# NICEATM Update:
# ICCVAM Public Forum 2026

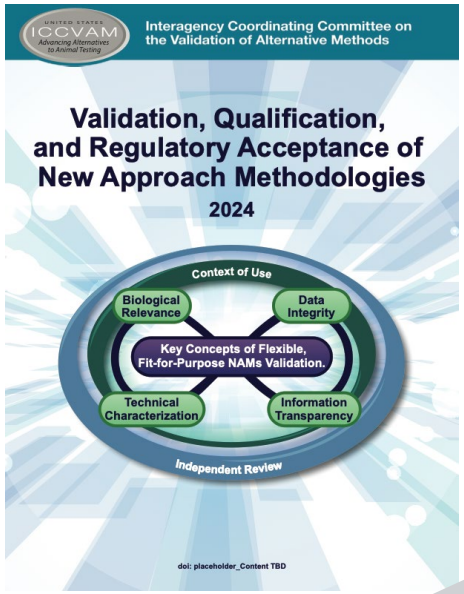
Helena Hoegberg-Durdock

Acting Director

NTP Interagency Center for the Evaluation
of Alternative Toxicological Methods
(NICEATM)

# NICEATMs Activities





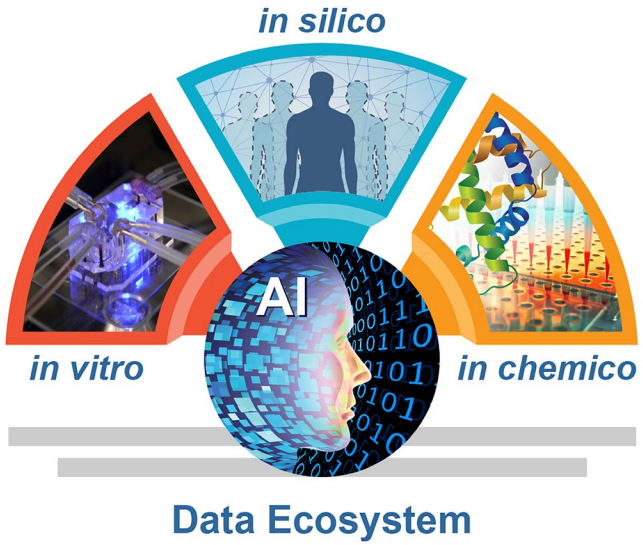

FDA U.S. FOOD & DRUG ADMINISTRATION

CONSUMER PRODUCT SAFETY COMMISSION UNITED STATES

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

OECD

etc.




Research

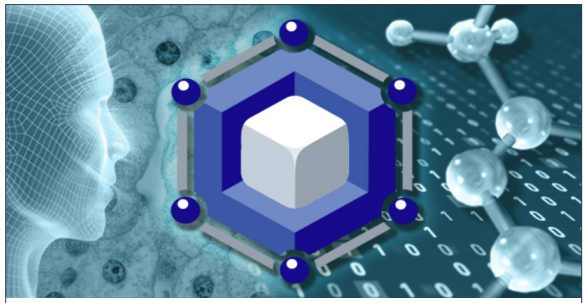
Validation/ Qualification

Adoption & Implementation

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

# NICEATM Scientific Tools

National Institutes of Health
*Division of Program Coordination, Planning, and Strategic Initiatives*

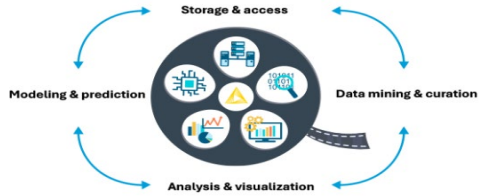


### NIH Integrated Chemical Environment (NICE)

NICE is an open-access, user-friendly platform developed by 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.

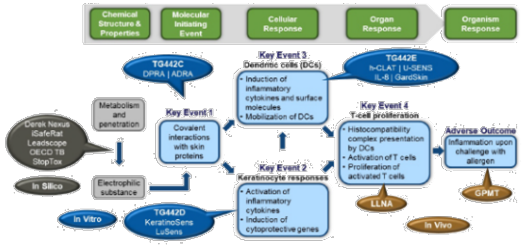



### Modeling and Visualization (MoVIZ) Pipeline

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.

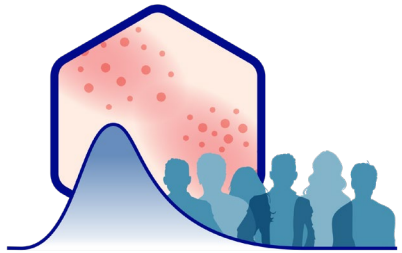
### Collection of Alternative Methods for Regulatory Application (CAMERA)

CAMERA is an interactive database and user interface providing online access to validation alternative methods for regulatory and other contexts of use. Users can access validation study reports, data, protocols/SOPs, and information on regulatory guidance.



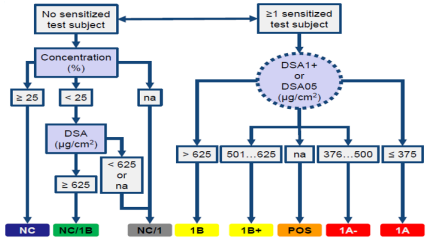

### The DASS App

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 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.



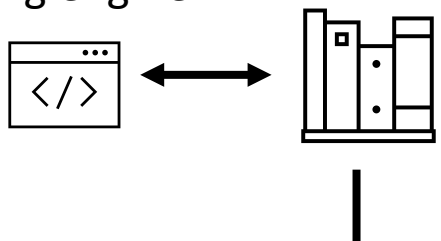

### The HPPT App

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.

