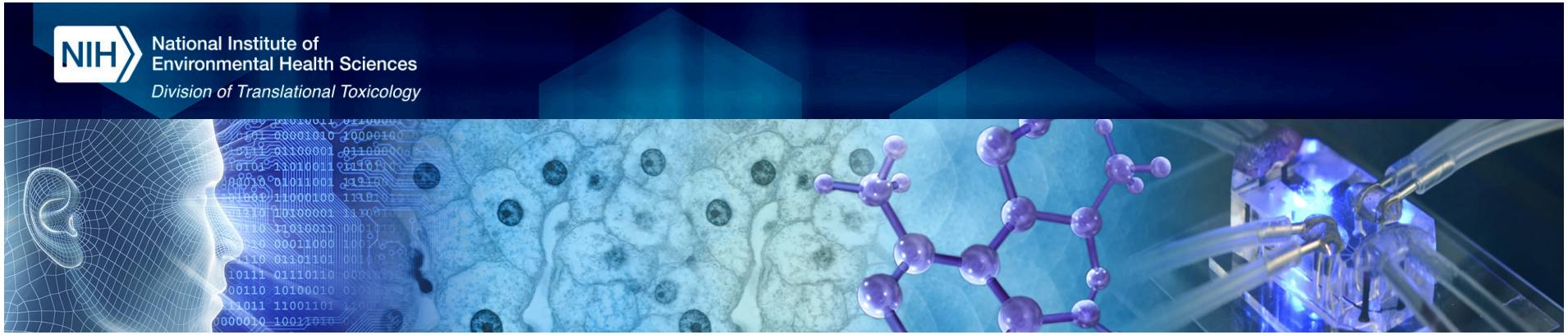

Augmented Intelligence and the Environmental Health Sciences

Nicole C. Kleinstreuer, PhD

Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

National Institutes of Health • U.S. Department of Health and Human Services

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NICEATM and ICCVAM

- National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (**NICEATM**), supporting the Interagency Coordinating Committee for the Validation of Alternative Methods (**ICCVAM**)
- ICCVAM Authorization Act of 2000: To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new and revised toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing (**3Rs**) animal tests and ensuring human safety and product effectiveness.

7 Regulatory Agencies

Consumer Product Safety Commission
Department of Agriculture
Department of the Interior
Department of Transportation
Environmental Protection Agency
Food and Drug Administration
Occupational Safety and Health Administration

*Other participants include: NCATS, Tox21 Representatives

10 Research Agencies

Agency for Toxic Substances and Disease Registry
National Institute for Occupational Safety and Health
National Cancer Institute
National Institute of Environmental Health Sciences
National Library of Medicine
National Institutes of Health
Department of Defense
Department of Energy
National Institute of Standards and Technology
Veterans Affairs Office of Research and Development

More information: https://ntp.niehs.nih.gov/go/iccvam

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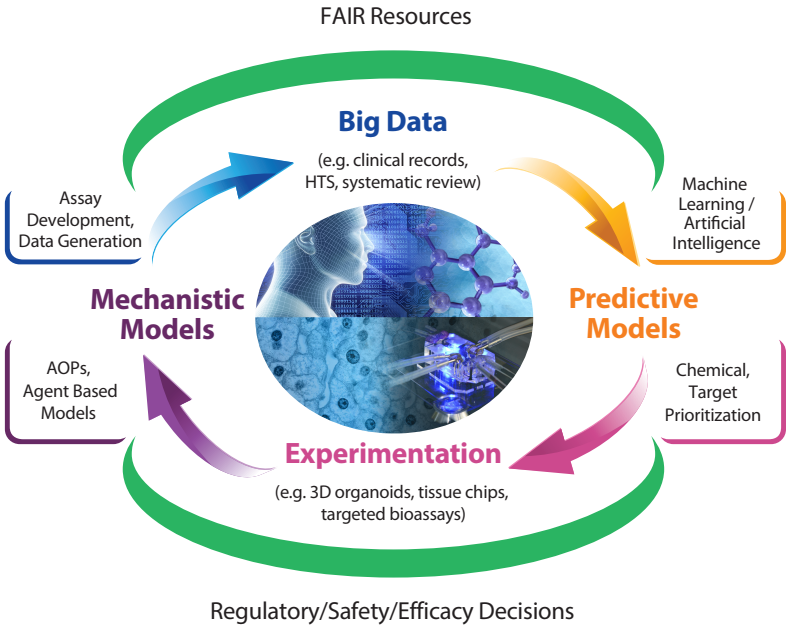
Ongoing NICEATM and ICCVAM Projects

- Integrated Chemical Environment
- OPERA (QSAR/QSPR)
- Computational Chemistry
- Quantitative IVIVE
- Reference data curation
- Variability of in vivo data
- Acute Systemic Toxicity
- Dermal absorption
- Eye and skin irritation
- Skin sensitization
- Ecotoxicology
- Carcinogenesis
- Cardiovascular Toxicity
- Developmental Toxicity
- DNT Testing Battery
- Zebrafish models
- Animal-free affinity reagents
- Microphysiological Systems
- Evolving Process of Validation



https://ntp.niehs.nih.gov/go/2021iccvamreport

ICCVAM Workgroups

- Acute Toxicity
- Consideration of Alternative Methods
- Ecotoxicity
- In Vitro to In Vivo Extrapolation
- Nanomaterials
- Validation
- NAMs for PFAS

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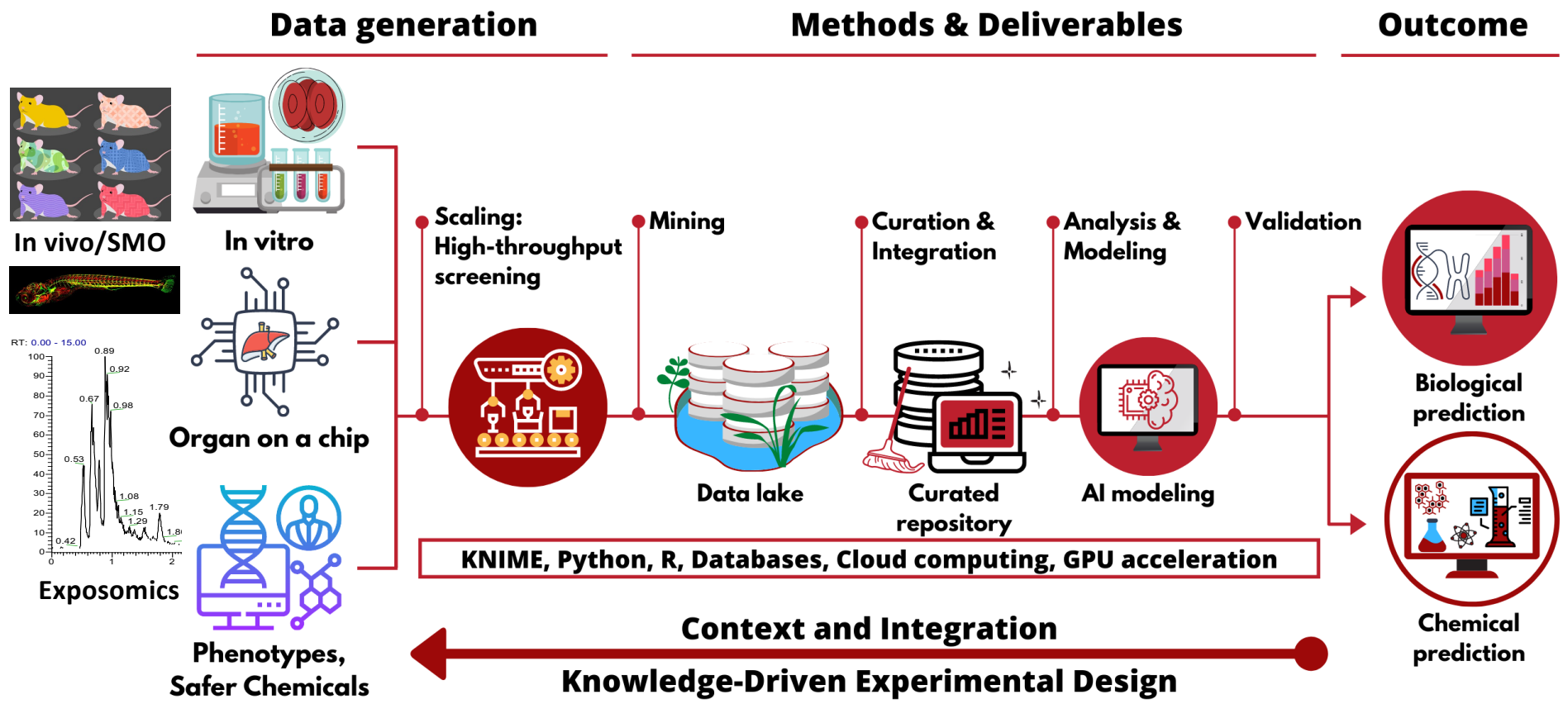
The Essentiality of Computational Resources



