AFRL

PREDICTIVE RISK APPROACHES FOR OPERATIONAL CHEMICAL RISK ASSESSMENT

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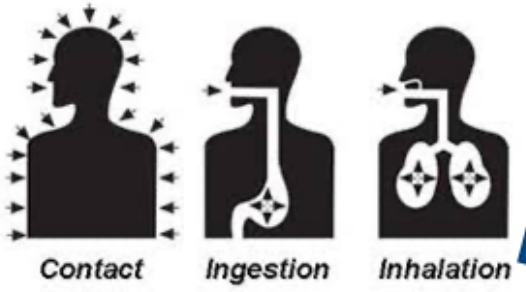
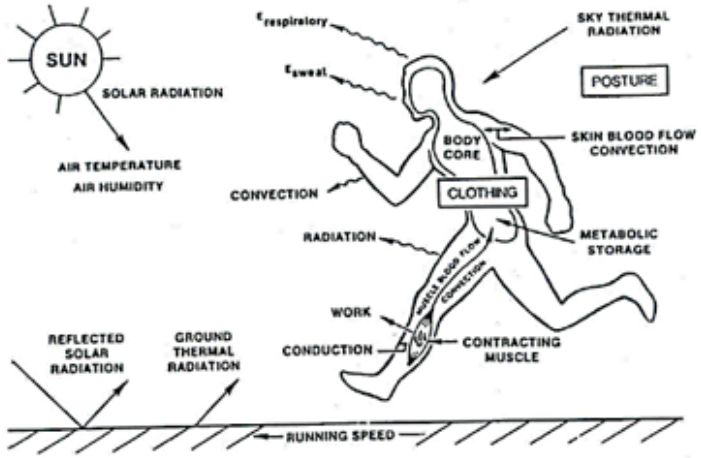
Operational Chemical Risk Assessment



ISBN 978-81-947760-7-9



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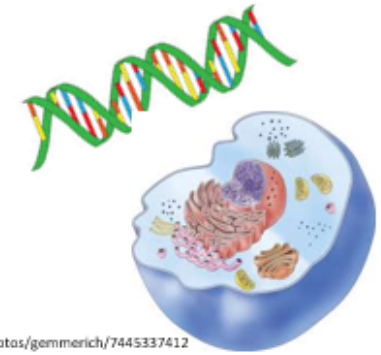

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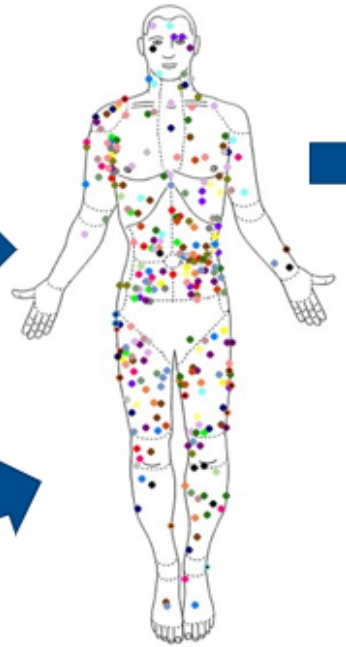

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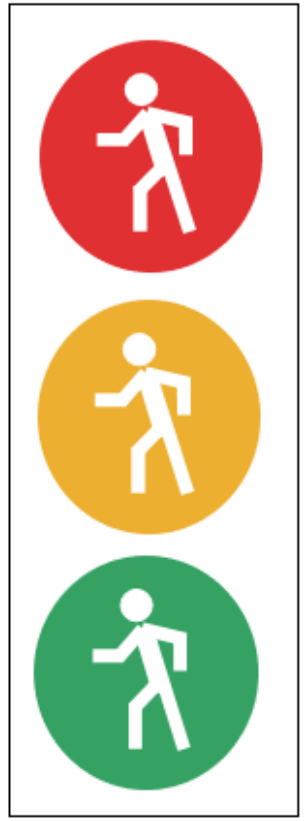
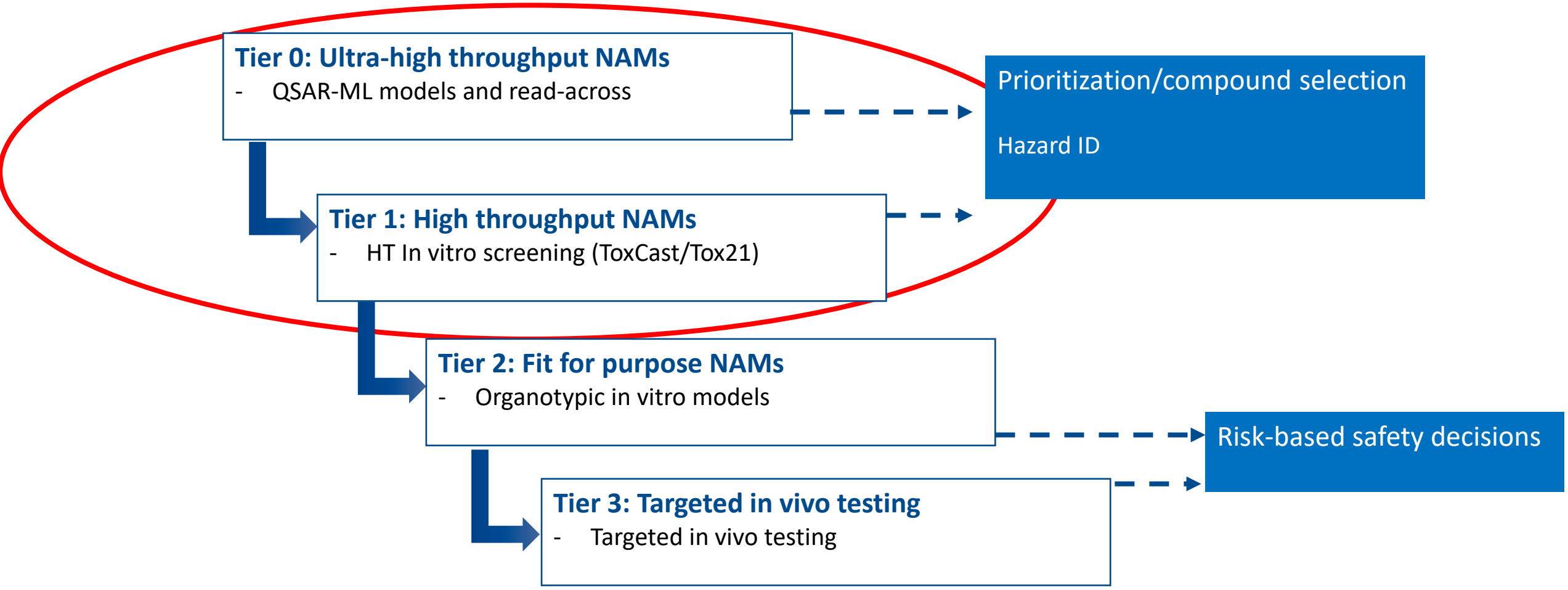
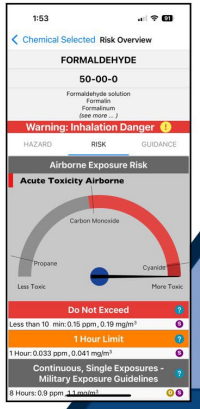


Modernized Tiered Risk Assessment



Predictive Risk Products



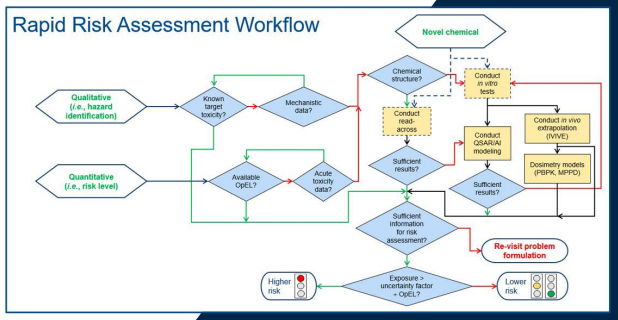
ToxAdvisor-lite
(Mobile app)

