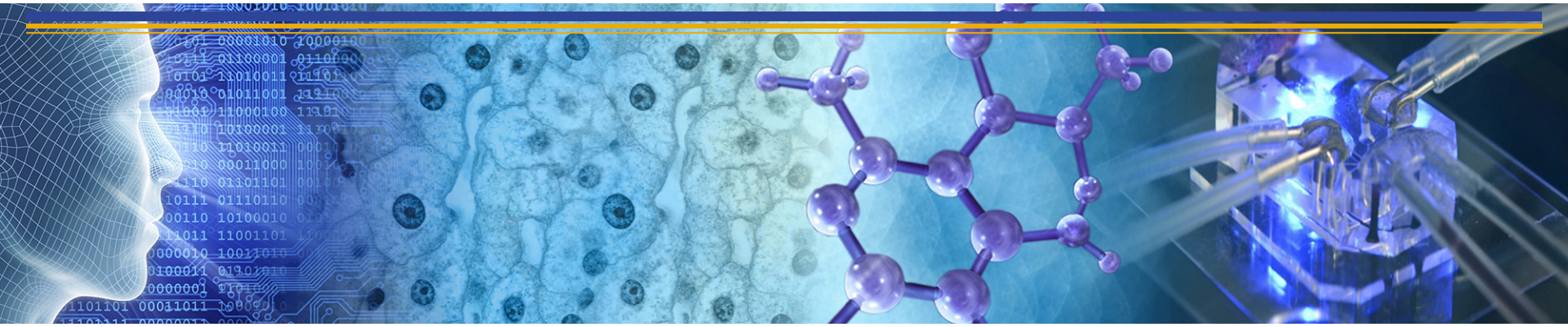
NTP
National Toxicology Program



Collaborative modeling project for predicting acute oral toxicity (CATMoS)

Kamel Mansouri
LEAD COMPUTATIONAL CHEMIST, ILS IN SUPPORT OF NICEATM

Disclaimer: ILS staff provide technical support for NICEATM, but do not represent NIEHS, NTP, or the official positions of any federal agency.

Collaborative projects

CERAPP

Collaborative Estrogen Receptor Activity Prediction Project **(2015/16)**

Mansouri et al. (https://doi.org/10.1289/ehp.1510267)

CoMPARA

Collaborative **M**odeling **P**roject for **A**ndrogen **R**eceptor **A**ctivity **(2017/18)**

Mansouri et al. (https://doi.org/10.1289/EHP5580)

CATMoS

Collaborative **A**cute **T**oxicity **Mo**deling **S**uite **(2017/18)**

Kleinstreuer et al. (https://doi.org/10.1016/j.comtox.2018.08.002)
Mansouri et al. (in preparation)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