Adapted from Alves et al. 2021

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A Slightly Different Definition of AI: Augmented Intelligence

The use of computational tools, information technology, and cognitive algorithms such as machine learning and artificial intelligence to **complement** and **enhance** human intelligence.

W. Ross Ashby:
Intelligence Amplification (1956)
J. C. R. Licklider:
Man-Computer Symbiosis (1960)
Douglas Engelbart:
Augmenting Human Intellect (1962)

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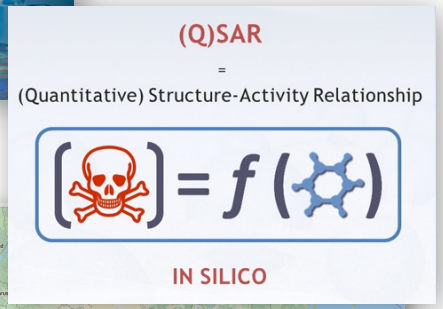
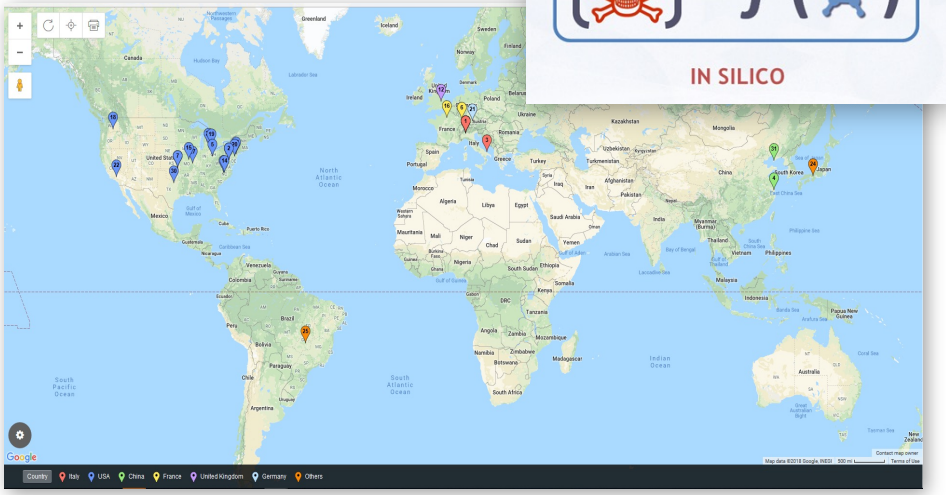
AI Example: Global Crowdsourcing Predictive Models





- 35 Groups: academia, industry, govt
- Curate reference data to train & test models: >10k chemicals
- Use molecular structure and chemical properties to predict toxicity (e.g. endocrine disruption, acute systemic effects)
- Combine best models together into “ensemble” approaches
- Create open access AI/ML modeling suite

OPERA
OPEn (q)saR App

https://github.com/NIEHS/OPERA

Kleinstreuer et al. Comp Tox (2018); Mansouri et al. J Cheminform (2018), Env Health Persp (2020, 2022)

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International collaborative projects

CERAPP

Collaborative **E**strogen **R**eceptor **A**ctivity **P**rediction **P**roject **(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 **(2019/20)**

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

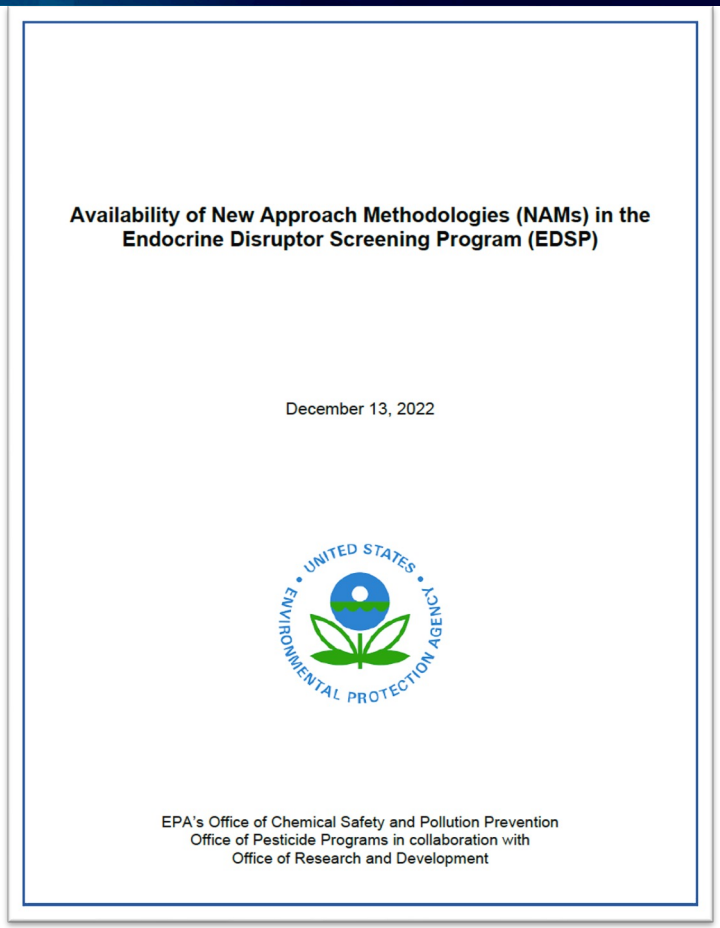
UNITED STATES ICCVAM *Advancing Alternatives to Animal Testing*

Acute Toxicity Workgroup: alternative methods

ICCVAM: Interagency Coordinating Committee on the Validation of Alternative Methods

EDSP whitepaper

- Certain NAMs have been validated by EPA and may now be accepted by EPA as alternatives for certain EDSP Tier 1 assays, while other NAMs are useful for prioritization under the EDSP and for consideration as OSRI in WoE evaluations.
- **NAMs Acceptable for Priority Setting and WoE Analysis:**
  - *In Silico* Qualitative Structure Activity Relationship Consensus Models for ER and AR. Available in the OPERA tool.



