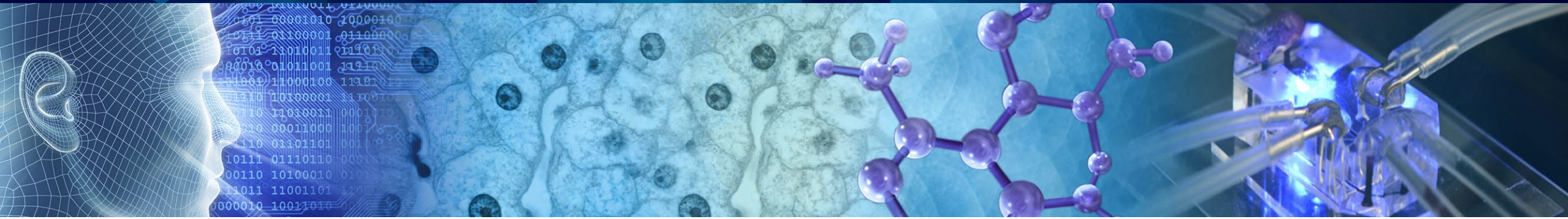
National Institute of Environmental Health Sciences
Division of Translational Toxicology

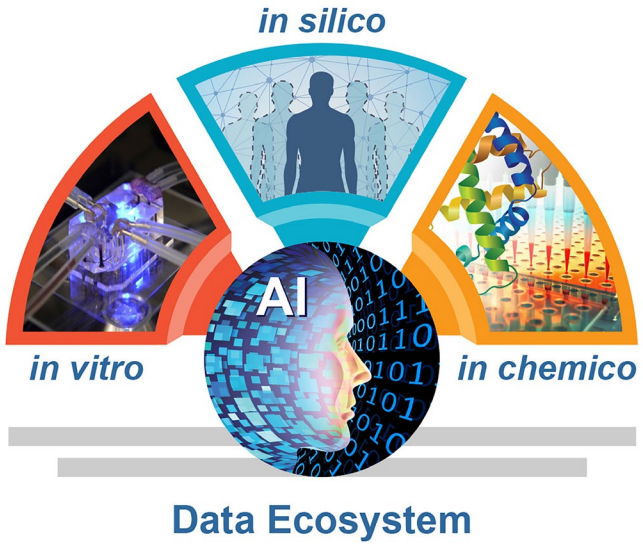


NICEATM Update: ICCVAM Public Forum 2025

Helena Hoegberg-Durdock

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

NICEATM's Activities



U.S. FOOD & DRUG ADMINISTRATION

CONSUMER PRODUCT SAFETY COMMISSION UNITED STATES

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

OECD

etc.

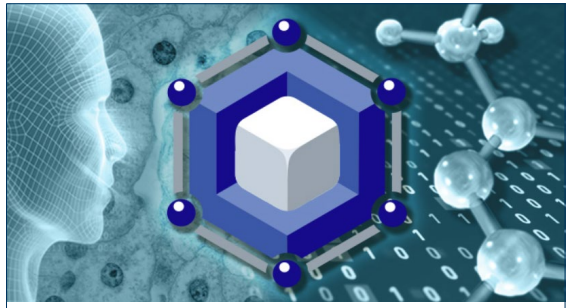
Research

Validation/ Qualification

Adoption & Implementation

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

NICEATM Scientific Tools

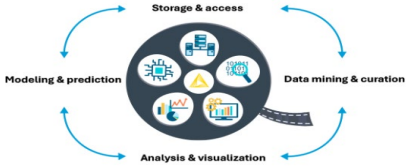


Integrated Chemical Environment (ICE)

ICE is an open-access, user-friendly platform developed by NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) that provides curated toxicologically relevant data and interactive computational tools to support development and evaluation of new testing approaches.

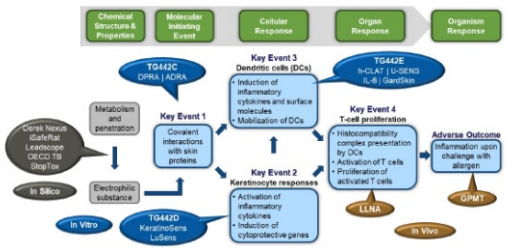
Open (Quantitative) Structure-activity/property Relationship App (OPERA)

OPERA is a free and open-source/open-data suite of QSAR models providing predictions for physicochemical properties, environmental fate parameters, and toxicity endpoints to support non-animal approaches for predicting toxicity.



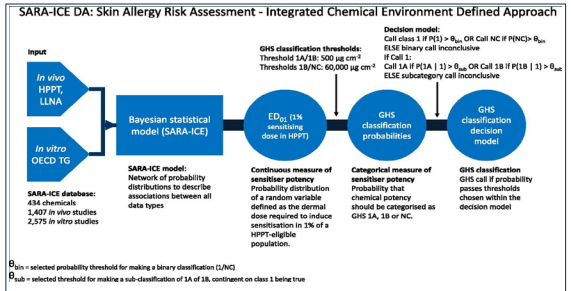
Modeling and Visualization (MoVIZ) Pipeline

MoVIZ is a cheminformatics pipeline developed using the free and open-source KNIME analytics platform and aims to democratize computational methods through intuitive, well-documented, and user-friendly graphical interfaces. Among MoVIZ tools is a workflow facilitating chemical grouping based on supervised and unsupervised machine learning approaches.



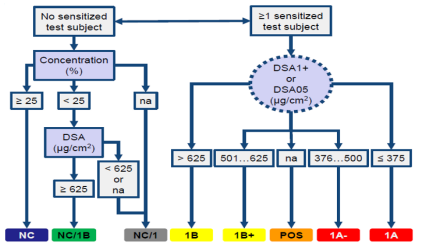
The DASS App

The DASS App is an open-source web application to predict skin sensitization using defined approaches. It enables users to apply validated non-animal approaches to their own data.



The Skin Sensitization Risk Assessment – Integrated Chemical Environment (SARA-ICE)

SARA-ICE is an open access web tool for quantitative prediction of a chemical's potential to cause skin sensitization in humans. It uses a Bayesian statistical model developed by NICEATM and Unilever to estimate human-relevant metric of skin sensitizer potency.



The HPPT App (Coming Live Soon)

The HPPT App is an open-source web application that helps classify human predictive patch test (HPPT) data for skin sensitization potency using a WoE approach. It enables users to apply a GHS based approach for assigning skin sensitization potency subcategorizations to their own data.

Integrated Chemical Environment

ICE Data

- Curated in vivo, in vitro, and in silico toxicity data
- Measured and predicted chemical properties
- Predicted exposure
- Reported and predicted chemical use categories

Chemical Quick Lists

- Reference and Non-reference chemical lists
- Support the development and evaluation of new test methods

Data and quick lists are accessible across ICE tools.

Search | Chemical Quest | Curve Surfer | PBPK | IVIVE | Chemical Character-ization

- Explore ICE data through interactive visualizations
- Identify structurally similar chemicals
- Leverage computational models without coding
- Access data through APIs and bulk data downloads

Tool Inter-connectivity: Send chemical and assay selections between tools.