- Exposure guidelines
- Risk predictions
- Recommend next steps

Adapted from https://pxhere.com/en/photo/937444
https://commons.wikimedia.org/wiki/File:Lax_33014_elife-33014-fig6-v1.jpg

CERA toolbox
(Desktop application)

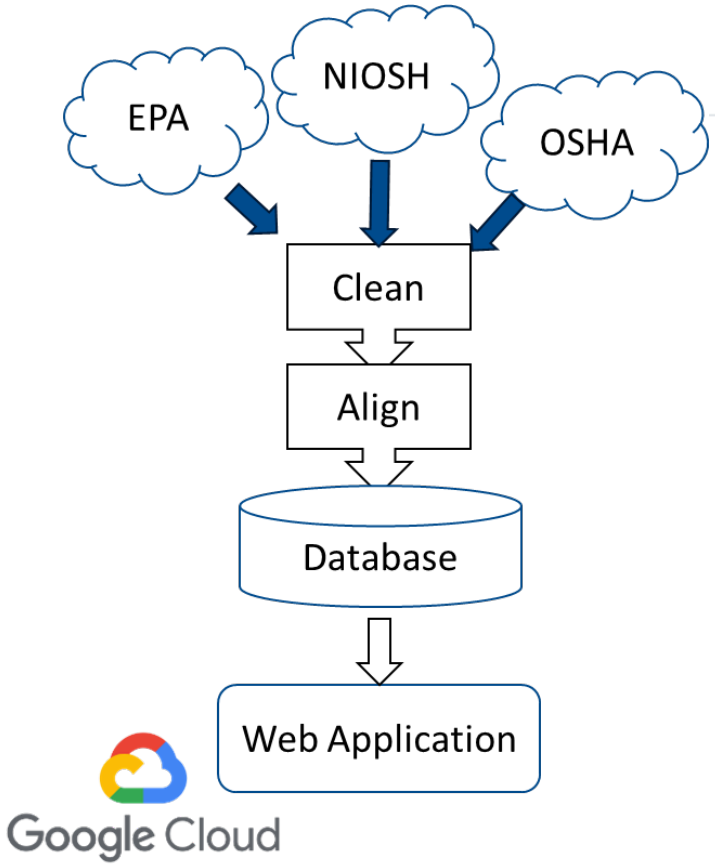
- Exposure guidelines
- Curated risk predictions and models
- Risk calculations, workflows



Predictive Risk Capability Build

- Databases
- Risk prediction models
- Dosimetry models
- Exposure models
- Risk assessment workflows

Chemical Exposure Risk Assessment (CERA) Database



Chemical Exposure Risk Assessment (CERA) Database

Batch Search Results (221)

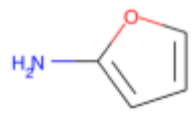
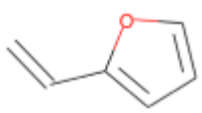
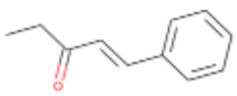
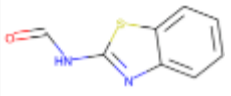
Download Full CSV

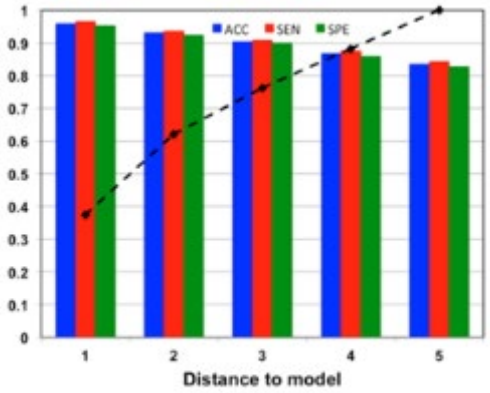
Search Term	Matches	Chemical Name	CAS
(+/-)-cis-Permethrin 61949-76-6	0	⚠ No matches found	
Permethrin 52645-53-1	1	Permethrin	52645-53-1
Trans-Permethrin 61949-77-7	0	⚠ No matches found	
Formaldehyde	7	⚠ Ambiguous search term Select Chemical(s)	
Cyfluthrin 68359-37-5	1	Cyfluthrin	68359-37-5

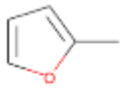
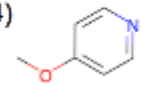
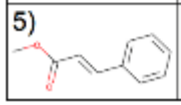
QSAR-ML Models for Acute Toxicity & Risk Mitigation

- Oxidative stress

Structural Alerts + Message Passing Neural Network Model (MPNN) → DrugBank repository

			
c1c(c(oc1N))		C=Cc1ccco1	
57	1	50	0.94
			
CCC(=O)C=Cc1ccc(cc1)		C(=O)Nc1nc2ccccc2s1	
28	1	26	1



1) 	Nitrofurantoin, Dantrolene, Mometasone furoate, Trioxsalen, Nitrofural, Benziodarone, Kinetin, Fluticasone furoate, Nifurtimox, Cefuroxime, Lapatinib, Diloxanide furoate
2) 	Alitretinoin, Tretinoin, Isotretinoin, Gestrinone, Acitretin, Medrogestone, Dydrogesterone, Colchiceine, Nomegestrol acetate, Cyproterone acetate, Ceftobiprole, Ceftobiprole medocaril
3) 	Tioconazole, Sitaxentan, Clotiazepam, Sertaconazole, Relugolix, Avatrombopag, Lornoxicam, Rivaroxaban, Lotilaner
4) 	Lansoprazole, Dexlansoprazole, Omeprazole, Esomeprazole, Rabeprazole, Simeprevir, Pantoprazole
5) 	Cinoxate, Octinoxate, Amiloxate, Rescinnamine, Ethyl ferulate

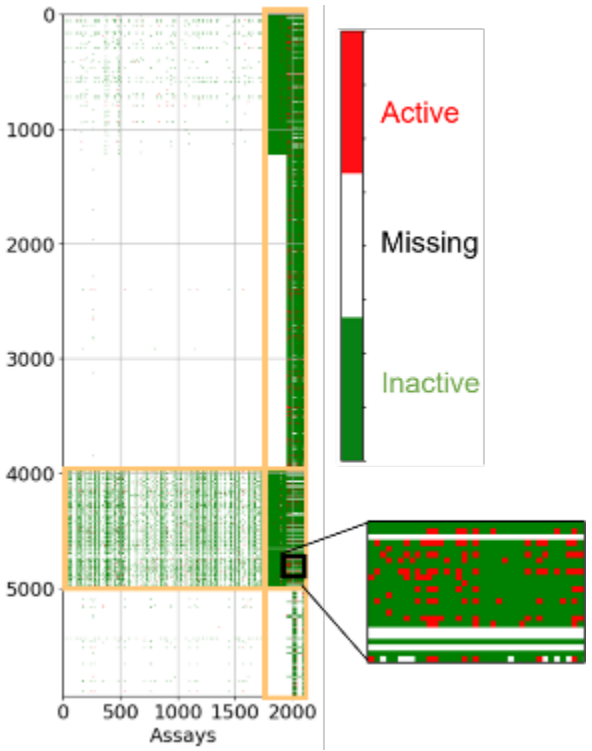
Models in development for:
Lung
Kidney
Neurotoxicity