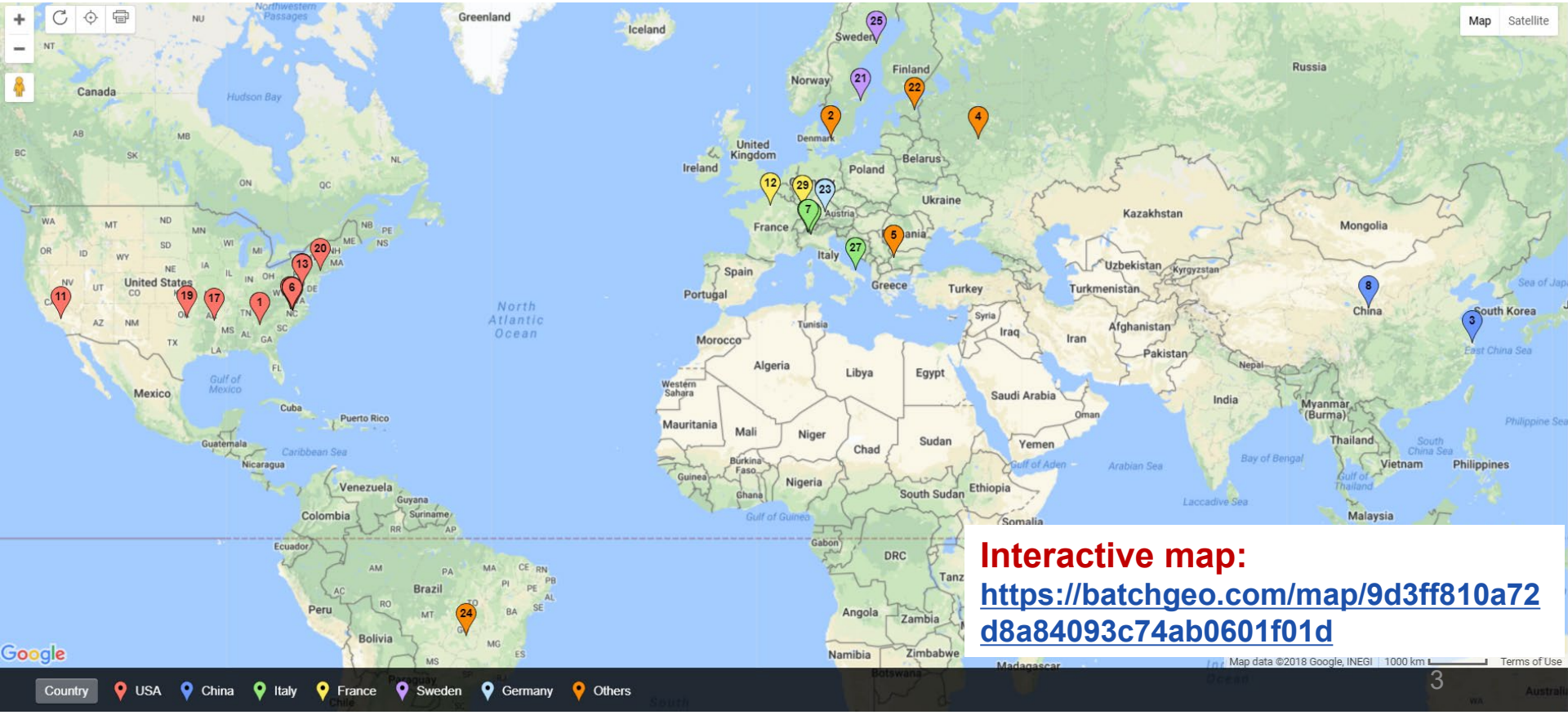
Endocrine Disruptor Screening Program

UNITED STATES ICCVAM Advancing Alternatives to Animal Testing

Acute Toxicity Workgroup: alternative methods

International Collaborators

Over 100 scientists from around the globe representing academia, industry, and government contributed



Interactive map:
https://batchgeo.com/map/9d3ff810a72d8a84093c74ab0601f01d

Acute Oral Toxicity: CATMoS

- ICCVAM is developing alternative test methods for the EPA's six pack tests: Acute oral, dermal, inhalation, eye & skin irritation and skin sensitization
- Acute Toxicity Workgroup: identifies federal agency requirements, needs, and decision contexts for using acute systemic toxicity data

Regulatory Toxicology and Pharmacology 94 (2018) 183–196

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Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Status of acute systemic toxicity testing requirements and data uses by U.S. regulatory agencies

Judy Strickland[a,*], Amy J. Clippinger[b], Jeffrey Brown[b], David Allen[a], Abigail Jacobs[c,1], Joanna Matheson[d], Anna Lowit[e], Emily N. Reinke[f], Mark S. Johnson[f], Michael J. Quinn Jr.[f], David Mattie[g], Suzanne C. Fitzpatrick[h], Surender Ahir[i], Nicole Kleinstreuer[j], Warren Casey[j]

Agency-Based Modeling Endpoint Selection

Binary Models

Hazard

Highly toxic (≤50 mg/kg)

Toxic (>50-5000 mg/kg)

+ Nontoxic (>2000 mg/kg)

Continuous Model

Point estimates of LD50 values

Categorical Models

Hazard

EPA Categories

Hazard

I (≤ 50 mg/kg)

II (>50 ≤ 500 mg/kg)

III (>500 ≤ 5000 mg/kg)

IV (>5000 mg/kg)

GHS Categories

Packing Group

I (≤ 5 mg/kg)

II (>5 ≤ 50 mg/kg)

III (>50 ≤ 300 mg/kg)

IV (>300 ≤ 2000 mg/kg)

NC (> 2000 mg/kg)