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

ICE Updates

ICE v4.1 August 2024

- Updated cHTS annotations from NCI Metathesaurus to OBO Foundry
- New PFAS chemical quick list and updated ROC chemical quick list
- ICE REST API updated to include Curve Surfer tool raw data
- Additional data visualizations in Search tool

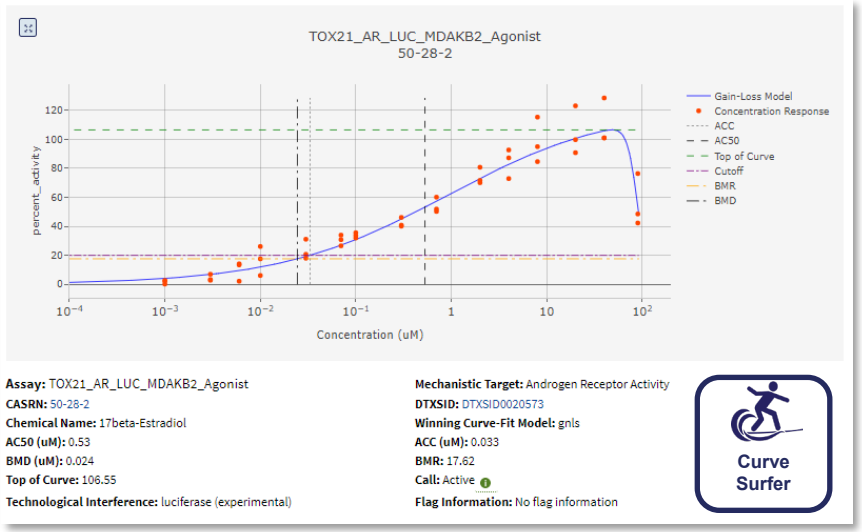
ICE v4.1.1 February 2025

- New download file with ClassyFire (Djoumbou Feunang et al. 2016) chemical taxonomies for over one million chemicals
- Updated all ICE Tool Help videos

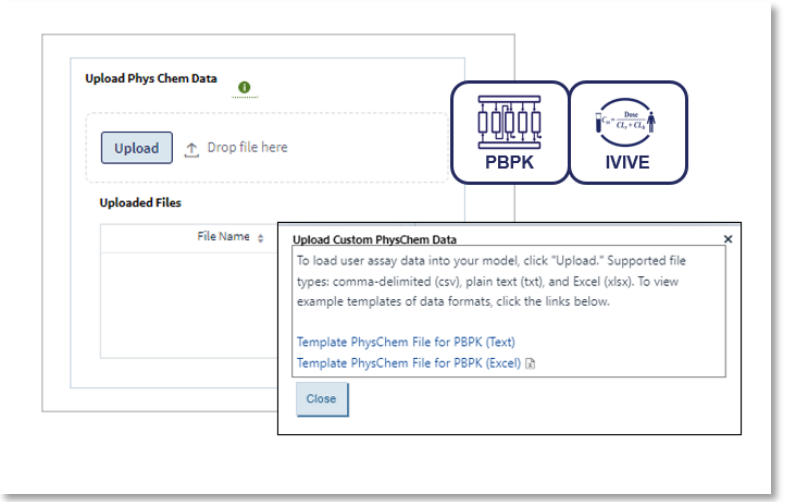
ICE v4.2 July 2025

- cHTS updated to invitrodb v4.2
- Option to upload user's physicochemical and ADME data to run PBPK/IVIVE
- Updated PCAs in Chemical Characterization
- Updated Tox21 Chemical Quick List

Curve Surfer cards show new points of departure, curation flags, and curve-fits



Upload custom physicochemical parameters to run PBPK and IVIVE



Curated High Throughput Screening (cHTS) data are annotated to OBO Foundry ontologies to provide biological relevance

OPERA as a Standalone Desktop Application

OPERA standalone application:

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

OPERA models:

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

Input options:

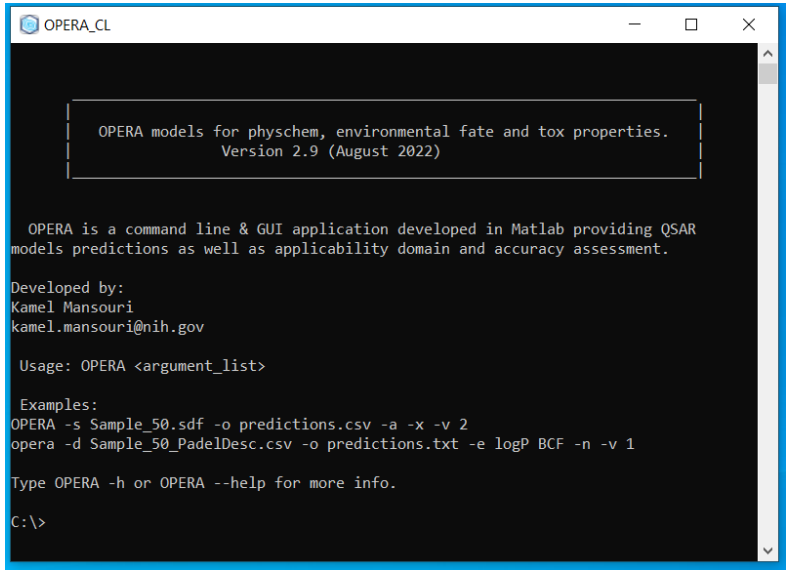
- Structure IDs (CAS, DTXSID, InChIKey)
- Structure files (SMILES, SDF, Mol)

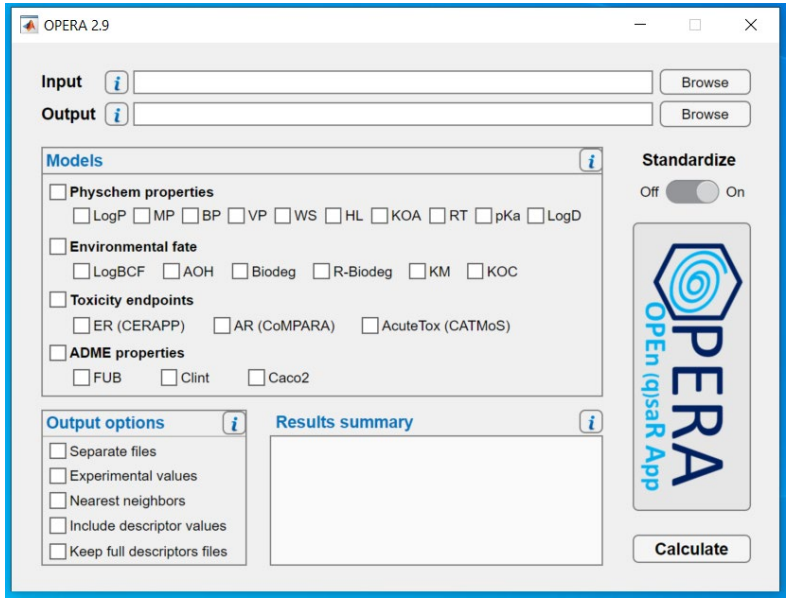
Download and learn more:

https://github.com/NIEHS/OPERA

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

Over 10,000 downloads





National Institute of Environmental Health Sciences
Division of Translational Toxicology

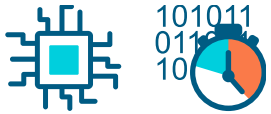
Modeling and Visualization (MoVIZ) Pipeline

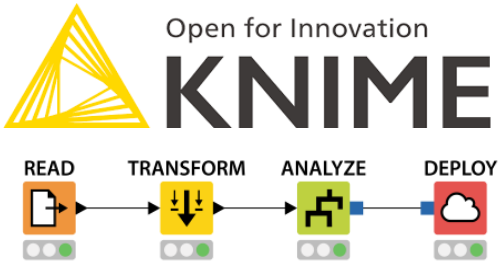
Download and learn more:

https://github.com/NIEHS/Chemical-grouping-workflow

Data storage and access

Modeling and prediction





Data mining and curation

Data analysis and visualization

Moreira-Filho *et al.*
Journal of Cheminformatics (2024) 16:101
https://doi.org/10.1186/s13321-024-00894-1

Journal of Cheminformatics

SOFTWARE Open Access

Democratizing cheminformatics: interpretable chemical grouping using an automated KNIME workflow

Mansouri *et al. Journal of Cheminformatics* (2024) 16:19
https://doi.org/10.1186/s13321-024-00814-3

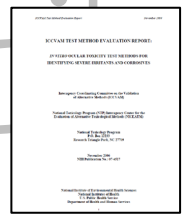
Journal of Cheminformatics

SOFTWARE Open Access

Free and open-source QSAR-ready workflow for automated standardization of chemical structures in support of QSAR modeling

LLMs to Extract Study Information

Corpora
Articles,
Reports, etc.