Availability of New Approach Methodologies (NAMs) in the Endocrine Disruptor Screening Program (EDSP)

December 13, 2022

EPA's Office of Chemical Safety and Pollution Prevention
Office of Pesticide Programs in collaboration with
Office of Research and Development

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Collaborative Acute Toxicity Modeling Suite (CATMoS)

Binary Models

Hazard

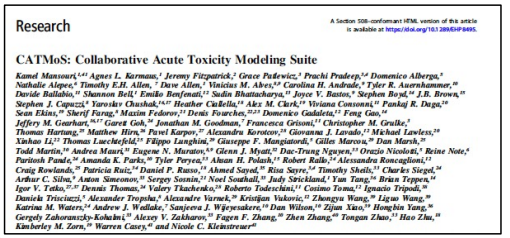
- Highly toxic (≤50 mg/kg)
- Toxic (>50-5000 mg/kg)

+ Nontoxic (>2000 mg/kg)

Continuous Model

Point estimates of LD50 values

Strickland et al. 2018



Mansouri et al. 2021

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

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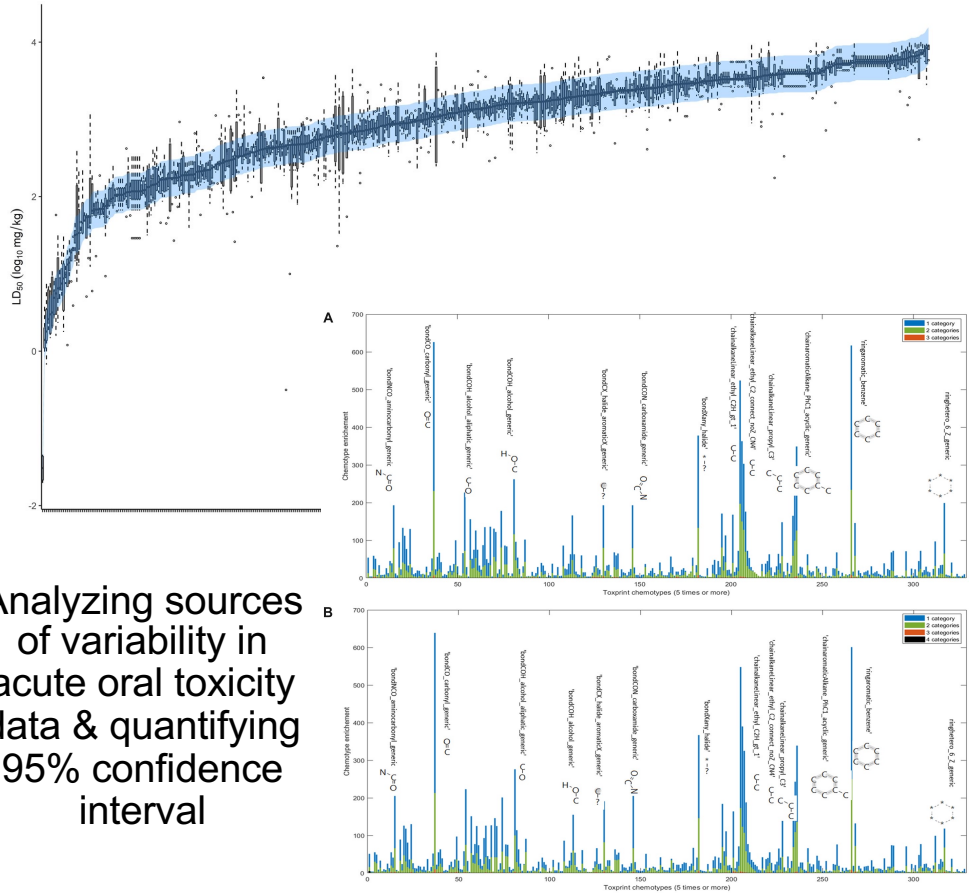
Characterizing Variability and Applying to Model Evaluation



Analyzing sources of variability in acute oral toxicity data & quantifying 95% confidence interval

Collaborative Acute Toxicity Modeling Suite (CATMoS) Performance

	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

CATMoS QSAR predictions perform just as well as replicate *in vivo* data at predicting oral acute toxicity outcome

Karmaus et al. Toxicol Sci. 2022; Mansouri et al. EHP 2021

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Application to Ecological Risk Assessment

- EPA's Office of Pesticide Programs (OPP) registers conventional pesticides and the Environmental Fate and Effects Division (EFED) conducts the needed ecological risk assessments
- Registrants submit required data, as specified in the Code of Federal Regulations (40 CFR 158), to assess risk to non-target animals and plants
- Rat in vivo acute oral toxicity LD50 data are used as a surrogate to assess risk to all mammalian wildlife
- The data are used for risk estimation (comparison of hazard and exposure) and precautionary and compulsory label statements to minimize the potential harm to non-target organisms
- EPA compared CATMoS results to OPP empirical data from in-vivo studies for 178 active ingredients
- CATMoS predictions of >2000 mg/kg-bw were reliable

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Predicting Acute Systemic Toxicity of Mixtures

Regulatory Toxicology and Pharmacology 125 (2021) 105007

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Performance of the GHS Mixtures Equation for Predicting Acute Oral Toxicity

Jon Hamm [a,*], David Allen [a], Patricia Ceger [a], Tara Flint [b], Anna Lowit [b], Lindsay O'Dell [b], Jenny Tao [b], Nicole Kleinstreuer [c]

[a] *ILS, P.O. Box 13501, Research Triangle Park, NC, 27709, USA*
[b] *Office of Pesticide Programs, U.S. Environmental Protection Agency, 1200 Pennsylvania Ave, NW, Washington, DC, 20460, USA*
[c] *National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709, USA*

ARTICLE INFO

Handling Editor: Dr. Lesa Aylward

Keywords:
Acute systemic toxicity
Alternative approaches
GHS Mixtures equation
Non-animal methods
Regulatory requirements

ABSTRACT

Acute oral toxicity classifications are based on the estimated chemical dose causing lethality in 50 % of laboratory animals tested (LD_{50}). Given the large number of pesticide registration applications that require acute toxicity data, an alternative to the *in vivo* test could greatly reduce animal testing. The United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Mixtures Equation estimates the acute toxicity of mixtures using the toxicities of mixture components. The goal of this study was to evaluate the concordance of LD_{50}s predicted using the GHS Mixtures Equation and LD_{50}s from the *in vivo* test results. Using the EPA classification system, concordance was 55 % for the full dataset (N = 671), 52 % for agrochemical formulations (N = 620), and 84 % for antimicrobial cleaning products (N = 51). Most discordant results were from substances LD_{50} > 2000 mg/kg (limit test) or 2000 < LD_{50} < 5000 mg/kg that were predicted as LD_{50} > 5000 mg/kg. A supplementary analysis combining all formulations with an LD_{50} > 500 mg/kg produced a concordance of 82 %. The lack of more toxic formulations in this dataset prevented a thorough evaluation of the GHS equation for such substances. Accordingly, our results suggest the GHS equation is helpful to predict the toxicity of mixtures, particularly those with lower toxicity.

- Promising approach for less toxic substances
- Within-class concordance was consistently over 85%
- Animal tests are inherently variable. Similar underclassification is observed following a repetition of the animal test.

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Predicting Acute Systemic Toxicity of Mixtures

Regulatory Toxicology and Pharmacology 125 (2021) 105007

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Performance of the GHS Mixtures Equation for Oral Toxicity

Jon Hamm [a,*], David Allen [a], Patricia Ceger [a], Tara Flint [b], A
Jenny Tao [b], Nicole Kleinstreuer [c]

[a] *ILS, P.O. Box 13501, Research Triangle Park, NC, 27709, USA*
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Acute oral toxicity classifications are
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Chemical Research in Toxicology

pubs.acs.org/crt

Article

In Silico Assessment of Acute Oral Toxicity for Mixtures

Yaroslav Chushak,* Jeffery M. Gearhart, and Darrin Ott

Cite This: https://dx.doi.org/10.1021/acs.chemrestox.0c00256

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ABSTRACT: While exposure of humans to environmental hazards often occurs with complex chemical mixtures, the majority of existing toxicity data are for single compounds. The Globally Harmonized System of chemical classification (GHS) developed by the Organization for Economic Cooperation and Development uses the additivity formula for acute oral toxicity classification of mixtures, which is based on the acute toxicity estimate of individual ingredients. We evaluated the prediction of GHS category classifications for mixtures using toxicological data collected in the Integrated Chemical Environment (ICE) developed by the National Toxicology Program (United States Department of Health and Human Services). The ICE database contains *in vivo* acute oral toxicity data for ~10,000 chemicals and for 582 mixtures with one or multiple active ingredients. By using the available experimental data for individual ingredients, we were able to calculate a GHS category for only half of the mixtures. To expand a set of components with acute oral toxicity data, we used the Collaborative Acute Toxicity Modeling Suite (CATMoS) implemented in the Open Structure–Activity/Property Relationship App to make predictions for active ingredients without available experimental data. As a result, we were able to make predictions for 503 mixtures/formulations with 72% accuracy for the GHS classification. For 186 mixtures with two or more active ingredients, the accuracy rate was 76%. The structure-based analysis of the misclassified mixtures did not reveal any specific structural features associated with the mispredictions. Our results demonstrate that CATMoS together with an additivity formula can be used to predict the GHS category for chemical mixtures.

