Collaborative Modeling Project for Predicting Acute Oral Toxicity (CATMoS)

Abstract 253

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OBJECTIVES

- Acute systemic toxicity tests are commonly required by regulatory authorities to characterize a chemical's toxicity.
- ICCVAM published a roadmap to establish alternative approaches for evaluating toxicity
- The goal of this project was to provide a computational tool for assessing acute oral toxicity
- A key aspect of this project was leveraging the collective expertise of collaborators from different sectors

APPROACH

- Data collected and curated by ICCVAM's Acute Toxicity Workgroup
- International collaborators were invited to form a modeling consortium
- Regulators and stakeholders were involved at early stages to ensure usability
- Crowdsourced models were evaluated and combined into a consensus model

MAIN RESULTS

- 35 international participating groups and over 100 scientists from government, academia and industry submitted models (n=139 total)
- The combined models provided high coverage and concordance for screened the lists of interest.
- The consensus model showed high performance and accuracy.

IMPACT

- Dialogue between regulators and computational scientists in a dedicated workshop: https://ntp.niehs.nih.gov/go/atwksp-2018
- Free and open-source/open-data consensus model available via a user-friendly app OPERA:https://github.com/NIEHS/OPERA
- Collaborative publication: https://doi.org/10.1289/EHP8495
- CATMoS is being tested for regulatory use

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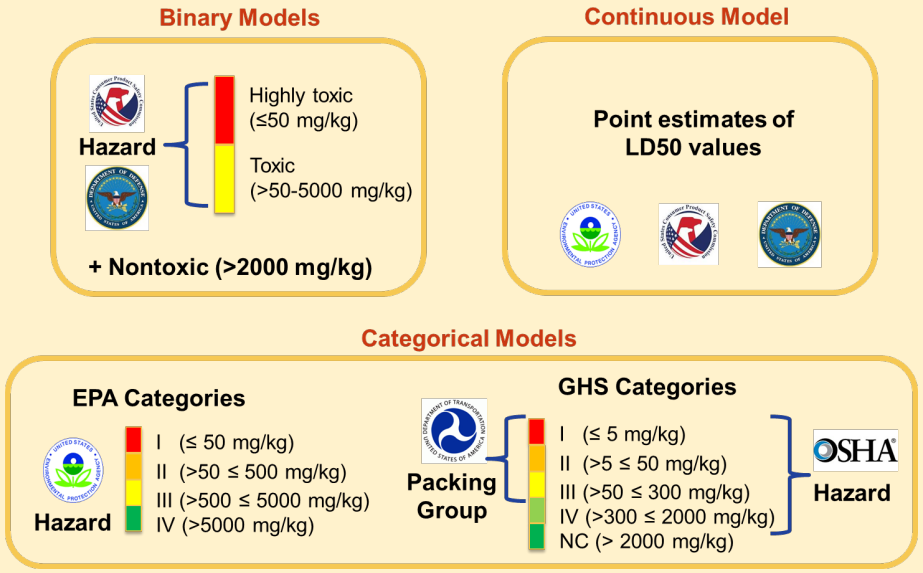
OBJECTIVES

- NICEATM supports ICCVAM's needs for the development and evaluation of new and revised alternative methods for the implementation of new approach methodologies (NAMs) for chemical safety.
- ICCVAM is developing alternative test methods for the EPA's six pack tests: Acute oral, dermal, inhalation, eye & skin irritation and skin sensitization
- In order to fulfill the pressing need to accurately assess chemicals for acute oral toxicity potential, NICEATM and the ICCVAM Acute Toxicity Workgroup organized the Collaborative Acute Toxicity Modeling Suite (CATMoS) project to develop in silico models as alternatives to predict LD50 and bridge data gaps.
- ICCVAM's Acute Toxicity Workgroup identified federal agency requirements, needs, and decision contexts for using acute systemic toxicity data



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APPROACH

- Endpoints: five endpoints were selected by the ICCVAM ATWG member agencies to serve as endpoints for predictive modeling within the CATMoS project.
- Data: collected and curated data for 11,992 chemicals split into training (75%) and evaluation (25%) sets.

Model evaluation procedure

Qualitative evaluation:

- Documentation
- Defined endpoint
- Unambiguous algorithm
- Availability of code
- Defined applicability domain
- Availability of input data used for modeling
- Mechanistic interpretation

Quantitative evaluation:

- Goodness of fit: training (Tr) statistics
- Predictivity: Evaluation set statistics (Eval)
- Robustness: balance between (Goodness of fit) & (Predictivity)

Steps for combining the models into consensus

Initial models & predictions

- VT (32 models)
- NT (33 models)
- GHS (23 models)
- EPA (26 models)
- LD50 (25 models)

Combining models (per endpoint)

Step 1

Weighted average /majority rule

Endpoint consensus models/predictions

- VT
- NT
- GHS
- EPA
- LD50

A consensus model per endpoint (~20-~30 models)

Weight of Evidence approach (WoE)