OSHA®

Hazard

Available data for modeling

Rat oral LD50s:
16,297 chemicals total
34,508 LD50 values

15,688 chemicals total
21,200 LD50 values

QSAR-ready standardization

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

11992 chemicals with accurate structures

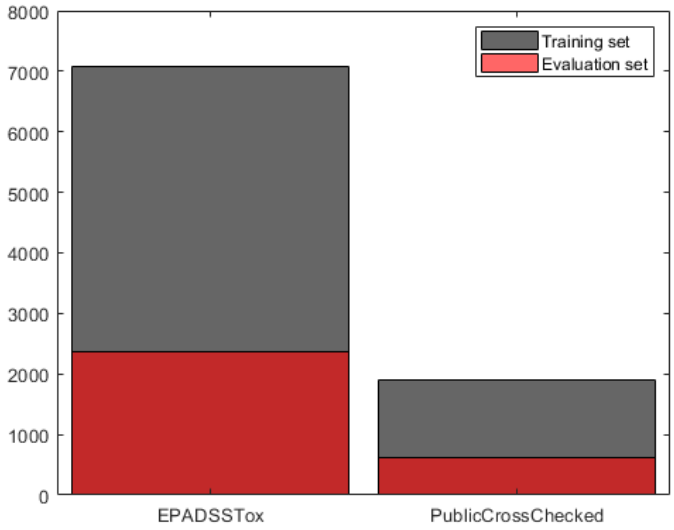
- Very toxic endpoint: 11886 entries (binary, 0/1)
- Non-toxic endpoint: 11871 entries (binary, 0/1)
- EPA endpoint: 11755 entries (categorical, 4 categories)
- GHS endpoint: 11845 entries (categorical, 5 categories)
- LD50 endpoint: 8908 entries (continuous values)

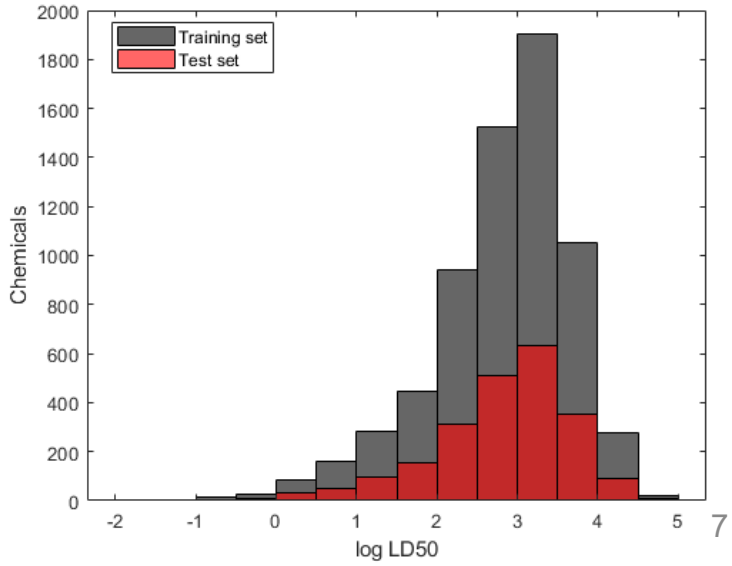
Establishing Modeling Dataset

- **Training and evaluation sets:**

- 11,992 chemicals from the final inventory of chemicals with QSAR-ready structures having rat oral acute toxicity data were split into training and test sets:
  - 75% training set: 8,994 chemicals
  - 25% evaluation set: 2,998 chemicals

- All endpoints training data included in same structure file
- Similar distributions and variability for values and categories
- Similar distribution of chemical structures sources





Establishing Modeling Dataset

- **Prediction set:**

Included lists of regulatory interest:

- ToxCast/Tox21
- EDSP
- TSCA
- Substances on the market (EPA Dashboard list)

After QSAR-ready standardization:

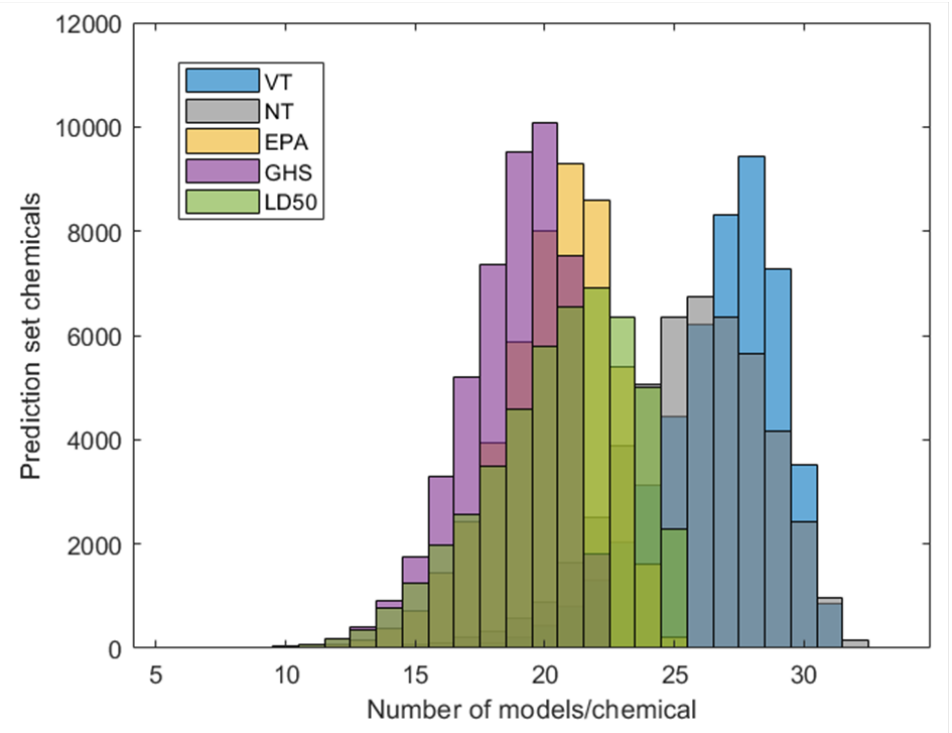
48137 structures to be predicted (including the evaluation set)

