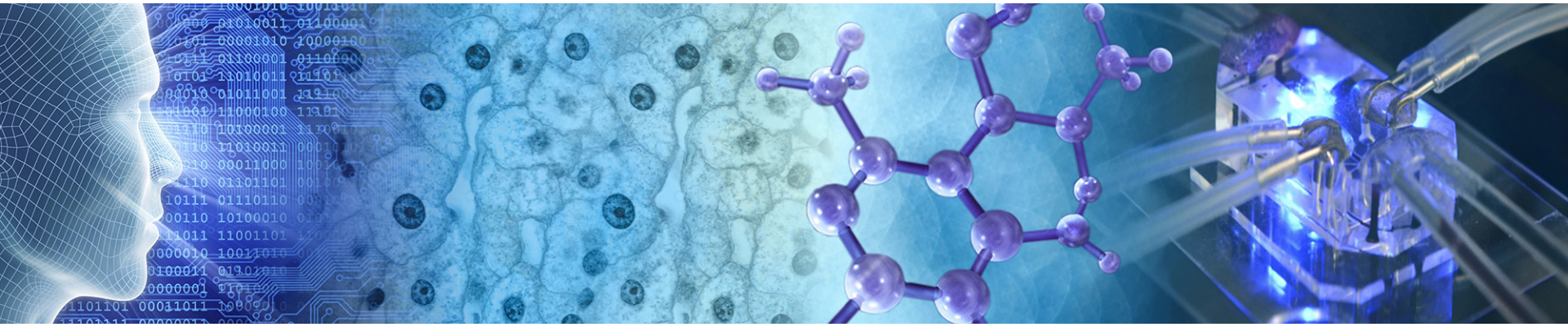
NTP
National Toxicology Program



Application of CATMoS to Ecological Risk Assessment

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The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of US EPA or any federal agency.

Motivations

- Organic **pollutants** with exposure potential may **accumulate** in body tissues
  - ➢ Cause **toxic effects** to wildlife and humans
- **Several toxicological endpoints**
  - ➢ Important to **risk assessment** of chemicals
- Existence of **gaps in the experimental data** for environmental endpoints
  - ➢ Need to fill the data gaps and bridge the **lack of knowledge**
- **Regulatory** requirements:
  - ➢ Reduce **animal** testing**, time** and **costs**

Alternative

(Q)SAR

=

(Quantitative) Structure-Activity Relationship

IN SILICO

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. (https://doi.org/10.1289/EHP8495)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Endocrine Disruptor Screening Program