# LLMs and AI to Match Expert Languages

National Institutes of Health
*Division of Program Coordination, Planning, and Strategic Initiatives*

Language matching engine



## AOP Language Matching

Match and expand ontologies

- NICE cHTS annotations

## NICEATM's NICE

- Chemical information
- cHTS curation flags

NIH Integrated Chemical Environment

## Data Object Creation

NICE cHTS mapping to OHT 201

- 9,614 of Chemicals
- 1,203 of Assays

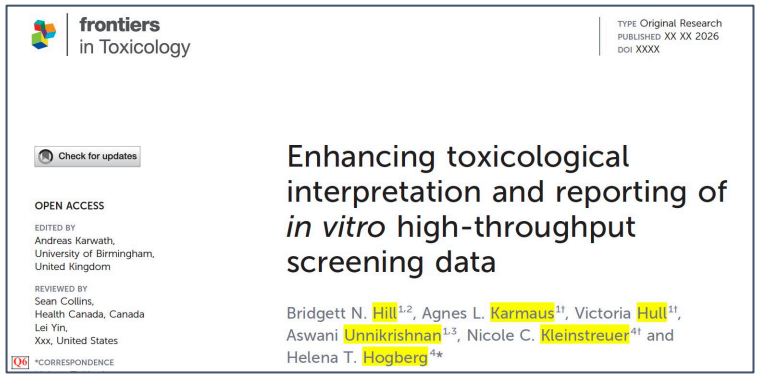
## IUCLID Dossier Submission

REST API

KNIME Data Uploader

Existing Entity Matching

**OHT 201 Chemical + Assay Record**


frontiers in Toxicology

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EDITED BY
Andreas Karwath,
University of Birmingham,
United Kingdom

REVIEWED BY
Sean Collins,
Health Canada, Canada
Lei Yin,
Xxx, United States

*CORRESPONDENCE

Enhancing toxicological interpretation and reporting of *in vitro* high-throughput screening data

Bridgett N. Hill[1,2], Agnes L. Karmaus[1†], Victoria Hull[1†], Aswani Unnikrishnan[1,3], Nicole C. Kleinstreuer[4†] and Helena T. Hogberg[4*]

*Hill et al., 2026, Front. Toxic.*

TABLE 2 Examples of the translation between the Mechanistic Target annotation terms and OHT 201 *Process* and *Object* fields. *Process* and *Object* fields are intended to describe the mechanism that can be measured using the assay. At the time of publication, some of the selected terms were not part of the template picklist. Blank spaces indicate that a term was not selected.

| Mechanistic target term | OHT 201 *Process* term* | OHT 201 *Object* term* |
|---|---|---|
| Energy homeostasis | Energy homeostasis | Cell morphology |
| Extracellular matrix organization | Extracellular matrix organization | Matrix metalloproteinase |
| Neural precursor cell proliferation | Cell proliferation | |
| p53 signaling pathway | Signaling | p53 protein |
| Regulation of angiogenesis | Regulation of angiogenesis | Vascular cell adhesion protein 1 |
| Thyroxine deiodinase activity | Enzyme activity | Type III thyroxine deiodinase |

*These terms may or may not be included in the current inventory of the pick-list. Our research supports diversifying the inventory of available terms; thus, these standardized fields may be subject to future refinement.