ICE GHS Category	Predicted GHS Category 1	2	3	4	5
1	0	0	0	0	0
2	1	0	1	0	0
3	0	0	22	6	2
4	0	1	8	85	47
5	0	0	7	67	256

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OPERA v2.9 Models

Physchem properties		Chemicals	Version
BP	**Boiling Point**	**7860**	**2.9**
HL	**Henry's Law Constant**	**2233**	**2.9**
LogP	**Octanol-water Partition Coefficient**	**18154**	**2.9**
MP	**Melting Point**	**22554**	**2.9**
VP	**Vapor Pressure**	**6764**	**2.9**
WS	**Water Solubility**	**9943**	**2.9**
pKa	Acid Dissociation Constant	6503	2.6
KOA	Octanol/Air Partition Coefficient	270	2.6

Environmental fate		Chemicals	Version
AOH	Atmospheric Hydroxylation Rate	692	2.6
BCF	Bioconcentration Factor	626	2.6
BioHL	Biodegradation Half-life	150	2.6
RB	Ready Biodegradability	1603	2.6
KM	Fish Biotransformation Half-life	541	2.6
KOC	Soil Adsorption Coefficient	728	2.6

ADME properties		Chemicals	Version
FUB	**Fraction unbound**	**3229**	**2.8**
Clint	**Intrinsic clearance**	**1346**	**2.8**
CACO2	**Caco-2 permeability**	**4601**	**2.8**

Toxicity endpoints		Chemicals	Version
ER	Estrogen Receptor Activity	32464	2.6
AR	Androgen Receptor Activity	47673	2.6
AcuteTox	Acute Oral Systemic Toxicity	50660	2.6

Future models	
Inhalation	Acute Inhalation Systemic Toxicity
SixPack	Acute Toxicity Six-Pack Endpoints
UGT	Glucuronidation: substrate selectivity
SULT	Sulfation: substrate selectivity

https://github.com/NIEHS/OPERA

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PFAS in OPERA models

	Models	PFAS/Total
BP	Boiling Point	346/7860
LogP	Octanol-water Partition Coef.	97/18154
MP	Melting Point	409/22554
VP	Vapor Pressure	178/6764
WS	Water Solubility	105/9943

VP Vapor Pressure

Deviation of log*p* (…urements at 25 °C

	COSMOtherm	EPI Suite	NICEATM	ACD/Labs	TEST	OPERA
MAE	1.22	1.08	1.46	1.53	1.31	0.95
RMSE	1.48	1.48	2.06	1.99	1.91	1.26

LogP Octanol-water Coef

Deviation of octanol–water partition ratio (log K_{OW}) estimates from experimental measurements at 25 °C

	COSMOtherm	EPI Suite	NICEATM	ACD/Labs	OPERA	LSER
MAE	0.41	0.25	0.68	0.61	0.21	0.33
RMSE	0.50	0.29	1.13	0.70	0.28	0.36

WS Water solubility

Deviation of water solubility (log *S*; mg/L) estimates from experimental measurements at 25 °C

	COSMOtherm	EPI Suite	NICEATM	TEST[a]	OPERA
MAE	0.35	1.82	2.38	0.95	0.23
RMSE	0.41	2.20	2.55	1.36	0.36

Environmental Chemistry

Property Estimation of Per- and Polyfluoroalkyl Substances: A Comparative Assessment of Estimation Methods

Alina Lampic and J. Mark Parnis*

Chemical Properties Research Group (Canadian Environmental Modelling Centre), Department of Chemistry, Trent University, Peterborough, Ontario, Canada

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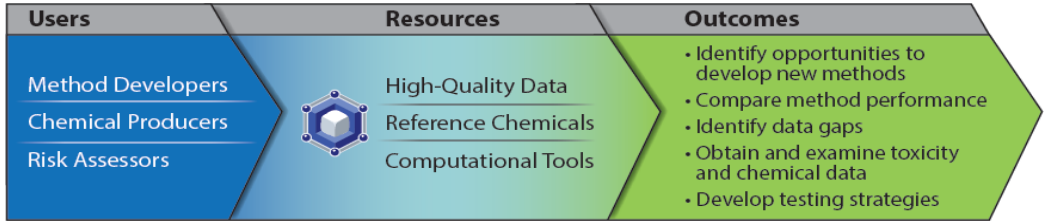
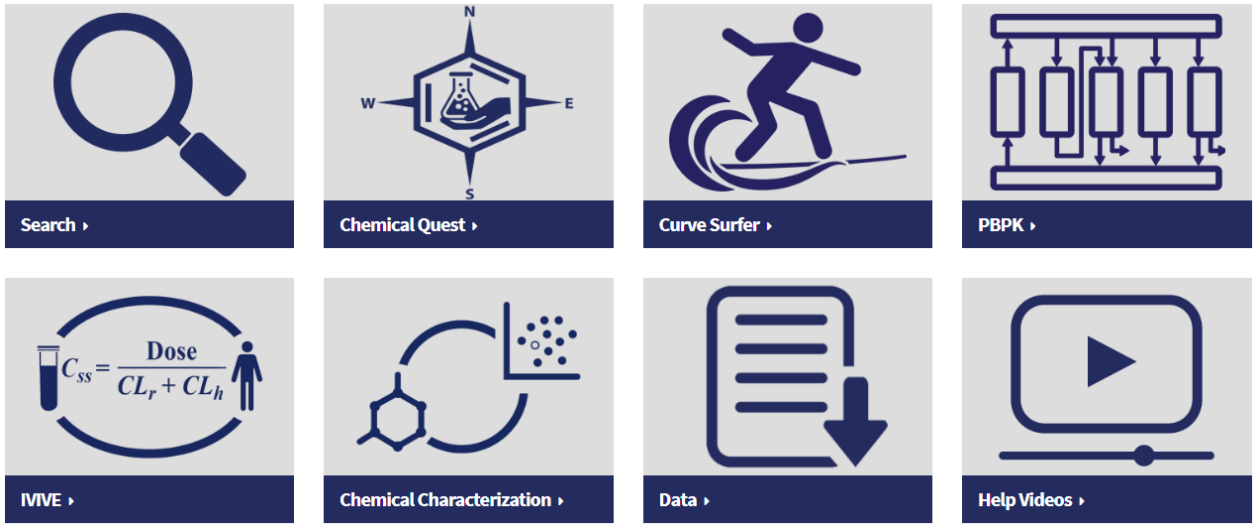
ICE: The Integrated Chemical Environment



Integrated
Chemical
Environment

ICE v4.0
March 17th



Bell et al. 2017 EHP
Bell et al. 2020 Tox In Vitro
Abedini et al. 2021 Comp Tox
Daniel et al. 2022 Front Toxicol