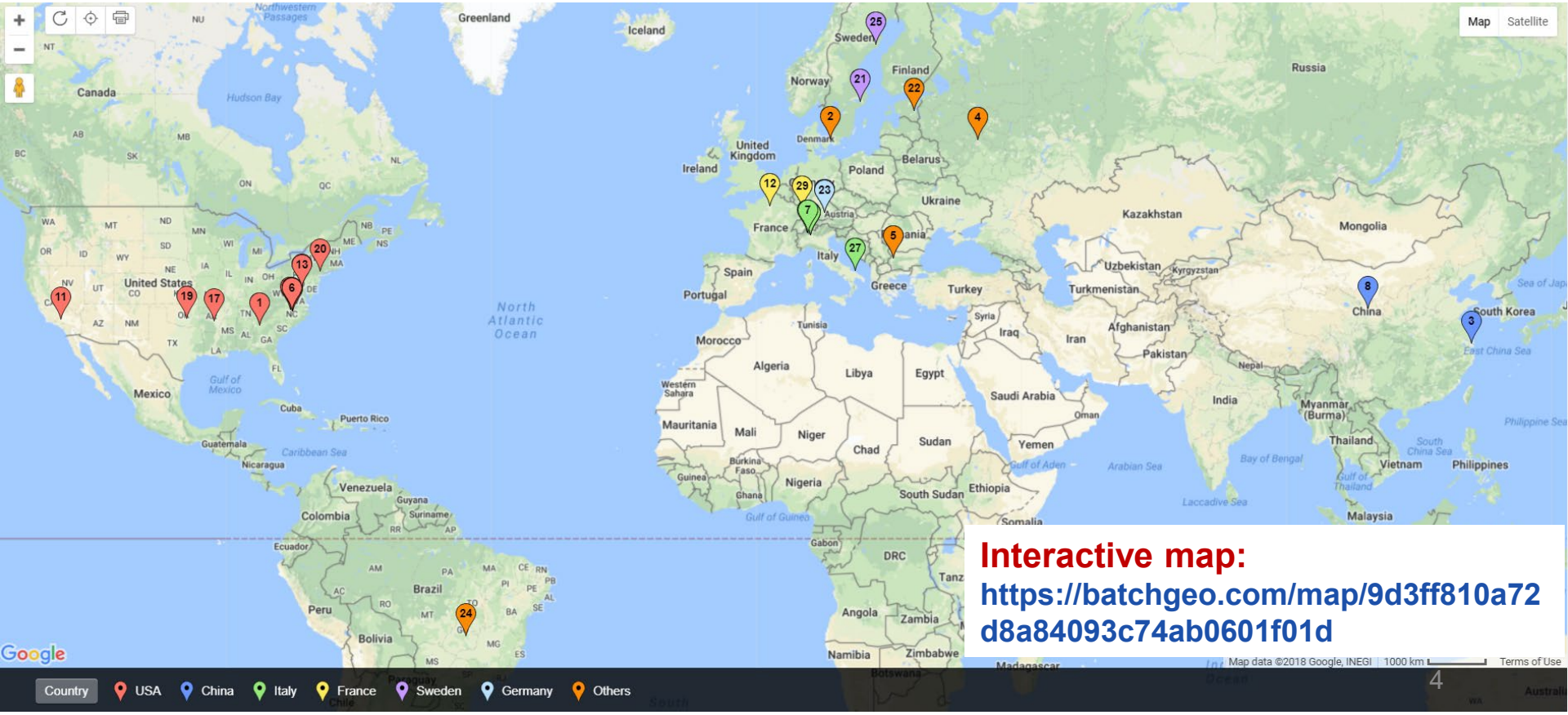
UNITED STATES ICCVAM Advancing Alternatives to Animal Testing

Acute Toxicity Workgroup: alternative methods

ICCVAM: Interagency Coordinating Committee on the Validation of Alternative Methods

International Collaborators

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



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

Contents lists available at ScienceDirect

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

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)