# DTT/NIEHS Screening Efforts in a Battery of DNT In Vitro Assays

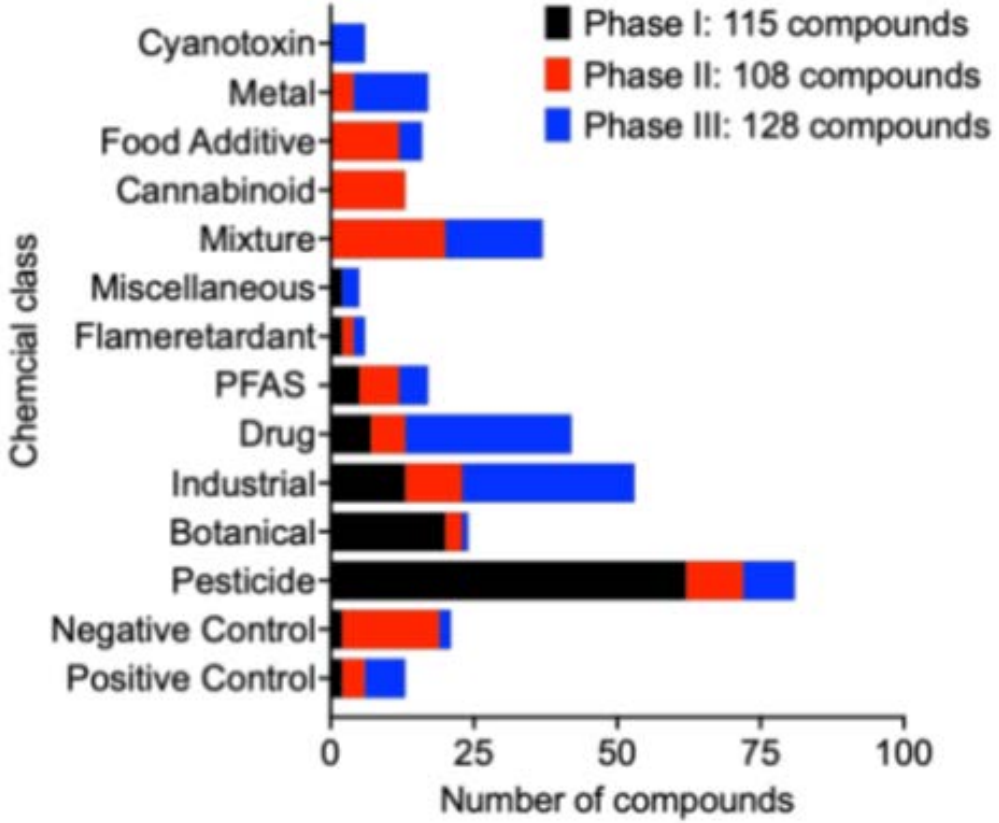


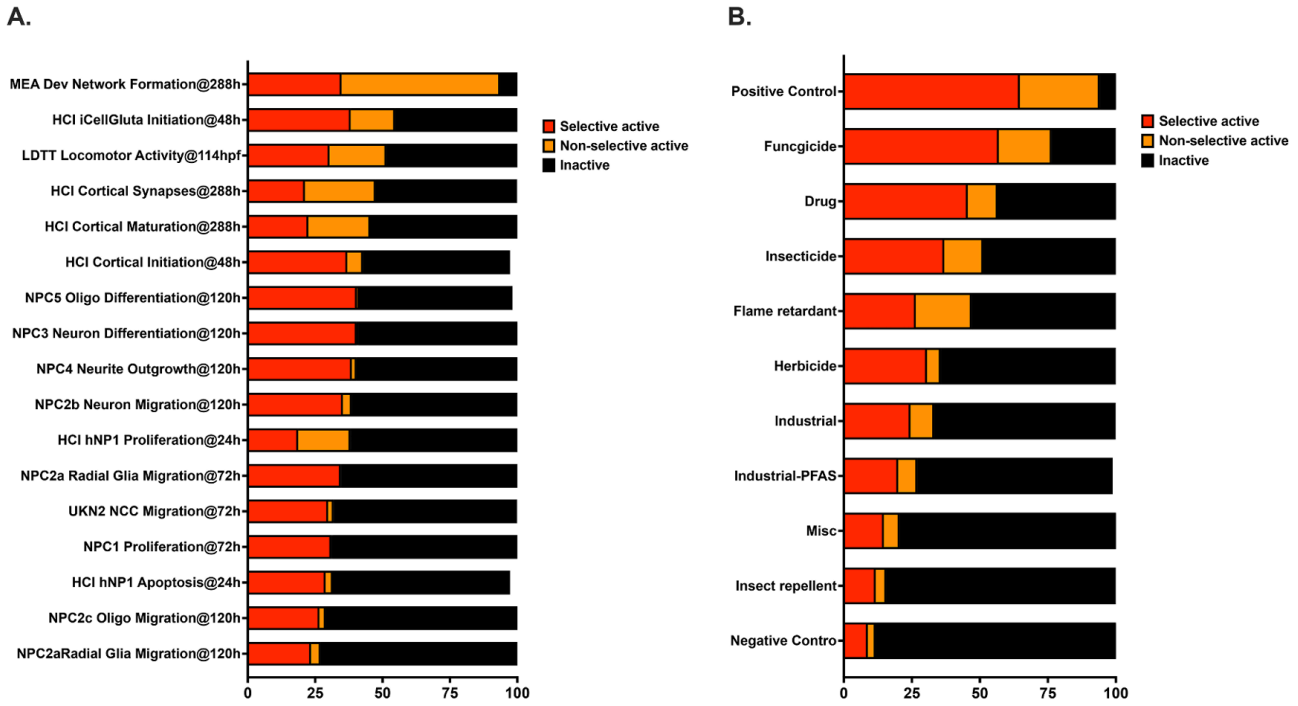
Neurotoxicology 115 (2026) 103485
Contents lists available at ScienceDirect
Neurotoxicology
journal homepage: www.elsevier.com/locate/neuro

*Hall et al., 2026, Neurotox.*

Prioritizing chemicals for developmental neurotoxicity by integrating data from a new approach methods (NAMs) battery covering key cellular events in neurodevelopment

Laura A. Hall [a], Jui-Hua Hsieh [b], Skylar W. Marvel [b], Mamta Behl [c,d], Ellen Fritsche [e], Katharina Koch [f], Anna Kreutz [g], Marcel Leist [h], Arantza Muriana [i], Timothy J. Shafer [j], Jason P. Stanko [a], Robert C. Sills [k], Helena T. Hogberg [l], Christopher A. McPherson [m,*]




87.8% of in vivo actives also active in vitro

# In Vitro to In Vivo Extrapolation (IVIVE)



## A Comparison of PBK Models

- Developed a DNT-IVIVE approach linking in vitro concentrations to human-equivalent doses across brain development
- Transferred the approach across PBK platforms, with expected differences due to lipophilicity and partitioning methods
- Confirmed strong concordance between DNT-IVIVE estimates and *in vivo* observations

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

*Toxicological Sciences*, 2026, **209(2)**, kfaf147
https://doi.org/10.1093/toxsci/kfaf147
Advance Access Publication Date: October 27, 2025
**Research article**

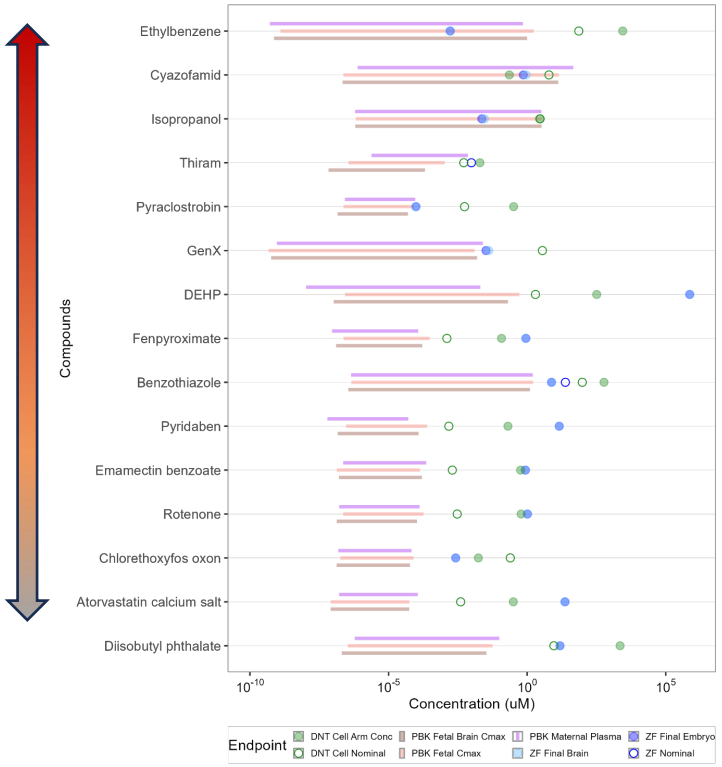
**Comparison of physiologically based pharmacokinetic modeling platforms for developmental neurotoxicity in vitro to in vivo extrapolation**

