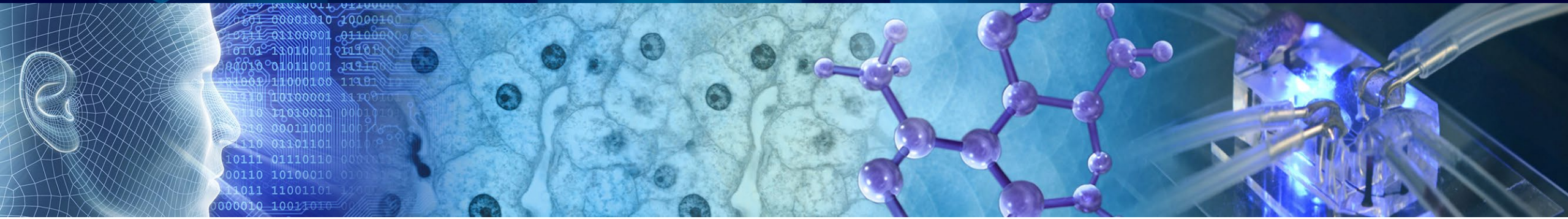
National Institute of Environmental Health Sciences
Division of Translational Toxicology

ECETOC Workshop
16th October, 2024



From Data to Decisions: AI's Role in Modern Toxicology

Nicole C. Kleinstreuer, PhD

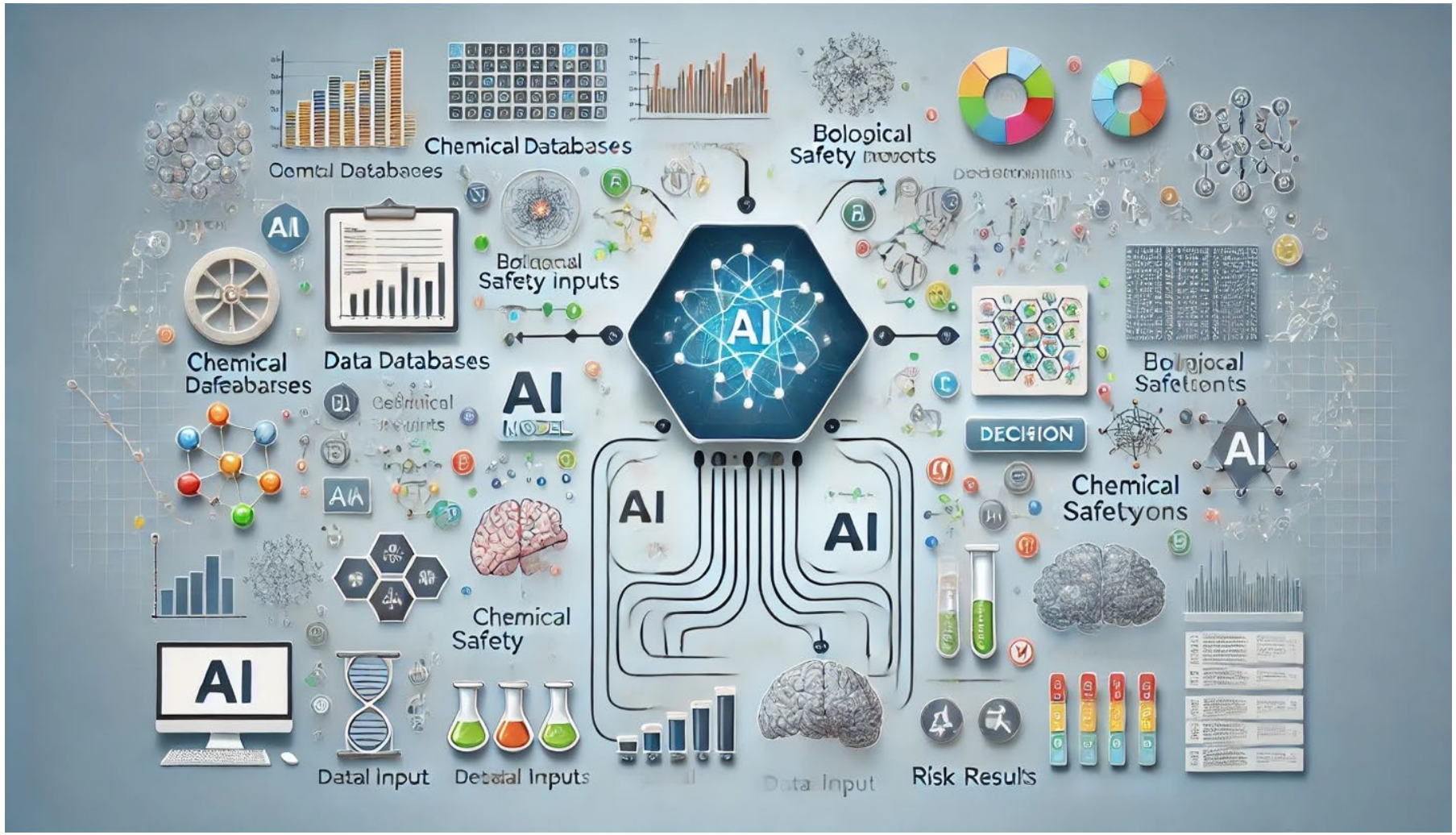
Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

Executive Director, Interagency Coordinating Committee for the Validation of Alternative Methods

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

AI's Role in Modern Toxicology

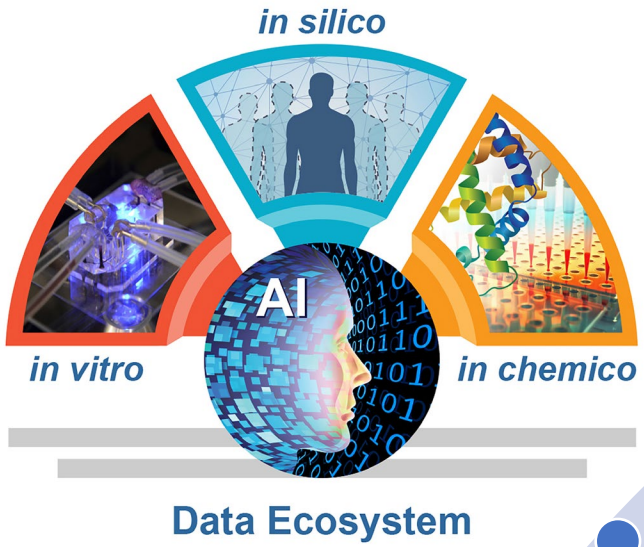
(As envisioned by ChatGPT4.0)



A 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)



Biomedical Research

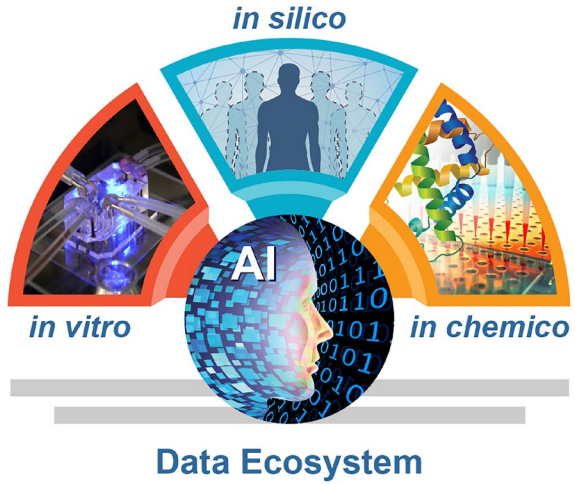
Validation/ Qualification

Adoption & Implementation

The NAMs Confidence Continuum: from *Biomedical Research* to *Validation/Qualification* to *Adoption & Implementation*

Complement-ARIE: Complement Animal Research in Experimentation

Purpose: To catalyze the development, standardization, validation and use of **human-based new approach methodologies (NAMs)** that will transform the way we do basic, translational, and clinical sciences



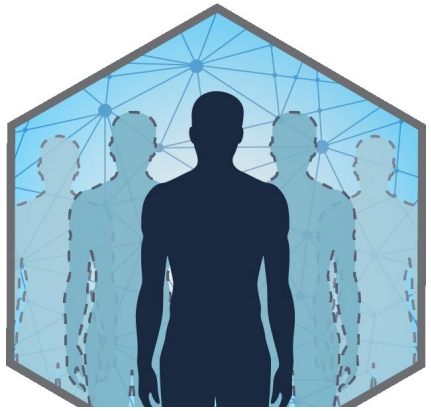
Goals:

1. Better model and **understand human health and disease** outcomes **across diverse populations**.
2. Develop NAMs that **provide insight into specific biological processes** or disease states.
3. Validate mature NAMs to **support regulatory use** and standardization.
4. Complement traditional models and **make biomedical research more efficient and effective**.

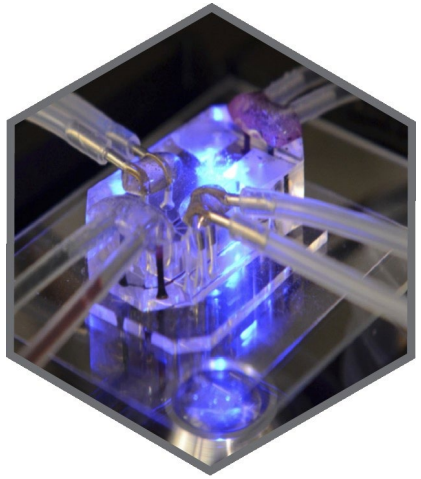
https://commonfund.nih.gov/complementarie

Build on existing NAMs activities

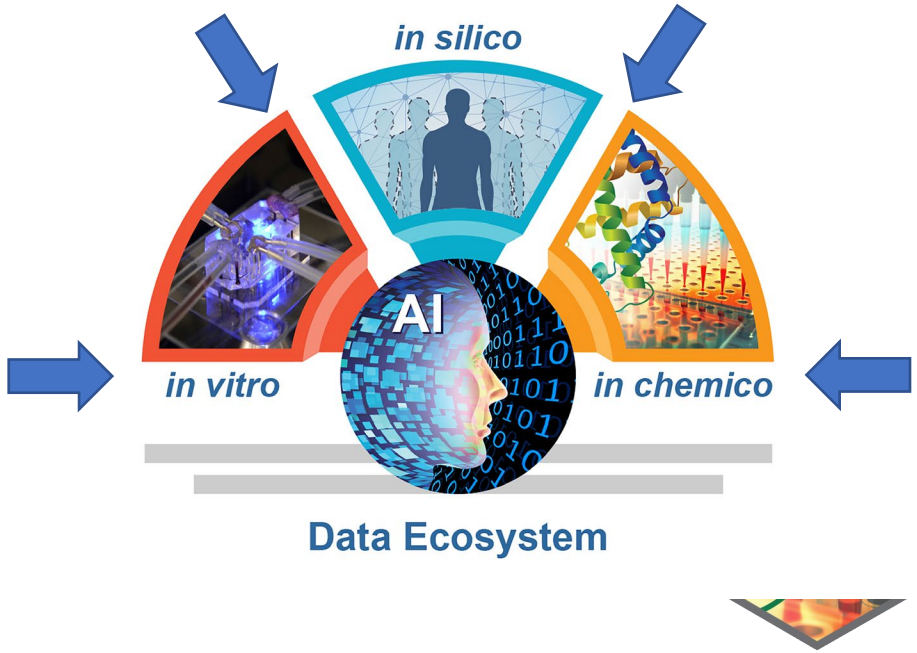
Digital Twin Models
Digital Twins for treatment of cancers and neuropsychiatric diseases, host-gut microbiome studies



In Silico Models
In silico and ML/AI models for neurodegenerative disease, wound healing, learning/behavior, SARS-CoV-2 propagation, many other diseases



Complex In
MPS and 3D
for multiple t
and disease

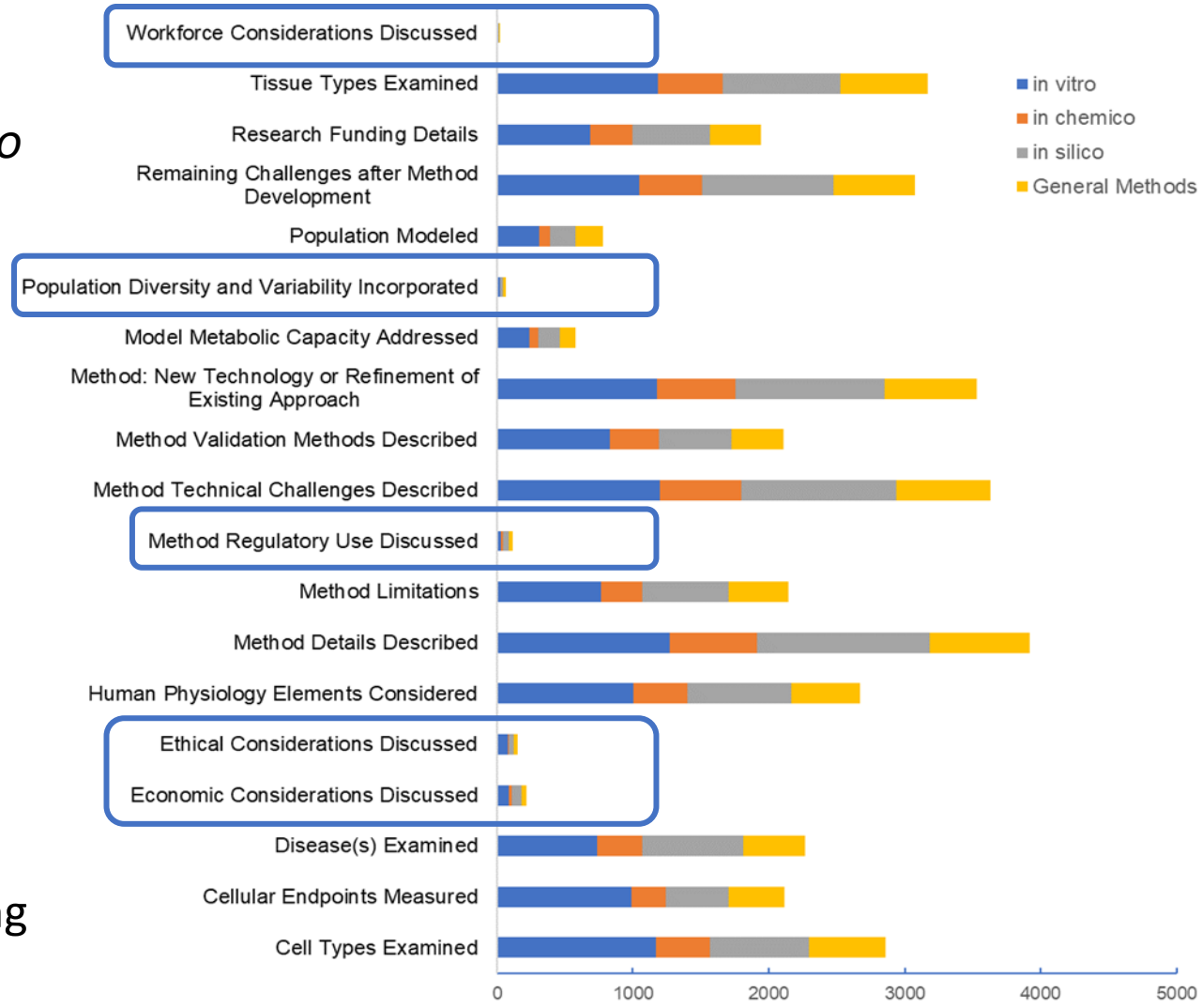


In Chemico Screening
Tox21 high-throughput studies, biochemical assays for skin irritation, ocular toxicity