Multi-layer Document Image/Text Object
- embed metadata for grounding
- markdown conversion: GROBID

LiteLLM Structured Data Extraction
- 100s of LLMs
- Configured Model Characteristics

LiteLLM

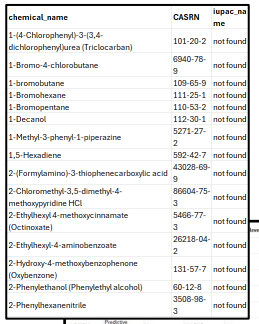
Optimize Prompts and Model x Task

Structured Data Output
- Extraction formatted data from LLM output

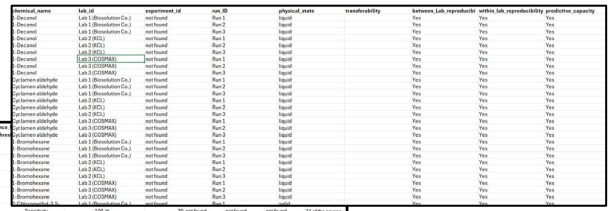
Fuzzy Performance Analysis
- Evaluate predicted matches
- Estimate performance
- Review Prompt Changes

Human Centered Review and QC

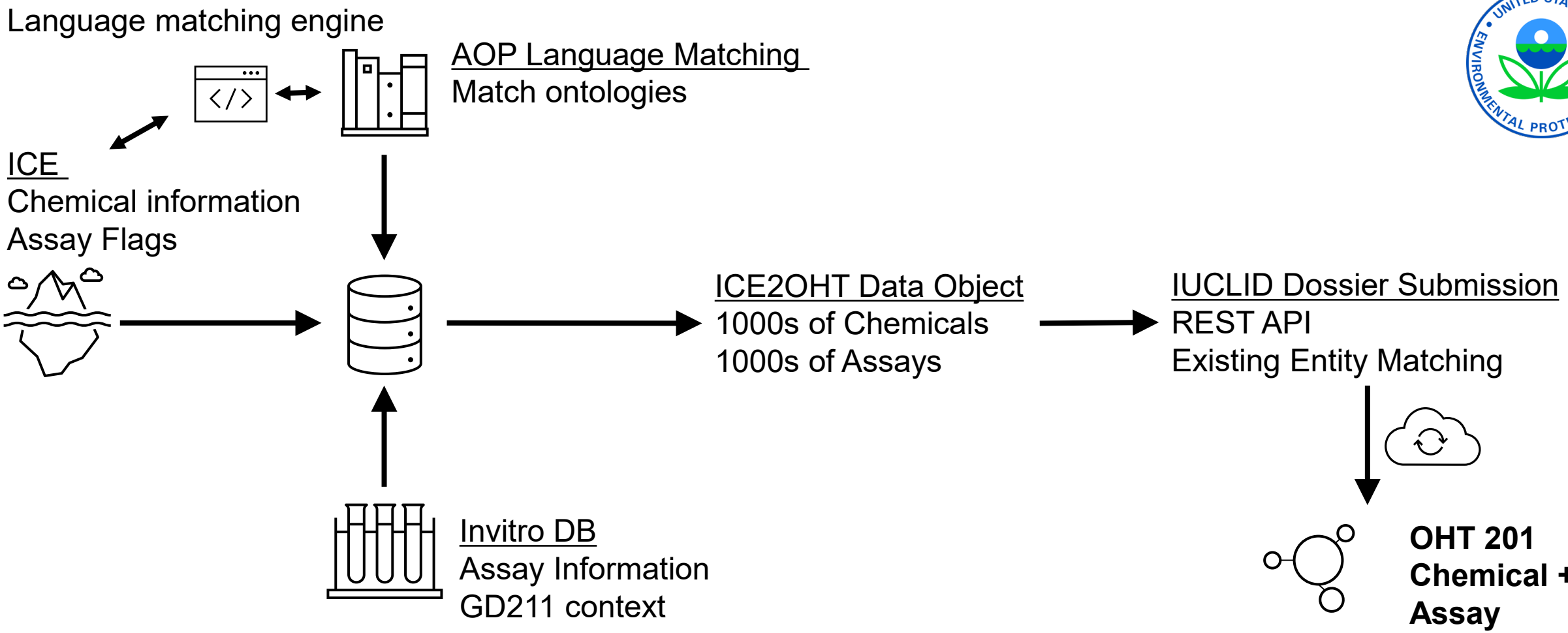
Database ingestion



chemical_name	CASRN	iupac_name
1-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)urea (Triclocarban)	101-20-2	not found
1-Bromo-4-chlorobutane	6940-78-9	not found
1-bromobutane	109-65-9	not found
1-Bromohexane	111-25-1	not found
1-Bromopentane	110-53-2	not found
1-Decanol	112-30-1	not found
1-Methyl-3-phenyl-1-piperazine	5271-27-2	not found
1,5-Hexadiene	592-42-7	not found
2-(Formylamino)-3-thiophenecarboxylic acid	43028-69-9	not found
2-Chloromethyl-3,5-dimethyl-4-methoxypyridine HCl	86604-75-3	not found
2-Ethylhexyl-4-methoxycinnamate (Octinoxate)	5466-77-3	not found
2-Ethylhexyl-4-aminobenzoate	26218-04-2	not found
2-Hydroxy-4-methoxybenzophenone (Oxybenzone)	131-57-7	not found
2-Phenylethanol (Phenylethyl alcohol)	60-12-8	not found
2-Phenylhexanenitrile	3508-98-3	not found



LLMs and AI to Match Expert Languages



National Institute of Environmental Health Sciences
Division of Translational Toxicology

Computational Models in Collaboration with UNC

EHP PUBLISHING

ehp Environmental Health Perspectives

Research | 19 May 2025

DeTox: an *In-Silico* Alternative to Animal Testing for Predicting Developmental Toxicity Potential

Authors: Ricardo Scheufen Tieghi, Marielle Rath, José Teófilo Moreira-Filho, James Wellnitz, Holli-Joi Martin, Kathleen Gates, Helena T. Hogberg, Nicole Kleinstreuer, Alexander Tropsha, and Eugene N. Muratov | AUTHORS INFO & AFFILIATIONS

Publication: Environmental Health Perspectives • https://doi.org/10.1289/EHP15307

Model	# Compounds (Nontoxic/Toxic)	Accuracy	Sensitivity	Specificity	Positive Prediction Value	Negative Prediction Value
Overall	213 (63/150)	0.78	0.96	0.37	0.78	0.79
First Trimester	228 (67/161)	0.67	0.72	0.53	0.79	0.45
Second Trimester	256 (75/181)	0.74	0.82	0.53	0.81	0.56
Third Trimester	257 (76?181)	0.77	0.92	0.39	0.79	0.70

https://detox.mml.unc.edu/

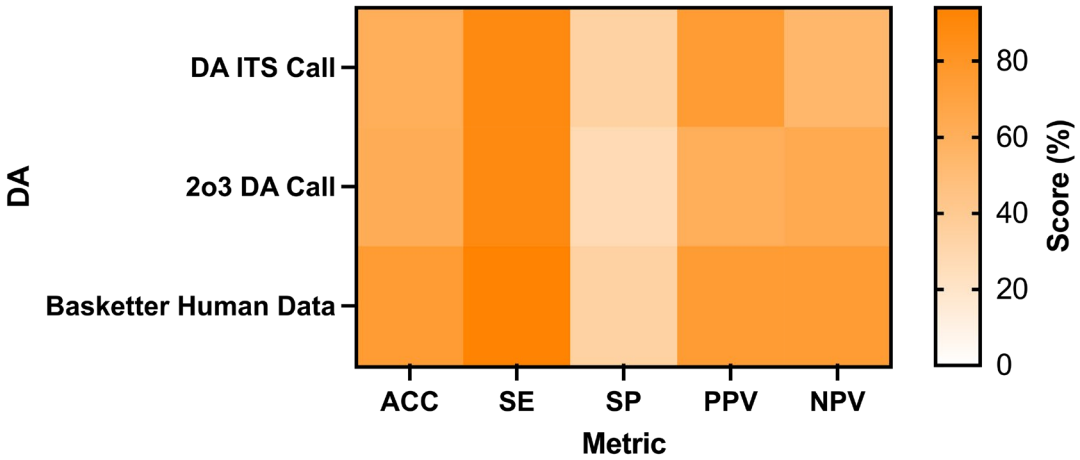
SCAN ME

toxics MDPI

Article

A Novel Machine Learning Model and a Web Portal for Predicting the Human Skin Sensitization Effects of Chemical Agents