Anna Kreutz[1,*], Xiaoqing Chang[1], Michael Lawless[2], Susana Proença[3], Stephan Schaller[3], Nicole Kleinstreuer[4,5], Helena T. Hogberg[4]

*Kreutz et al., 2026, Tox Sci.*

## DNT-IVIVE for the DTT/NIEHS Screening Battery

- Expanded DNT-IVIVE to chemicals from the Phase 1 screen
- Adapted the approach for zebrafish behavioral assays using a zebrafish PBPK model
- Integrated cell-based, zebrafish, and human dose estimates for cross-species risk assessment
- Flagged priority chemicals with overlapping human exposures and DNT activity concentrations, indicating potential health concerns




*Kreutz et al., manuscript in prep*

# Moving DNT Forward

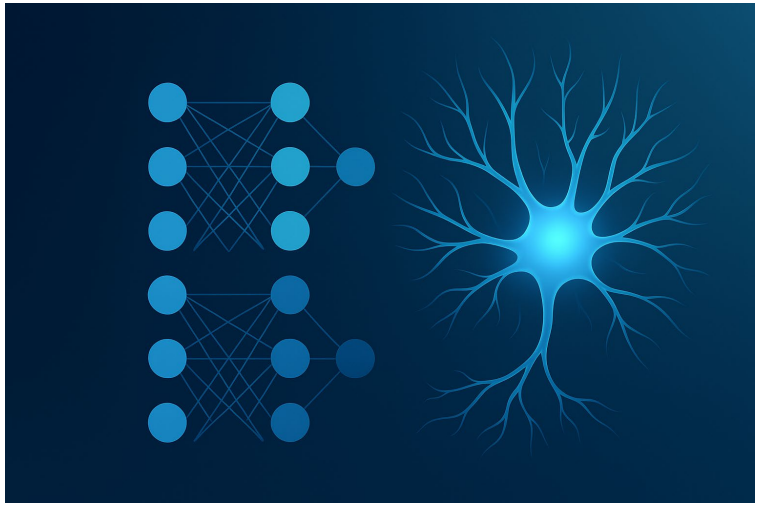


## Incorporation of Lactational Exposure

- Develop a lactational PBPK model that includes a maternal breast compartment
- In vitro to in vivo extrapolation (IVIVE) approach to reduce uncertainties in DNT risk assessment for infants

## A Data-driven Approach to Prioritizing Assays

- Proof-of-concept, develop a conditional generative adversarial network (cGAN) applied to subset of assays
- Expand to the whole battery



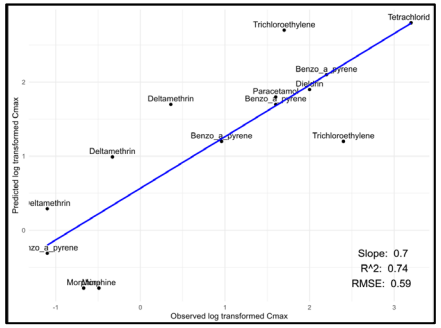
# Predicting Chemical Distribution



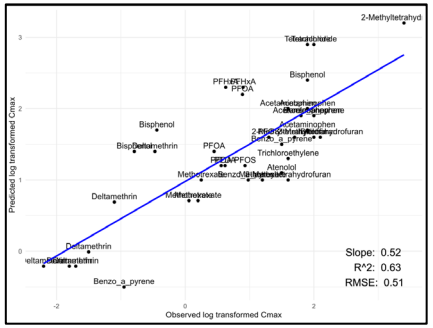
## Brain-Adipose PBK Model

- 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
- Evaluated to in vivo data for adipose, brain, and plasma concentrations

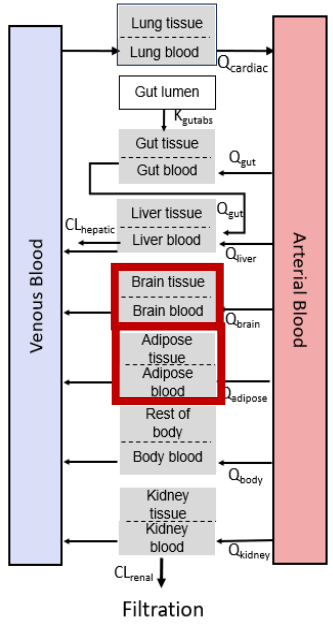
Log10 Predicted vs Observed Adipose




Log10 Predicted vs Observed Brain

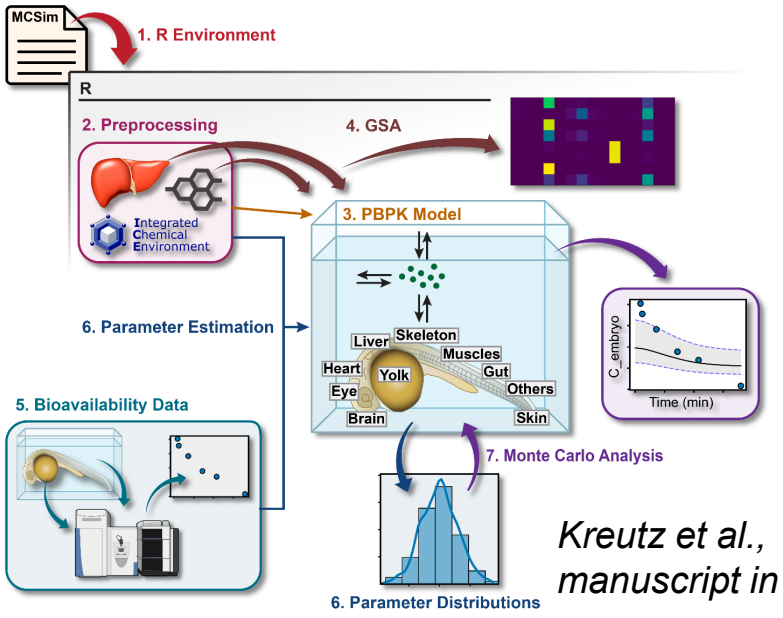



*Unnikrishnan et al., under revision at Front. Pharmacol.*




## Zebrafish PBK Model

- Provides pharmacokinetic predictions for 10 organs and experimental compartments
- Incorporates developmental changes and metabolism
- Model revised to several hundred chemicals