Strategic planning activities: AI-enabled Landscape Analysis

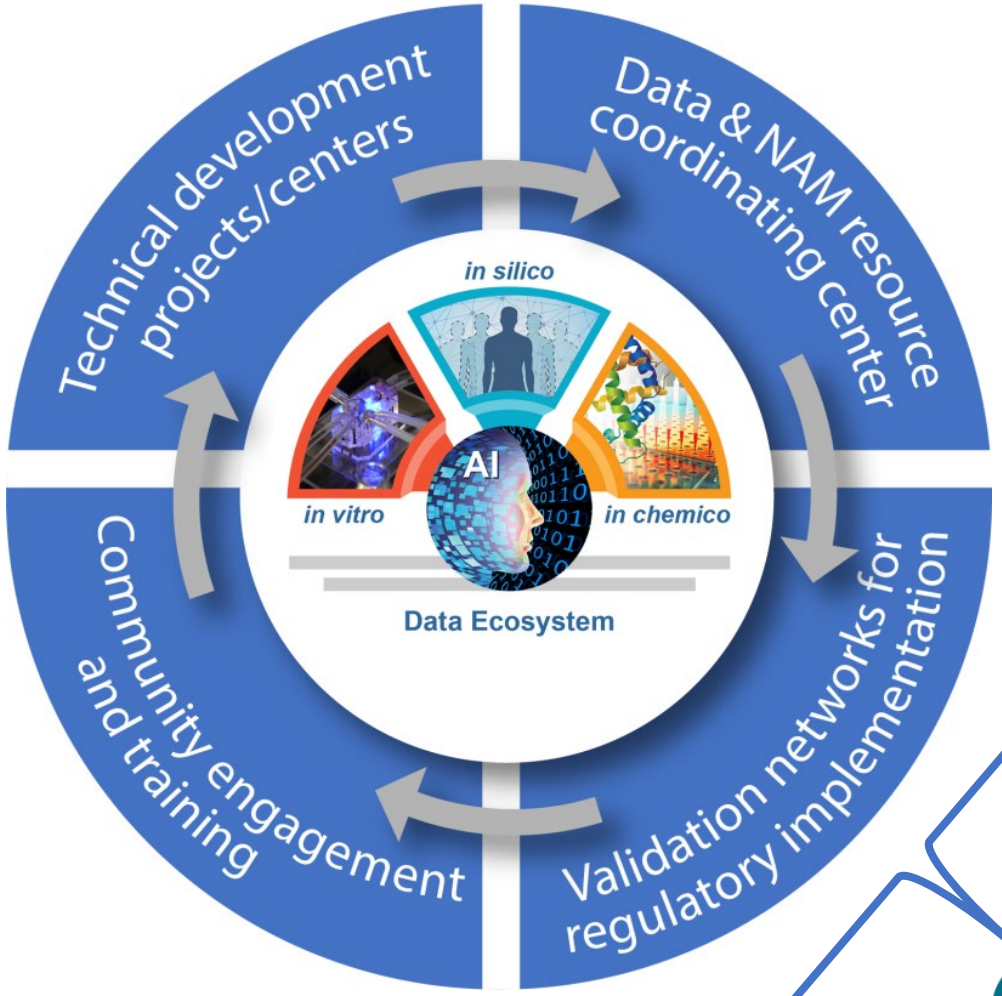
Describe existing efforts, and highlight gaps, challenges, and opportunities in the areas of human-relevant *in vitro, in chemico,* and *in silico* NAMs, and FAIRness of data resources

- **Comprehensive Scientific Lit Review**
  - Delivered via interactive Tableau dashboard
- **Current Focal Areas**
  - e.g., cell lines, organoids/MPS, AI/ML, HTS, specific disease types
- **Future Directions**
  - e.g., clinical translation, immune components, digital twins, combinatorial NAMs
- **FAIRness** of data resources
  - Application of FAIR assessment rubric to existing resources (e.g. HuBMAP = 100% FAIR)



https://commonfund.nih.gov/complementarie/strategicplanning/landscape-analysis

Complement-ARIE: Comprehensive center model



- Comprehensive centers will require embedded projects on *in vitro*, *in chemico*, and *in silico* approaches plus combinatorial approaches.
- Cores will include administrative, validation, resources, and training components.
- Phased milestone-driven projects that pilot some of the truly innovative approaches can also be transitioned for integration with the centers.

UNITED STATES ICCVAM Advancing Alternatives to Animal Testing

Key partners for validation networks include: ICCVAM, FDA, ICATM members, OECD, etc.

U.S. Validation Body: ICCVAM Authorization Act of 2000

PUBLIC LAW 106–545 (42 U.S.C. 285/-3)

"To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness."

ICCVAM Co-chairs

Suzy Fitzpatrick
FDA/CFSAN

Natalia Vinas
DoD

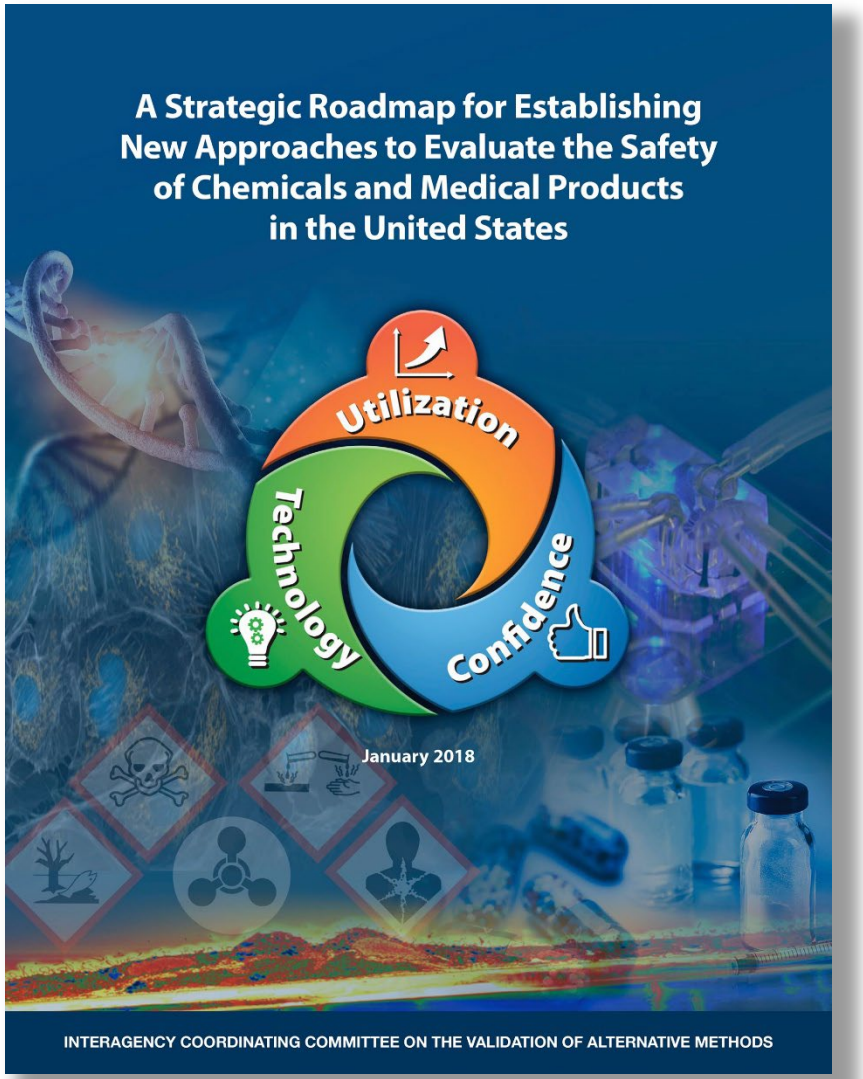
- Consumer Product Safety Commission
- Department of Agriculture
- Department of the Interior
- Department of Transportation
- Environmental Protection Agency
- Food and Drug Administration
- Occupational Safety and Health Administration
- National Institute for Occupational Safety and Health
- Agency for Toxic Substances and Disease Registry
- National Cancer Institute

- National Inst of Environmental Health Sciences
- National Library of Medicine
- National Institutes of Health
- Department of Defense
- Department of Energy
- National Institute of Standards and Technology (since 2017)
- Dept of Veterans Affairs Office of Research and Development (since 2020)
- National Center for Advancing Translational Sciences (since 2024)

Nicole Kleinstreuer
Executive Director, ICCVAM
Director, NICEATM

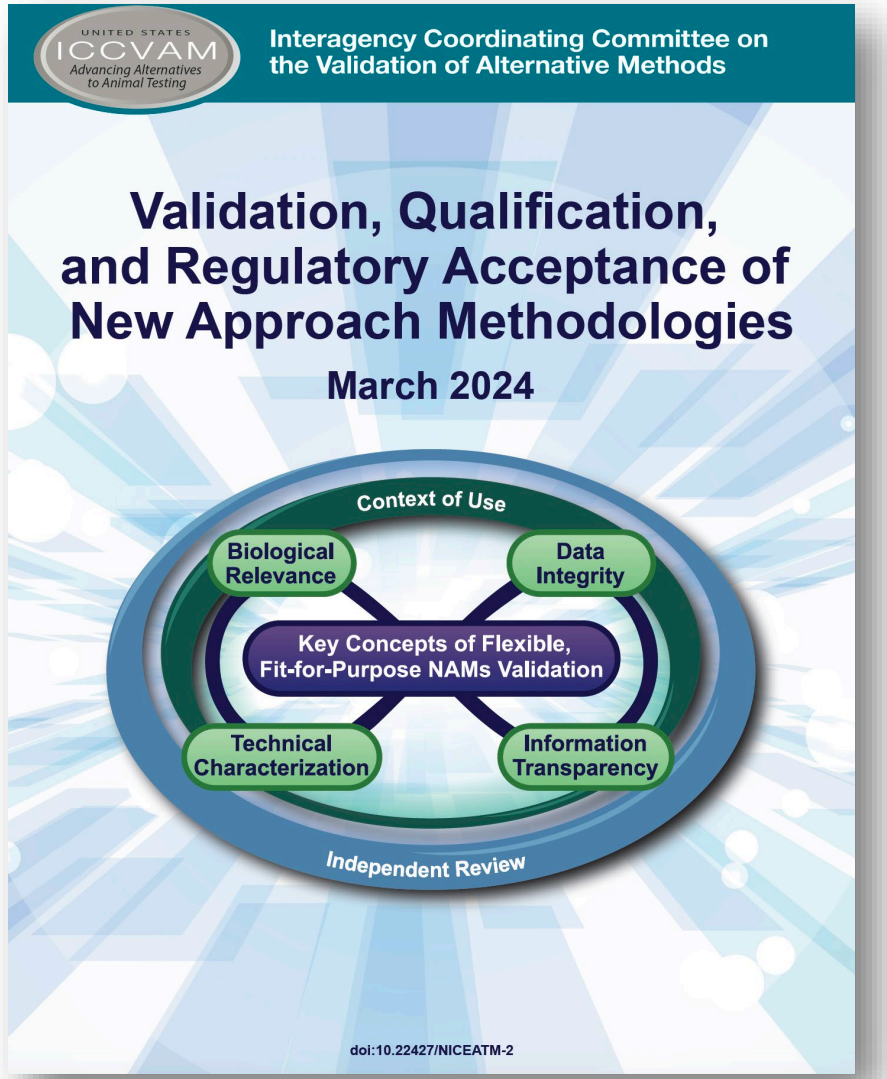
More information: https://ntp.niehs.nih.gov/go/iccvam

Interagency Coordinating Committee on the Validation of Alternative Methods



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

- **Connect end users with the developers of alternative methods**
- **Establish new validation approaches that are more flexible and efficient**
- **Ensure adoption and use of new methods by both regulators and industry**



https://ntp.niehs.nih.gov/go/ICCVAM-submit

International collaborative projects

CERAPP

Collaborative Estrogen Receptor Activity Prediction Project (2015/16)

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

CoMPARA

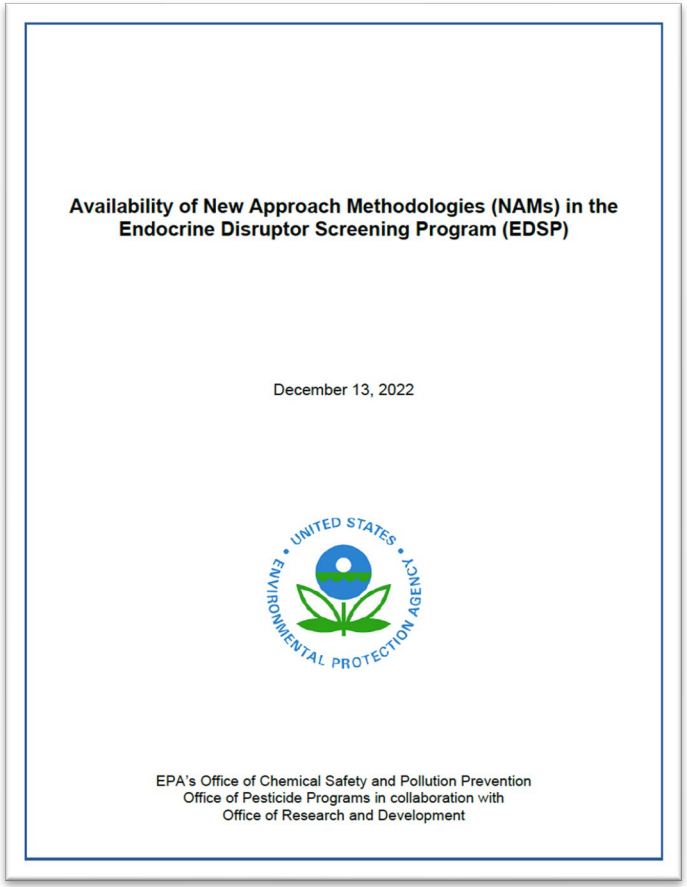
Collaborative Modeling Project for Androgen Receptor Activity (2017/18)

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

CATMoS

Collaborative Acute Toxicity Modeling Suite (2019/20)

Kleinstreuer et al. (https://doi.org/10.1016/j.comtox.2018.08.002)
Mansouri et al. (https://doi.org/10.1289/EHP8495)


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

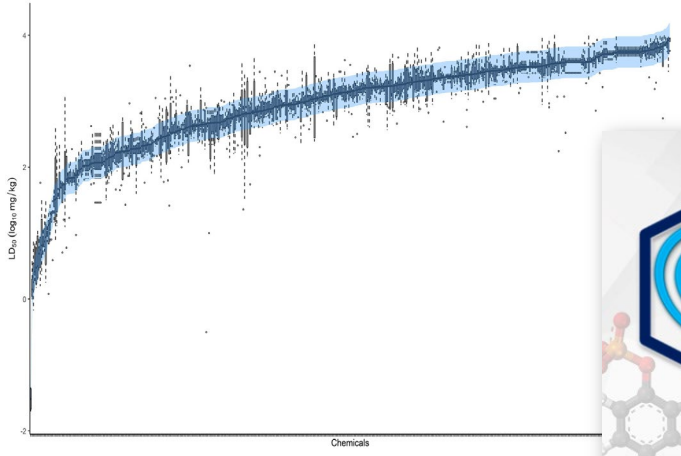
REACH COMPLIANCE

OPERA
OPEn (q)saR App

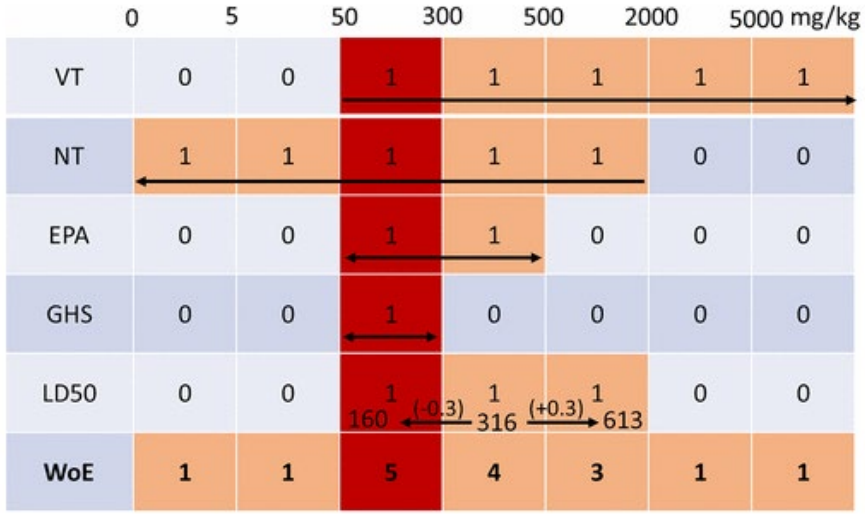
https://github.com/NIEHS/OPERA

Reference Data Variability as a Benchmark

Data-driven Confidence Intervals for Model Evaluation/Predictions



Analyzing sources of variability in acute oral toxicity data & applying 95% confidence interval to predictions