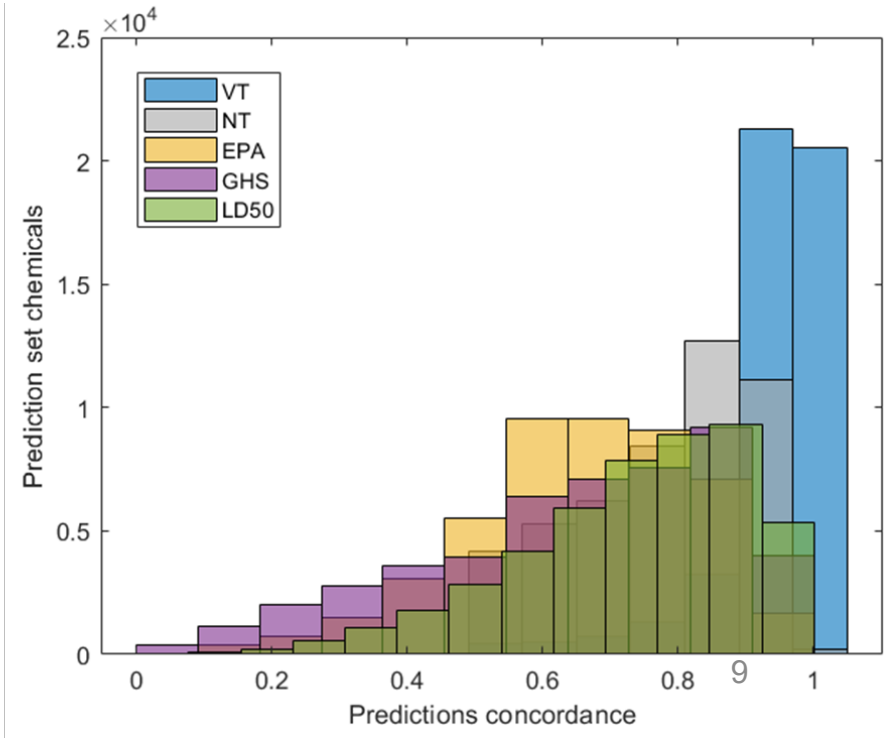
Coverage and concordance of the models

Consortium Comprised 35 Participants/Groups

- Very Toxic: 32 models
- Non-toxic: 33 models
- EPA categories: 26 models
- GHS categories: 23 models
- LD50: 25 models