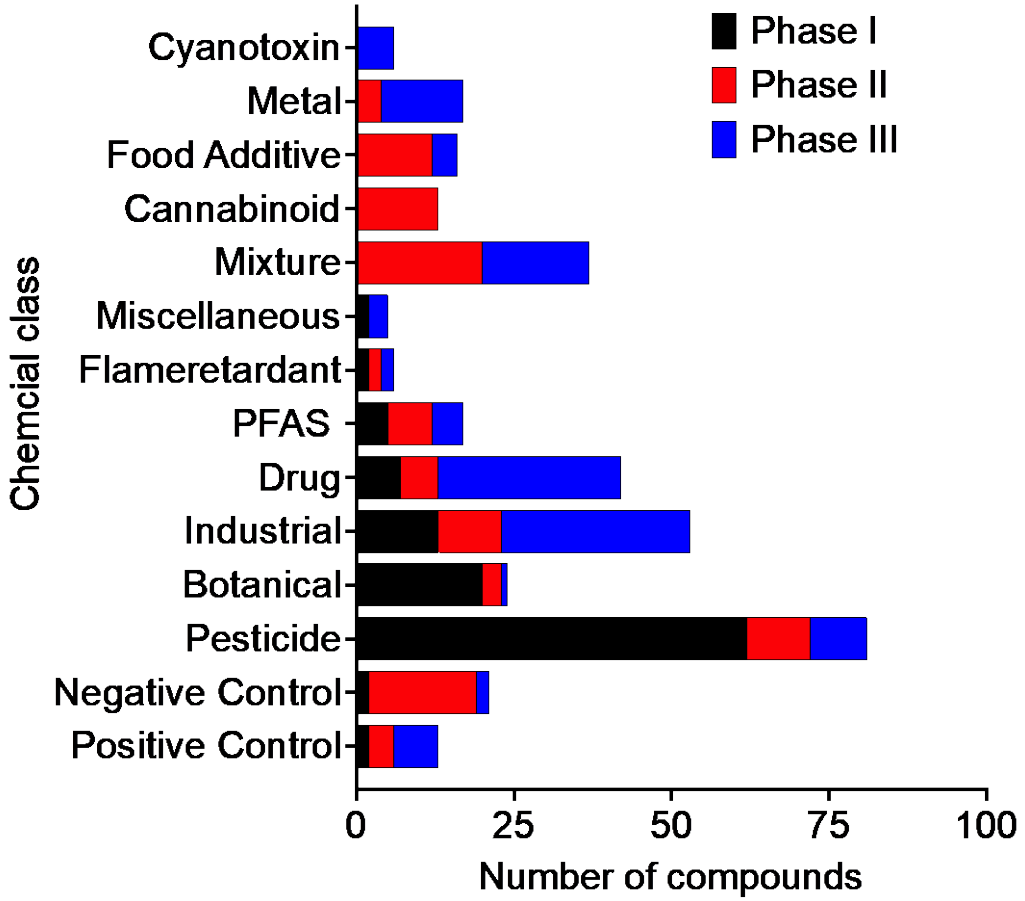
Ricardo Scheufen Tieghi [1,2], José Teófilo Moreira-Filho [1], Holli-Joi Martin [2], James Wellnitz [2], Miguel Canamary Otoch [2], Marielle Rath [2], Alexander Tropsha [2,3,*], Eugene N. Muratov [2,*] and Nicole Kleinstreuer [1,*]



https://husspred.mml.unc.edu/

DTTs Screening Efforts in a Battery of DNT In Vitro Assays

https://www.niehs.nih.gov/research/atniehs/dtt/strategic-plan/health/developmental



Phase I: 115 Chemicals

Phase II: 108 Chemicals

Phase III: 128 Chemicals

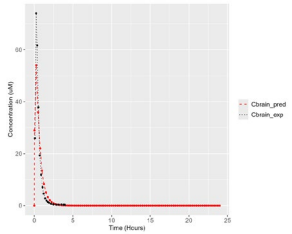
National Institute of Environmental Health Sciences
Division of Translational Toxicology

Predicting Chemical Distribution for Developmental Neurotoxicity (DNT)

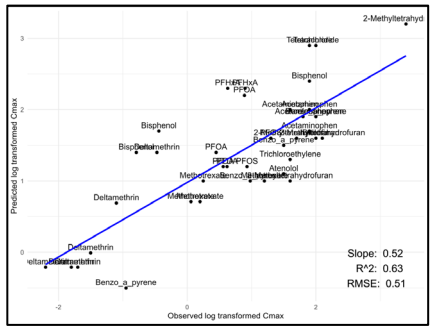
Brain-Adipose Physiologically Based Kinetic (PBK) Model

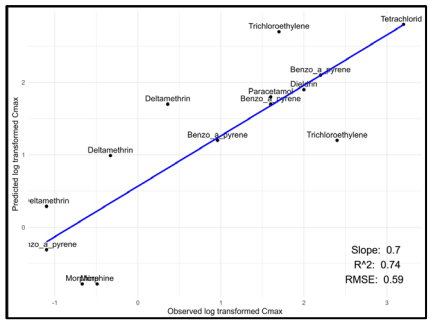
- Built upon generic PBK model from EPA's httk R package (v2.2.2)
- Addition of brain and adipose compartments
- Diffusion-Limited brain compartment considering blood brain barrier permeability
- Validation using in vivo data for adipose, brain, and plasma concentrations

Acetaminophen Pred vs Obs Brain

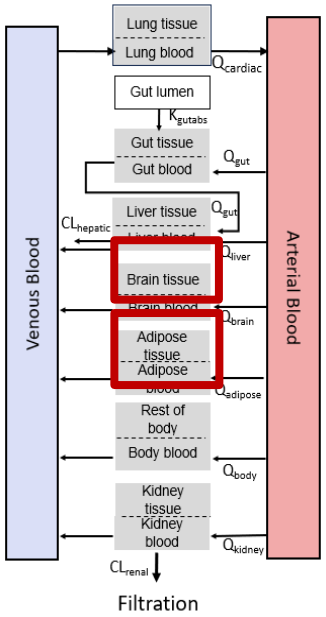


Log10 Predicted vs Observed Brain



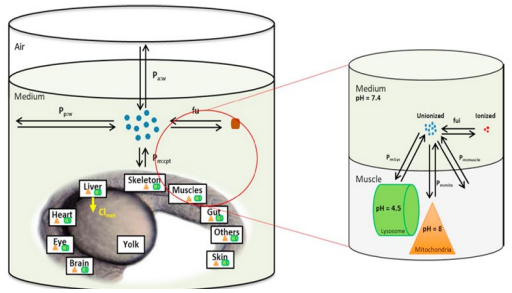


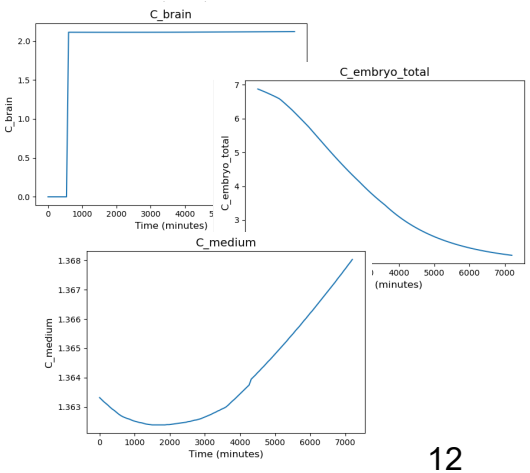
Log10 Predicted vs Observed Adipose



Zebrafish PBK Model

- Model developed by Simeon et al., 2020
- Predictions for 10 organs and medium concentrations
- Incorporates developmental changes and metabolism
- Refining model with bioavailability data to expand applicability domain
- Applying to screening data from zebrafish behavioral assays conducted in extended DNT in vitro battery