	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

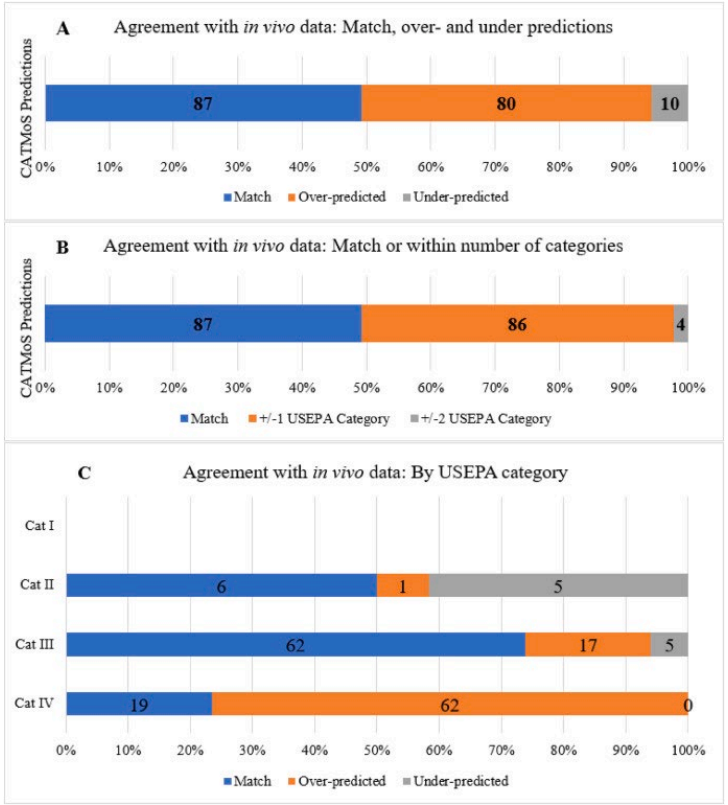
Karmaus et al. Toxicol Sci. 2022; Mansouri et al. EHP 2021

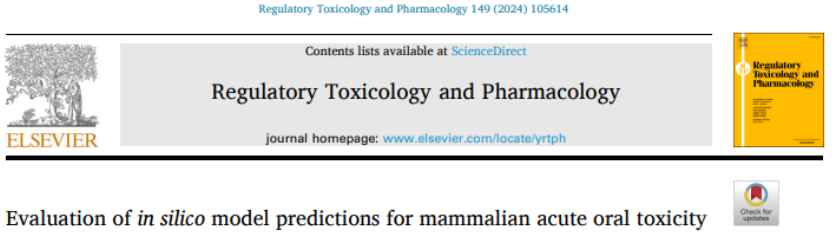
Application of CaTMOS to Pesticide AIs

EPA Case Study

- Comparative analysis of 177 pesticides with LD_{50} data between CaTMOS and EPA database
- 88% categorical concordance for 165 chemicals with empirical *in vivo* LD_{50} values ≥ 500 mg/kg

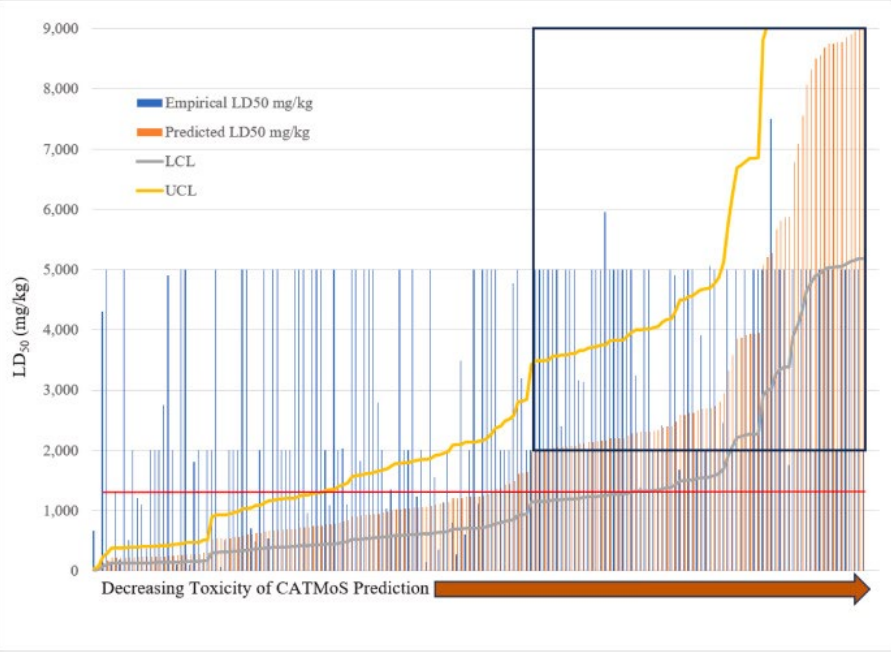
Toxicity Category based on CATMoS Prediction	Number of predictions	Toxicity Category based on Empirical *In Vivo* Test Data			
		I	II	III	IV
I (<50 mg/kg)	2	-	1	1	-
II (50-500 mg/kg)	25	-	**6**	16	3
III (>500-5,000 mg/kg)	126	-	5	**62**	59
IV (>5,000 mg/kg)	24	-	-	5	**19**
III and IV combined	150	-	5	145	




Regulatory Toxicology and Pharmacology 149 (2024) 105614
Contents lists available at ScienceDirect
Regulatory Toxicology and Pharmacology
journal homepage: www.elsevier.com/locate/yrtph
ELSEVIER

Evaluation of *in silico* model predictions for mammalian acute oral toxicity and regulatory application in pesticide hazard and risk assessment

Patricia L. Bishop [a,*], Kamel Mansouri [b], William P. Eckel [c], Michael B. Lowit [c], David Allen [d,1], Amy Blankinship [c], Anna B. Lowit [e], D. Ethan Harwood [c], Tamara Johnson [c], Nicole C. Kleinstreuer [b]



Bishop et al., Reg. Tox. Pharm., 2024 https://doi.org/10.1016/j.yrtph.2024.105614

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

National Institute of Environmental Health Sciences
Division of Translational Toxicology

OPERA predictions online

National Toxicology Program
U.S. Department of Health and Human Services

QSAR TOOLBOX

Input | Profiling | Data | Category definition | Data Gap Filling | Report

Gap Filling: Trend analysis | Read across | (Q)SAR
Workflow Editor: Automated | Standardized | New | Import | Export | Delete

Documents
Document 1
[C: 1;Md: 0;P: 0] CAS: 58082

Filter endpoint tree...
Structure
Structure info
Parameters
Physical Chemical Properties
Autoflammability / Self-ignition tempera...
Boiling point
Chemical reactivity
Density
Dissociation Constant (pKa)
Explosive properties
Flammability
Flash point
Melting / freezing point
Oxidation reduction potential
Oxidising properties
Particle size
Partition Coefficient:
Solubility in organic solvents / fat solubil...
Stability in organic solvents and identity...
Surface tension
Vapour pressure
Viscosity
Water solubility
Environmental Fate and Transport
Ecotoxicological Information
Human Health Hazards

Data Gap Filling Settings
Only endpoint relevant
At this position:
QSARs 2
Automated workflows 0
Standardized workflows 0

Details for 2 (Q)SAR models

QSAR name	#	Predicted	Domain	QMRF	Test set	Training set
Boiling Point Adapted Stein and Brown Method (EPISUITE) (1.0)						
Opera BP (2.6)						

EPA United States Environmental Protection Agency

Endosulfan
115-29-7 | DTXSID1020560
Searched by DSSTox Substance Id.

ToxCast: Models
ToxCast Model Predictions

Toolbox Repository

Tools / QSARs / OPERA models

OPERA models

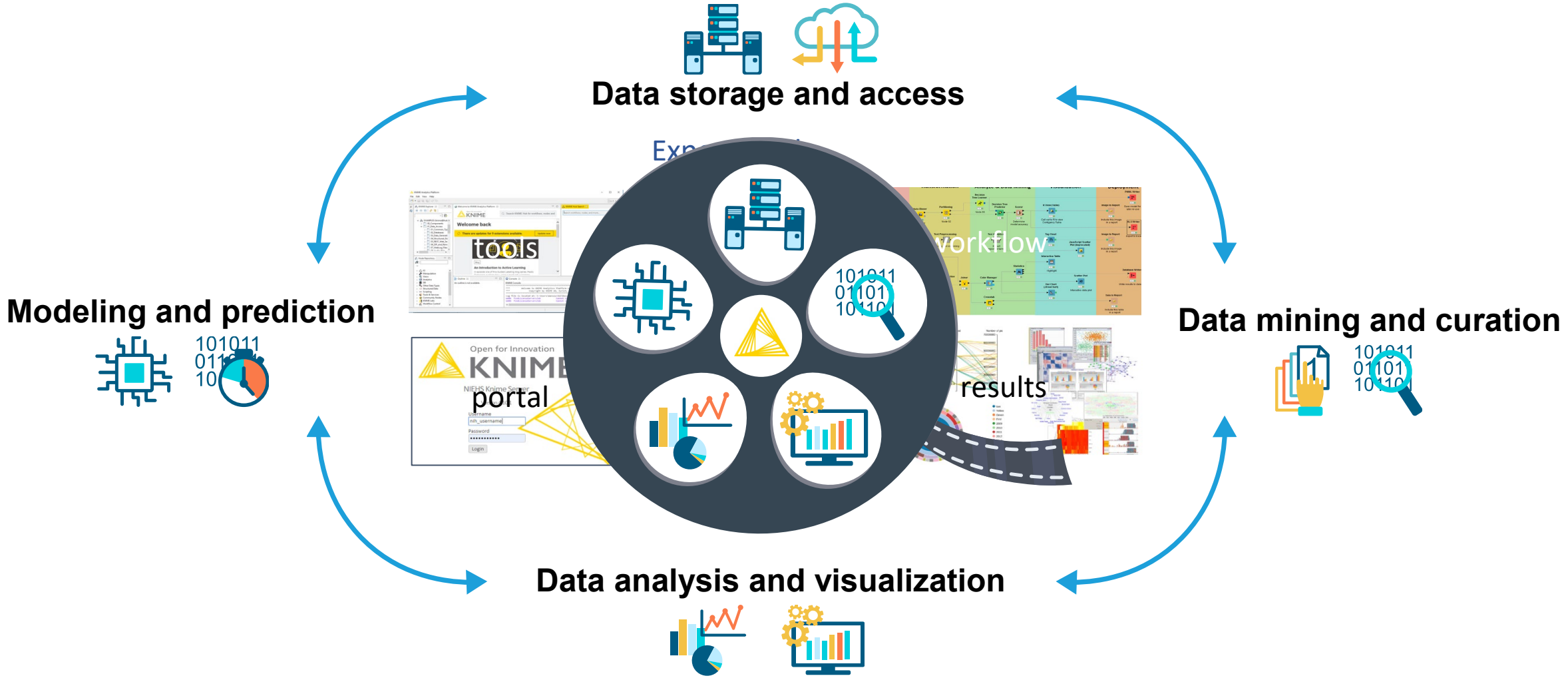
OPERA
OPEn (q)saR App

Current version: 1.0
Supported Toolbox versions: 4.5
Developer: NIEHS
Category: QSARs
Downloads: 57
Rating: ☆☆☆☆☆ 0
Description:
OPERA is a free and open-source/open-data suite
physicochemical properties, environmental fate, ADME
information including applicability domain and accuracy
data and standardized QSAR-ready chemical structures.
friendly graphical interface for Windows and Linux operati

Executions 1203
Spec | Executions (10) | Readme
DEFAULT INSTANCE TYPE: baseline-4
HAS INTERNET ACCESS: No
INPUTS
string Input file format REQUIRED
OUTPUTS
file OPERA output tarball REQUIRED

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Modeling and Visualization (MoVIZ) Pipeline



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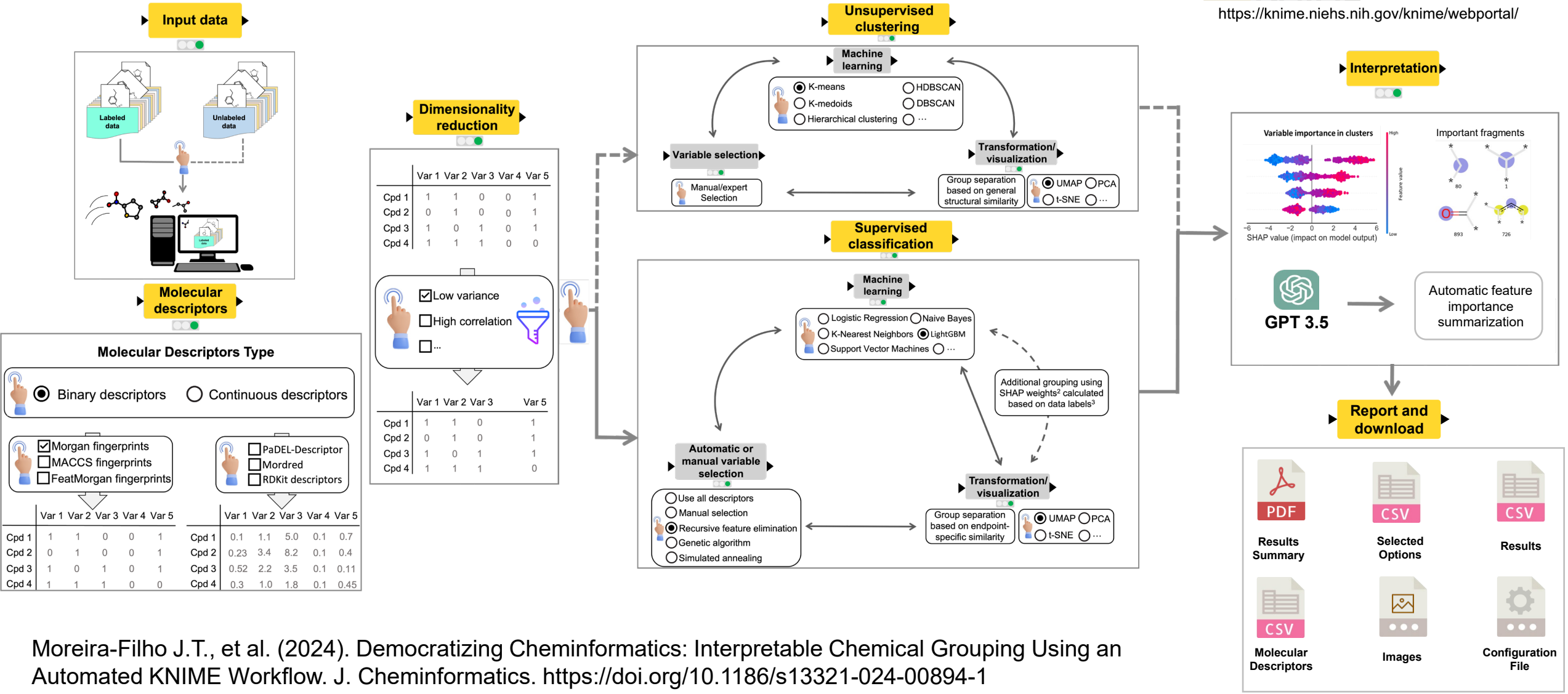
Chemical Grouping Workflow

Open for Innovation KNIME **KNIME Server**
https://knime.niehs.nih.gov/knime/webportal/



Moreira-Filho J.T., et al. (2024). Democratizing Cheminformatics: Interpretable Chemical Grouping Using an Automated KNIME Workflow. J. Cheminformatics. https://doi.org/10.1186/s13321-024-00894-1