At distance 0.3, 76% ACC = 0.90, SEN = 0.91 and SPE = 0.90, for 76% of chemicals

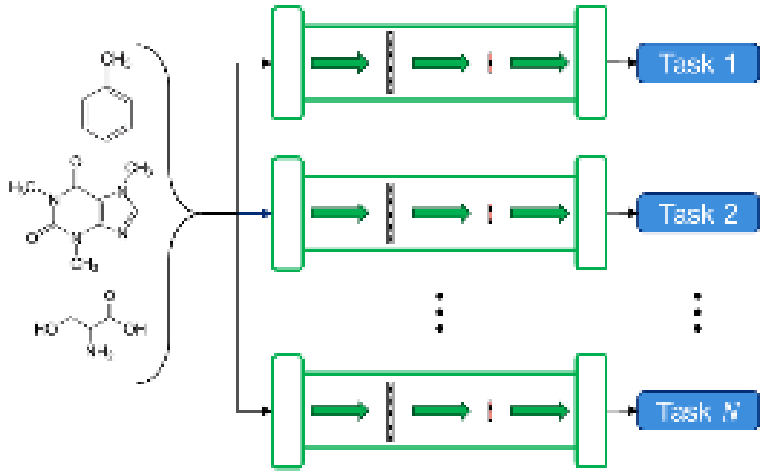
Chushak and Clewell 2024
https://doi.org/10.1016/j.ailsci.2024.100097

Multi-tasking ML Models for Data Poor Endpoints
(with JHU APL)

Available data

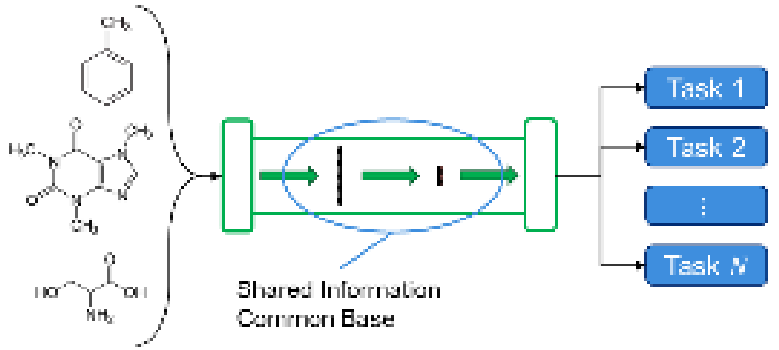


Single-Task (ST)



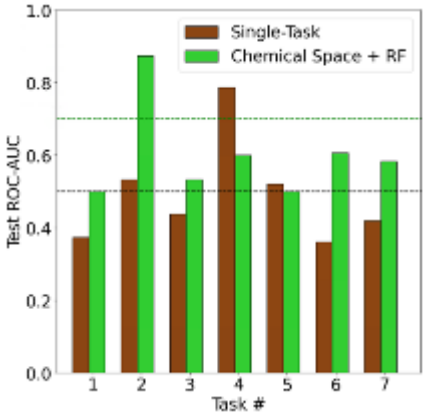
One Model per Task

Multi-Task (MT)



One Model for Multiple Tasks

ST vs. MT – low density data

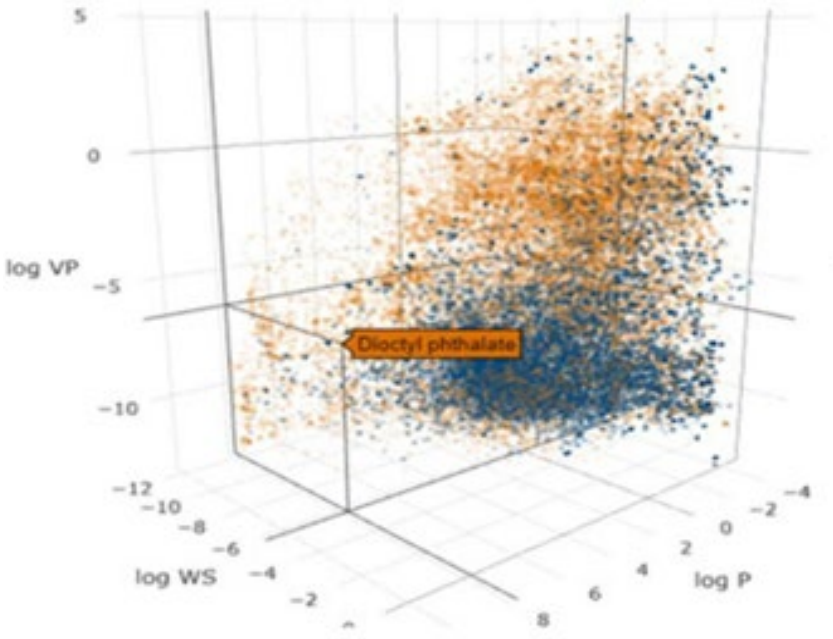


Main Goal: Generalizable prediction models

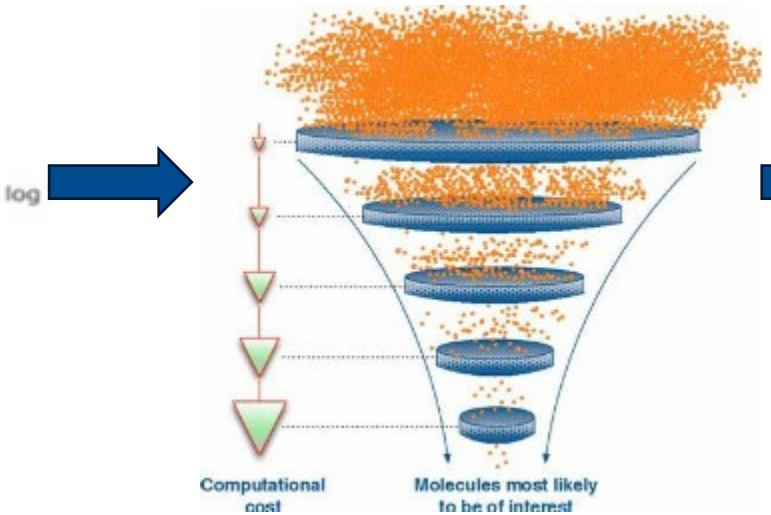
ML Models to Identify Minimum Tests for Novel Chemicals

(with RTI International)

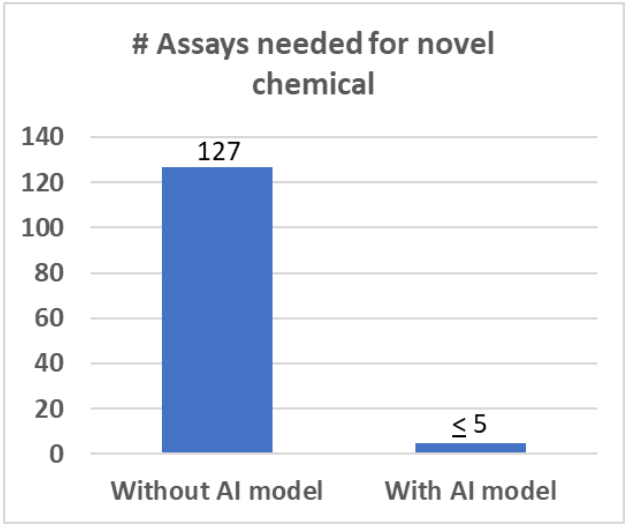
Main Goal: Strategy to maximize efficiency of testing for chemical risk