Hazard

OSHA®

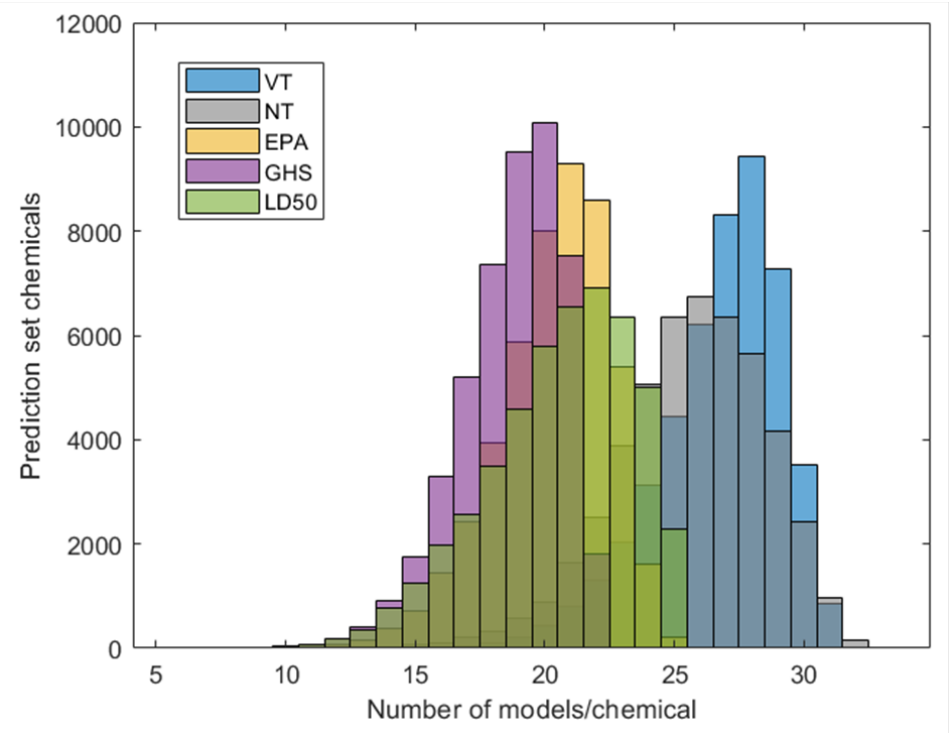
Hazard

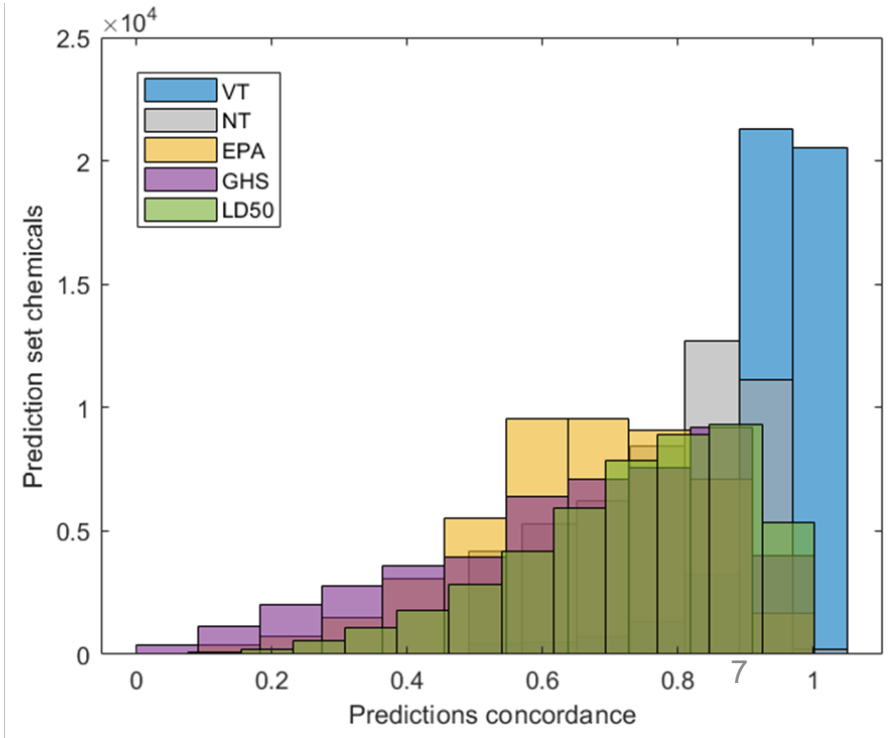
Coverage and concordance of the models

Consortium Comprised 35 Participants/Groups

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

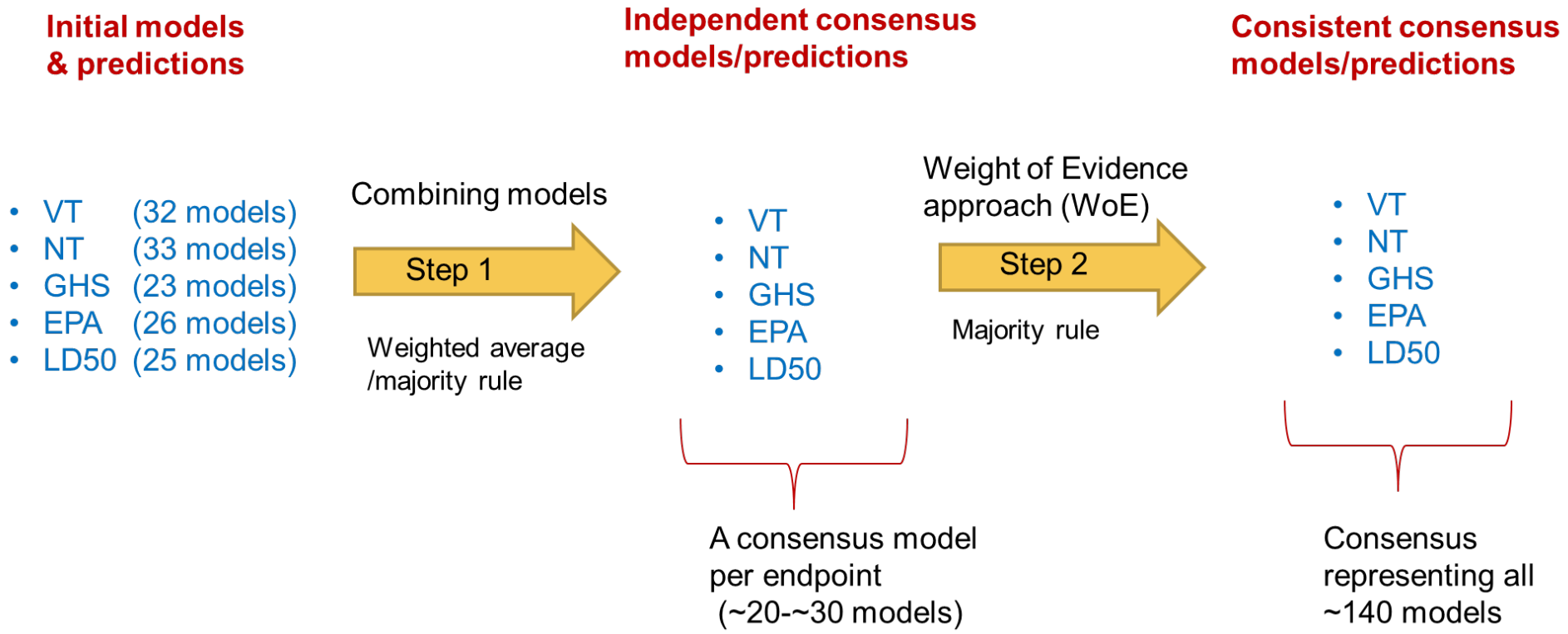
Total: 139 models