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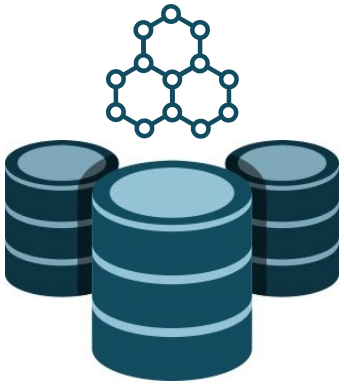
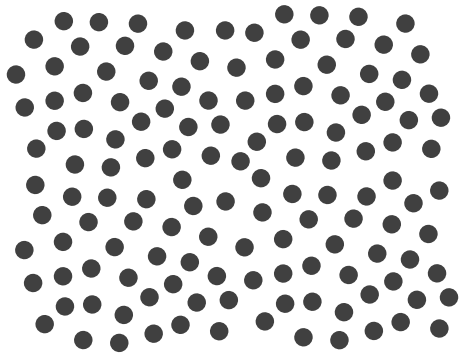
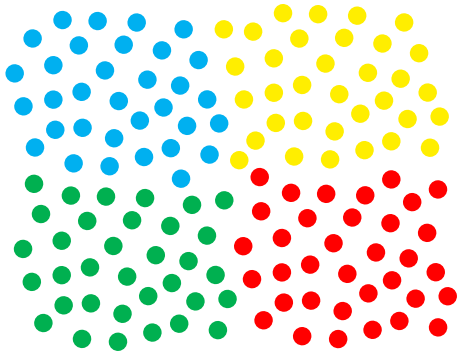
Application – DTT HTS initiative



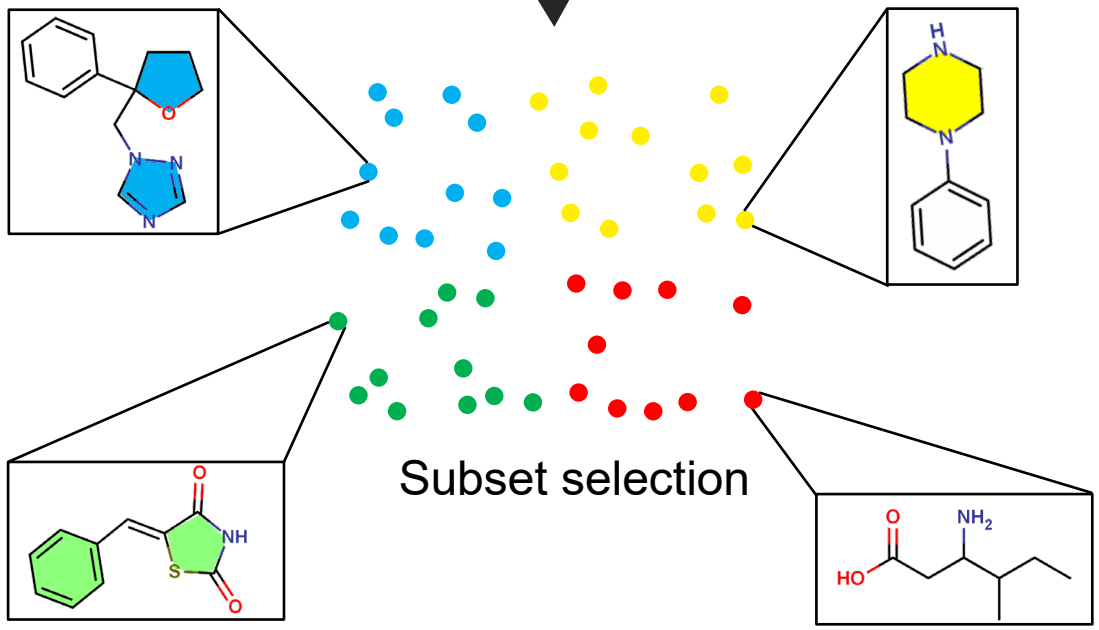
Chemical database



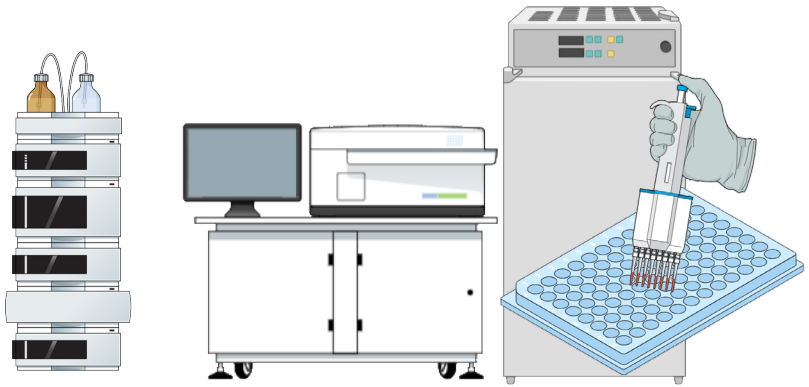
Chemical space



Cluster compounds

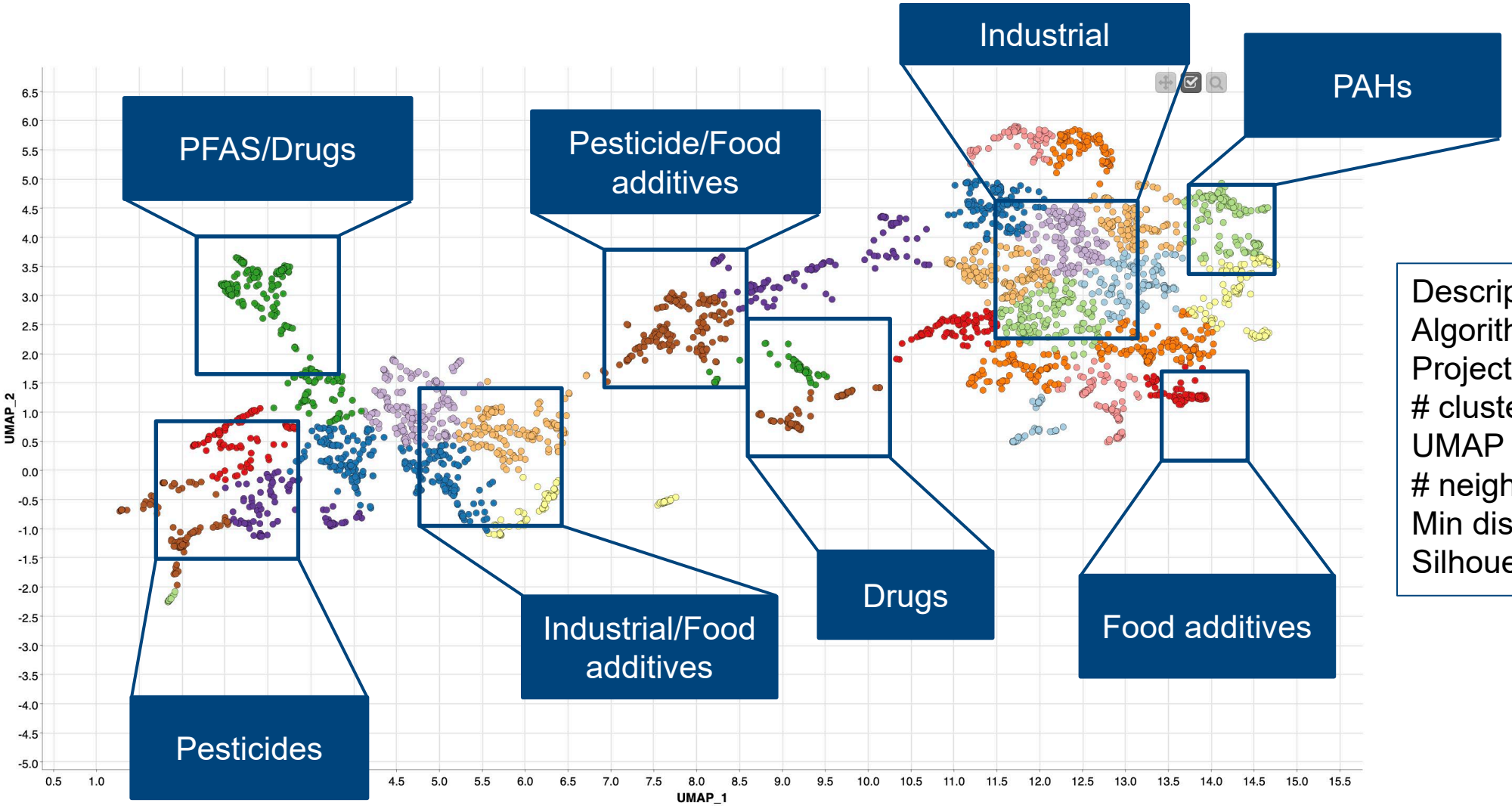


Subset selection



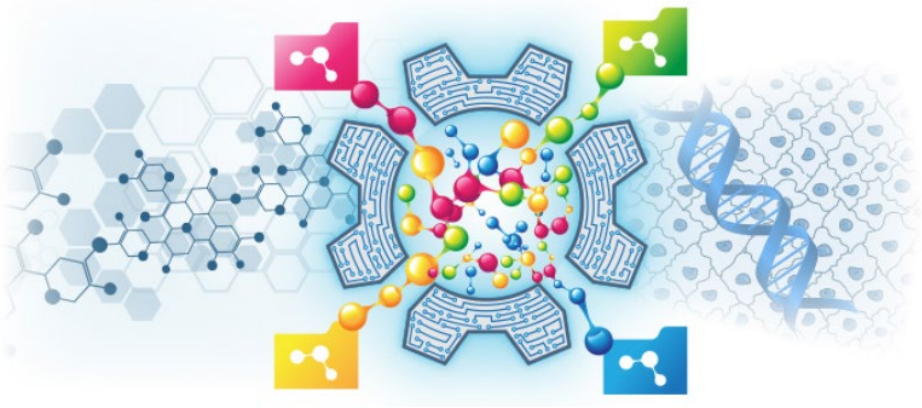
Experimental testing

Unsupervised Clustering



Descriptor: **Morgan (2048 bit)**
Algorithm: **K-means**
Projection: **UMAP**
clusters: **32**
UMAP metric: **dice**
neighbors: **28**
Min distance: **0.01**
Silhouette score: **0.47**

Clustering and Classification Workshop



https://www.niehs.nih.gov/news/events/pastmtg/2022/nams2022/index.cfm

Convened international experts to discuss methods, their applications to guide toxicology research and inform hazard and risk assessment.

Accomplishments:

- Defined the concept similarity for supervised and unsupervised approaches
- Introduced different approaches, corrected some misconceptions
- Involved both NAM developers and users
- Established a consortium and a community for increasing communication and collaboration across sectors
- *Ongoing and future:* develop and share new ideas/concepts (best practices & innovation)

Mansouri K., et al. (2024). Unlocking the Potential of Clustering and Classification Approaches: Expert Insights and Applications. Environmental Health Perspectives. doi:10.1289/EHP14001

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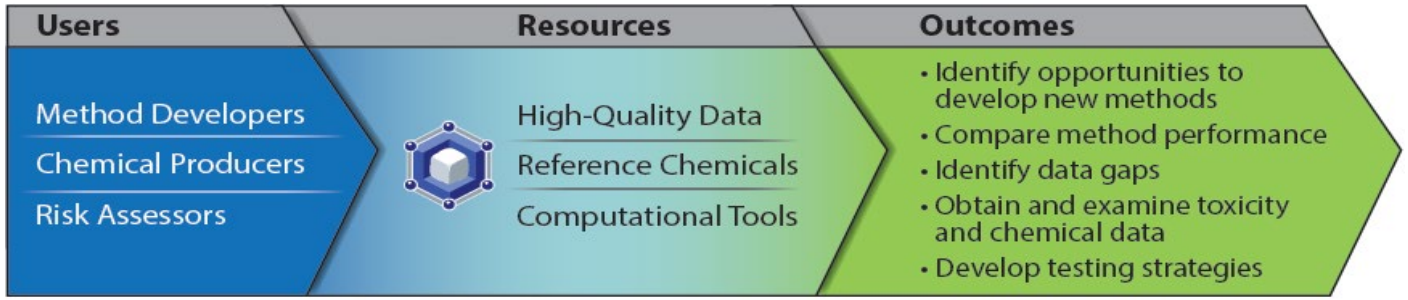
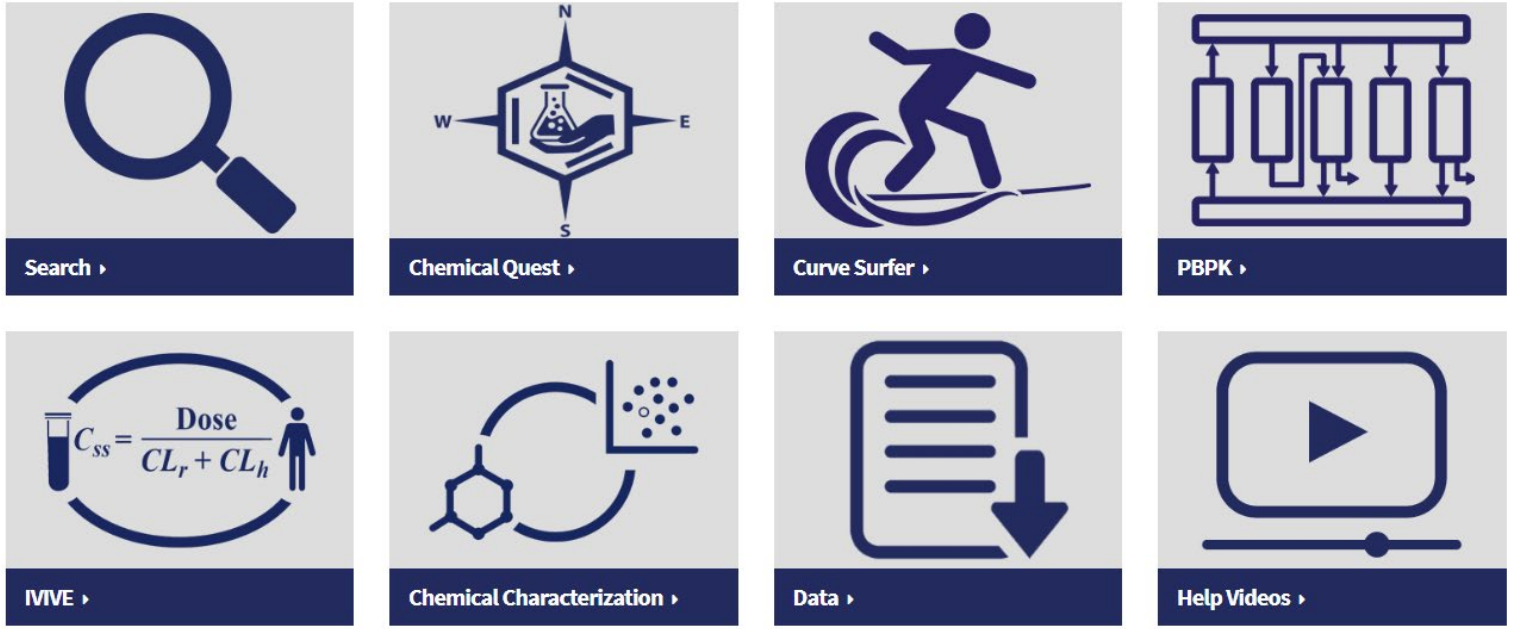
ICE: The Integrated Chemical Environment