Step 2

Majority rule

Consistent consensus models/predictions

- VT
- NT
- GHS
- EPA
- LD50

Consensus representing all 139 models

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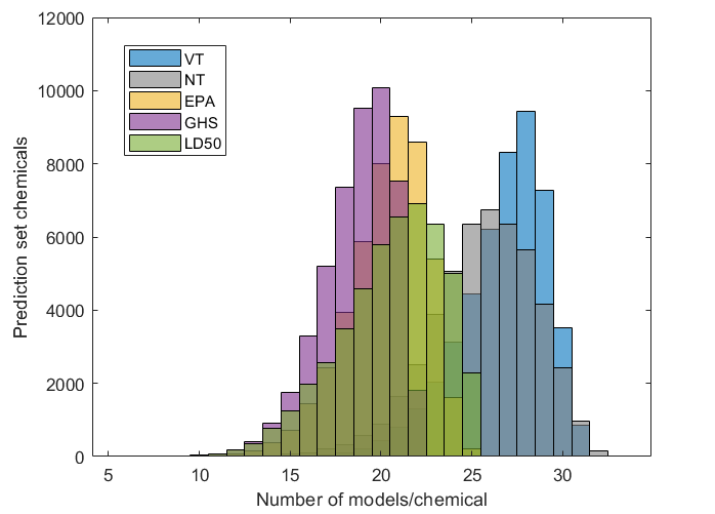
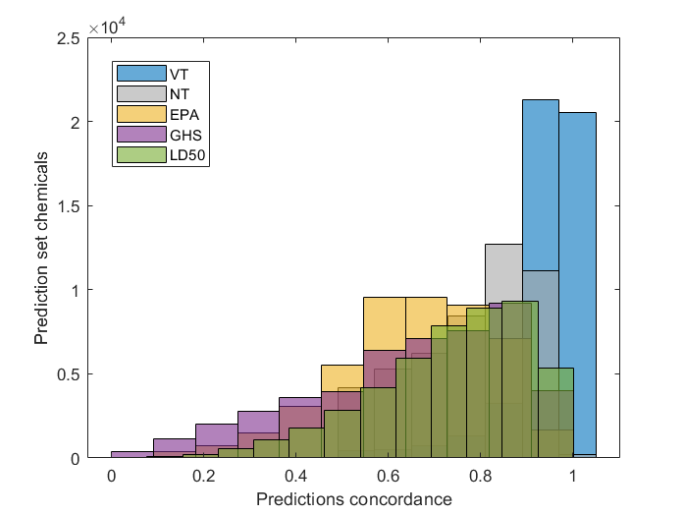
MAIN RESULTS

Coverage and concordance of the models (139 models received)





- Participants from 35 international groups submitted a total of 139 predictive models.
- Predictions within the applicability domains of the submitted models were evaluated, then combined into consensus predictions based on a weight-of-evidence approach.
- The resulting consensus model, forming CATMoS, leverages the strengths and overcomes the limitations of individual modeling approaches.
- The consensus predictions are fully reproducible and performed as well as independent replicate in vivo acute oral toxicity assays.

CATMoS Performance 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

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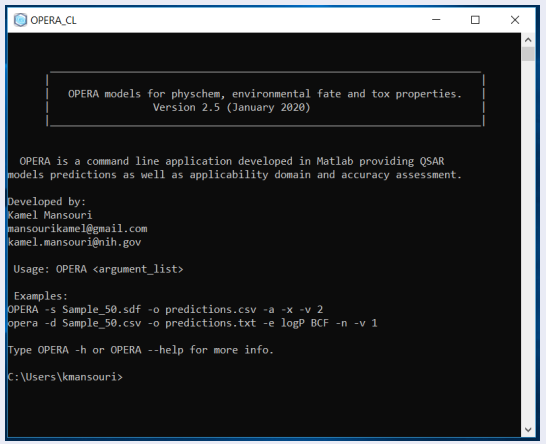
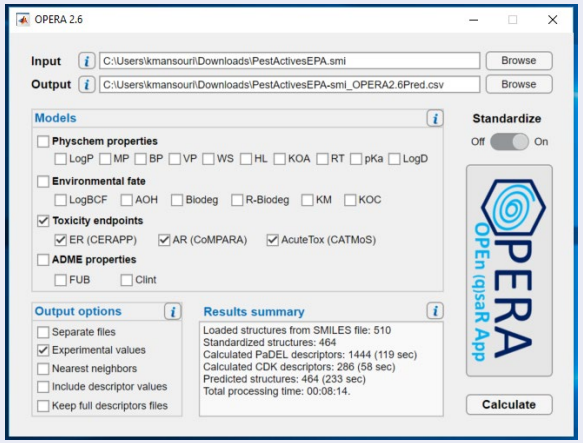
CATMoS implementation in OPERA

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 in Java, C, C++, and Python

IMPACT





Collaboration with ATWG partners and ICCVAM agencies

Agency	No. Substances	Agency	No. Substances
Air Force	421	EPA OPP	36
Army Public Health Command	18	EPA OPPT	8
Army Edgewood Chemical Biological Center	42	EPA NCCT	4815
CPSC	110	EPA EFED	160
DOT	3671	FDA CFSAN	22

Progress made with EPA EFED

- Compared CATMoS predictions to risk assessment data on 160 pesticides registered in the last 25 years.
- Determined overlap and discordance leading to additional curation and improvement of the used data and predictions.