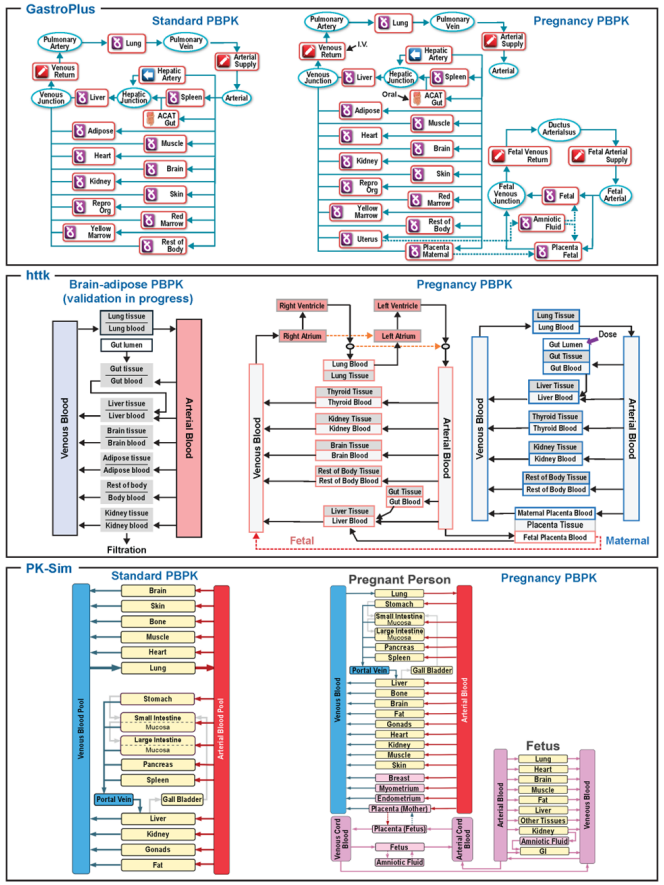




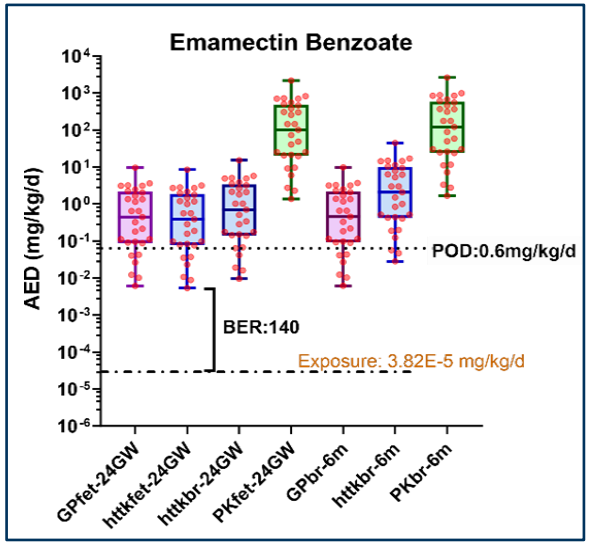
In Vitro to In Vivo Extrapolation (IVIVE) for Developmental Neurotoxicity

A Comparison of PBK Models

- DNT-IVIVE approach established to translate in vitro DNT activity doses into in vivo human doses that considers the site and period of brain development
- PBK models compared for DNT-IVIVE approach
- Chemicals bioactive in DNT NAMs from EPA with experimental toxicokinetic data
- Findings
  - In vivo data fall in the range of human administered equivalent dosages (AEDs), showing the concordance of DNT-IVIVE predictions with in vivo data
  - Approach relatively transferable across platforms, with differences explained by lipophilicity and partitioning algorithms
  - Uncertainties exist due to the lack of data available for validation



Manuscript submitted to Tox Sci.



Next Steps To Expand the Regulatory Applicability for DNT

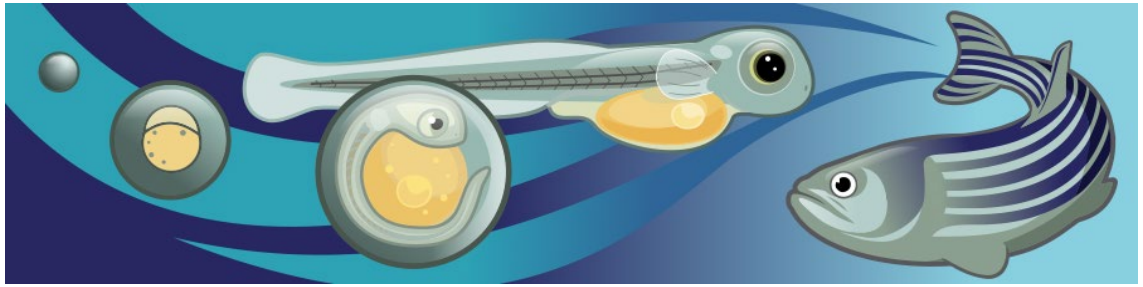
DNT IATA Framework Template and Guidance of Support

- EU (EFSA) and US (NICEATM) lead project, approved by WHPA in June 2024
- Develop an IATA framework template specific for DNT
  - Advance and provide guidance to address QIVIVE
  - Standardize uncertainty analyses for integration in WoE assessment
- Leverage on the existing and development of new DNT IATA case studies
- IATA framework template specific to the DNT regulatory endpoint
  - Several information sources
  - Multiple problem formulations
  - Consistent way to integrate data

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Systematic Evaluation of the Application of Zebrafish In Toxicology (SEAZIT)

- Promotes broader adoption of zebrafish screening in toxicology.
- Interlaboratory studies were conducted to evaluate influence of experimental protocols on the assessment of developmental toxicity.
- Study design and data analysis approaches have been published.
- Results from the interlaboratory studies including a landscape analysis of phenotype responses are ongoing.



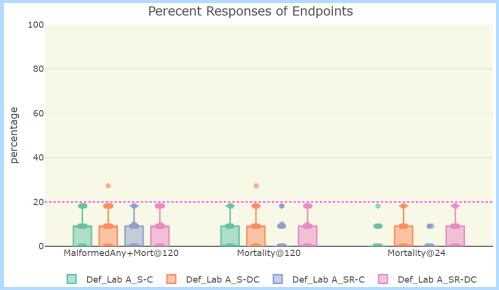
Open Access | Feature Paper | Editor's Choice | Article

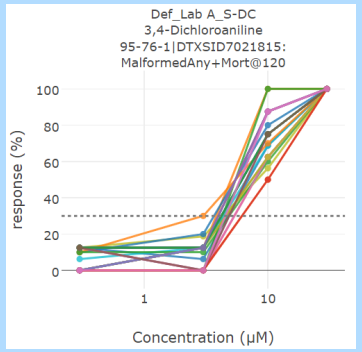
Interlaboratory Study on Zebrafish in Toxicology: Systematic Evaluation of the Application of Zebrafish in Toxicology's (SEAZIT's) Evaluation of Developmental Toxicity