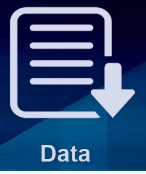
Integrated Chemical Environment



Findable Accessible Interoperable Reusable

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/



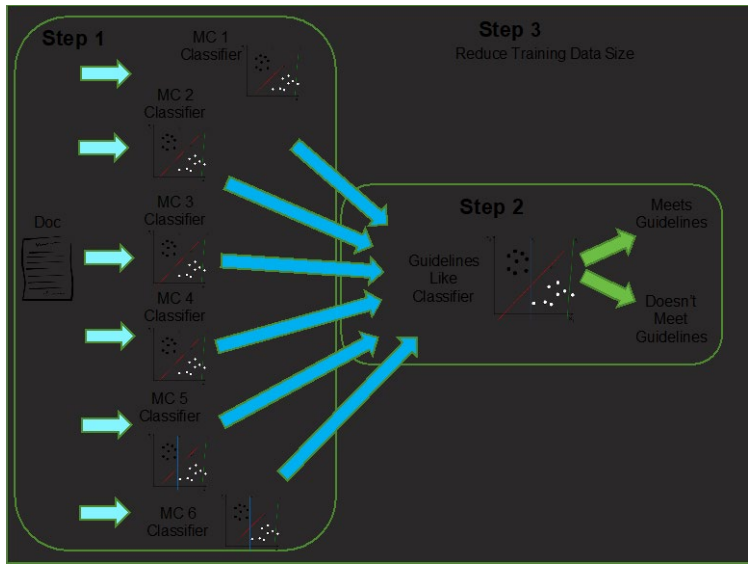
ICE Data (In Vivo and In Vitro)

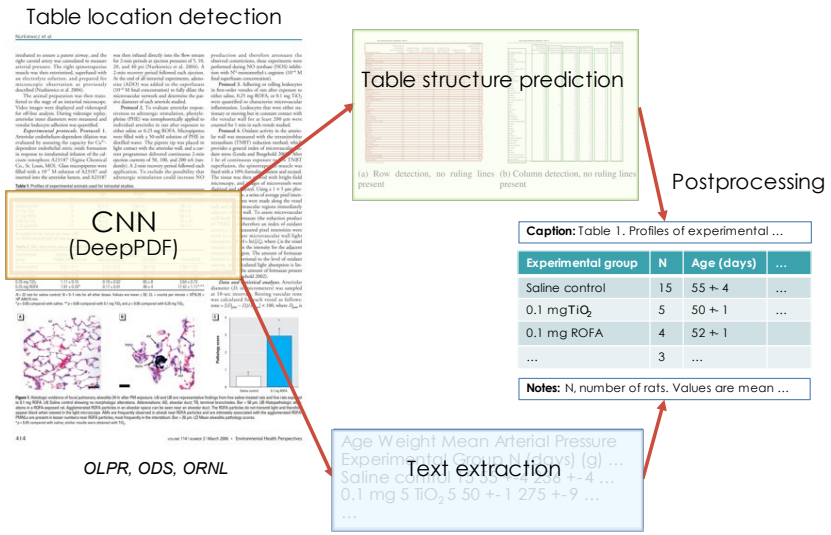
Toxicity endpoint	Assays	# of chemicals
Chemical Parameters	Experimental physicochemical properties	~20000
ADME Parameters	Fu, intrinsic clearance, Caco2 permeability	~3000
Acute Toxicity	In vivo acute oral, dermal, and inhalation toxicity	~10000
Cancer	In vivo and in vitro cancer, and Weight of Evidence	3038
DART	In vivo and in vitro DART	628
Skin Sensitization	In vivo and in vitro skin sensitization	1771
Skin Irritation	In vivo and in vitro skin irritation/corrosion	595
Eye Irritation	In vivo and in vitro eye irritation/corrosion	455
Endocrine	In vivo and low throughput in vitro data on AR and ER agonist and antagonist activity	384
cHTS	Curated US EPA's ToxCast and Federal Tox21 assays (in vitro)	~10000

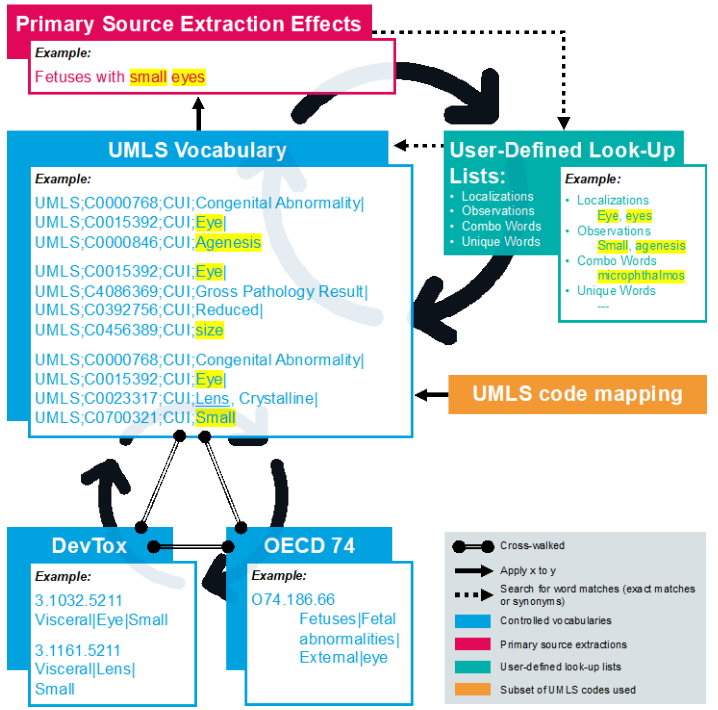
National Institute of Environmental Health Sciences
Division of Translational Toxicology

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

Foster et al. 2024 Env Health Persp

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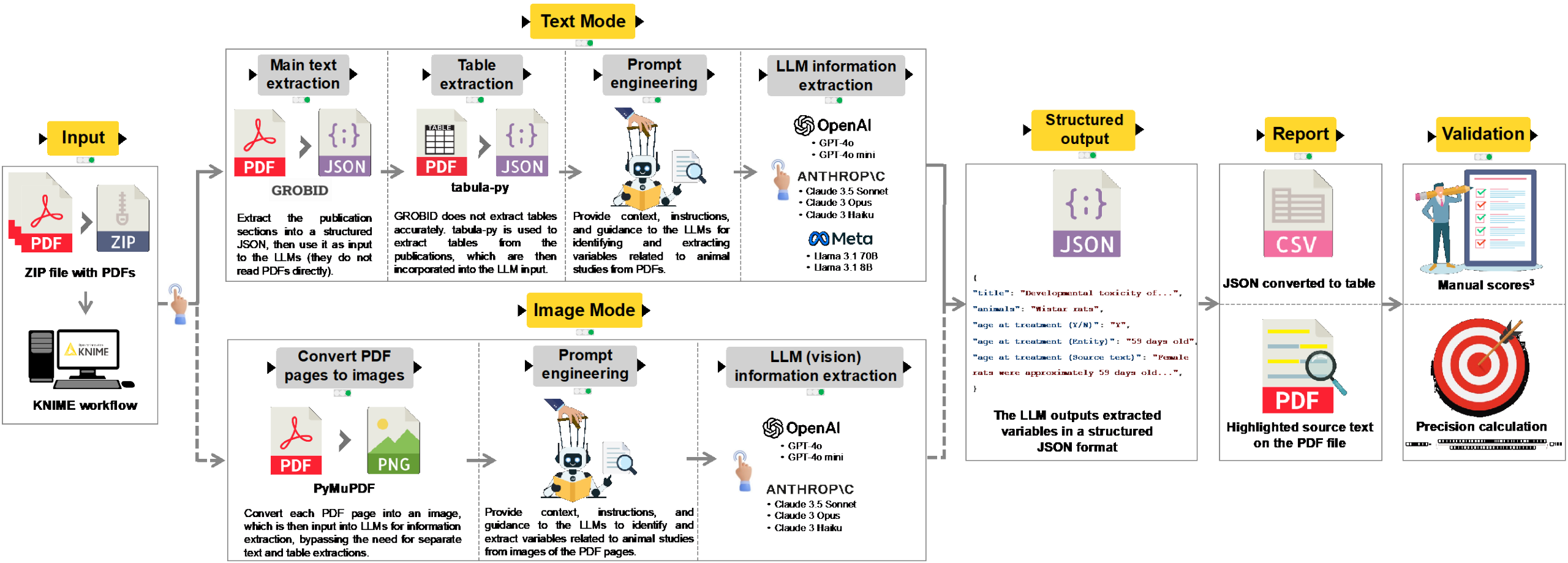
Extraction workflow



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Landing page and prompts

Automatic Information Extraction

ZIP File Upload

Use the file browser below to upload the data.

Choose File Sample_1.zip Size: 5.45 MB

Extraction Modes

- (•) Text Mode (Extract text from PDF)
- ( ) Image Mode (Analyze PDF pages as images)

Refresh

LLM Model

- ( ) GPT-4
- (•) GPT-4o mini
- ( ) Claude 3.5 Sonnet
- ( ) Claude 3 Opus
- ( ) Claude 3 Haiku
- ( ) Llama 3.1 70B
- ( ) Llama 3.1 8B

API Key

INSERT_YOUR_API_KEY_HERE

Guide

1. File Upload

Upload a ZIP file containing the PDF files you want to process.

2. Extraction Modes

Our workflow offers two modes for extracting information from scientific publications:

- **Text Mode:** Extracts the text from the PDF file and processes it using a Large Language Model (LLM) to extract the required information.
- **Image Mode:** Converts PDF pages to images and uses a Large Language Model with vision capabilities to extract the required information.

▸ Details

3. API Keys for LLM Providers

Our workflow uses models from multiple providers to offer you the best possible results. You'll need to provide API keys for the respective models you select:

- **OpenAI:** Powers GPT models like GPT-4o, and GPT-4o mini
- **Anthropic:** Offers the models Claude 3.5 Sonnet, Claude 3 Opus, and Claude 3 Haiku
- **Meta:** Provides free and open-source models Llama 3.1 70B, and Llama 3.1 8B

▸ Details

Automatic Information Extraction

Info Extraction - Prompt

System Prompt (editable)
Sets the context and behavior for the AI model.

System prompt

```
You are a scientific assistant and toxicologist expert in reviewing scientific publications and extract and analyze specific relevant information out of PDFs in valid JSON format. Be careful with numbers.
```

User Prompt (editable)
Specific instruction you want the AI to address for each document.

Guides the model in extracting the desired information from the PDFs.

User prompt - instruction

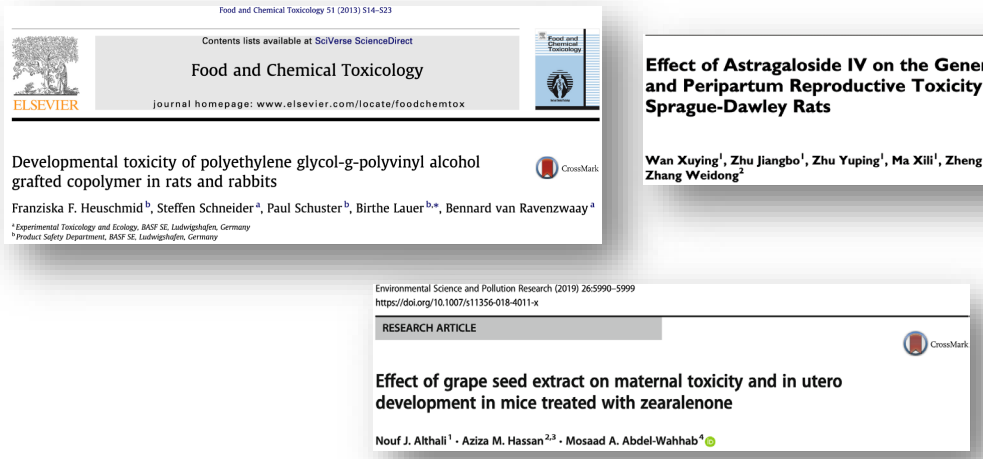
```
Analyze the input JSON file (data) and extract the specified variables to create a new JSON output. Follow these guidelines:

1. Output Format:
   - Return only a valid JSON object.
   - Do not include any additional text before or after the JSON output.
2. JSON Structure:
   - Each variable becomes a key-value pair in the JSON object.
   - Use the exact variable names provided in the list below.
3. Data Handling:
   - Use 'N/A' for missing or null values.
   - Ensure uniform formatting for similar types of variables.
   - Include only the specified variables in the output.
   - Combine related variables into a single value without nesting (e.g., combine "specie 1" and "specie 2" into a single "Animal" value).
4. Value Extraction Guidelines:
   - For 'Y/N' variables: Use 'Y' if information is present, 'N' if absent.
   - For entity variables: Provide specific values or ranges (e.g., '8 weeks', '200 grams').
   - For source text variables: Provide the exact relevant text snippet from the input.
5. Specific Variable Handling:
   - 'Animal': Provide species as a single string (e.g., 'Rat', 'Mouse'). Separate multiple species with commas.
   - 'Number of animals per treatment group': Specify as '10M and 10F' or '20 overall evenly split' if applicable.
   - 'Dose': Include amount and units (e.g., '10 mg/kg').
   - 'Dose day': Specify the exact days of administration.
6. Complex Data Handling:
   - For variables with multiple related pieces of information, combine them into a coherent, comma-separated string.
   - If information is spread across multiple sections in the input, consolidate it into a single, comprehensive value.
7. Consistency and Accuracy:
   - Maintain consistent formatting across similar variables.
   - Double-check extracted values against the source text to ensure accuracy.
8. Error Handling and Reporting:
   - If unable to extract a value due to complexity or lack of clear information, use 'Unable to determine' instead of 'N/A'.

Examples of Correct Extractions:

- "Animal": "Sprague-Dawley rats"
- "Age at treatment (Entity)": "8-10 weeks"
- "Body weight at treatment (Entity)": "180-220 grams"
- "Dose": "10 mg/kg, 50 mg/kg, 100 mg/kg"
- "Dose day": "GD 6-15"
- "Number of animals per treatment group": "25 females per dose group"
- "Body weight at treatment? (entity)": "Rats: 160 g, Mice: 20 g"

Variables to extract:
```

User prompt - variables

```
[
  'Title',
  'Animal',
  'Age at treatment (Y/N)',
  'Age at treatment (Entity)',
  'Age at treatment (Source text)',
  'Body weight at treatment? (Y/N)',
  'Body weight at treatment (Entity)',
  'Body weigh at treatment (Source text)',
  'Number of animals per treatment group (note if this is given as #M and #F, or # overall evenly split between the two)',
  'Route of administration',
  'Dose',
  'Daily dosing? (Y/N)',
  'Dose day',
  'Animal checks during treatment? (Y/N)',
  'Animal checks during treatment (Entity)',
  'Animal checks during treatment? (Source text)',
  'Body weights during treatment? (Y/N)',
  'Body weights during treatment (Entity)',
  'Body weights during treatment (Source text)',
  'Food consumption during treatment? (Y/N)',
  'Food consumption during treatment (Entity)',
  'Food consumption during treatment (Source text)',
  'Sacrifice (Y/N)',
  'Sacrifice (Entity)',
  'Sacrifice (Source text)',
  'Maternal body weight at sacrifice? (Y/N)',
  'Maternal body weight at sacrifice (Entity)',
  'Maternal body weight at sacrifice (Source text)',
  'Fetal body weight at sacrifice, individual? (Y/N)',
  'Fetal body weight at sacrifice, individual (Entity)',
  'Fetal body weight at sacrifice, individual (Source text)',
  'Fetal body weight at sacrifice, combined? (Y/N)',
  'Fetal body weight at sacrifice, combined (Entity)',
  'Fetal body weight at sacrifice, combined (Source text)',
  'Uterine weight? (Y/N)',
  'Uterine weight (Entity)',
  'Uterine weight (Source text)',
  'Organ weights? (any in addition to uterus, Y/N)',
  'Organ weights? (any in addition to uterus, entity)',
  'Organ weights? (any in addition to uterus, source text)',
  'Pregnancy status (Y/N)',
  'Pregnancy status (Entity)',
  'Pregnancy status (Source text)',
  'Number/count of live fetuses? (Y/N)',
  'Number/count of live fetuses (entity)',
  'Number/count of live fetuses (source text)',
  'Number/count of dead fetuses? (Y/N)',
  'Number/count of dead fetuses (Entity)',
  'Number/count of dead fetuses (Source text)',
  'Fetal sex (Y/N)',
  'Fetal sex (Number of males and females, entity)',
  'Fetal sex (Source text)',
```