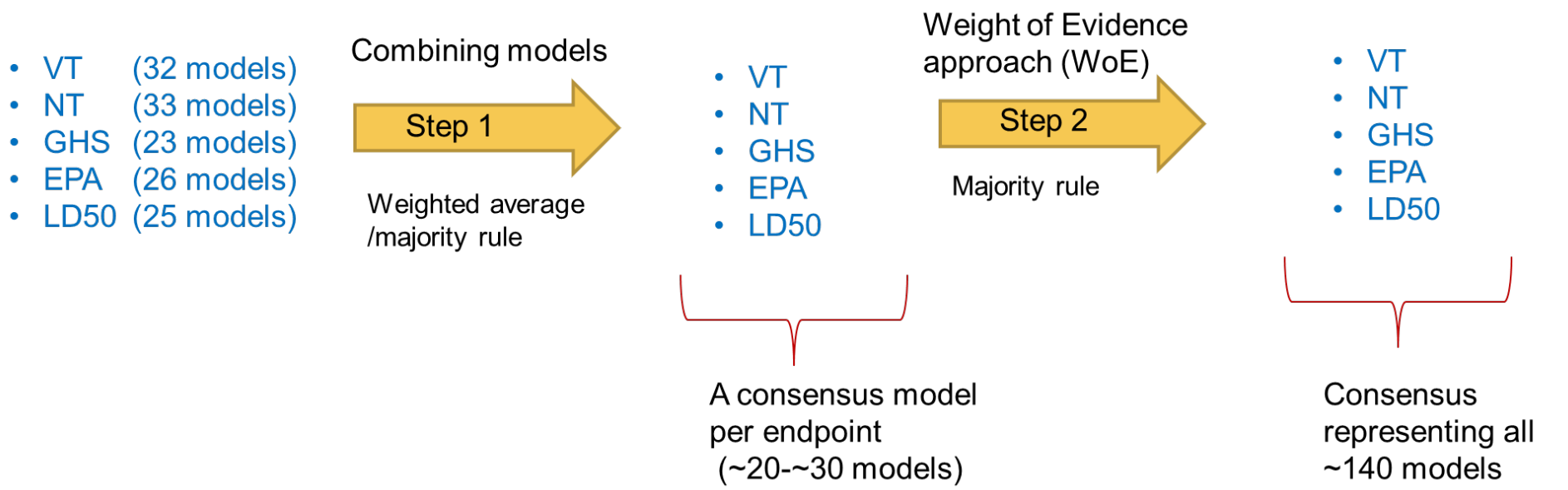
Total: 139 models





CATMoS consensus modeling

Steps of combining the single models into consensus



Learn more:

https://www.piscltd.org.uk/wp-content/uploads/2020/01/2020.01.22_CATMoS_Webinar.pdf
https://youtu.be/KjbTnfRTY-0

Performance Assessment

Consensus Model Statistics

	Very Toxic		Non-Toxic		EPA		GHS	
	Train	Eval	Train	Eval	Train	Eval	Train	Eval
Sensitivity	0.87	0.70	0.88	0.67	0.81	0.62	0.80	0.58
Specificity	0.99	0.97	0.97	0.90	0.92	0.86	0.95	0.90
Balanced Accuracy	0.93	0.84	0.92	0.78	0.87	0.74	0.88	0.74
***In vivo* Balanced Accuracy**	0.81		0.89		0.82		0.79	

	LD50 values		LD50 values
	Train	Eval	***In Vivo***
R2	0.85	0.65	0.80
RMSE	0.30	0.49	0.42

The consensus predictions perform just as well as replicate *in vivo* data do at predicting oral acute toxicity outcome

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.

Running CATMoS Consensus and other OPERA models

OPERA standalone application:

- Free, opensource & open-data
- Command line & Graphical user interface
- Single chemical and batch mode
- Multiple platforms (Windows and Linux)
- Embeddable libraries (java, C, C++, Python)
- **New: QSAR-ready standardization**

OPERA models:

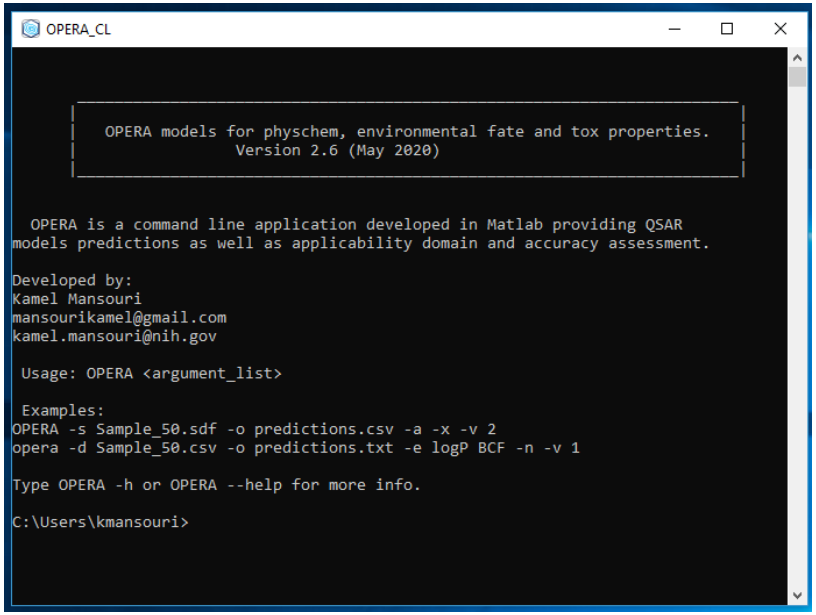
- Physicochemical properties
- Environmental fate
- ADME properties
- Toxicity endpoints