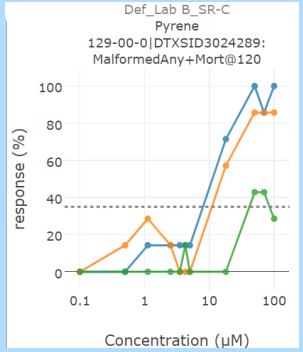
by Jon T. Hamm [1], Jui-Hua Hsieh [2], Georgia K. Roberts [2], Bradley Collins [2], Jenni Gorospe [3], Barney Sparrow [3], Nigel J. Walker [2], Lisa Truong [4], Robyn L. Tanguay [4], Sylvia Dyballa [5], Rafael Miñana [5,6], Valentina Schiavone [5], Javier Terriente [5], Andrea Weiner [7], Arantza Muriana [7], Celia Quevedo [7] and Kristen R. Ryan [2,*]

Launch of SEAZIT-DIVER tool:

Explore and download protocol information, data, and visualizations







https://seazit.dtt.niehs.nih.gov/seazit/

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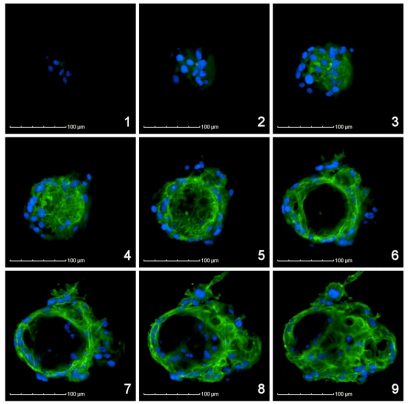
Inter-laboratory Transferability Study of Human Thyroid Microtissue Assay

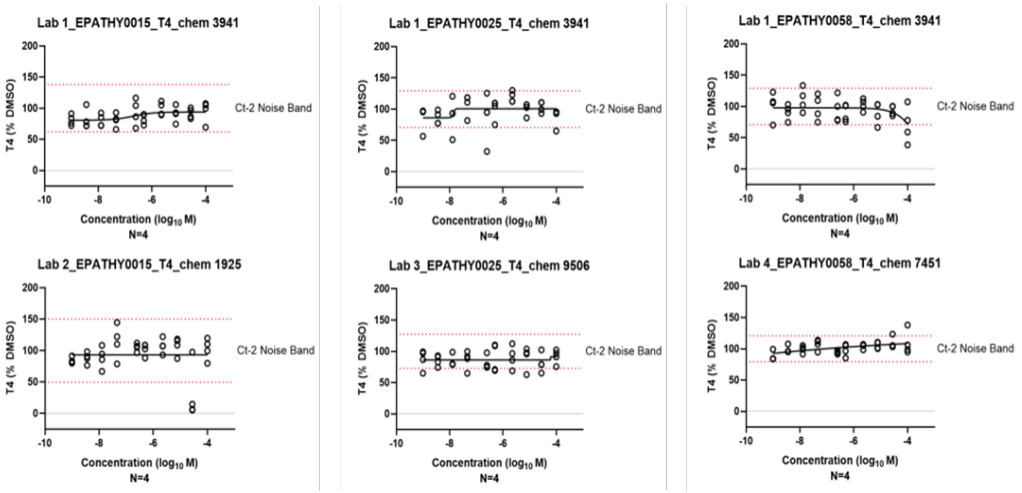
OXFORD SOT Society of Toxicology
academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 2019, 1–16
doi: 10.1093/toxsci/kfz238
Advance Access Publication Date: December 6, 2019
Research Article

Development of an *In Vitro* Human Thyroid Microtissue Model for Chemical Screening

Chad Deisenroth ,*,[1] Valerie Y. Soldatow,[†] Jermaine Ford,[‡] Wendy Stewart,* Cassandra Brinkman,* Edward L. LeCluyse,[†] Denise K. MacMillan,[‡] and Russell S. Thomas *





Team Members

Coordinator: NICEATM

Method Developer
Lab 1

Lab 2

Lab 3

Lab 4

LifeNet Health®
Saving Lives. Restoring Health. Giving Hope.

CORTEVA™ agriscience

Status:

- Phase 1.2 complete (initial transfer phase, lab 2)
- Phase 1.3 complete (secondary transfer phase, labs 3 and 4)
- Phase 1.4 complete (transferability study)
- Pre-validation report and peer review publication are being drafted

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Adoption and Implementation

Home » NICEATM: Alternative Methods » Test Method Evaluations » **Skin Sensitizers**

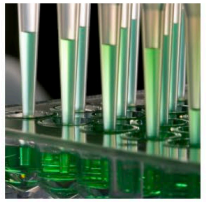
Identification of Skin Sensitizers

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

Substances with the potential to cause allergic contact dermatitis (ACD) are skin sensitizers; the process by which they cause ACD is skin sensitization. Non-animal approaches to identify potential skin sensitizers are becoming widely accepted. NICEATM, ICCVAM, and ICCVAM agencies have been at the forefront of advancing these non-animal approaches.

GARD Models for Identifying Sensitizers

The GARD®skin assay uses a genomic profile to identify potential skin sensitizers. A NICEATM report evaluates the assay. Read more »

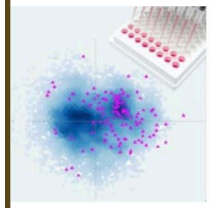


Electrophilic Allergen Screening Assay (EASA)

The EASA is a chemical assay that measures a chemical's tendency to bind to proteins, the first step in skin sensitization. Read More »

Human Skin Sensitization Data

NICEATM and collaborators compiled human data as a resource to evaluate new testing approaches for skin sensitizers. Read More »



Defined Approaches to Identify Potential Skin Sensitizers

A defined approach uses input data and a data interpretation procedure to identify potential skin sensitizers. NICEATM and ICCVAM have developed and evaluated defined approaches. Read More »

OECD Topics Countries & regions Publications Data News & events About English

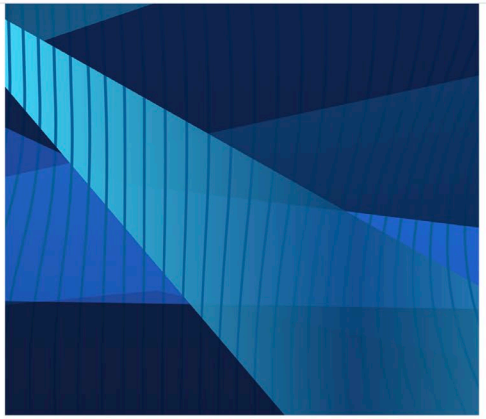
OECD › Publications › Guideline No. 497: Defined Approaches on Skin Sensitisation

Guideline No. 497: Defined Approaches on Skin Sensitisation

Report

More info

OECD Guidelines for the Testing of Chemicals, Section 4 • 25 June 2025



HPPT Database and Publications

Human Skin Sensitization Data

NICEATM and collaborators compiled human data as a resource to evaluate new testing approaches for skin sensitizers.
Read More »

Database and proposed HPPT GHS classification approach

Archives of Toxicology (2023) 97:2825–2837
https://doi.org/10.1007/s00204-023-03530-3

REVIEW ARTICLE

A database of human predictive patch test data for skin sensitization

Judy Strickland[1] · Jaleh Abedini[1] · David G. Allen[1] · John Gordon[2] · Victoria Hull[1] · Nicole C. Kleinstreuer[3] · Hon-Sum Ko[4] · Joanna Matheson[2] · Hermann-Josef Thierse[5] · James Truax[1] · Jens T. Vanselow[5] · Matthias Herzler[5]

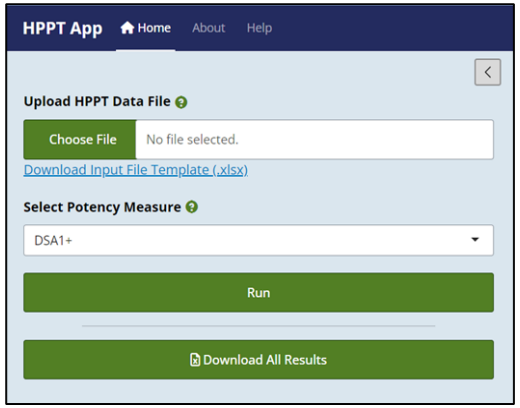
Archives of Toxicology (2024) 98:1253–1269
https://doi.org/10.1007/s00204-023-03656-4