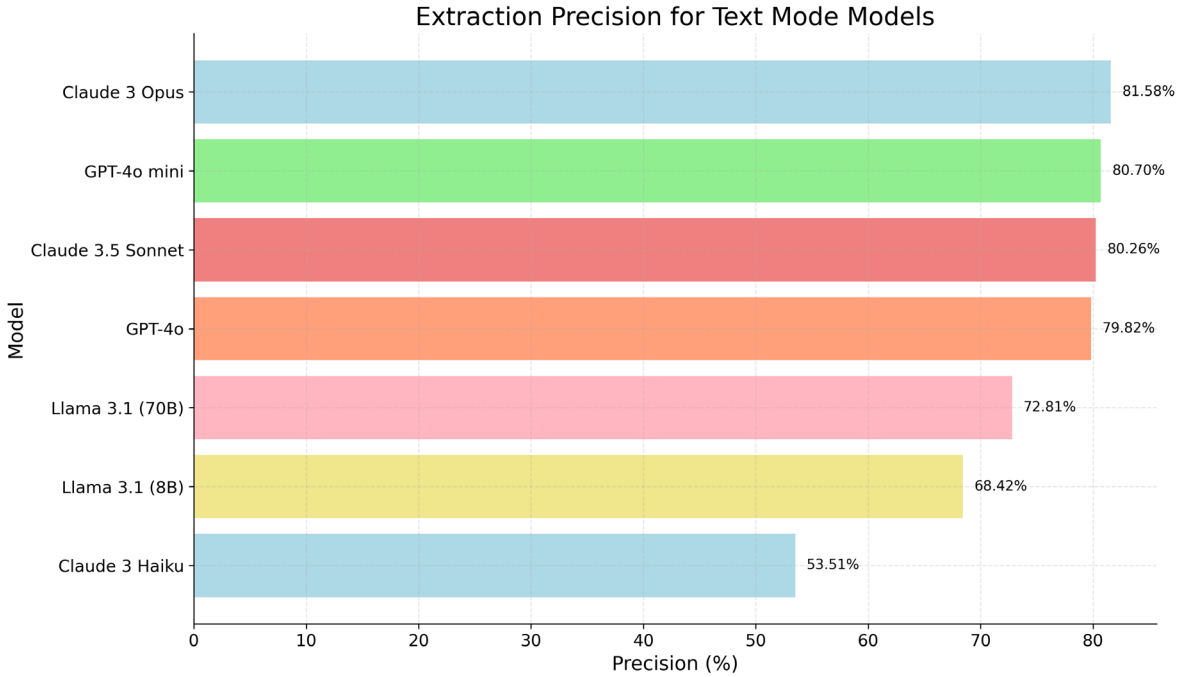
Variables to Extract (editable)
Define the specific information you want to extract from each document.
Will be consistently extracted across all processed PDFs, allowing for structured data output.

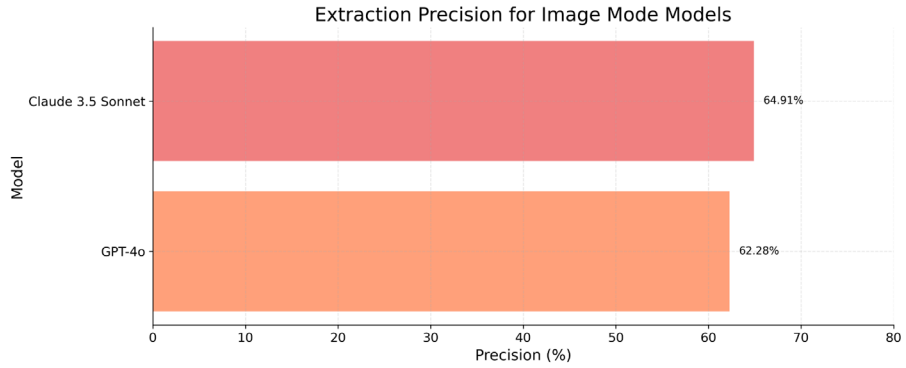
Validation - precision



❖ Extracted if the following variables are present (Y/N), the entity, and the source text:

- Title
- Animal
- Age at treatment
- Body weight at treatment
- Number of animals per treatment group
- Route of administration
- Dose
- Daily dosing
- Dose day
- Animal checks during treatment
- Body weights during treatment
- Food consumption during treatment
- Sacrifice
- Maternal body weight at sacrifice
- Fetal body weight at sacrifice, individual
- Fetal body weight at sacrifice, combined
- Uterine weight
- Organ weights
- Pregnancy status
- Number of Live fetuses
- Number of Dead fetuses
- Fetal sex
- Number of Implantation sites
- Number of Corpora lutea
- Number of Resorptions
- Placental evaluation
- Fetal exam, any type
- Fetal external examination
- Fetal visceral examination
- Fetal skeletal examination





Data

ICE Data (In Silico Models/Integrated Approaches)

Endpoint	Model	# of chemicals
Physicochemical Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Structural Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Predicted ADME Properties	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Environmental Fate	OPEn (q)saR App (OPERA) Mansouri et al. J Cheminform 2018	1M+
Acute Oral Toxicity	Collaborative Acute Toxicity Modeling Suite (CATMoS) - Rat acute oral toxicity. Mansouri et al. EHP 2021	1M+
Endocrine	Estrogen Receptor pathway Model. Browne et al. ES&T 2015	1812
	Androgen Receptor Pathway Model. Kleinstreuer et al. Chem Res Tox 2017	1855
	Collaborative Estrogen Receptor Activity Prediction Project (CERAPP). Mansouri et al. EHP 2016	1M+
	Collaborative Modeling Project for Androgen Receptor Activity (COMPARA). Mansouri et al. EHP 2020	1M+
Exposure Predictions	Systematic Empirical Evaluation of Models (US EPA'S SEEM3). Ring et al. Environ Sci Technol 2019	475,000+

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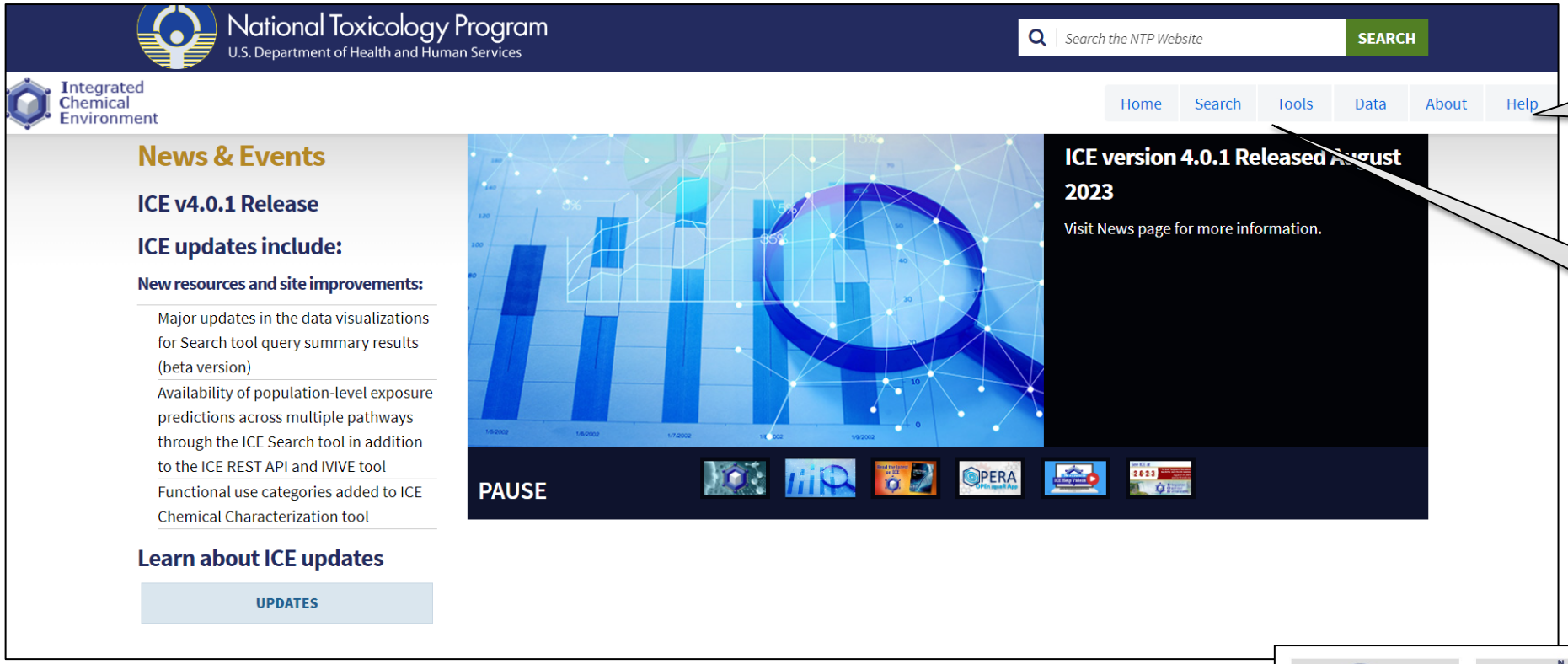
Accessing ICE Tools

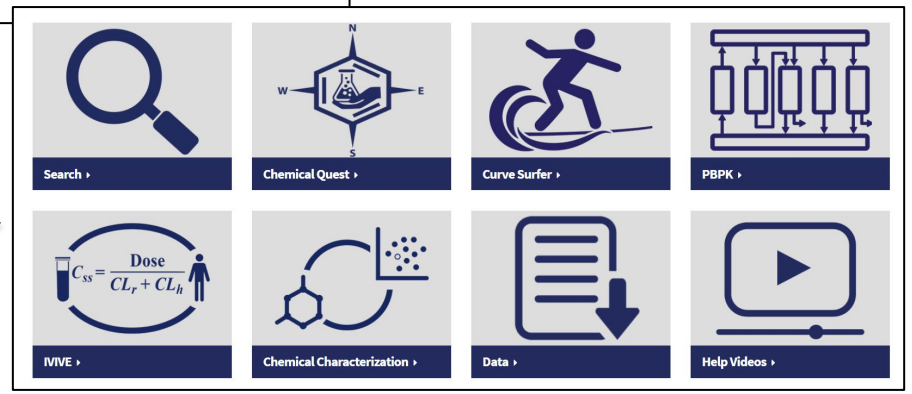


Detailed information on each tool is available as individual user guides and videos through the help tab.

Search and other tools can also be accessed through the search tab and tools tab, respectively.

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

The tools can be accessed through ICE homepage by clicking the respective icons.



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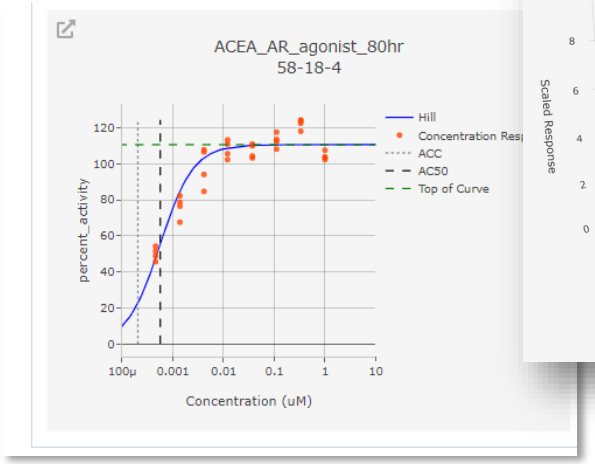
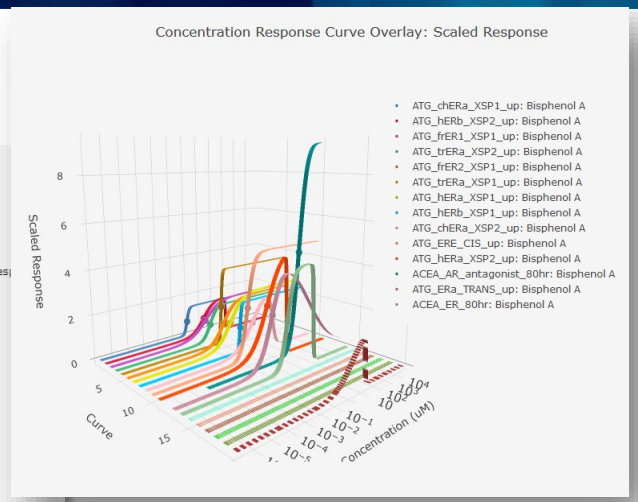
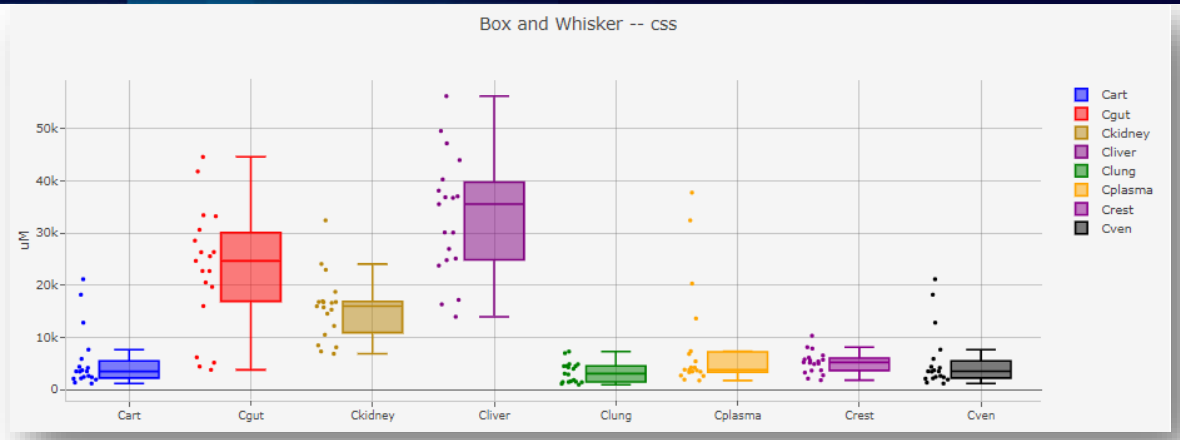
ICE Tools: Examples