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

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:

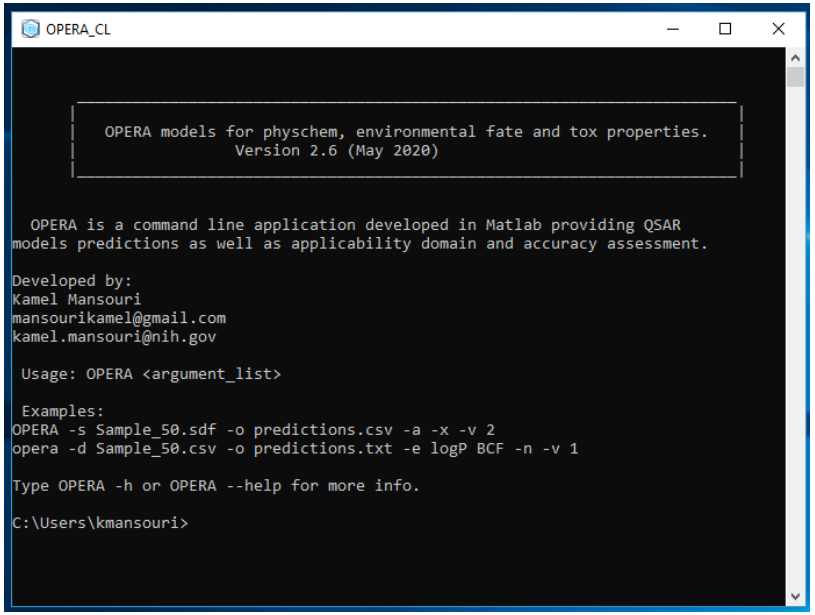
- Physicochemical properties
- Environmental fate
- ADME properties
- Toxicity endpoints

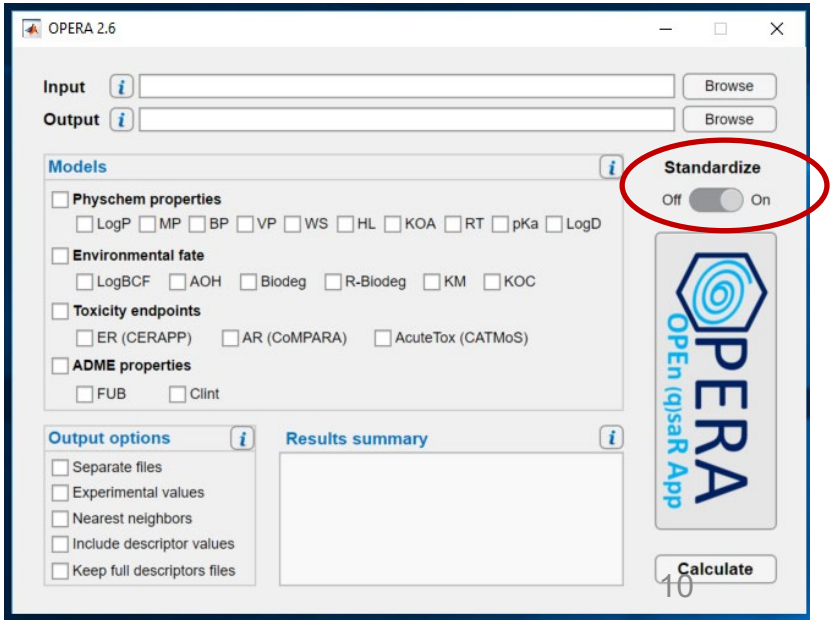
Input options:

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

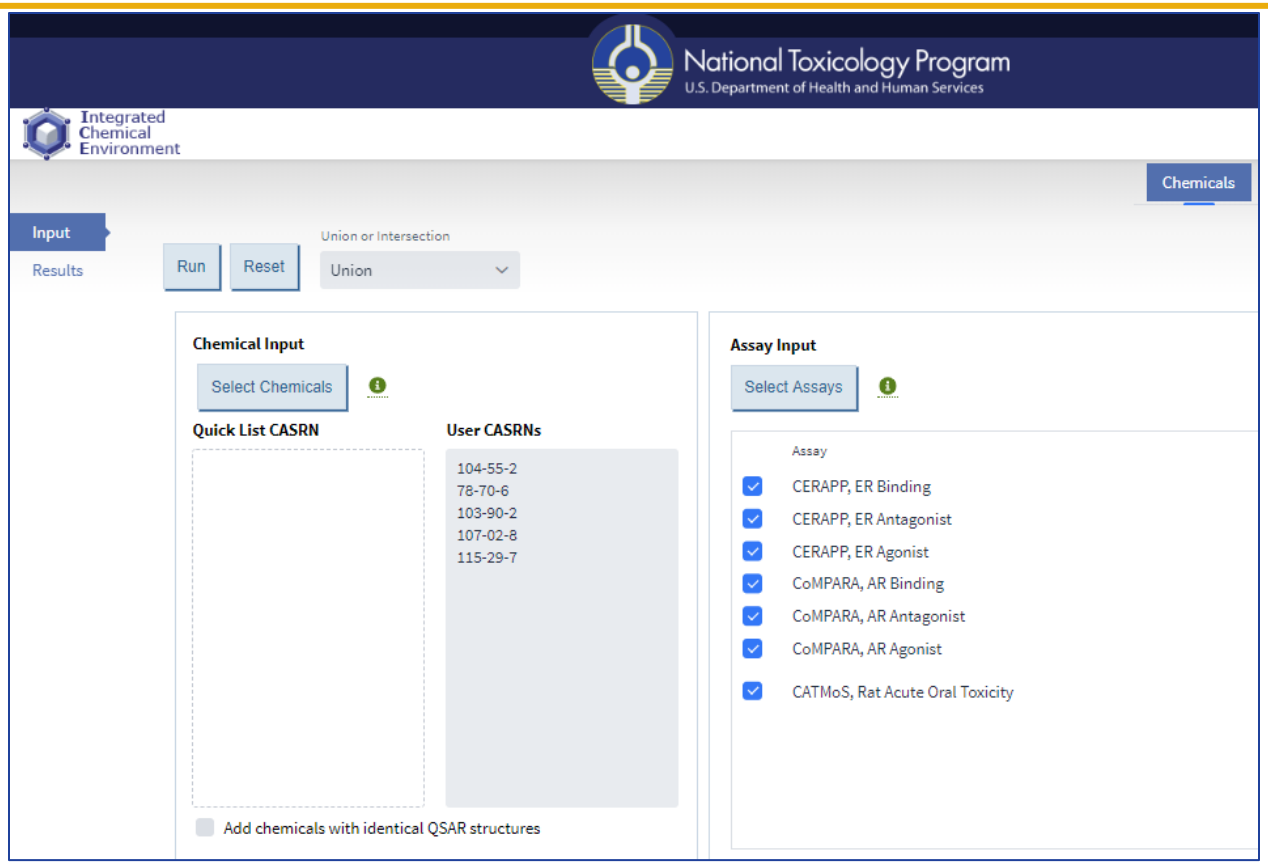
Links:

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





Predictions on NTP/ICE

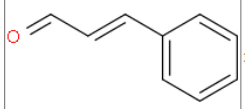
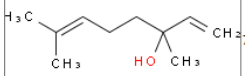
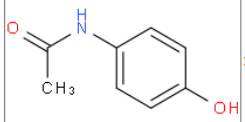
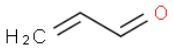
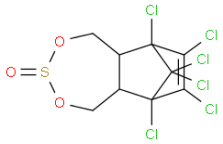


https://ice.ntp.niehs.nih.gov/Search

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

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

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	195
DOT	3671	FDA CFSAN	22

Progress made with EPA EFED and Humane Society of the US:

- Compared mammalian acute toxicity risks based on CATMoS predictions to those based on rat LD50 tests for 178 pesticides registered in the last 25 years.
- Determined overlap and discordance leading to additional curation of the data and prediction assessments.

The dataset: collection and curation

Initial steps:

- Initial list of 195 pesticides registered from 1998 to 2020
- Rodenticides and soil fumigants were removed
- Entries with conflicting or inadequate information were removed
- Certain entries adjusted or corrected based on alternate resources.

Curated dataset:

- Final list included 178 conventional pesticides
- 57 with LD50 point estimate values. Range: 62 mg/kg to >7500 mg/kg
- 121 with limit test LD50. 42 estimated at >2000 mg/kg and 79 at >5000 mg/kg
- 140 pesticides with publicly-available ecological RAs

EPA category	**I**	**II**	**III**	**IV**
Pesticides	0	12	84	82

The evaluation and analysis

The approach:

- Quantitative: Comparing risk quotients (RQs) based on predicted and empirical rat LD50s as available in the RAs (N = 100)
- Semi-quantitative: comparison made on worst-case scenario (N = 12)
- Qualitative: pesticides with no RAs or RQs calculated (N = 66)

The analysis steps:

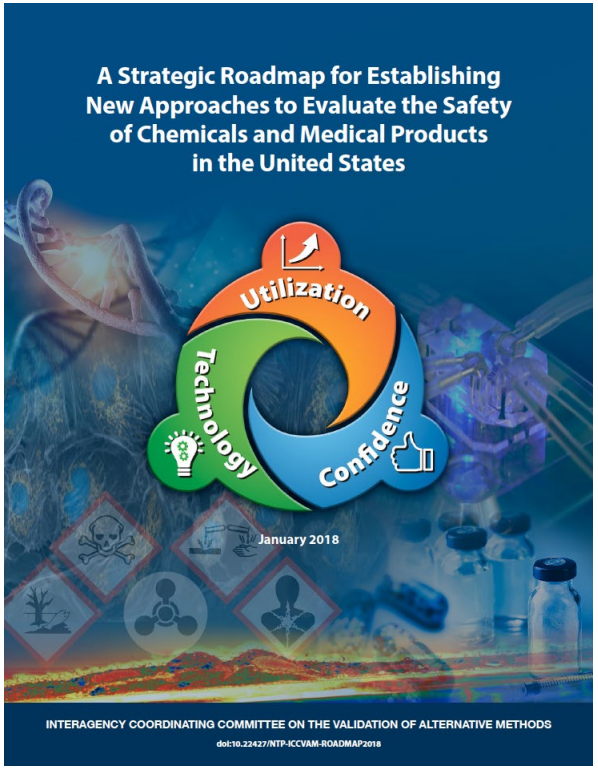
- Evaluate concordance of empirical LD50s values used in the ecological RAs Vs the input data used for developing CATMoS
- Identify the CATMoS predictions that would and would not have affected the acute mammalian toxicity RA of the analyzed pesticides
- Characterize the model's success in predicting risk in all or some of the exposure scenarios
- In discordant cases, identify whether the model tends to be more or less conservative than the available RAs.
- Use the quantified margin of uncertainty around in vivo LD50s to estimate the overlap between predictions and empirical values

Next steps and goals

- Evaluate the applicability of CATMoS estimates as a potential replacement of the rat acute single oral dose study for establishing the effects endpoint in ecological risk assessments of conventional pesticides
- Iterative evaluation process to determine how and under what scenarios CATMoS may or may not be able to inform any future data needs for in vivo studies

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

- Patricia Bishop (Humane Society of the US)
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- Amy Blankinship (EPA)
- Nicole Kleinstreuer (DNTP/NICEATM)
- David Allen (ILS)

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