REVIEW ARTICLE

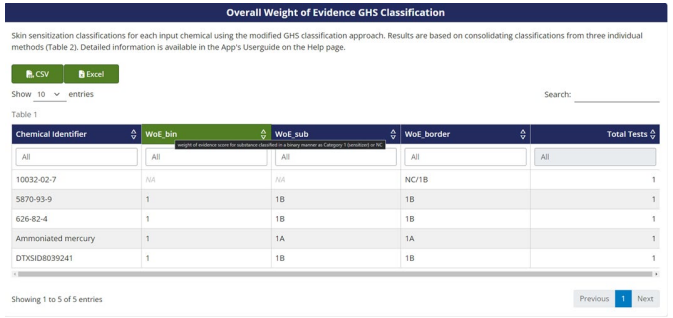
Use of human predictive patch test (HPPT) data for the classification of skin sensitization hazard and potency

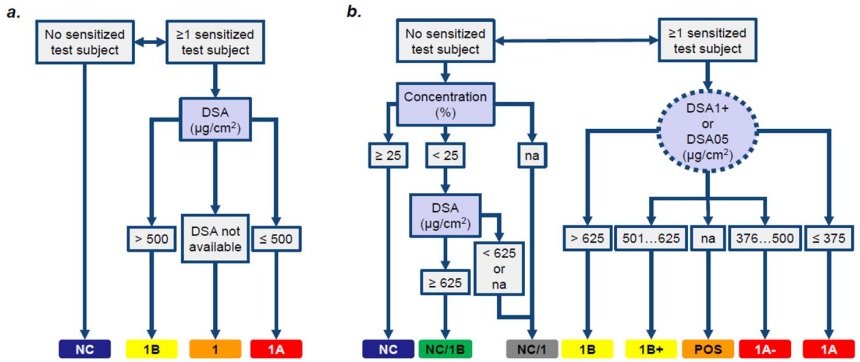
Matthias Herzler[1] · Jaleh Abedini[2] · David G. Allen[2] · Dori Germolec[3] · John Gordon[4] · Hon-Sum Ko[5] · Joanna Matheson[4] · Emily Reinke[2] · Judy Strickland[2] · Hermann-Josef Thierse[1] · Kim To[2] · James Truax[2] · Jens T. Vanselow[1] · Nicole Kleinstreuer[6]

HPPT App (Rshiny tool) under development



Chemical Identifier	Conc (%)	DSA (ug/cm2)	No. Test Subjects	No. Positive	Call	DSA1+	DSA5%	Ex.C	WES_indiv
All	All	All	All	All	All	All	All	All	All
5870-93-9	12	8100	24	5	Active	1620	1944	1B	1
626-82-4	4	2700	30	2	Active	1350	2025	1B	1
Ammoniated mercury	2	1296	100	14	Active	93	463	1A	2
DTXSID8039241	4	2700	25	1	Active	2700	3375	1B	1
10032-02-7	6	3888	25	0	Inactive	NA	NA	NC/1B	0.5

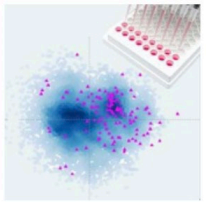




(a) Standard GHS Classification Approach (b) Modified Classification Approach

National Institute of Environmental Health Sciences
Division of Translational Toxicology

The Skin Allergy Risk Assessment (SARA) – ICE Model



Defined Approaches to Identify Potential Skin Sensitizers

A defined approach uses input data and a data interpretation procedure to identify potential skin sensitizers. NICEATM and ICCVAM have developed and evaluated defined approaches.
Read More »

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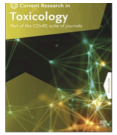
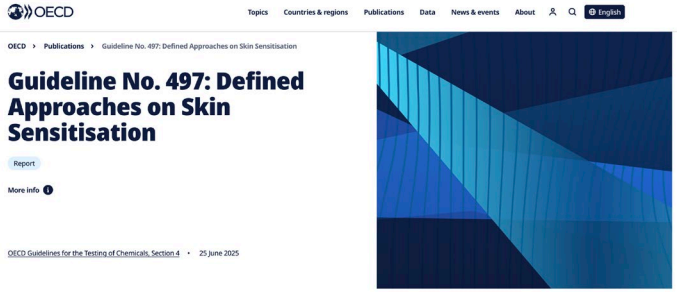


Research Paper

The skin allergy risk assessment-integrated chemical environment (SARA-ICE) defined approach to derive points of departure for skin sensitization

Emily N. Reinke [a,*], Joe Reynolds [b], Nicola Gilmour [b], Georgia Reynolds [b], Judy Strickland [a,1], Dori Germolec [c], David G. Allen [a,2], Gavin Maxwell [b], Nicole C. Kleinstreuer [c]



A SARA-ICE is a Bayesian statistical model which infers a human-relevant metric of sensitiser potency (termed ED_{01}), the dose with a 1% chance of human skin sensitisation.

- Accounts for variability of the input data and explicitly quantifies uncertainty
- Utilises any combination of human repeat insult patch test (HRIPT), LLNA, direct peptide reactivity assay (DPRA), KeratinoSens™, h-CLAT, U-SENS™ data
- Derive a Point-of-departure for use in risk assessment (geometric mean)

Steps for Using the SARA-ICE Tool

Steps 1-4 outline the process for conducting an analysis using the SARA-ICE tool. Refer to the User Guide for the purpose of the tool, the types of data that can be analyzed, how to use the tool and underlying models, and additional details on each step:

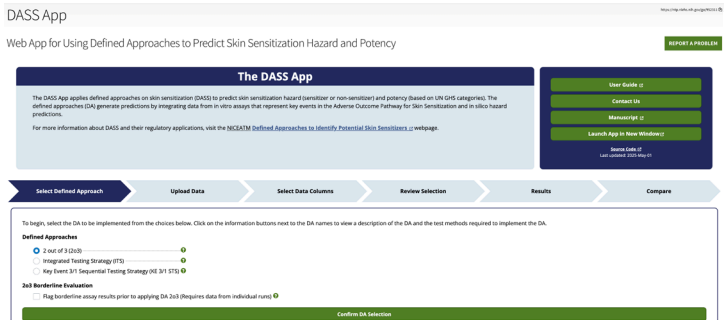
Download User Guide

1. Create and Select Input File
2. Select Model either the 'SARA-ICE OECD TG 497 Defined Approach (version 1.0)' or the 'SARA-ICE Extended Model (version 1.0)'
3. After selecting a model, the analysis will automatically start running. You can View Analysis during and after processing
4. After analysis is finished, you can Download Analysis

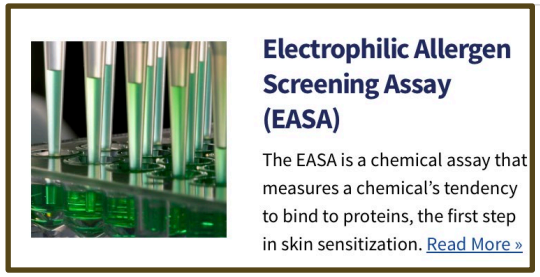
Help & Support

Have questions or need to report an issue? Please email ICE-support@niehs.nih.gov