HTS Data Exploration

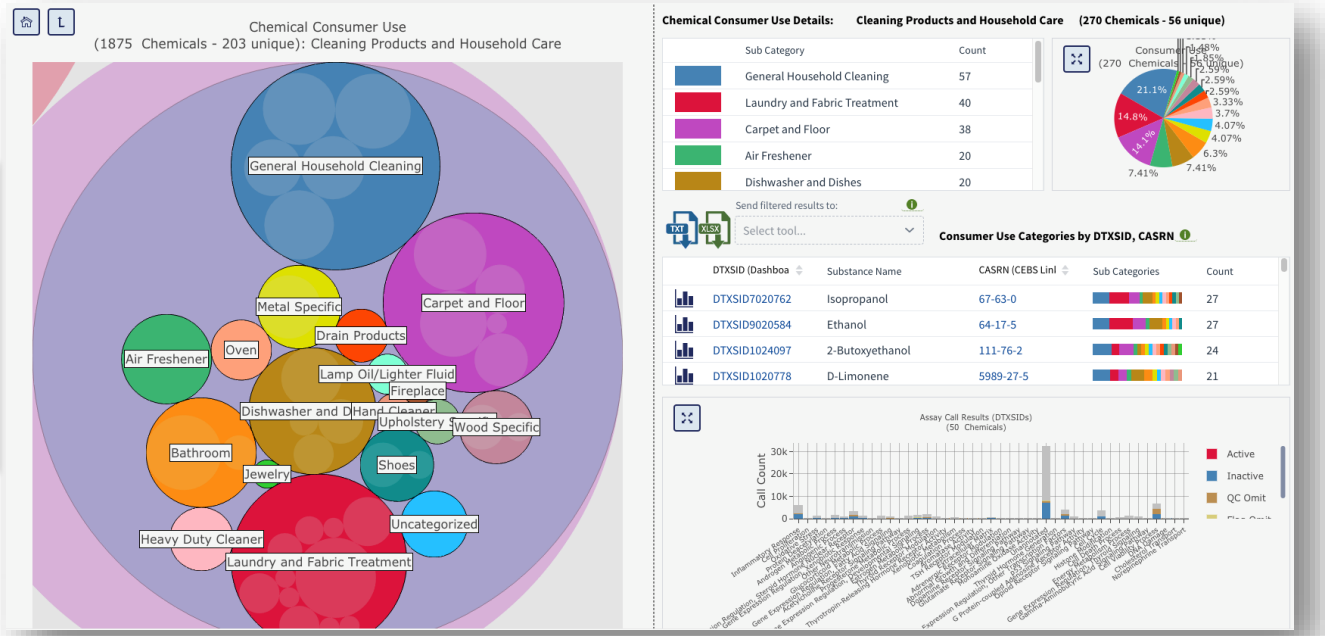






Predicting Chemical Exposure: Body Tissues, Consumer Products

Chemical Similarity



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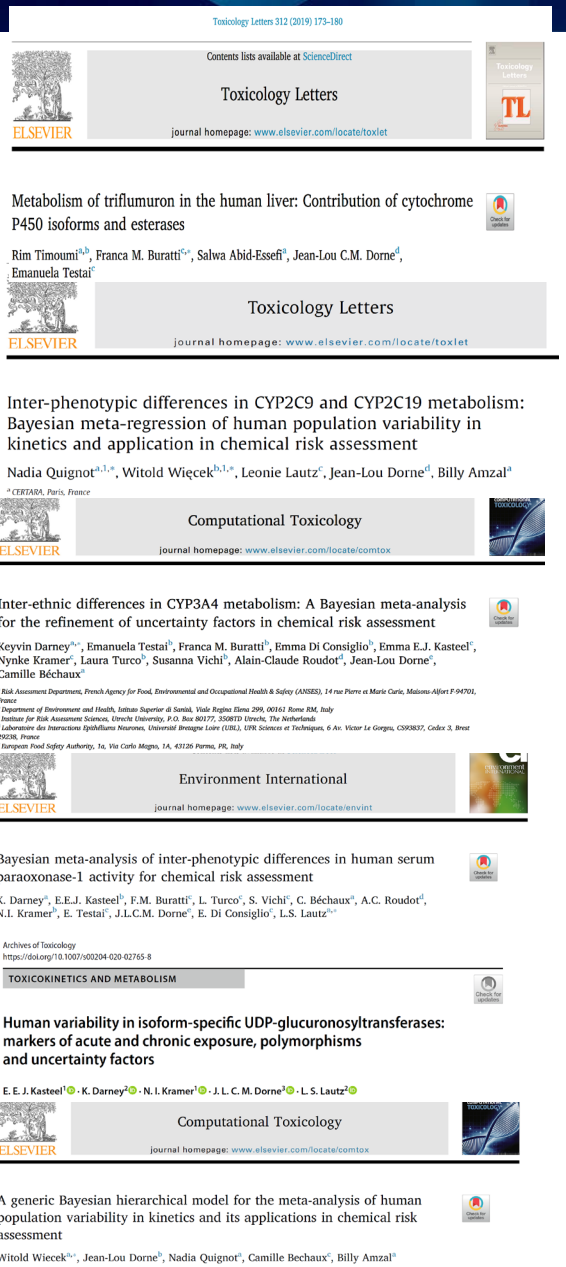
TK to Connect Metabolism and Variability


Toxicology Letters 312 (2019) 173–180

Contents lists available at ScienceDirect

Toxicology Letters

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

Metabolism of triflumuron in the human liver: Contribution of cytochrome P450 isoforms and esterases

Rim Timoumi[a,b], Franca M. Buratti[c,*], Salwa Abid-Essefi[a], Jean-Lou C.M. Dorne[d], Emanuela Testai[c]

Toxicology Letters

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

Inter-phenotypic differences in CYP2C9 and CYP2C19 metabolism: Bayesian meta-regression of human population variability in kinetics and application in chemical risk assessment

Nadia Quignot[a,1,*], Witold Więcek[b,1,*], Leonie Lautz[c], Jean-Lou Dorne[d], Billy Amzal[a]

[a] CERTARA, Paris, France

Computational Toxicology

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

Inter-ethnic differences in CYP3A4 metabolism: A Bayesian meta-analysis for the refinement of uncertainty factors in chemical risk assessment

Keyvin Darney[a,*], Emanuela Testai[b], Franca M. Buratti[b], Emma Di Consiglio[b], Emma E.J. Kasteel[c], Nynke Kramer[c], Laura Turco[b], Susanna Vichi[b], Alain-Claude Roudot[d], Jean-Lou Dorne[e], Camille Béchaux[a]

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[b] Department of Environment and Health, Istituto Superior di Sanità, Viale Regina Elena 299, 00161 Rome RM, Italy
[c] Institute for Risk Assessment Sciences, Utrecht University, P.O. Box 80177, 3508TD Utrecht, The Netherlands
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[e] European Food Safety Authority, 1a, Via Carlo Magno, 1A, 43126 Parma, PR, Italy

Environment International

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

Bayesian meta-analysis of inter-phenotypic differences in human serum paraoxonase-1 activity for chemical risk assessment

K. Darney[a], E.E.J. Kasteel[b], F.M. Buratti[c], L. Turco[c], S. Vichi[c], C. Béchaux[a], A.C. Roudot[d], N.I. Kramer[b], E. Testai[c], J.L.C.M. Dorne[e], E. Di Consiglio[c], L.S. Lautz[b,*]

Archives of Toxicology
https://doi.org/10.1007/s00204-020-02765-8

TOXICOKINETICS AND METABOLISM

Human variability in isoform-specific UDP-glucuronosyltransferases: markers of acute and chronic exposure, polymorphisms and uncertainty factors

E. E. J. Kasteel[1] · K. Darney[2] · N. I. Kramer[1] · J. L. C. M. Dorne[3] · L. S. Lautz[2]

Computational Toxicology

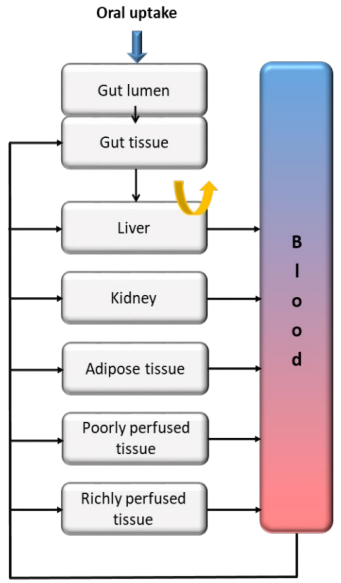
journal homepage: www.elsevier.com/locate/comtox

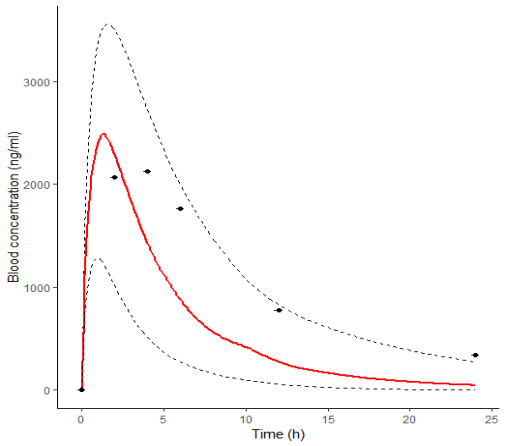
A generic Bayesian hierarchical model for the meta-analysis of human population variability in kinetics and its applications in chemical risk assessment

Witold Wiecek[b,*], Jean-Lou Dorne[b], Nadia Quignot[a], Camille Bechaux[c], Billy Amzal[a]

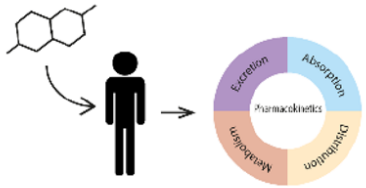
Covering Phase I CYP450 and Phase II UGTs enzymes

PBPK models + virtual population



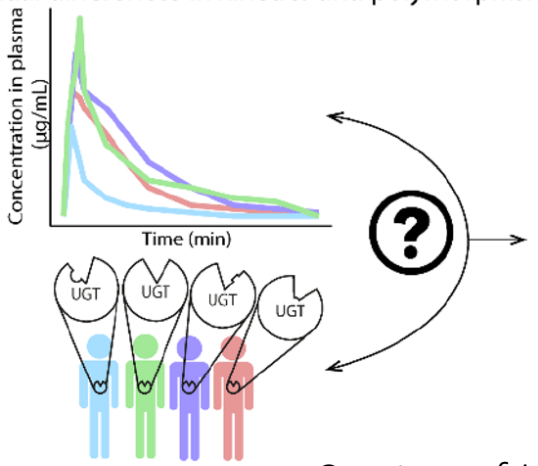


Pharmacokinetic data on compounds metabolised by UGT isoforms is collected and summarised in a database



Data on polymorphism frequencies in different populations is collected and summarised

Interindividual differences in kinetics and polymorphisms



UGT-related uncertainty factors

Courtesy of Jean-Lou Dorne

efsa European Food Safety Authority

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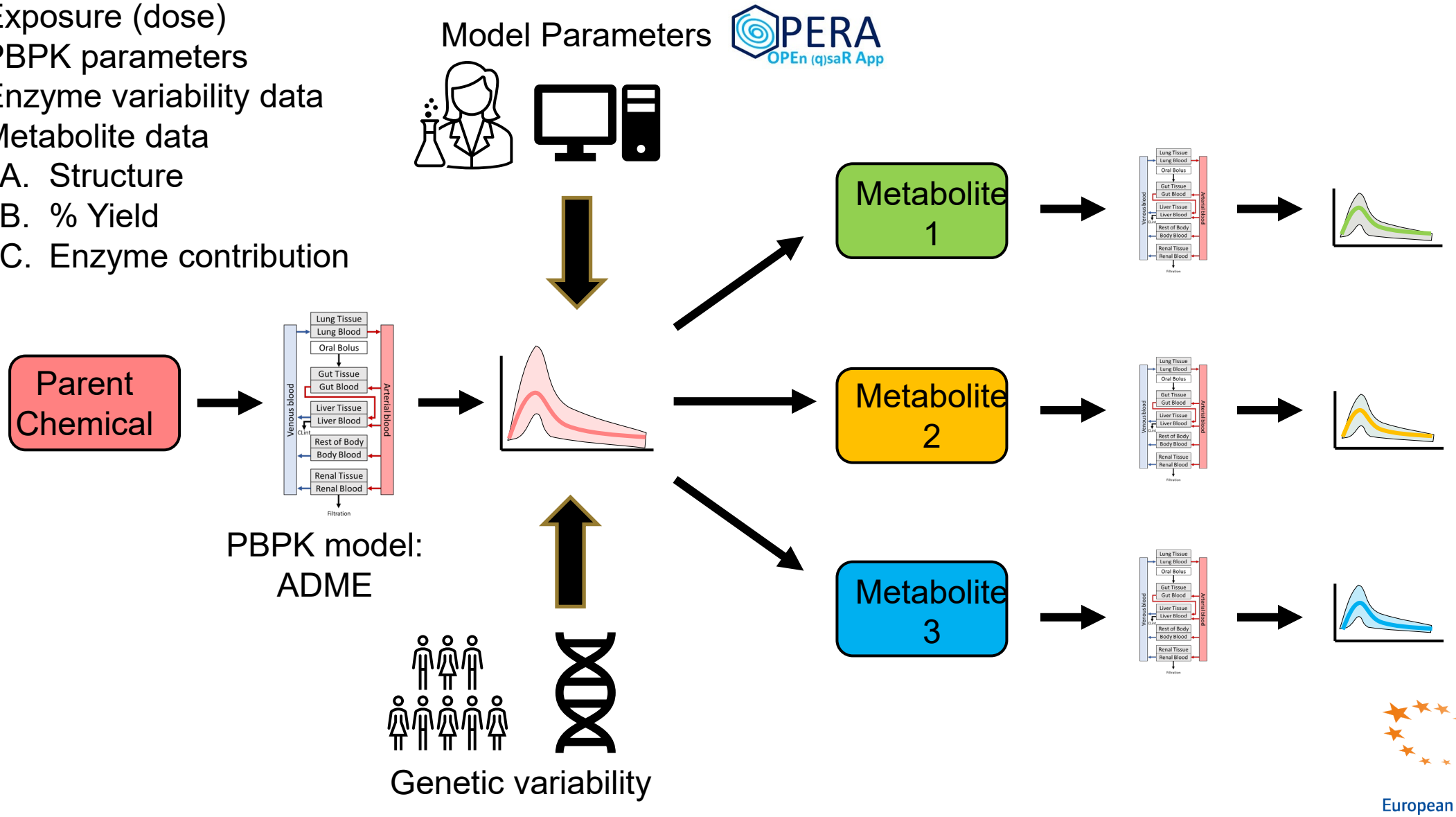
TK to Connect Metabolism and Variability

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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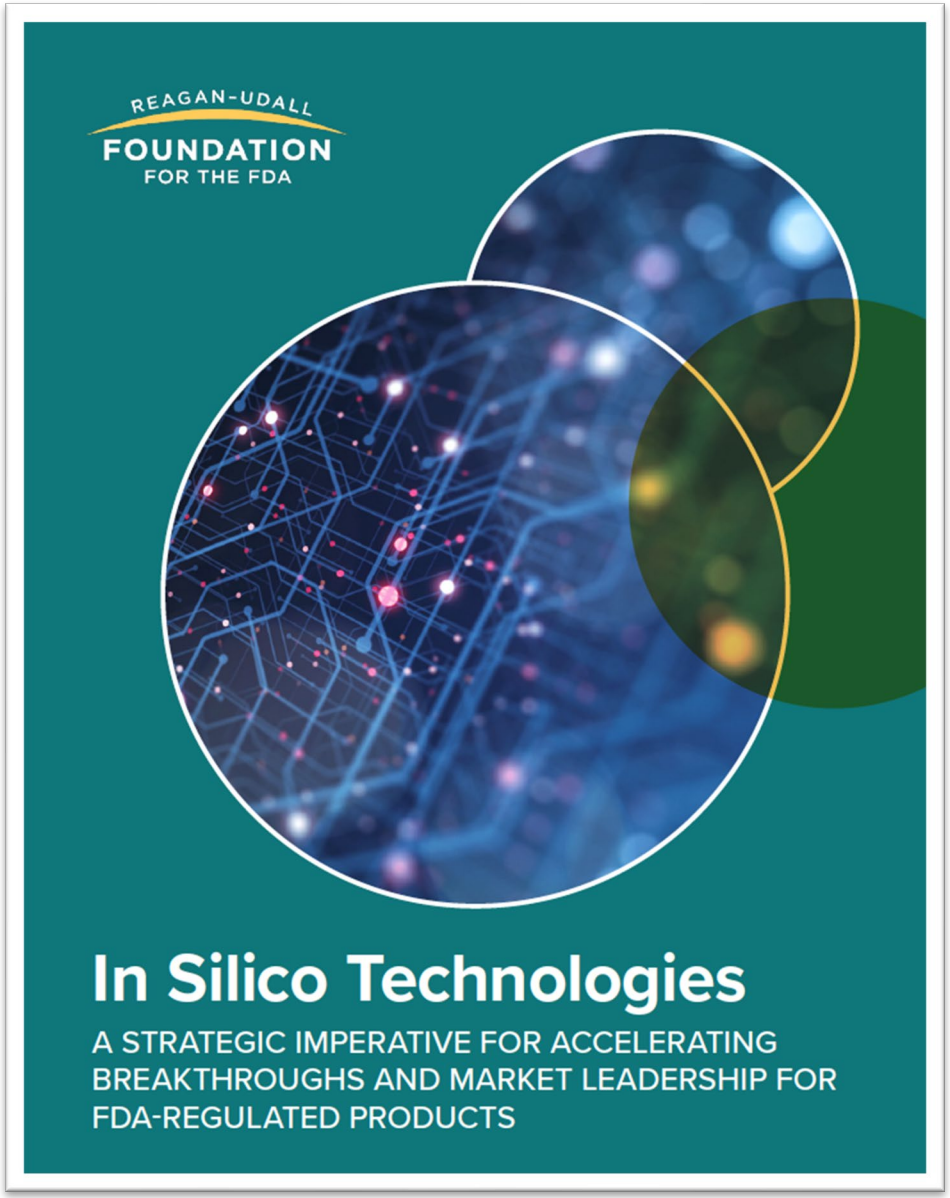
Newly Published Whitepaper