https://doi.org/10.3389/ftox.2022.894569



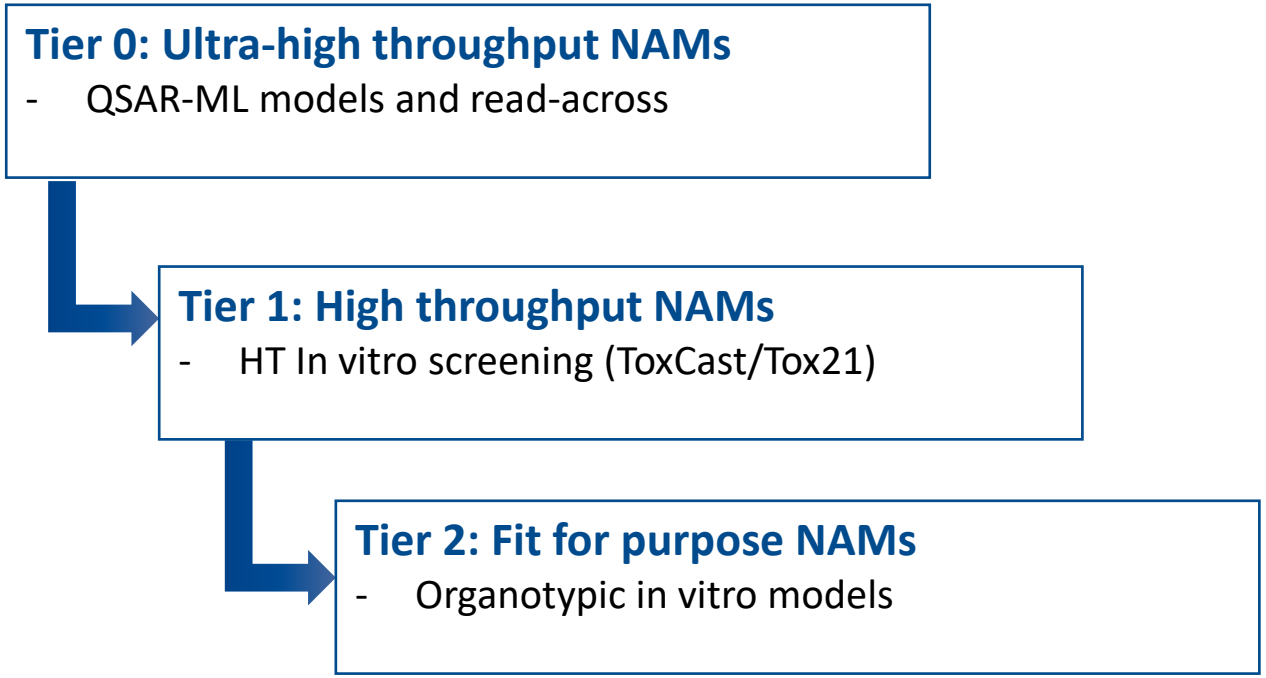
https://doi.org/10.1016/j.commatsci.2019.02.040



Edwards et al., 2022, PMID: 35295211

Case Study - Tiered Screening for Rapid Assessment of Novel Chemicals
(With JHU APL)

Main Goal: Validate utility of tiered assessment developed by the PRCB

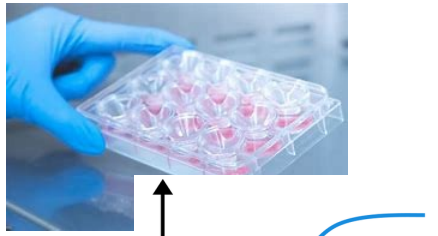


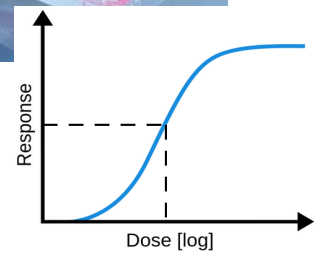
Rapid Dosimetry Models for In Vitro Tests

(Collaboration with USEPA)

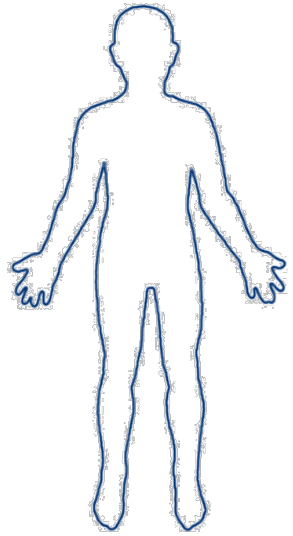
Main Goal: Enable rapid estimate of exposure limits for chemicals with in vitro data – in population of interest

- AF population
- Space flight





https://www.iecfrance.com/en/in-vitro-testing/



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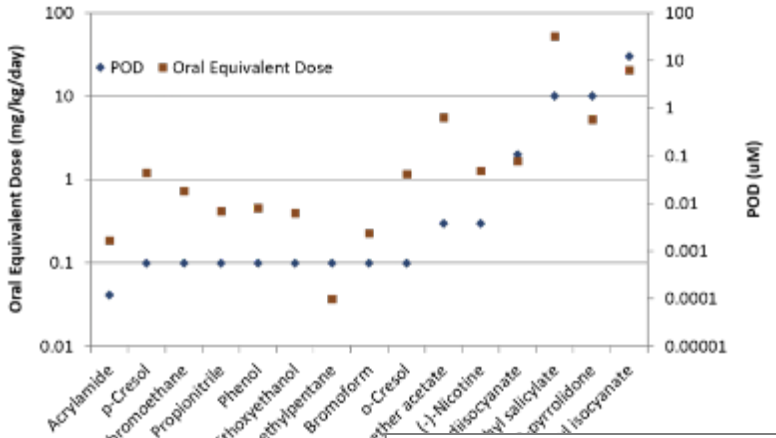
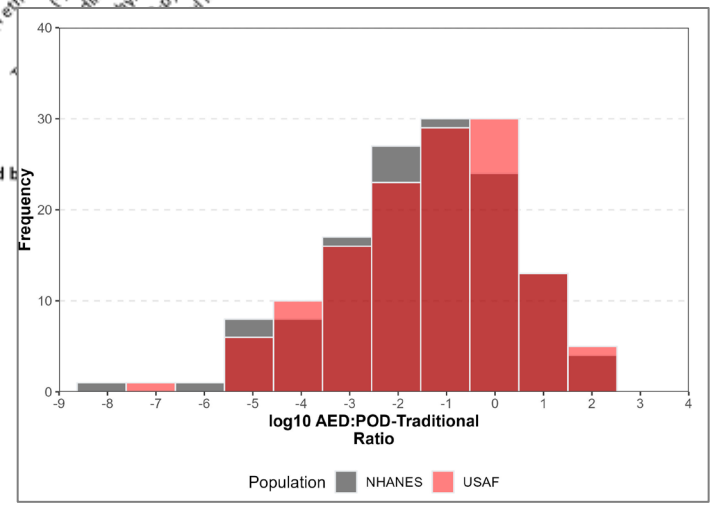
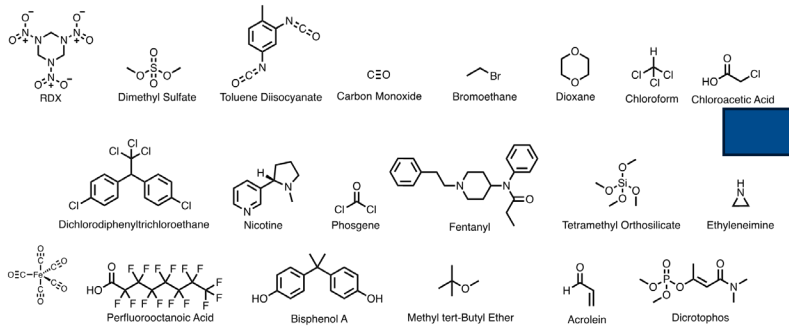