*Kreutz et al., manuscript in prep*

# Systematic Evaluation of the Application of Zebrafish in Toxicology (SEAZIT)



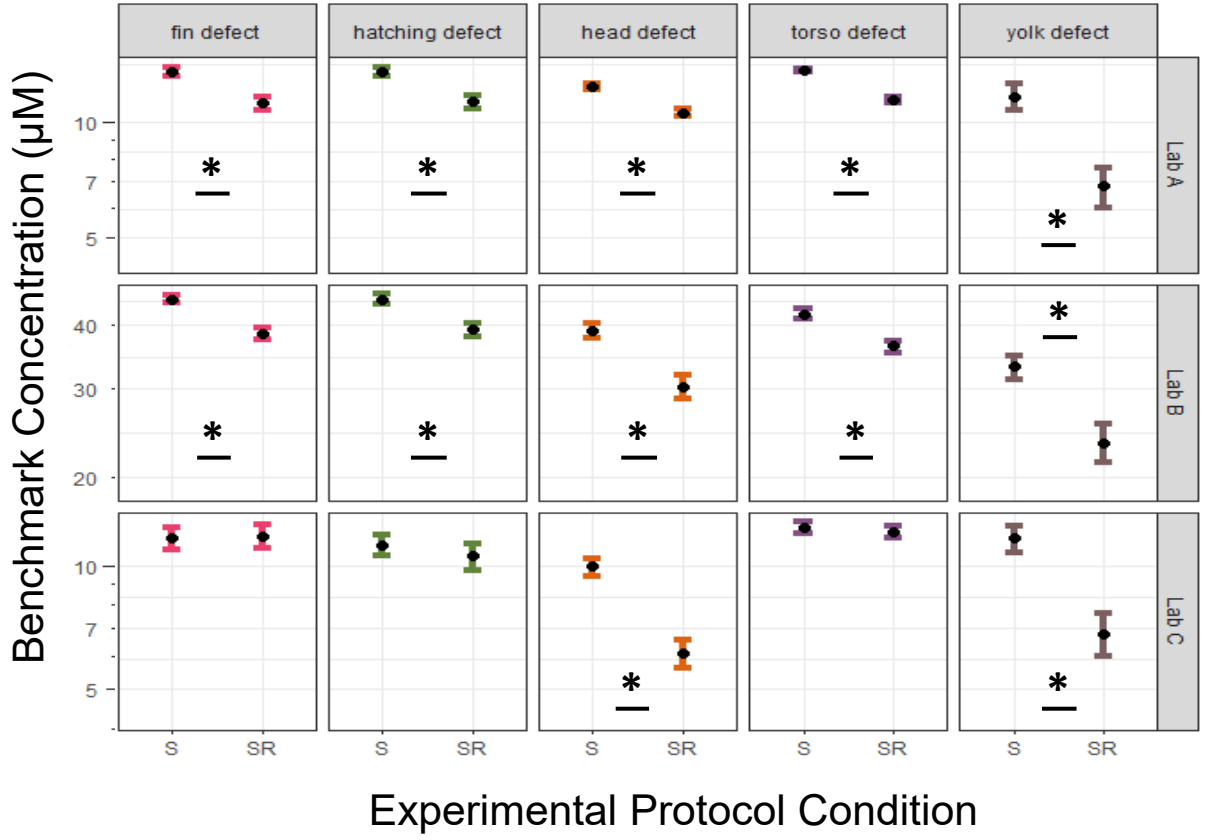
- An interlaboratory case study with vehicle and positive controls to understand the landscape of variability among phenotype assessment terms and varying experimental protocols
- While laboratories differed in responses, there were two consistent observations:
  1) Renewing media daily increased potency of positive control across many phenotypes
  2) Head defects were noted to be a sensitive endpoint for both controls
- Data can be explored through the SEAZIT-DIVER Tool: https://seazit.dtt.niehs.nih.gov/seazit/

NIH NIEHS

*Hill et al.,*

*manuscript in prep*

Mean positive control response (benchmark concentrations, µM ± standard error) across harmonized assessment terms

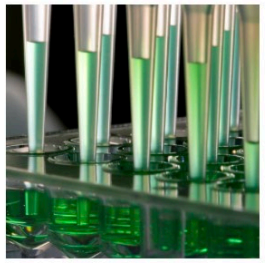



S = static media protocol (no media replacement)
SR = static renewal media protocol (daily replacement of chemical media)
* statistical difference between protocol

# Validation/Qualification Support (1)

NIH National Institutes of Health
*Division of Program Coordination, Planning, and Strategic Initiatives*

## Electrophilic Allergen Screening Assay



**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 »

OECD Topics Countries &

OECD › Publications › Test No. 442C: In Chemico Skin Sensitisation

**Test No. 442C: In Chemico Skin Sensitisation**

Assays addressing the Adverse Outcome Pathway key event on covalent binding to proteins

Report

## Respiratory Sensitization

**Evaluation of the Genomic Allergen Rapid Detection (GARD™)skin Test Method Using Substances of Regulatory Interest**

**National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)**

**National Institute of Environmental Health Sciences**
**National Institutes of Health**
**Department of Health and Human Services**

**June 2025**


## Skin Sensitization AgChem Formulations

OECD › Publications › Test No. 442D: In Vitro Skin Sensitisation

**Test No. 442D: In Vitro Skin Sensitisation**

Assays addressing the Adverse Outcome Pathway Key Event on Keratinocyte activation