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Acknowledgments

The NICEATM Group

Dr. Tina Morrison
U.S. FDA
Senior Science Advisor, Office of the Chief Scientist

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Advancing Alternatives to Animal Testing

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Extra Slides

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OPERA and ICE Used Worldwide

Environmental Science & Technology

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Article

Two-Stage Machine Learning-Based Approach to Predict Points of Departure for Human Noncancer and Developmental/Reproductive Effects

Jacob Kvasnicka, Nicolò Aurisano, Kerstin von Borries, En-Hsuan Lu, Peter Fantke, Olivier Jolliet, Fred A. Wright, and Weihsueh A. Chiu*

Cite This: https://doi.org/10.1021/acs.est.4c00172

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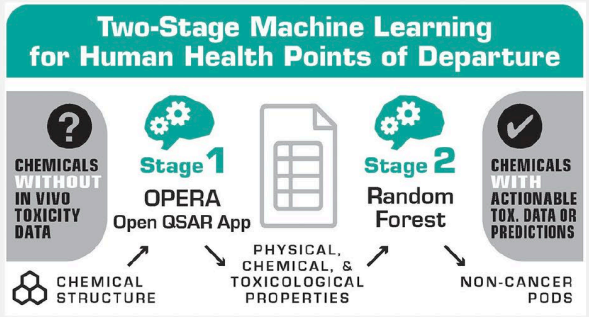
ABSTRACT: Chemical points of departure (PODs) for critical health effects are crucial for evaluating and managing human health risks and impacts from exposure. However, PODs are unavailable for most chemicals in commerce due to a lack of *in vivo* toxicity data. We therefore developed a two-stage machine learning (ML) framework to predict human-equivalent PODs for oral exposure to organic chemicals based on chemical structure. Utilizing ML-based predictions for structural/physical/chemical/toxicological properties from OPERA 2.9 as features (Stage 1), ML models using random forest regression were trained with human-equivalent PODs derived from *in vivo* data sets for general noncancer effects (n = 1,791) and reproductive/developmental effects (n = 2,228), with robust cross-validation for feature selection and estimating generalization errors (Stage 2). These two-stage models accurately predicted PODs for both effect categories with cross-validation-based root-mean-squared errors less than an order of magnitude. We then applied one or both models to 34,046 chemicals expected to be in the environment, revealing several thousand chemicals of *moderate* concern and several hundred chemicals of *high* concern for health effects at estimated median population exposure levels. Further application can expand by orders of magnitude the coverage of organic chemicals that can be evaluated for their human health risks and impacts.



KEYWORDS: *QSAR model, machine learning, toxicity prediction, chemical risk assessment, high-throughput screening, life cycle impact assessment (LCIA)*

- **OPERA** predicted properties used as features in ML model to predict PODs for thousands of chemicals
- US EPA SEEM3 exposure data downloaded from **ICE** to facilitate comparisons

OPERA
OPEn (q)saR App

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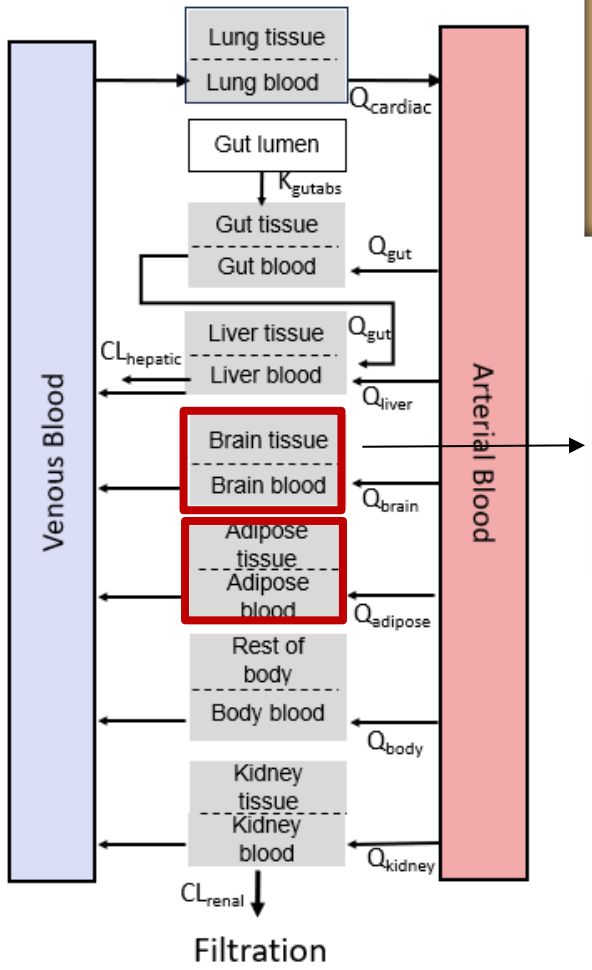
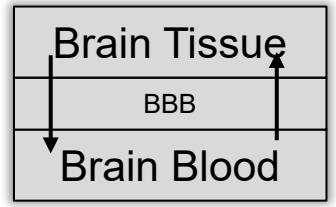
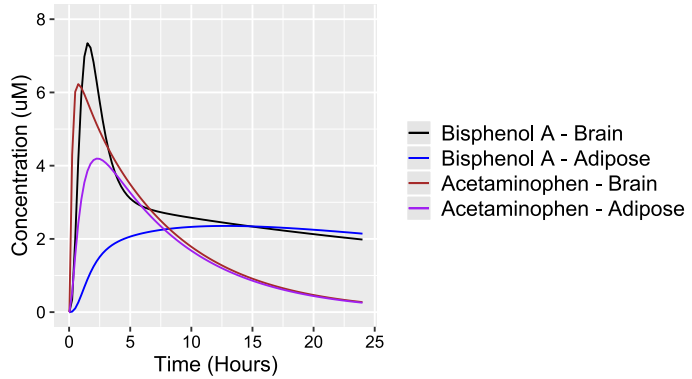
Predicting Chemical Distribution in Brain and Adipose Compartments



- Perfusion-limited model with brain and adipose compartments (Simple Model)
- Build upon generic PBPK model from EPA's httk R package (v2.2.2)



- Diffusion-Limited brain compartment considering blood brain barrier permeability (Complex Model)
- Predicts brain tissue distribution of chemicals from capillary blood

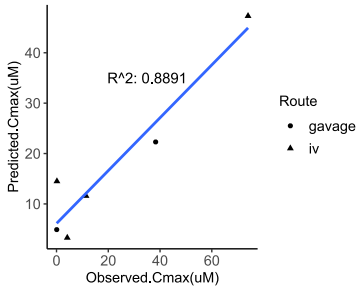


Model output includes time series concentration graphs

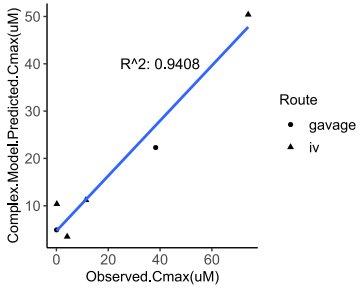
Ongoing Updates

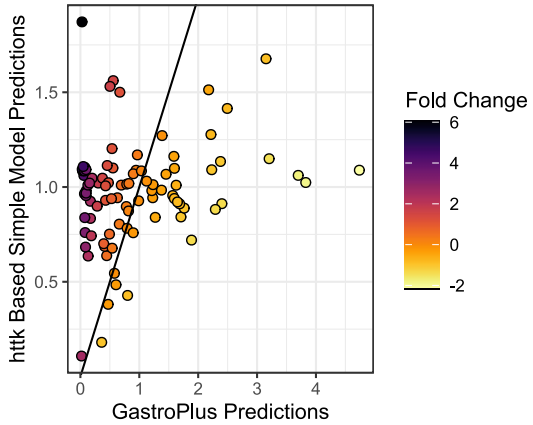
- Incorporation of predicted BBB permeability coefficient values in addition to measured.
- Exploration of additional validation criterions applied for other commercial brain models.
- Efforts for further comparisons using pharmacokinetic time series data from additional chemicals to provide greater confidence in these models.

Simple Model Predicted Brain Cmax Vs Observed Data

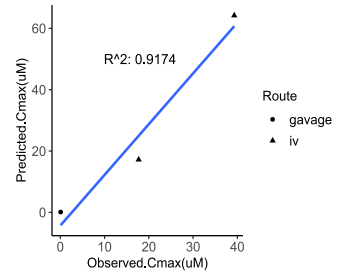


Complex Model Predicted Brain Cmax Vs Observed Data





Simple Model Predicted Adipose Cmax Vs Observed Data



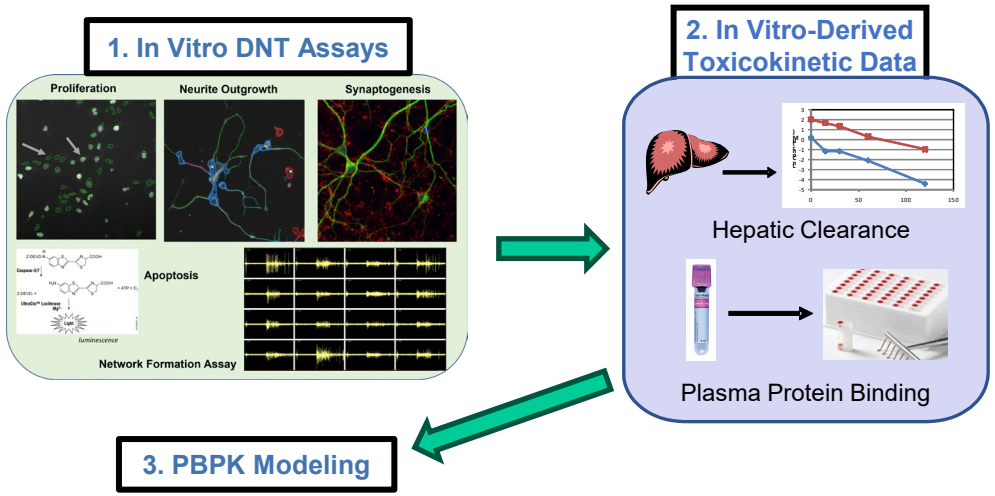
National Institute of Environmental Health Sciences
Division of Translational Toxicology

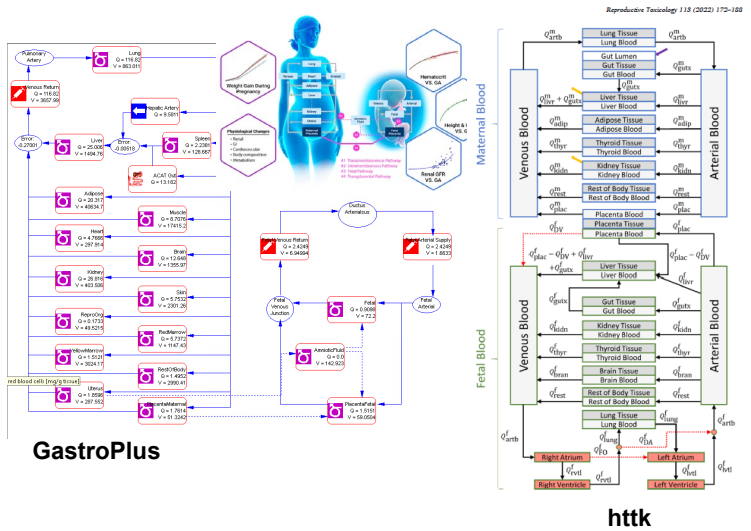
In Vitro to In Vivo Extrapolation (IVIVE) for Developmental Neurotoxicity

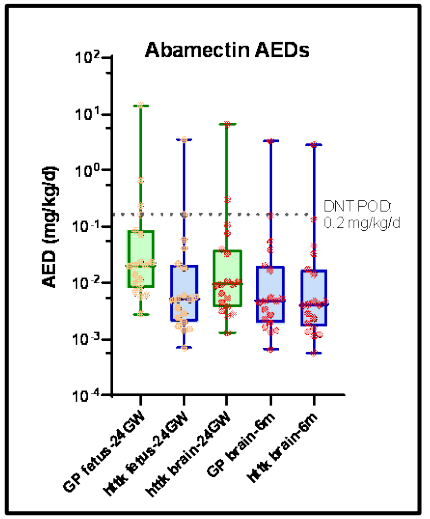
A Comparison of Physiologically Based Pharmacokinetic Models

- Physiologically-based pharmacokinetic (PBPK) models compared for DNT-IVIVE approach
- Chemicals bioactive in DNT NAMs from EPA with experimental toxicokinetic data
- Findings
  - Chemicals preferentially partition into the brain
  - In vivo DNT points of departure fall within the range of human administered equivalent dosages (AEDs) for bioactive endpoints for both programs, showing the concordance of in vitro-derived, DNT-IVIVE predictions with in vivo data
  - GastroPlus & httk perform similarly, though httk provides somewhat more conservative estimates

Manuscript in preparation







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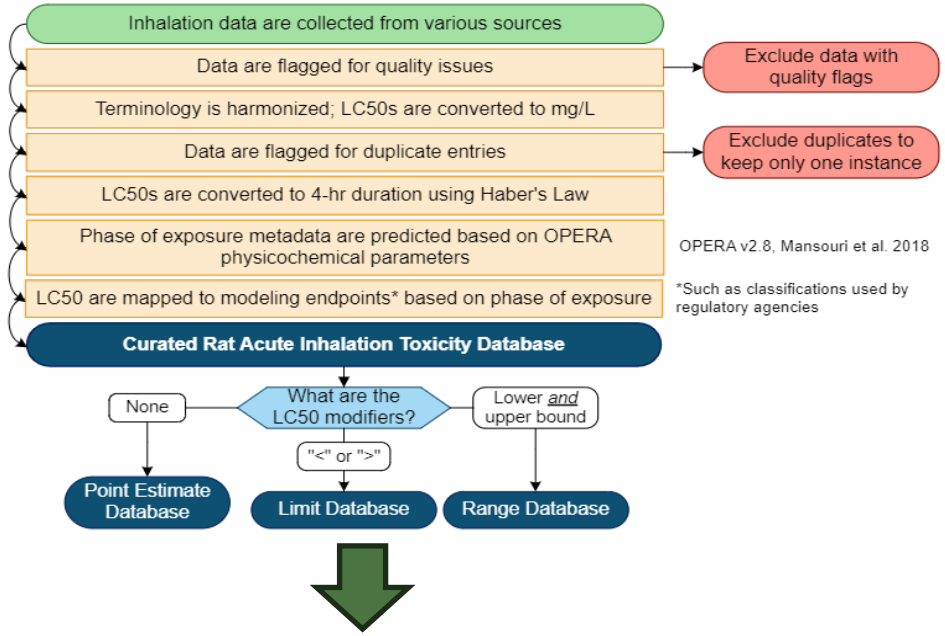
Acute Inhalation Toxicity Database

Data Source	Data Records	Unique Substances
Legacy data from ChemIDplus (now integrated into PubChem)	2036	1249
National Institute for Occupational Safety and Health Pocket Guide	136	649
European Chemicals Agency Registration, Evaluation, Authorisation and Restriction of Chemicals Database	3016	611
U.S. Environmental Protection Agency Acute Exposure Guideline Levels	1682	271
U.S. Department of Defense	47	13



Database Summary

- 1025 unique chemicals
- ~760 chemicals will be used to support a collaborative modeling effort
- The database can be downloaded and explored on ICE

Download the Rat Acute Inhalation Database from ICE.
https://ice.ntp.niehs.nih.gov/DATASETDESCRIPTION