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

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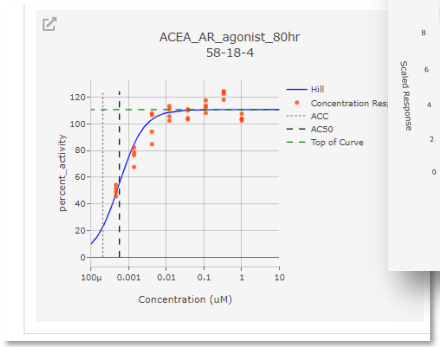
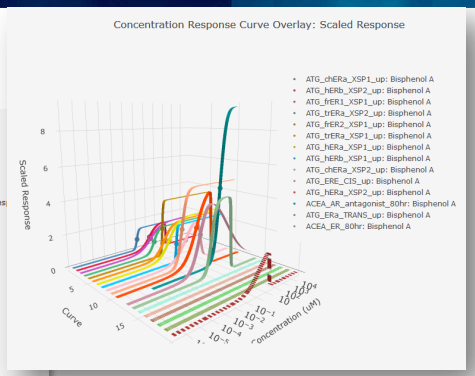
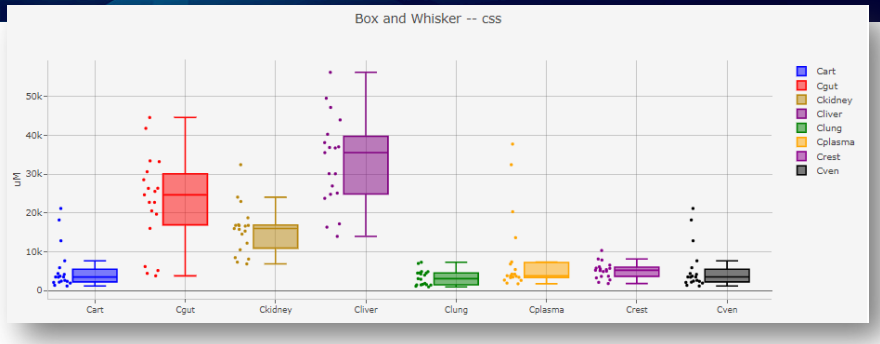
ICE Tools

HTS Data Exploration

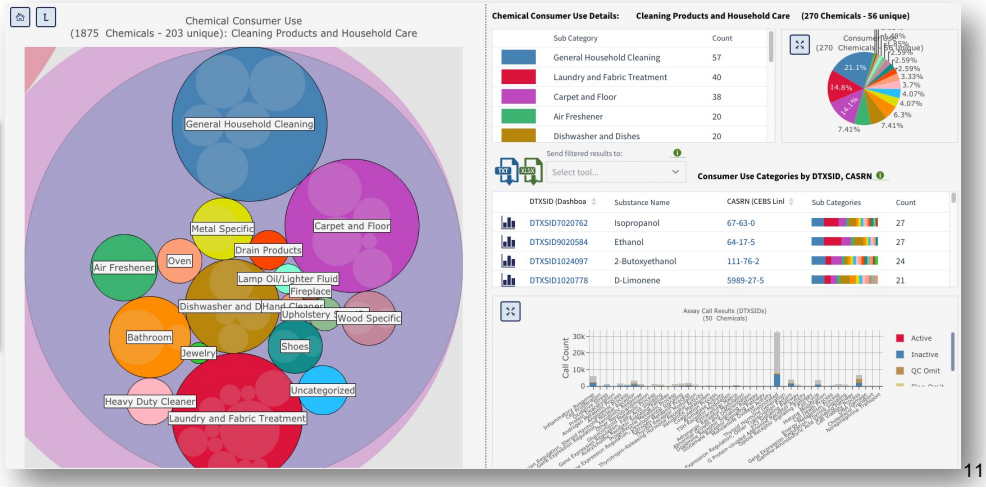






Predicting Chemical Exposure: Body Tissues, Consumer Products

Chemical Similarity



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ICE v4.0: New Features

Search Results Redesign (beta):

- A completely redesigned Search results interface features new summary interactive visualizations.

PBPK and IVIVE Tools Feature Enhancements:

- ICE PBPK and IVIVE tools now incorporate a gestational model from U.S. EPA's httk package (v2.2.2; released February 2023).
- Updated dosing options for users modeling inhalation exposure (dose units of ppmv in addition to µM).

Exposure Predictions:

- ICE tools integrate exposure predictions from the EPA's SEEM3 (Systematic Empirical Evaluation of Models) model (Ring et al. 2019).
- Download exposure predictions on the ICE Data Sets page and the ICE REST API.
- Predicted exposure data can also be compared to the equivalent administered doses (EADs) in the IVIVE tool.

Chemical Name Input Options:

- ICE tools and the ICE REST API now accept chemical names and synonyms as input along with other pre-existing input options like CASRN, DTXSID, SMILES, and InChIKeys.

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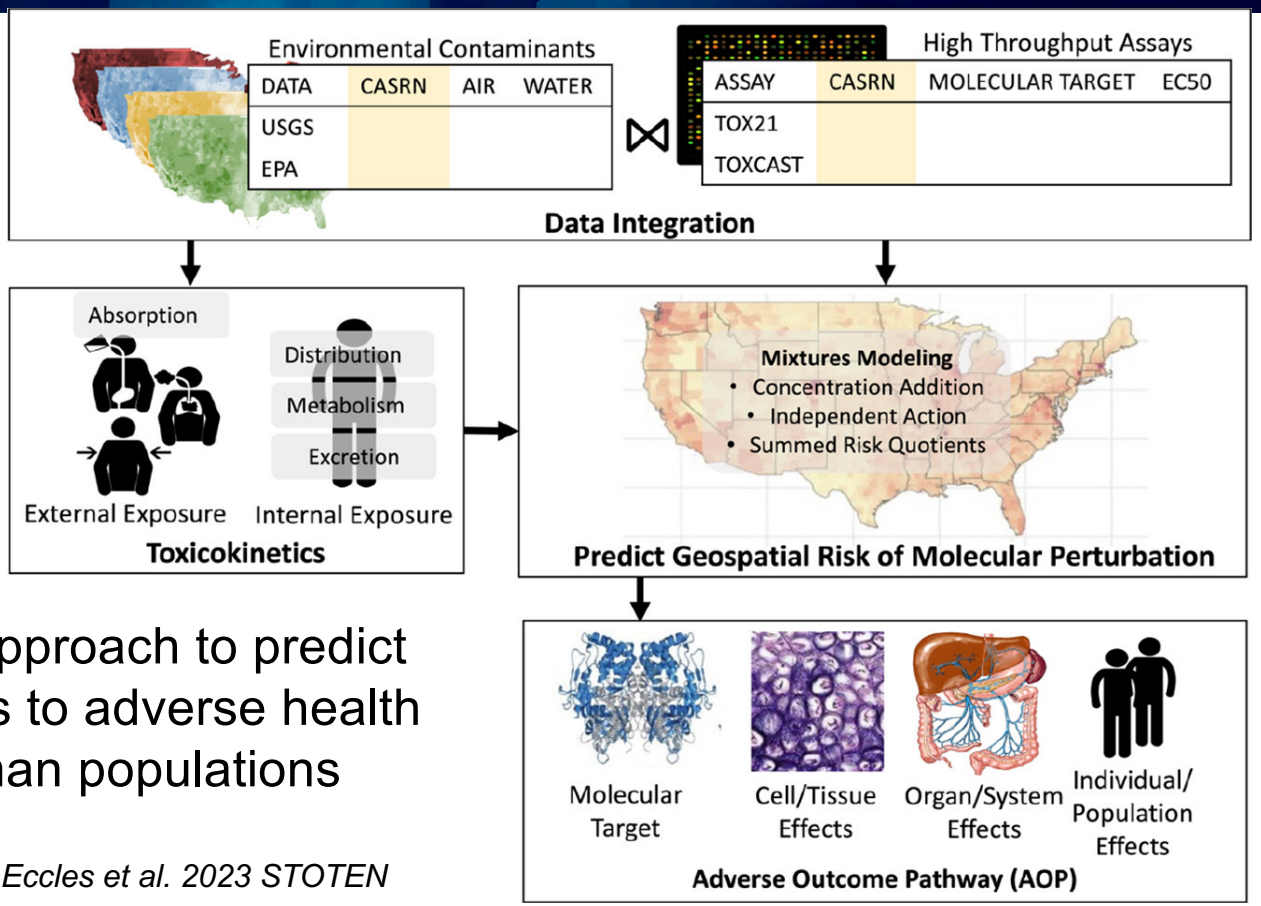
Geospatial Modeling Approach

Linking Tox21 *in vitro* HTS data and exposure information to predict geospatial risk of molecular perturbation.