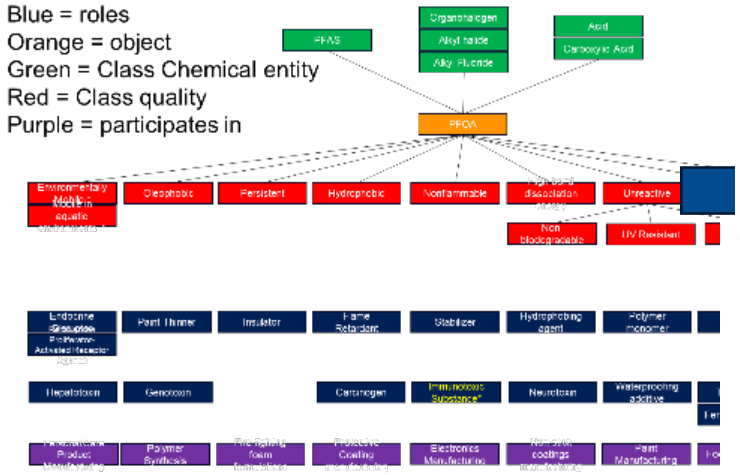
Forecasting Emerging Threats – AI- NLP Search and Analysis
(With JHU APL)

Main Goal: Proactively identify threats to Force health before they are widely incorporated into military materiel and processes

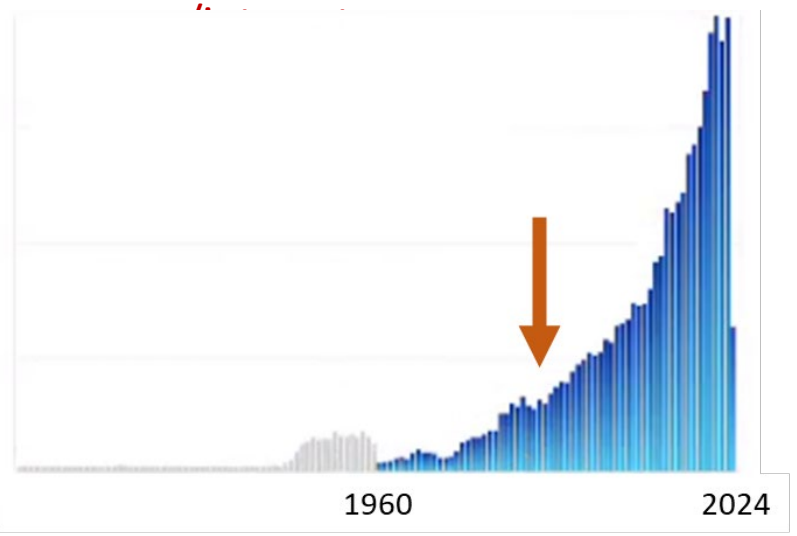
1) Identify classes of chemicals useful to AF



2) Build ontologies

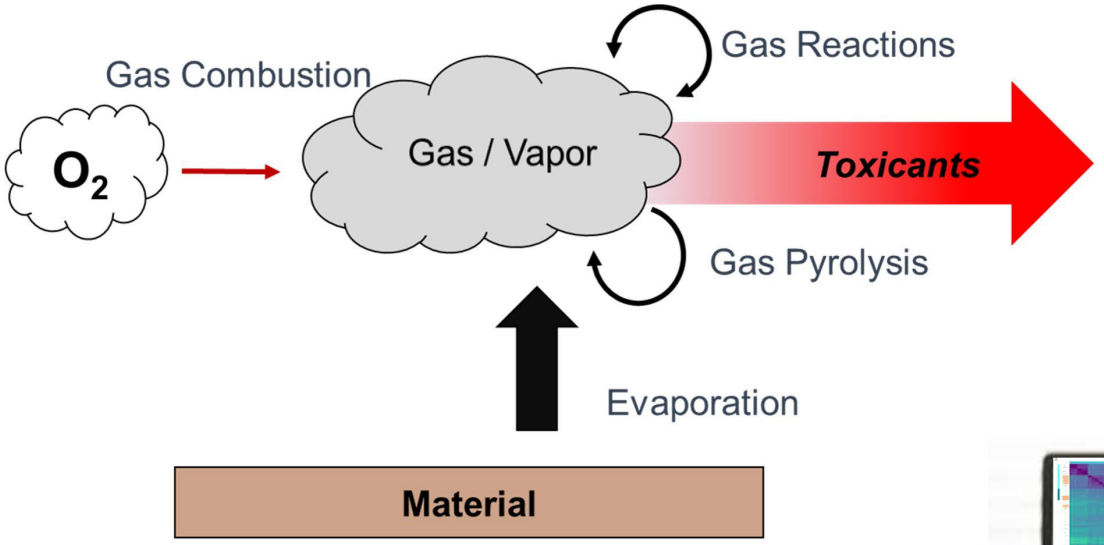


3) Citation burst indicates increased



4) Evaluate emerging chemicals in predictive risk models

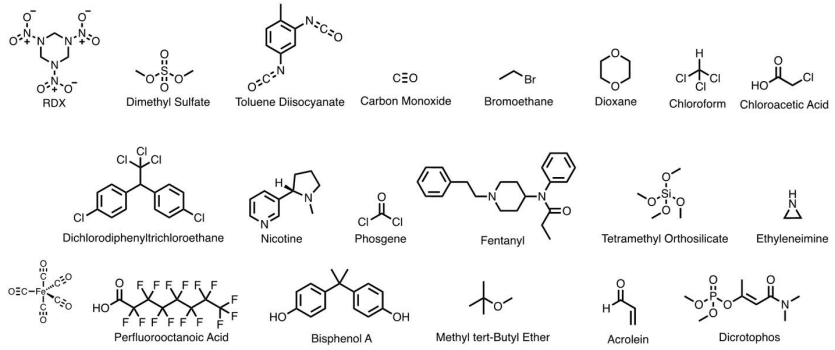
Predictive Chemistry for Thermal Degradation
(With JHU APL)



https://www.dvidshub.net/image/3530557/firefight er-exercise

https://www.dvidshub.net/

Adapted from https://pxhere.com/en/photo/937444
https://commons.wikimedia.org/wiki/File:Lax_33014_elife-33014-fig6-v1.jpg



Predictive Risk Team

AFRL/RHBAF

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- Nam Le
- Phillip Koshute
- Jordan L. Wesley

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- Stephen Comaty (DCPH-A)
- Matt McAtee (DCPH-A)
- John Reichard (NASA)
- John Wambaugh (USEPA)
- Caroline Ring (USEPA)
- Jayme Coyle
- Jeff Gearhart
- Janiece Hope
- Mike McCarthy
- Elaine Merrill
- Darrin Ott
- Megan Steele

Chemical Risk Assessment – past, present, and future

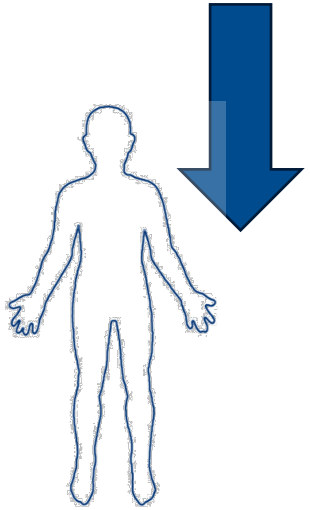
Pre-1970

http://resource.nlm.nih.gov/101447556

1901 – FDA “poison squad”
1906 – Pure Food and Drug Act -> FDA
1970 – Formation of EPA