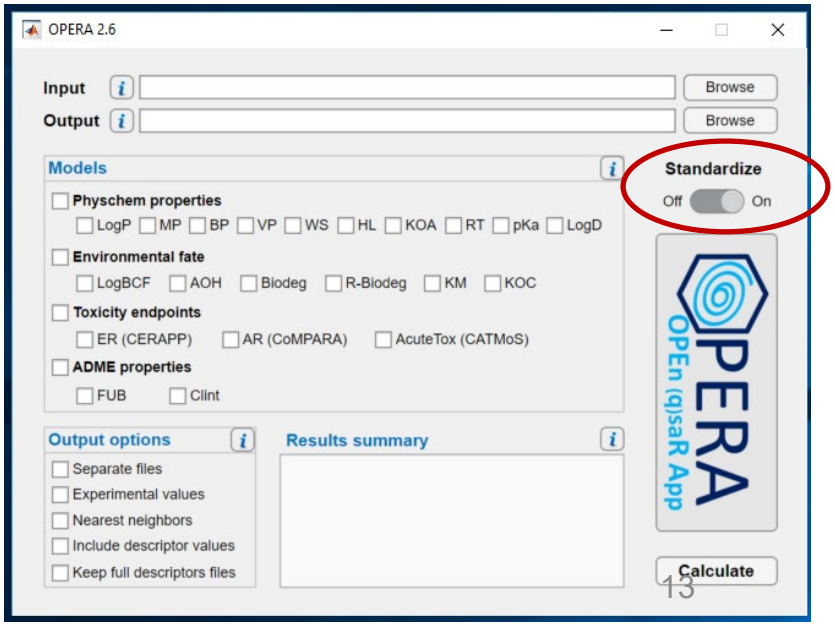
Input options:

- Structure IDs (CAS, DTXSID, InChIKey)
- Structure files (SMILES, SDF, Mol)

Links:

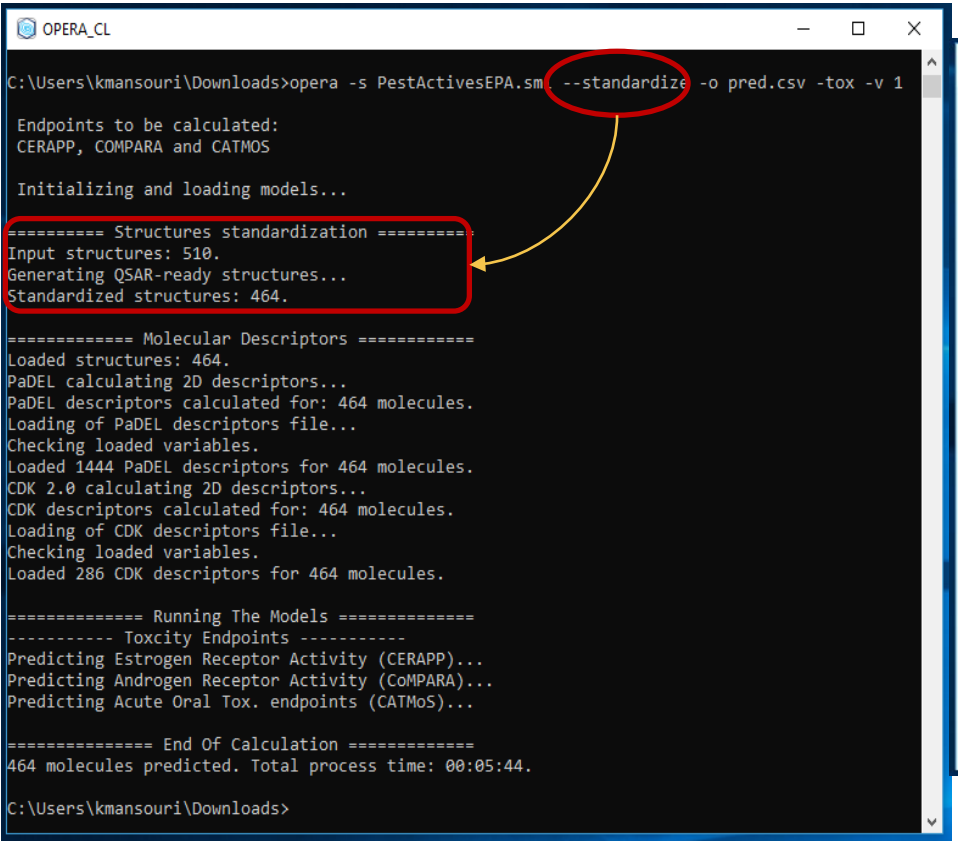
https://github.com/NIEHS/OPERA
https://ntp.niehs.nih.gov/go/opera
https://doi.org/10.1186/s13321-018-0263-1