Eventual goal: use approach to predict chemical contributions to adverse health outcomes across human populations

Eccles et al. 2023 STOTEN

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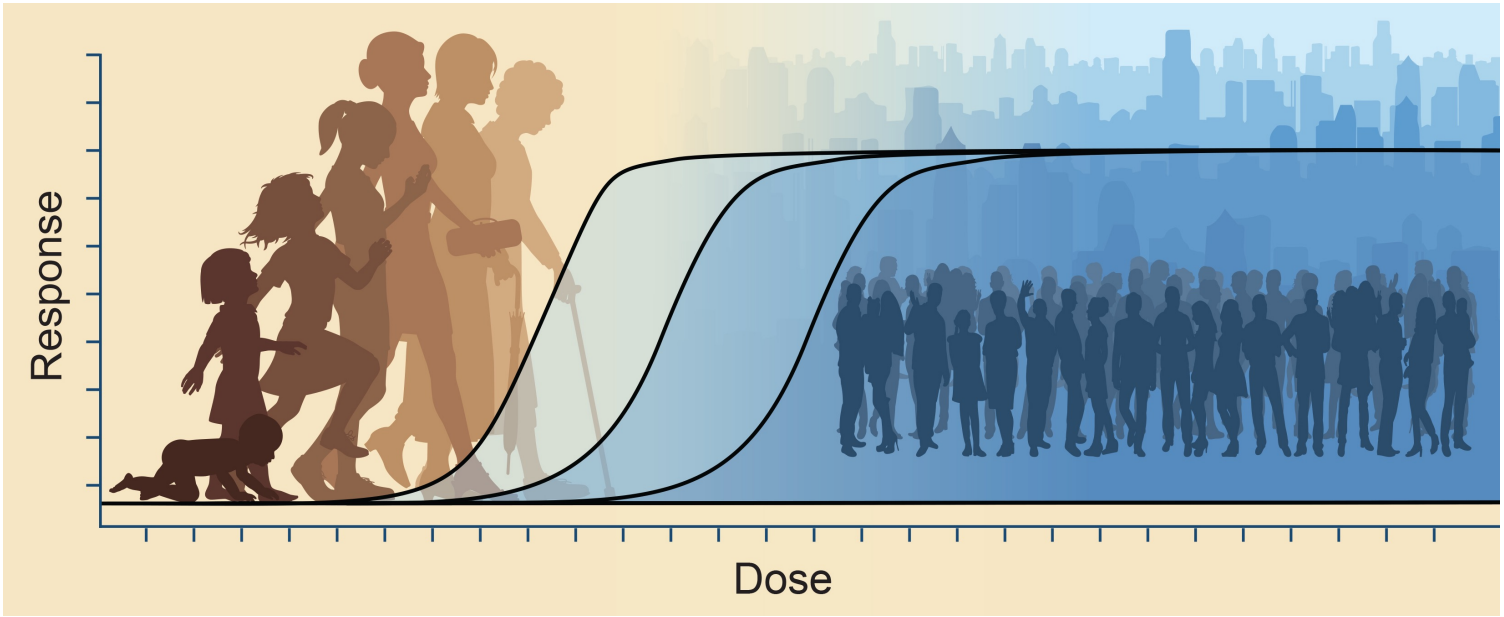
October 2022 NICEATM Workshop

Using New Approach Methodologies to Address Variability and Susceptibility Across Populations



https://ntp.niehs.nih.gov/go/popvar

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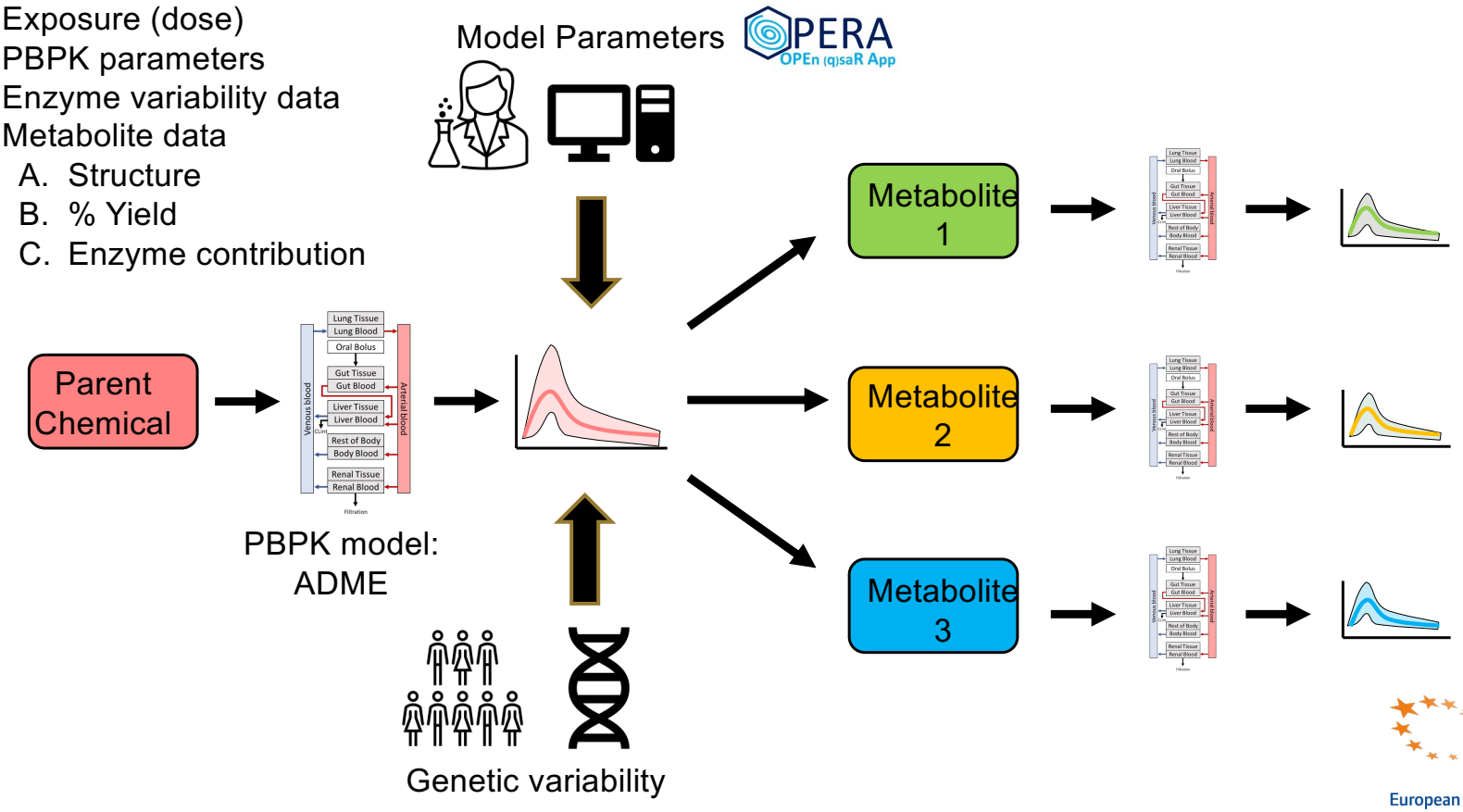
Incorporating Population Variability in Metabolism