1970-2000s

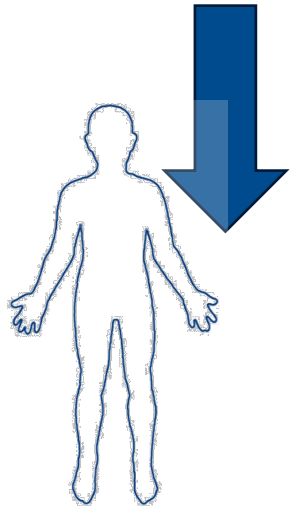
https://commons.wikimedia.org/wiki/File:Rat_togopic.png



https://www.deviantart.com/greyback-squirell/art/how-bout-deep-158236397

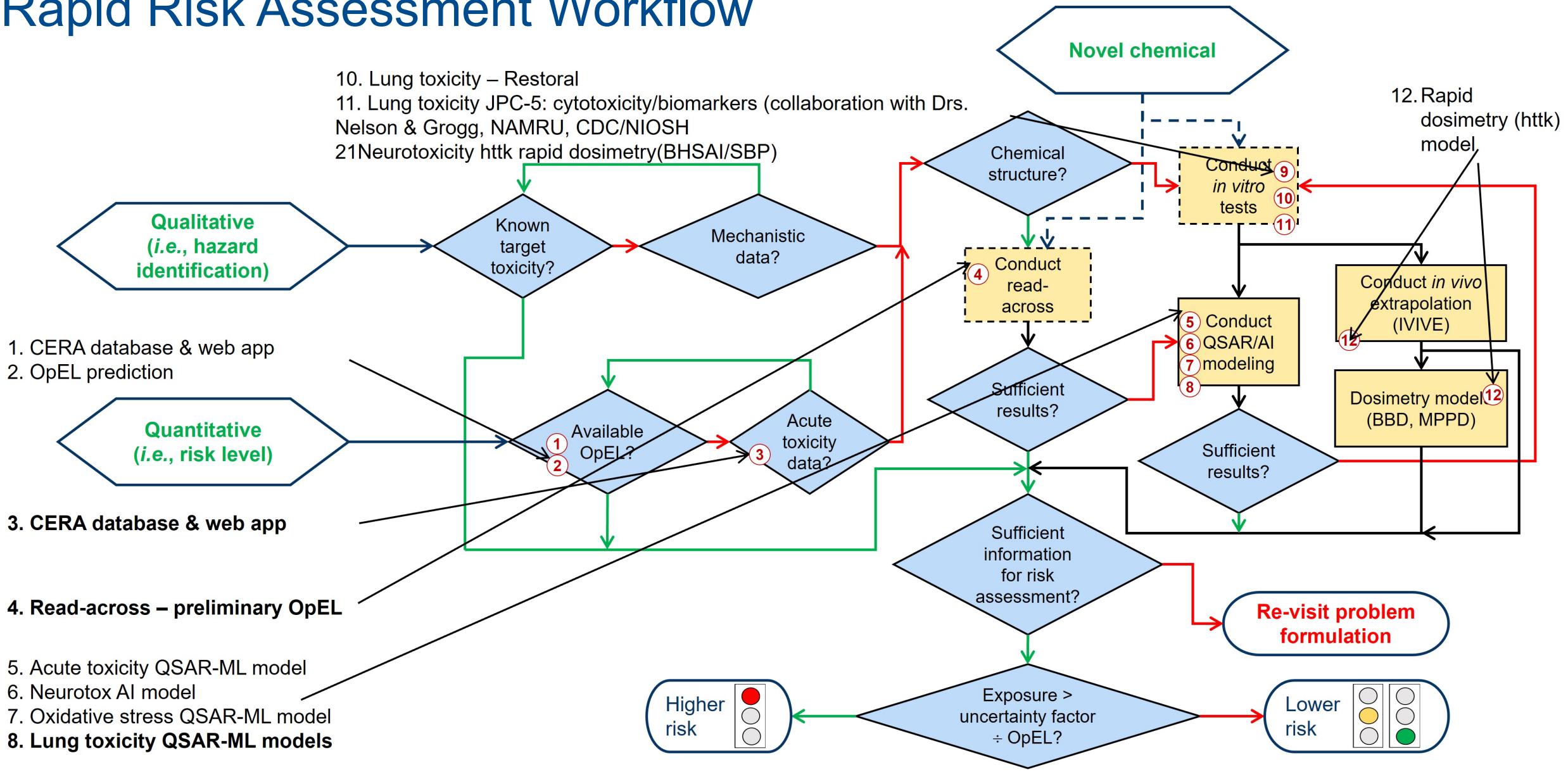
2000s & going forward

https://www.iecfrance.com/en/in-vitro-testing/