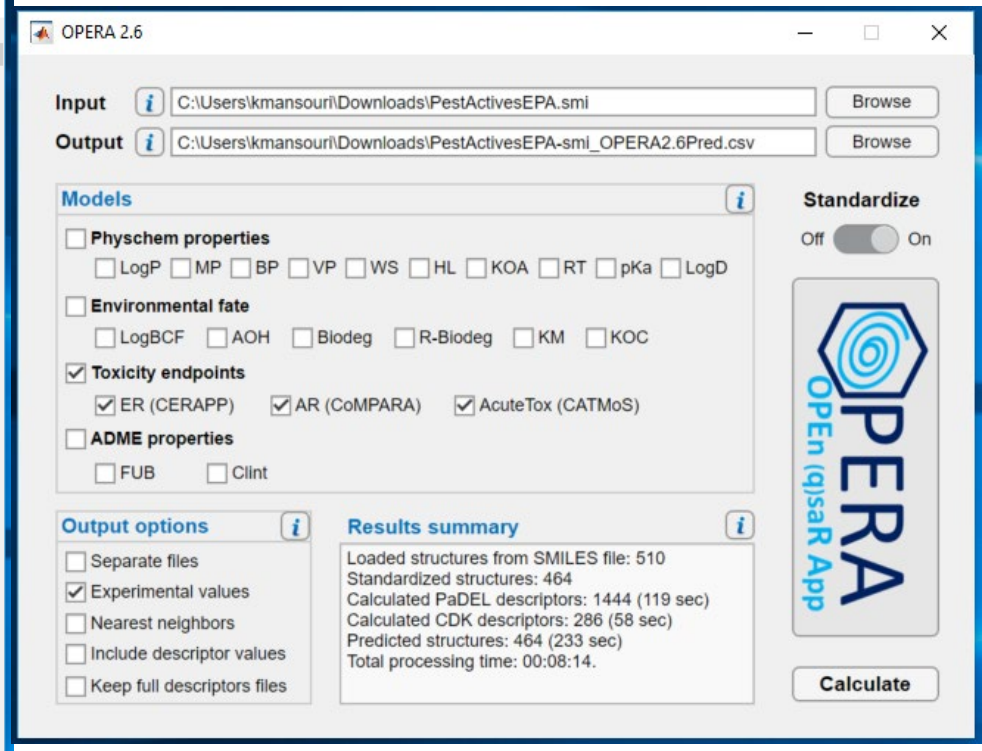




New in OPERA version 2.6

QSAR-ready standardization tool

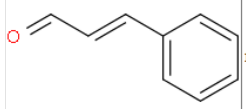
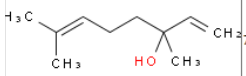
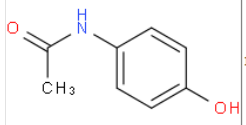
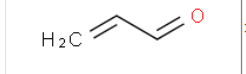
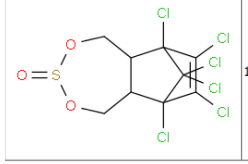