Inputs needed:

1. Exposure (dose)
2. PBPK parameters
3. Enzyme variability data
4. Metabolite data
   A. Structure
   B. % Yield
   C. Enzyme contribution



efsa
European Food Safety Authority

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Standardization Efforts at DTT

Getting to FAIR+ requires standard metadata, terminologies, and quality curation

NIH Office of Data Science Strategy FAIR checklist

- Establishment of a DTT Data Dictionary
  - e.g., populations, treatments, outcomes, endpoints
  - Incorporated into DSMPs
  - In-house expertise with ontologies

- Community is key, both local and global:
  - DTT Knowledge Management Team
  - DTT-EPA collaborations
  - Engagement with ontology communities, e.g.
    - Ontology for Biomedical Investigations (OBI)
    - Adverse Outcome Pathways (AOPs)
  - Engagement with NIEHS grantee communities
  - Environmental Health Language Collaborative

Courtesy of Charles Schmitt

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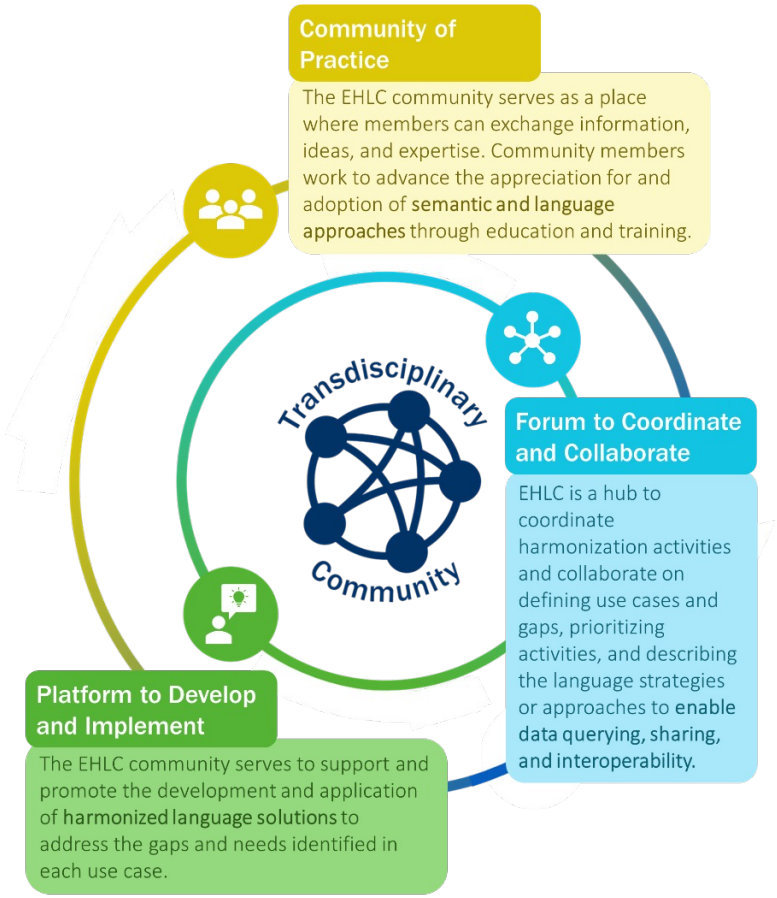
Environmental Health Language Collaborative



EHLC Mission: to advance integrative environmental health research by promoting access, use, and harmonization of data through interoperable terminologies and best practices.

Use Case	Champion
1. What data exists for a given chemical/endpoint/exposure scenario?	Michelle Angrish, EPA Shannon Bell, RTI
2. What are the biological processes and biomarkers associated with exposure and how do they relate to the potential for an adverse outcome associated with a given exposure	Steve Edwards, RTI Chirag Patel, Harvard University
3. How do we combine individual-level data from multiple independent studies to understand how exposures X+Y impact health outcome Z?	Jeanette Stingone, Columbia University

Contact: Stephanie Holmgren (Holmgren@niehs.nih.gov)

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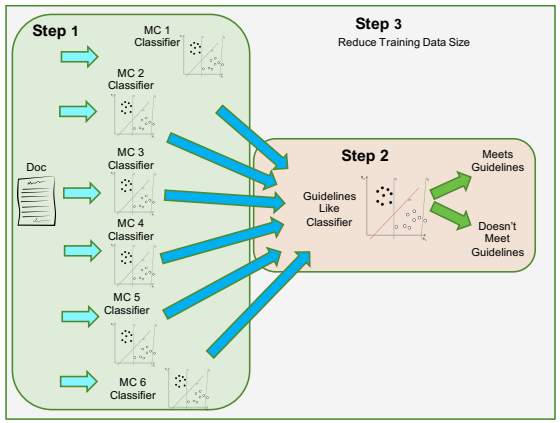
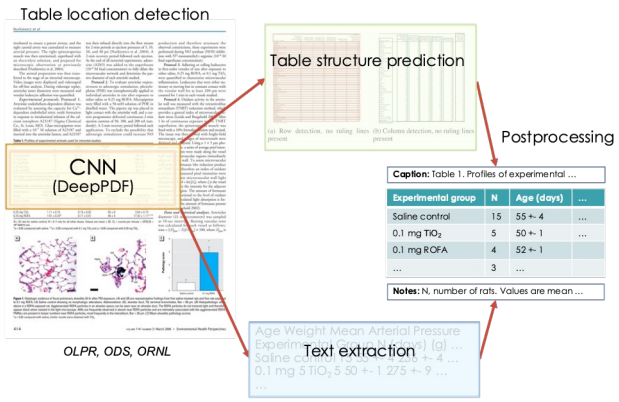
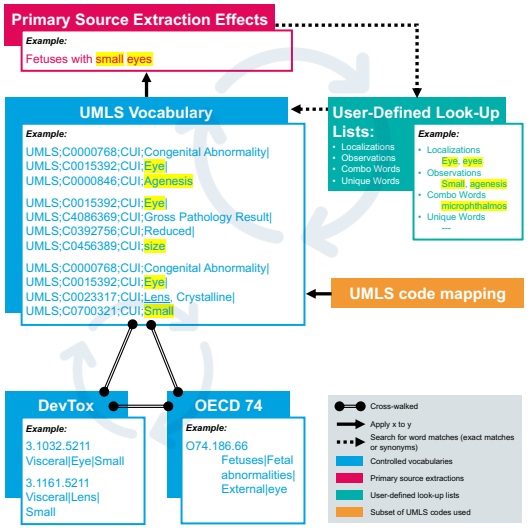
Machine Automating Study Data Curation

Identification → Extraction → Annotation







- Important for leveraging high-quality studies in the published literature
- Applications in systematic review of chemical effects
- Establishing reference datasets for validating new methods

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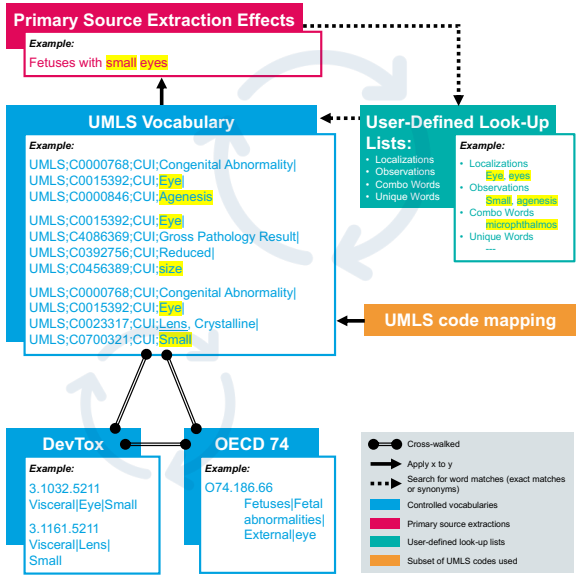
Study Extractions and Endpoint Mapping