OECD › Publications › Test No. 442E: In Vitro Skin Sensitisation

**Test No. 442E: In Vitro Skin Sensitisation**

In Vitro Skin Sensitisation assays addressing the Key Event on activation of dendritic cells on the Adverse Outcome Pathway for Skin Sensitisation

frontiers in Toxicology

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EDITED BY
Andy Nong,
Health Canada, Canada

REVIEWED BY
Anita Iskandar,
Philip Morris International, Switzerland
Doris Cerecedo,
National Polytechnic Institute (IPN), Mexico

*CORRESPONDENCE
Nuria Roldan,

**Establishing scientific confidence: human biological relevance of reconstructed human respiratory epithelium (RHRE) for assessing respiratory effects**

Nuria Roldan[1]*, Emily N. Reinke[2], Helena T. Hogberg[3], Andreas O. Stucki[1], Monique M. Perron[4] and Amy J. Clippinger[1]

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

PETA SCIENCE CONSORTIUM INTERNATIONAL e.V.

# Validation/Qualification Support (2)

NIH National Institutes of Health
*Division of Program Coordination, Planning, and Strategic Initiatives*

## Thyroid Microtissue

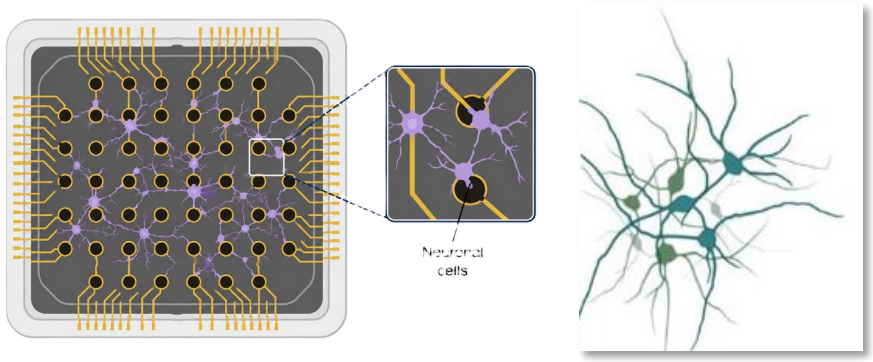
JOURNAL ARTICLE

**Interlaboratory validation of the human thyroid microtissue assay**

Chad Deisenroth ✉, Briana Foley, Eda Rogers, Julia Kühnlenz, Wei Chen, Madison Feshuk, Enrica Bianchi, Josiah McKenna, Bridgett N Hill, Jessica Larocca ... Show more

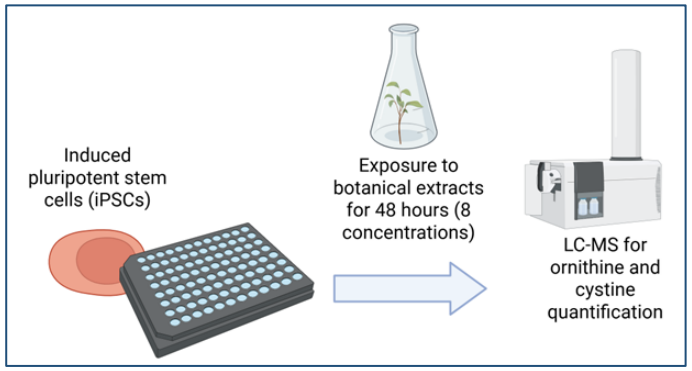
*Toxicological Sciences*, Volume 209, Issue 2, February 2026, kfaf166,
https://doi.org/10.1093/toxsci/kfaf166