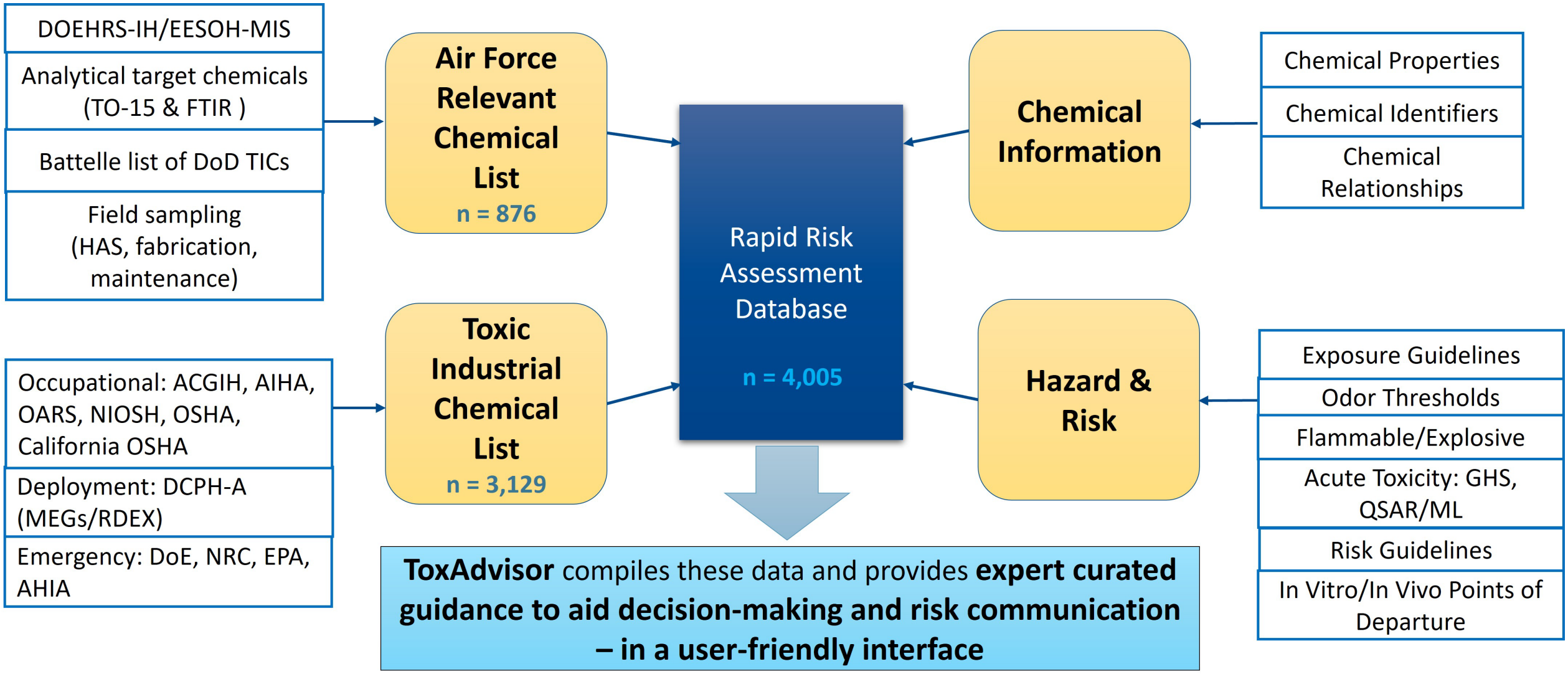


https://www.deviantart.com/greyback-squirell/art/how-bout-deep-158236397

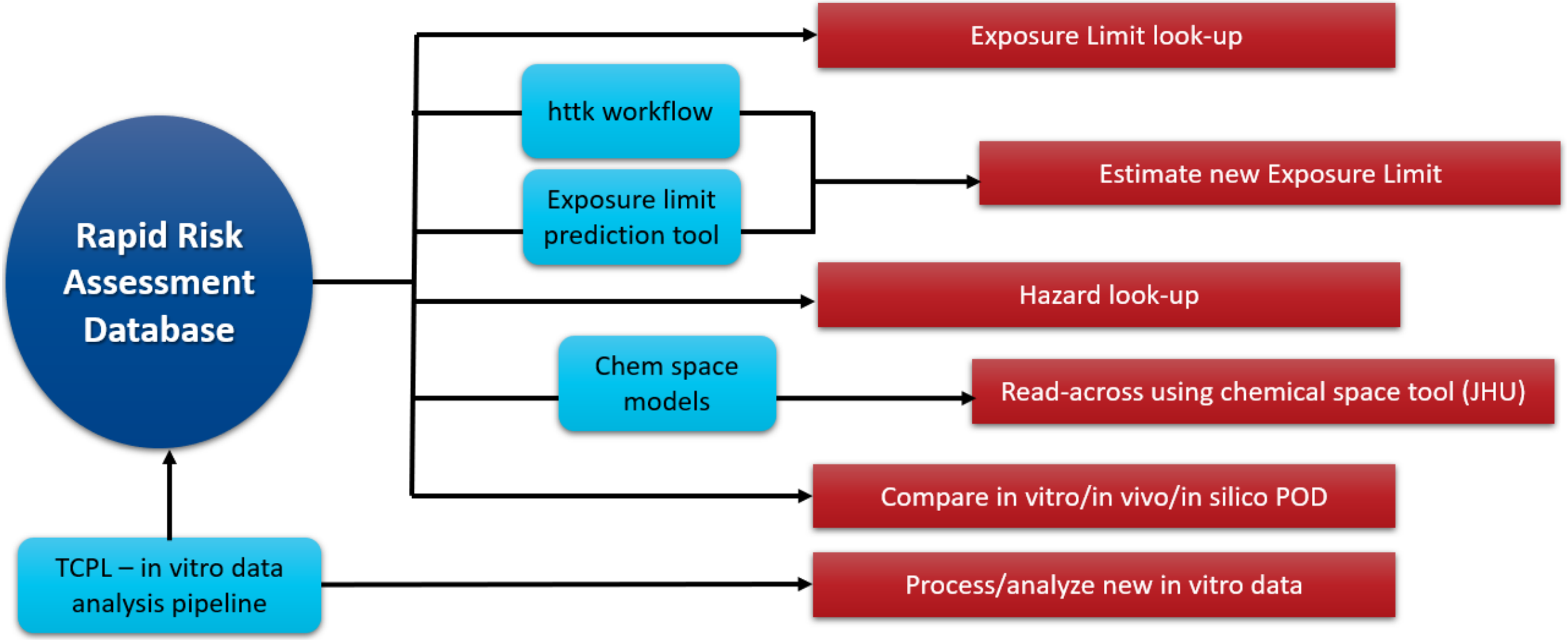
Rapid Risk Assessment Workflow



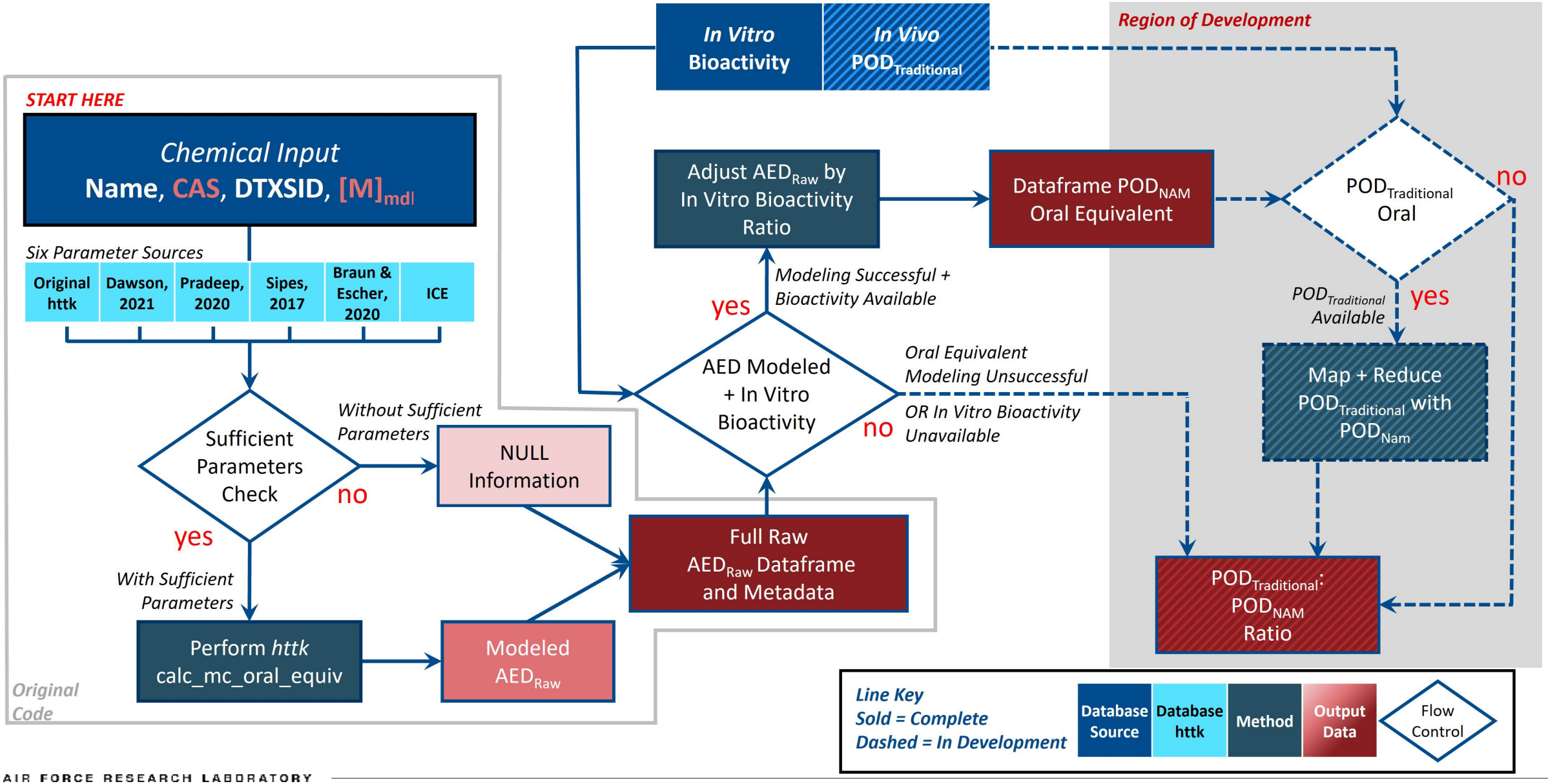
CERA (desktop): Searchable database + automated risk estimate paradigm