- Extract study details from prenatal developmental toxicity guideline studies
  - NTP legacy studies
  - ECHA submissions (expert reviewed for quality)
- Programmatically map results to controlled vocabularies/ontologies
  - UMLS (ToxRefDBv2.0)
  - EPA/BfR DevTox DB
  - OECD Harmonized Templates
- Code is plug-and-play



- 72% of all extractions received standardized controlled vocabulary mappings via the automation code.
- Time savings to map extracted information >500 hours

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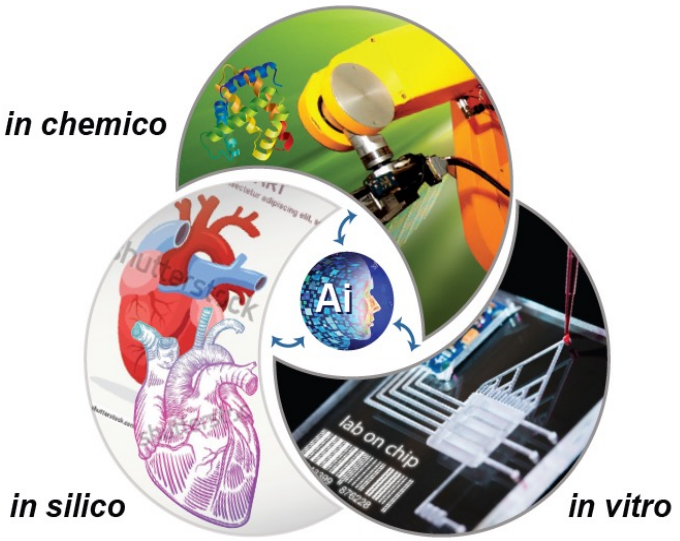
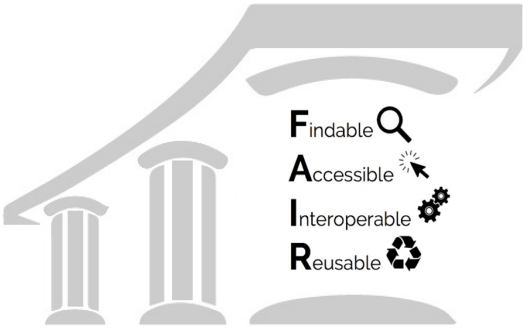
FAIR Data as the Foundation and AI as the Enabler

- Findable, Accessible, Interoperable, and Reusable data objects, e.g.
  - comparable, compatible, integrable multi-omic databases
- AI-enabled approaches that leverage the full technological toolbox and are iterative, e.g.
  - development of in silico “digital twins” of in vitro and in vivo systems
  - large language models (GPT-4) supporting hypothesis generation

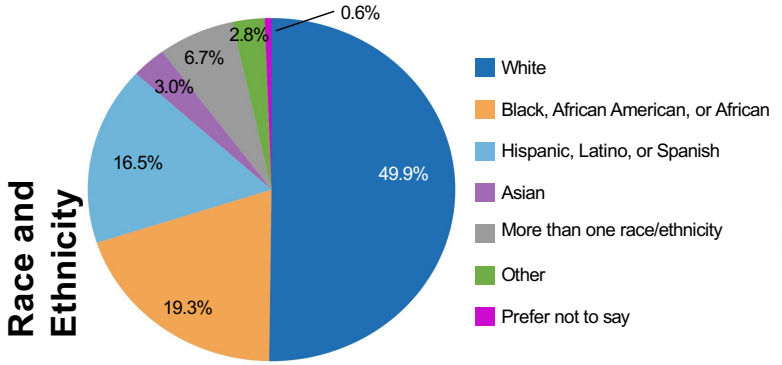


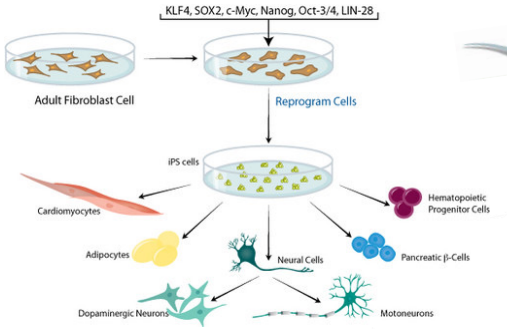


Digital and Tissue Chip Twins for Precision Medicine

"right medicine to right person at right time" $1.5B over 10 years

- Leveraging the NIH ***All of Us*** program: target >1M individuals across the United States
- (as of Sep 2022 >**535,000 participants**)





Tissue chip Twin

324,000+ Electronic Health Records

394,000+ Biosamples

Digital twin for an individual from **comprehensive longitudinal clinical record** such as medical imaging (e.g. MRI, ultrasound, CT scans); wearable technologies (e.g. smart watches, ECG monitors, glucose monitors); voice recordings; other clinical information; and/or, self-reported data

Collection of **blood, urine** samples for **omics analysis** (e.g., genomics (whole genome sequencing), transcriptomics, epigenomics, proteomics, metabolomics, microbiomics); **blood to iPSCs**

Courtesy of Dan Tagle

NIH National Center for Advancing Translational Sciences

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Accelerating AImplementation

Topic	Challenges	Opportunities
AI-ready data sets	Building these is not the norm; Incentives to invest; Coordination across groups	Eager modeling community; Industry partnerships; Infrastructure for data challenges
Standards	Under funded; Coordination across groups; Workplace skills; Incentives for Vendors to Adopt	Strengthen engagement with the standards efforts; NIH Common Data Elements; International efforts
Epidemiology and clinical data	Lack of models, tools, and common measures to bridge toxicology to clinical; Ensure data security	Exposome initiatives; Capture of mechanistic data on the Epi/Clinical side; Greater involvement of modeling/statistical community;
Knowledge Models (e.g., ontologies, AOPs)	Under funded; High human cost; Lack of training	Use of AI approaches; Industry partnerships; Better knowledge capture tools
Biomedical Data Ecosystem (FAIR+)	Federation of data has high costs & evolves slowly; Standardized protocols; Lack of cloud computing skills; Human focused data; Lack of industry data	NIH investments in data ecosystem; Cross-agency data federation; Industry involvement (increased data access)
Workforce/IT needs	Lack of data scientists, data-aware workforce to drive data sharing/use; Data security & QA	Workplace development efforts; training programs; hardware/software infrastructure

ICCVAM Public Forum

- ICCVAM's goals include promotion of national and international partnerships between governmental and nongovernmental groups, including academia, industry, advocacy groups, and other key stakeholders.
- To foster these partnerships ICCVAM holds an annual public forum (usually in May) to share information and facilitate direct communication of ideas and suggestions from stakeholders
- Recent meetings have included representatives from ≥15 ICCVAM agencies and participation from more than 100 stakeholders.
- Next meeting is **May 18-19, 2023** at NIH in Bethesda, MD

https://ntp.niehs.nih.gov/go/iccvamforum-2023

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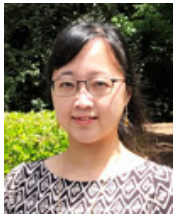
Acknowledgments

The NICEATM Group



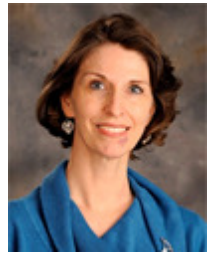
April 2022 DoD Future Directions Workshop Participants

NIEHS/ODS

Charles Schmitt

NCATS

Dan Tagle



Stephanie Holmgren

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