Version 0.2.5-beta

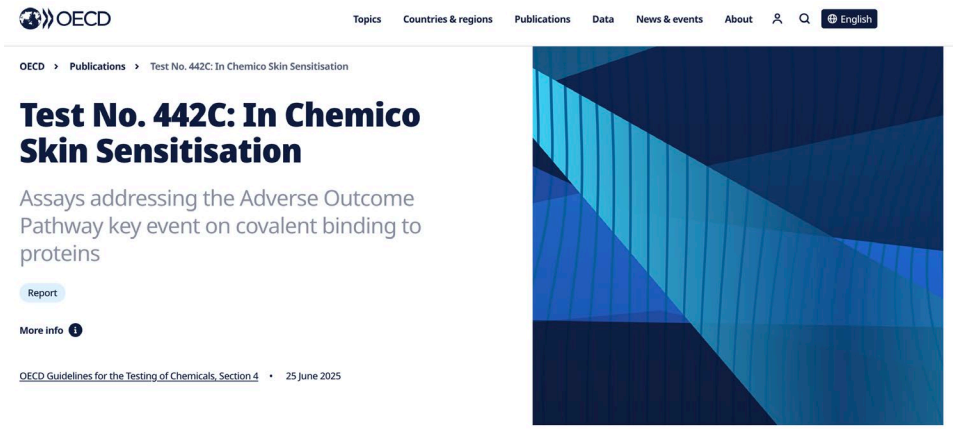


Electrophilic Allergen Screening Assay (EASA)



- Addresses KE1 in the Skin Sensitization AOP
- In chemico plate-based assay
  - Measures protein reactivity of a chemical via fluorescent or colorimetric probes
- Multi-lab validation study
  - Participating labs: U.S. FDA, DoD, CPSC/NIST, BRT, Inc.
  - Utilize 2019 OECD Performance Standards for KE1-based assays for validation study
  - Peer Review of validation study nearly finished
- Accepted on to 2024 OECD workplan for inclusion in TG 442C – meetings with expert group summer 2025

Lab #	Balanced Accuracy	Sensitivity	Specificity	Within Lab Reproducibility	Between Lab Reproducibility
1	76%	85%	67%	94%	96%
2	82%	92%	71%	100%	
3	84%	85%	83%	97%	
4	84%	85%	83%	94%	
Mean	**82%**	**87%**	**76%**	**96%**	



Defined Approaches for Predicting Eye Irritation Classifications

NICEATM, PETA Science Consortium International, and EPA Office of Pesticide Programs collaborated to test eye irritation/corrosion potential of 29 agrochemical formulations in a common set of in vitro methods

- Developed four defined approaches (DAs) applicable to GHS and EPA classification systems:
  - BCOP with histopathology (DA-BCOP+)
  - EO + BCOP with histopathology (DA-EO+)
  - TTL+ BCOP with histopathology (DA-TTL+)
  - EyeIRR-IS + BCOP with histopathology (DA-EyeIRR-IS+)
- Instead of evaluating direct concordance of the four individual DAs with historical in vivo data, for each formulation, we assessed orthogonal concordance of GHS and EPA classifications predicted across all five approaches
- Also evaluated associated hazard labeling (GHS) and PPE labeling (EPA) predicted across all five approaches
- All DAs performed **as well as or better** than the in vivo test and generally resulted in hazard/PPE labeling that is **more protective of human health**
- Publications:
  - NTP report (2021; addended 2025) https://doi.org/10.22427/NTP-NICEATM-1
  - van der Zalm et al. (2024) https://doi.org/10.1080/15569527.2023.2275029
  - Daniel et al. (2025) https://doi.org/10.1080/15569527.2025.2499552

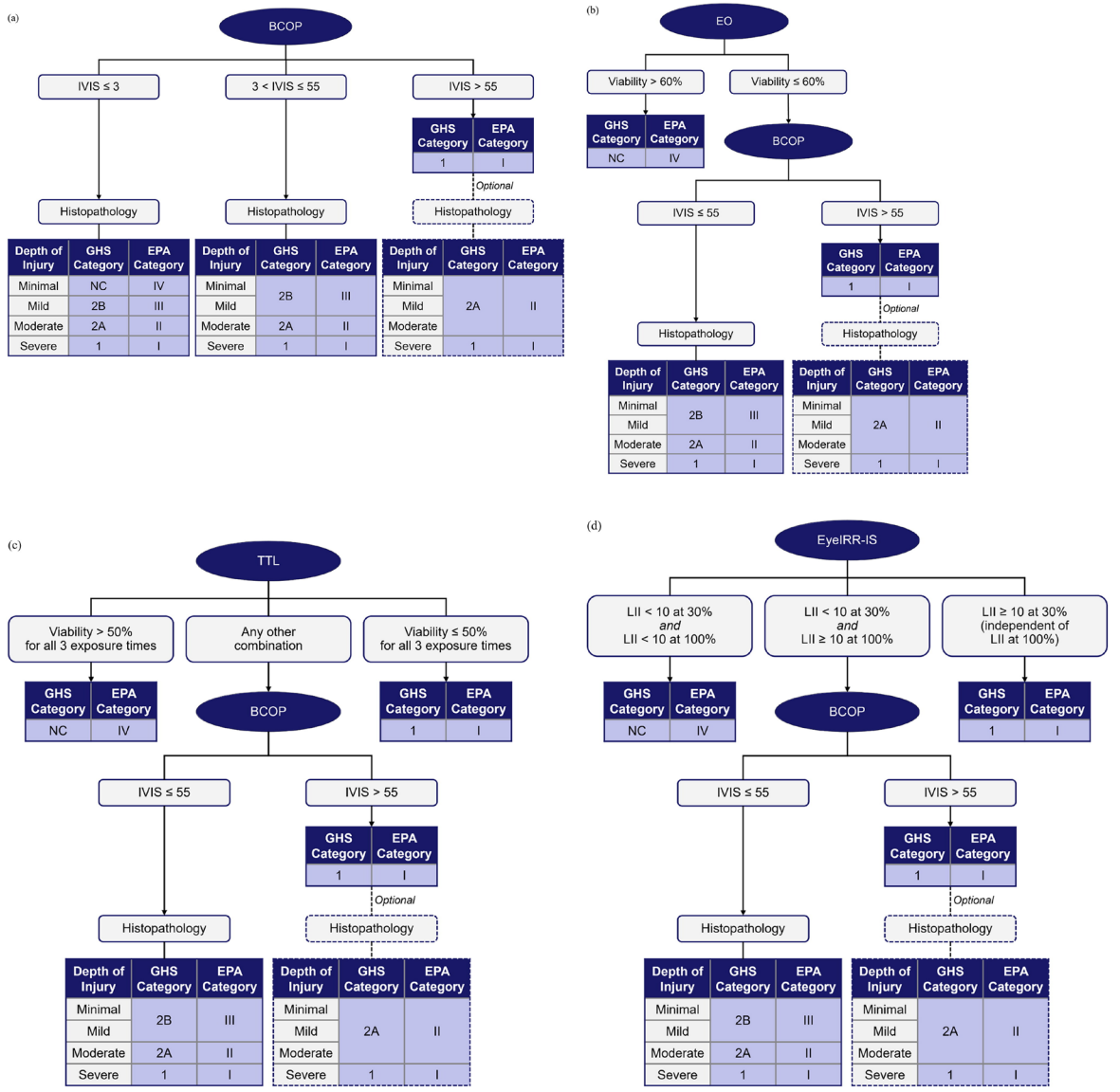


Figure 7 Daniel et al., 2025

Advancing Quantitative Analysis in Human Health Assessments through Probabilistic Methods

Workshop Monday, October 7-8, 2024

Convened international experts to facilitate discussion of probabilistic methods in human health risk assessment. The workshop provided examples of application of probabilistic methods in chemical risk assessments, highlighted ongoing research, and discussed the needs and challenges for the regular use of these methods.

Broken into four subtopics, the agenda featured sessions on:

- Probabilistic exposure
- Toxicokinetics
- Benchmark dose modeling
- Toxicity value determination

Accomplishments:

- Greater understanding of probabilistic methods within the context of human health assessments
- Guided discussion for how these methods may be implemented

https://ntp.niehs.nih.gov/whatwestudy/niceatm/3rs-meetings/past-meetings/probabilistic-methods-wksp

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Acknowledgments

The NICEATM Group

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UNITED STATES ICCVAM
Advancing Alternatives to Animal Testing

https://ntp.niehs.nih.gov/iccvamreport/2023

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