CERA (desktop): Searchable database + automated risk estimate paradigm



Estimating exposure limits



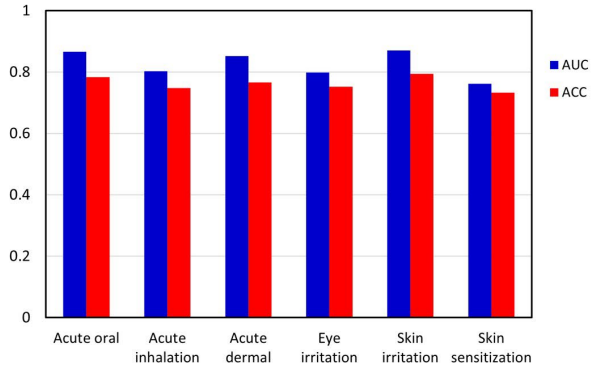
ML models for target acute toxicity

Models in development for Lung & Kidney

Acute Toxicity

Message passing neural network (MPNN) model

https://github.com/chaitjo/geometric-gnn-dojo/blob/main/geometric_gnn_101.ipynb

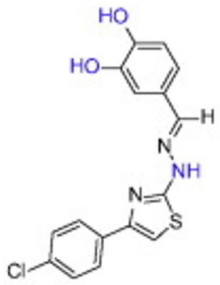


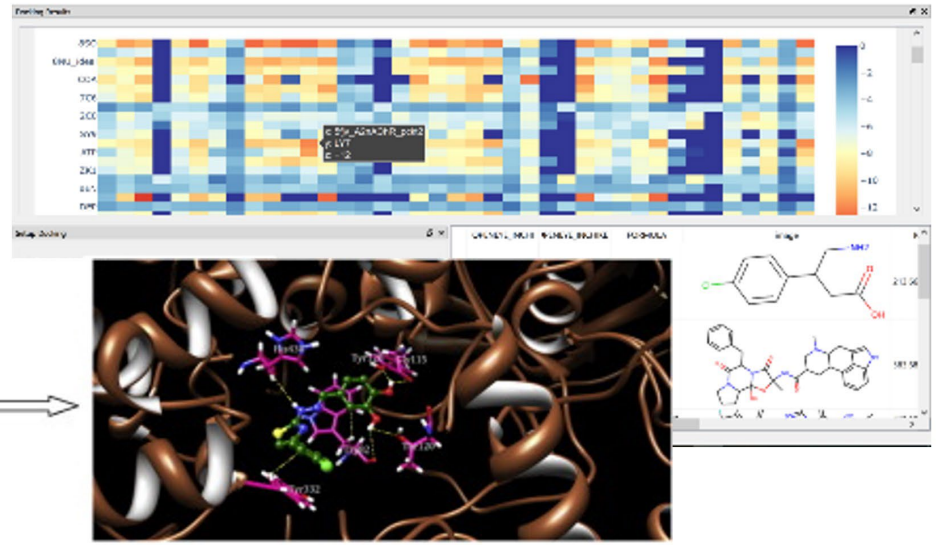
ACC = (TP+TN)/Nchem – accuracy

AUC = area under ROC curve

Chushak et al. 2023
https://doi.org/10.1016/j.comtox.2023.100280

Neurotoxicity





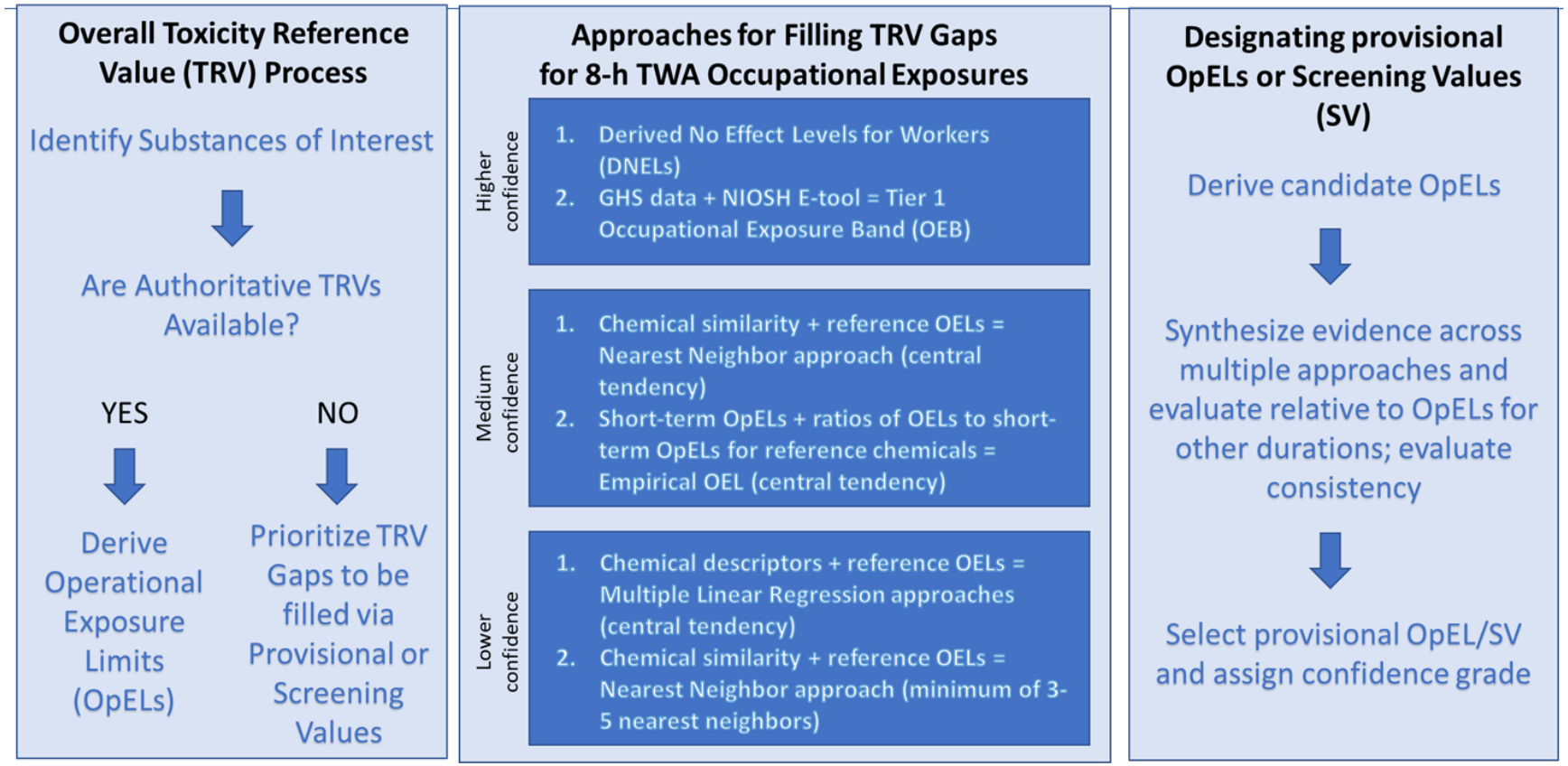
https://doi.org/10.1016/j.bioorg.2015.08.002

Neuro targets

- Acetylcholine
- AChE
- AMPA
- CHAT
- GABA

McCarthy et al. 2022
https://doi.org/10.1016/j.comtox.2022.100238

Exposure Limit Prediction



Conclusion: DNELs tended to be supported by other approaches. In the absence of DNELs, Nearest Neighbor approaches and Empirical Adjustment of Short Term OpELs were found to allow TRV estimation with reasonable confidence for nearly all substances in the test set.

Sweeney and Sterner. 2024. Toxicity Reference Values for Force Health Protection: Provisional Occupational Exposure Guidelines. Regul. Toxicol. Pharmacol.(submitted)