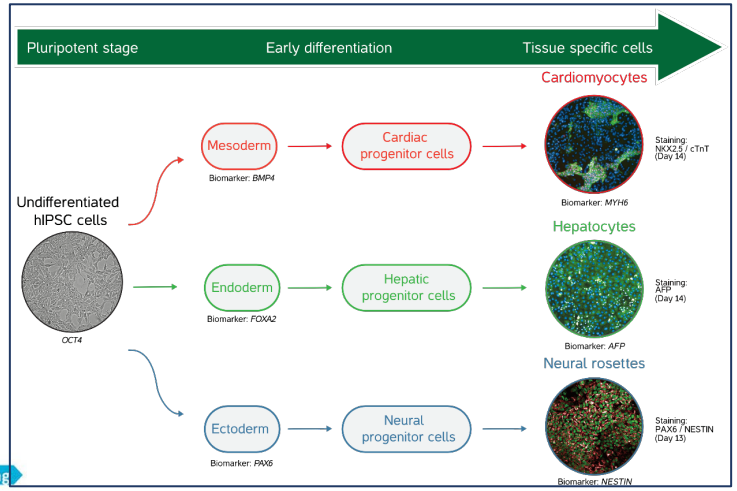
## DNT Network Formation Assay

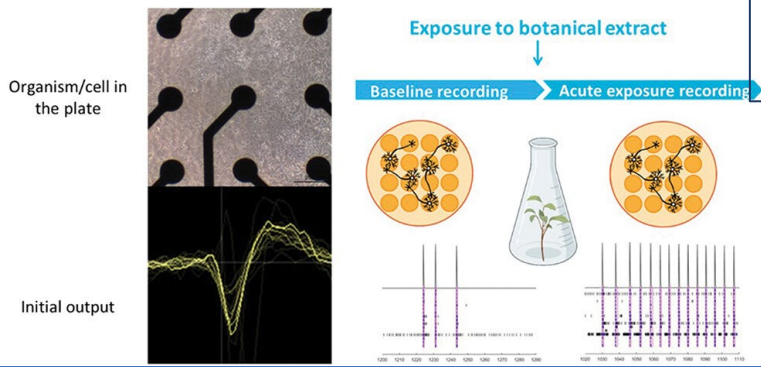



## Neuromuscular Junction-on-a-Chip
## Protein Digestibility Alternatives

## Botanicals
## Developmental Toxicity and Neurotoxicity



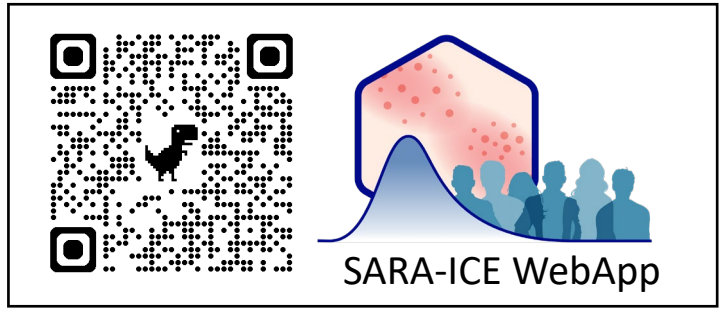

BOTANICAL SAFETY CONSORTIUM

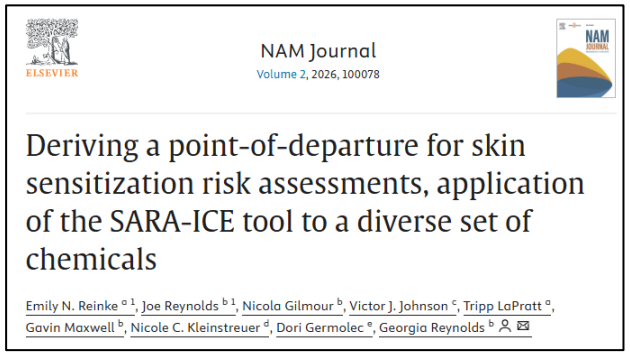
# The Skin Allergy Risk Assessment (SARA) – ICE Model

NIH National Institutes of Health
*Division of Program Coordination, Planning, and Strategic Initiatives*

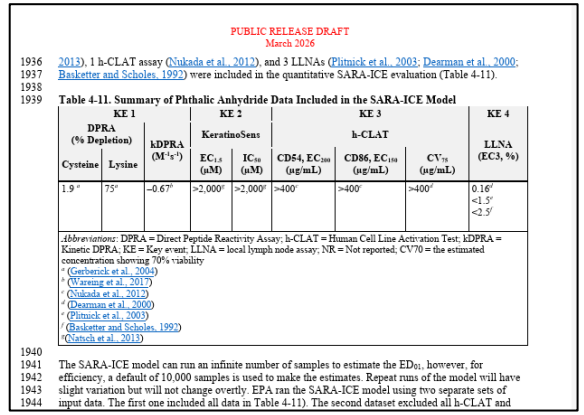
A SARA-ICE is a Bayesian statistical model which infers a human-relevant metric of sensitiser potency (termed $ED_{01}$), the dose with a 1% chance of human skin sensitisation.

- Utilises any combination of human repeat insult patch test (HRIPT), LLNA, direct peptide reactivity assay (DPRA), KeratinoSensTM, h-CLAT TM,
  U-SENS data – looking to add more inputs to the extended database this year, please contact NICEATM for details
- Derive a Point-of-departure for use in risk assessment (geometric mean)
- Included in OECD Test Guideline 497 – Defined Approaches for Skin Sensitisation https://doi.org/10.1787/b92879a4-en
- Application of SARA-ICE to agency partner dataset published January 2026 https://doi.org/10.1016/j.namjnl.2026.100078




**Regulatory Application: US EPA used SARA-ICE in a human hazard assessment for phthalic anhydride**


PUBLIC RELEASE DRAFT
March 2026

2013), 1 h-CLAT assay (Nukada et al., 2012), and 3 LLNAs (Plitnick et al., 2003; Dearman et al., 2000; Basketter and Scholes, 1992) were included in the quantitative SARA-ICE evaluation (Table 4-11).

**Table 4-11. Summary of Phthalic Anhydride Data Included in the SARA-ICE Model**

| KE 1 | | | KE 2 | | KE 3 | | | KE 4 |
|---|---|---|---|---|---|---|---|---|
| DPRA (% Depletion) | | kDPRA ($M^{-1}s^{-1}$) | KeratinoSens | | h-CLAT | | | LLNA (EC3, %) |
| Cysteine | Lysine | | $EC_{1.5}$ (µM) | $IC_{50}$ (µM) | CD54, $EC_{200}$ (µg/mL) | CD86, $EC_{150}$ (µg/mL) | $CV_{75}$ (µg/mL) | |
| 1.9 [a] | 75[a] | ~0.67[b] | >2,000[g] | >2,000[g] | >400[c] | >400[c] | >400[d] | 0.16[f]<br><1.5[e]<br><2.5[f] |

*Abbreviations:* DPRA = Direct Peptide Reactivity Assay; h-CLAT = Human Cell Line Activation Test; kDPRA = Kinetic DPRA; KE = Key event; LLNA = local lymph node assay; NR = Not reported; CV70 = the estimated concentration showing 70% viability
[a] (Gerberick et al., 2004)
[b] (Wareing et al., 2017)
[c] (Nukada et al., 2012)
[d] (Dearman et al., 2000)
[e] (Plitnick et al., 2003)
[f] (Basketter and Scholes, 1992)
[g] (Natsch et al., 2013)

