting UG	Germany
UCOL	University of Colorado	USA
DUT	Dalian University of Technology	China
DOW_AGRO	Dow Agrosciences	USA

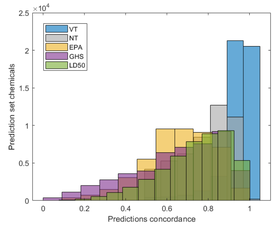
Consensus Modeling

Models received from participants. Participating groups submitted predictions for any one or up to all five of the acute toxicity endpoints.



Coverage and concordance of the models





Single model evaluation procedure

Qualitative evaluation:
- Documentation
- Defined endpoint
- Unambiguous algorithm
- Availability of code
- Applicability domain definition
- Availability of data used for modeling
- Mechanistic interpretation

Quantitative evaluation:
- Goodness of fit: training (Tr) statistics
- Predictivity: statistics on the evaluation set (Eval)
- Robustness: balance between (Goodness of fit) & (Predictivity)

$$S = 0.3 * (Goodness\ of\ fit) + 0.45 * (Predictivity) + 0.25 * (Robustness)$$

Categorical models (binary and multi-class):

$$Goodness\ of\ fit = 0.7 * (BA_{Tr}) + 0.3 * \left(1 - |\widetilde{Sn_{Tr} - Sp_{Tr}}|\right)$$

$$Predictivity = 0.7 * (BA_{Eval}) + 0.3 * \left(1 - |\widetilde{Sn_{Eval} - Sp_{Eval}}|\right)$$

$$Robustness = 1 - |BA_{Tr} - BA_{Eval}|$$

Continuous models:

$$Goodness\ of\ fit = R^2_{Tr}$$

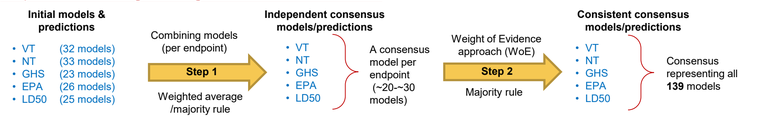
$$Predictivity = R^2_{Eval}$$

$$Robustness = 1 - |R^2_{Tr} - R^2_{Eval}|$$

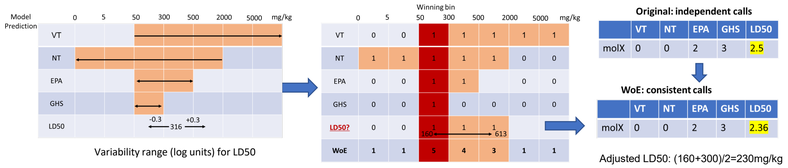
$$BA = \frac{(Sn + Sp)}{2} \qquad Sn = \frac{TP}{TP + FN} \qquad Sp = \frac{TN}{TN + FP} \qquad R^2 = 1 - \frac{\sum_{i=1}^{n_{Tr}} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n_{Tr}} (y_i - \bar{y})^2}$$

$\hat{y}_i$ and y_i are the estimated and observed responses

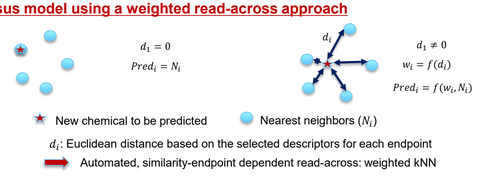
Steps for combining the single models into consensus



WoE approach to combine the five independent calls

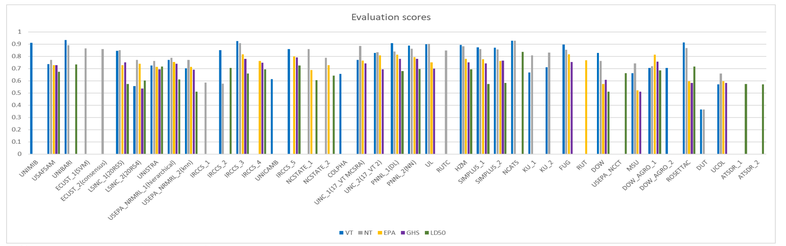


Extended consensus model using a weighted read-across approach



Models Performance Evaluation

Single models evaluation. Resulting scores (per model) from the evaluation procedure.



Consensus models evaluation

	LD50	
	Training	Evaluation
R^2	0.85	0.65
RMSE	0.30	0.49

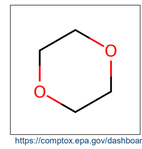
	VT		NT	
	Training	Evaluation	Train	Evaluation
Balanced accuracy (BA)	0.93	0.84	0.92	0.78
Sensitivity (Sn)	0.87	0.70	0.88	0.67
Specificity (Sp)	0.99	0.97	0.97	0.90

	EPA Training				EPA Evaluation			
	Cat 1	Cat 2	Cat 3	Cat 4	Cat 1	Cat 2	Cat 3	Cat 4
BA	0.87				0.74			
Sn	0.87	0.83	0.91	0.63	0.70	0.56	0.81	0.40
Sp	0.99	0.95	0.75	0.98	0.97	0.88	0.62	0.97

	GHS Training					GHS Evaluation				
	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5
BA			0.88					0.74		
Sn	0.73	0.75	0.84	0.80	0.88	0.50	0.53	0.56	0.66	0.67
Sp	0.99	0.99	0.92	0.89	0.96	0.99	0.97	0.89	0.74	0.90

CATMoS in Practice

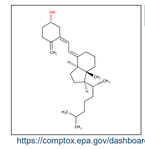
Example predictions. Structures taken from the EPA CompTox Chemicals Dashboard.



1,4-Dioxane
123-91-1 | DTXSID4020533
Molecular Formula: $C_4H_8O_2$
Average Mass: 88.106 g/mol

LD50: 4200 mg/kg
log10 LD50= 3.62

https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID4020533



Vitamin D3
67-97-0 | DTXSID6026294
Molecular Formula: $C_{27}H_{44}O$
Average Mass: 384.648 g/mol

LD50: 42 mg/kg
log10 LD50= 1.62

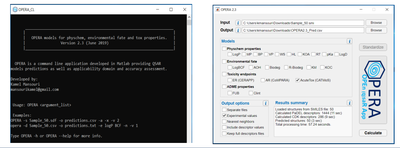
https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID6026294

Consensus output: Exported results sheet with predictions, applicability domain and accuracy estimates.

MoleculeID	CATMoS_VT_pred	CATMoS_NT_pred	CATMoS_EPA_pred	CATMoS_GHS_pred	CATMoS_LD50_pred	AD_CATMoS	AD_index_CATMoS	Conf_index_CATMoS
'123-91-1'	0	1	3	5	3.4053	1	1	0.9500
'67-97-0'	1	0	1	2	1.2845	1	1	0.8684

CATMoS implementation in OPERA

OPERA suite of models:
- Free, open-source and open-data
- Command line and GUI
- Single chemical and batch mode
- Windows OS and Linux
- Embeddable wrapper libraries (java, C/C++, Python)



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Acknowledgements

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