Command line

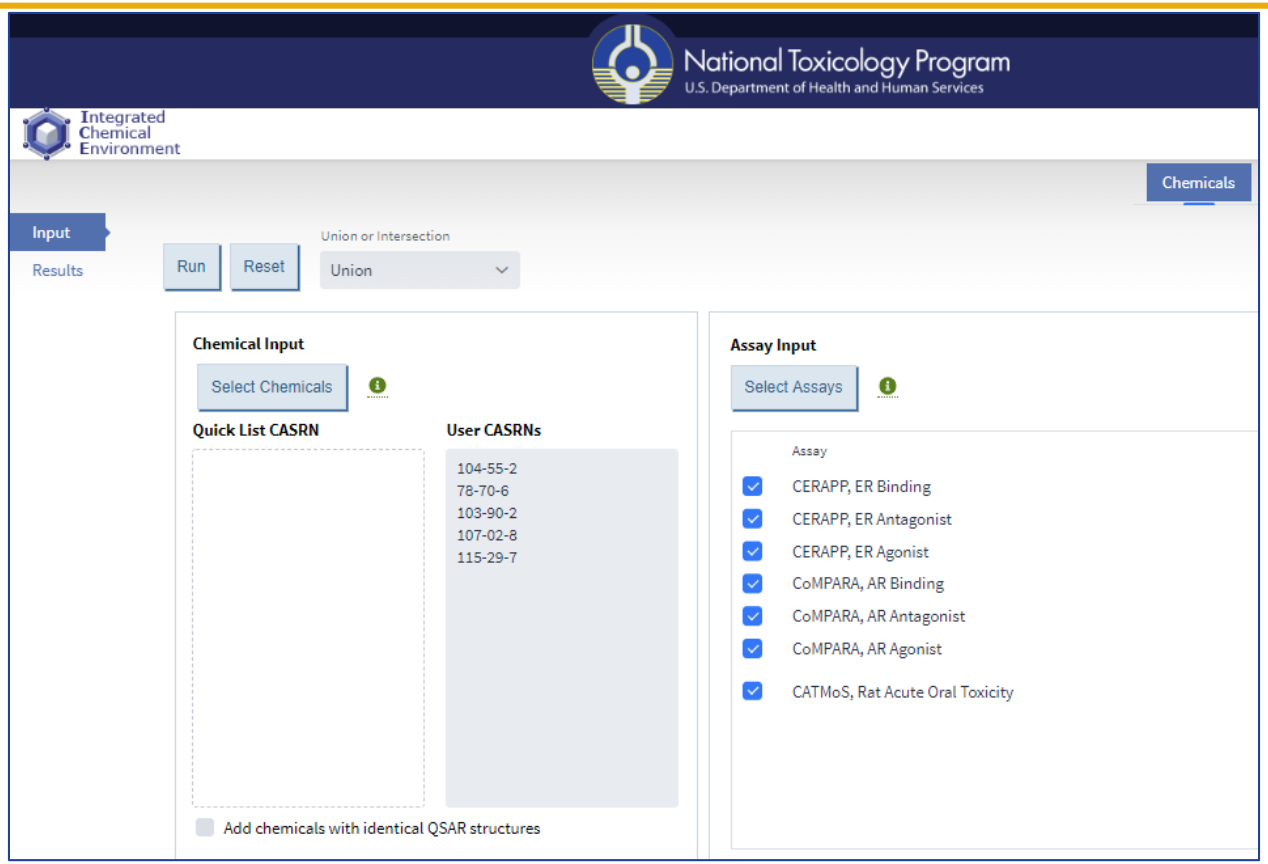
Graphical user interface

Example output

SMILES	MoleculeID	CATMoS_VT_pred	CATMoS_NT_pred	CATMoS_EPA_pred	CATMoS_GHS_pred	CATMoS_LD50_exp	CATMoS_LD50_pred	CATMoS_LD50_predRange	AD_CATMoS	AD_index_CATMoS	Conf_index_CATMoS
	104-55-2	0	1	3	5	2220	2,568	[1300-5100]	1	1	0.958
	78-70-6	0	1	3	5	2795	2,218	[1100-4400]	1	1	0.958
	103-90-2	0	0	3	4	501-5000	1,625	[810-3200]	1	1	0.964
	107-02-8	1	0	1	2	20	40	[20-80]	1	1	0.772
	115-29-7	1	0	1	1	NA	2.26	[1-4.5]	1	1	0.823

- Consensus predictions for the 5 endpoints
- LD50 confidence interval (based on in vivo data variability)
- Applicability domain assessment
- Experimental values, when available
- Nearest neighbors, optional

Predictions on NTP/ICE



https://ice.ntp.niehs.nih.gov/Search

Download | Query Mixtures | Clear Filter | Number of chemicals = 5

Substance Name	CASRN	DTXSID	CATMoS, Rat Acute Oral Toxicity LD50	CoMPARA, AR Agonist Call	CoMPARA, AR Antagonist Call	CoMPARA, AR Binding Call	CERAPP, ER Agonist Call	CERAPP, ER Antagonist Call	CERAPP, ER Binding Call
Acetaminophen	103-90-2	DTXSID2020006	1625	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Endosulfan	115-29-7	DTXSID1020560	2.26	Inactive	Inactive	Inactive	Inactive	Active	Active
3-Phenylprop-2-enal	104-55-2	DTXSID1024835	2568	Inactive	Inactive	Inactive	Inactive	Active	Active
Acrolein	107-02-8	DTXSID5020023	40	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Linalool	78-70-6	DTXSID7025502	2097	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive

The “3C” Concept at Work!

- Success of the projects was due in great part to the use of the 3C concept as well as up-front and continuous engagement of regulators in the process

Communication

Collaboration

Commitment

https://ntp.niehs.nih.gov/go/natl-strategy

Thank you for your attention!

Acknowledgements

- EPA/CCTE
- ICCVAM Acute Toxicity Workgroup
- NTP/NICEATM
- ILS
- ScitoVation
- All international collaborators

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- The Lush Prize 2017, young researchers, supporting animal free testing.