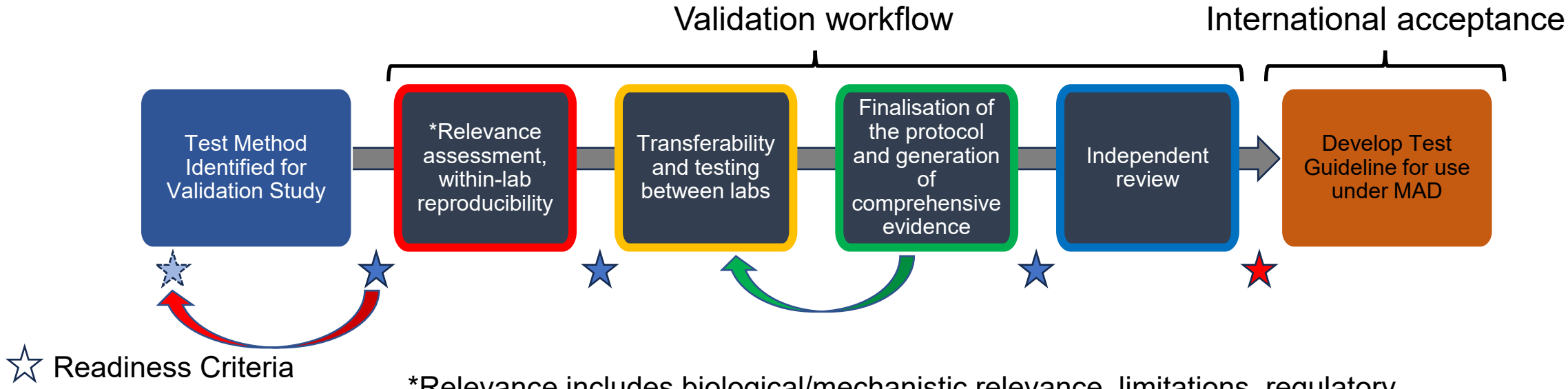
The SARA-ICE model can run an infinite number of samples to estimate the $ED_{01}$, however, for efficiency, a default of 10,000 samples is used to make the estimates. Repeat runs of the model will have slight variation but will not change overtly. EPA ran the SARA-ICE model using two separate sets of input data. The first one included all data in Table 4-11). The second dataset excluded all h-CLAT and

# Updates to Guidance Document 34



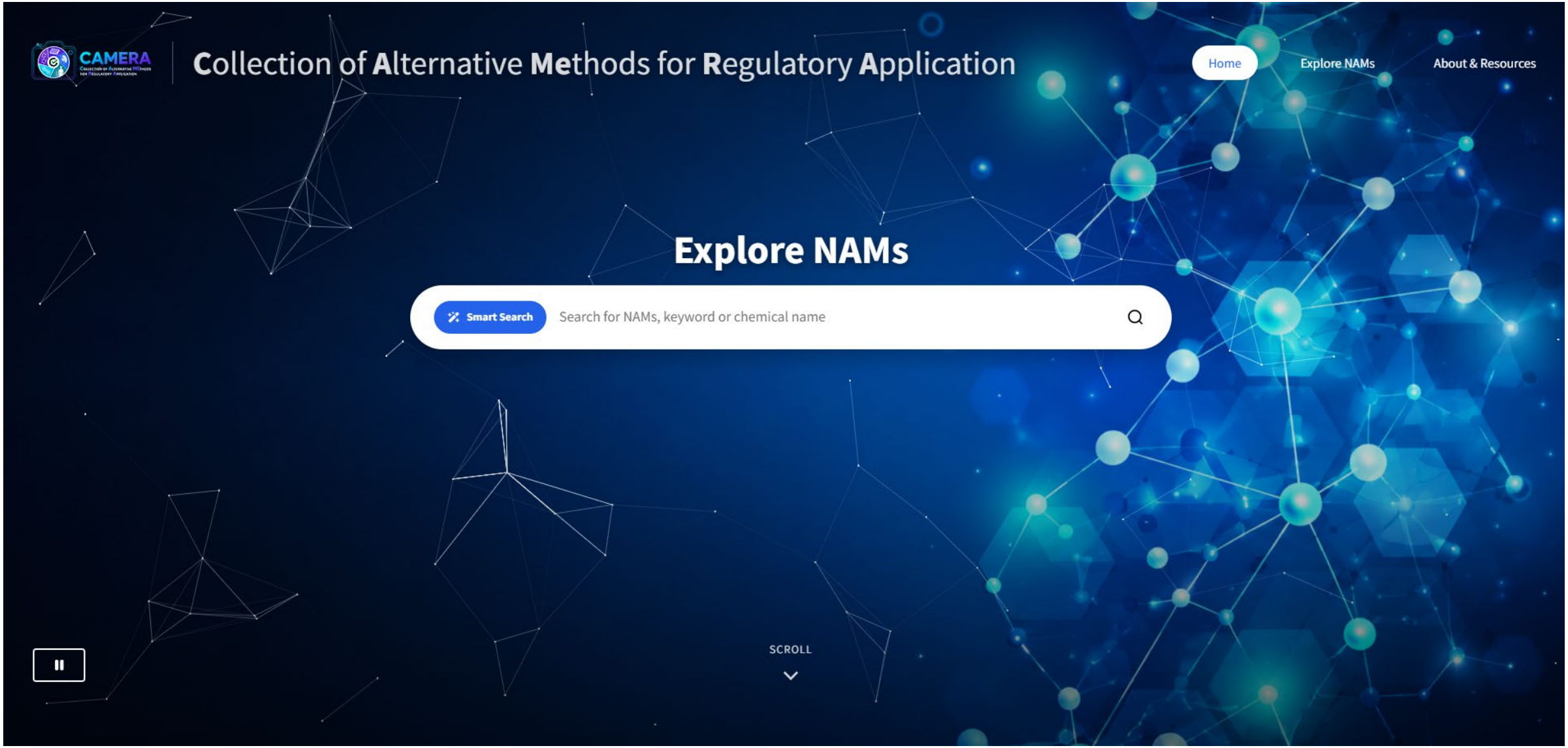
## New Sections and Guidance on Validation Process

- Revisions to Chapter 3 and Chapter 4 provide better guidance on types of validation covered and using a validation workflow
  - Adds defined approaches and increased coverage of in silico methodologies
- Development of readiness criteria covers the “requirements” for a methodology to advance in the workflow
- New guidance around quality processes




*Relevance includes biological/mechanistic relevance, limitations, regulatory relevance and regulatory application (incl. e.g., predictive capacity)

# CAMERA v2.0 (1)


CAMERA
Collection of Alternative Methods for Regulatory Application
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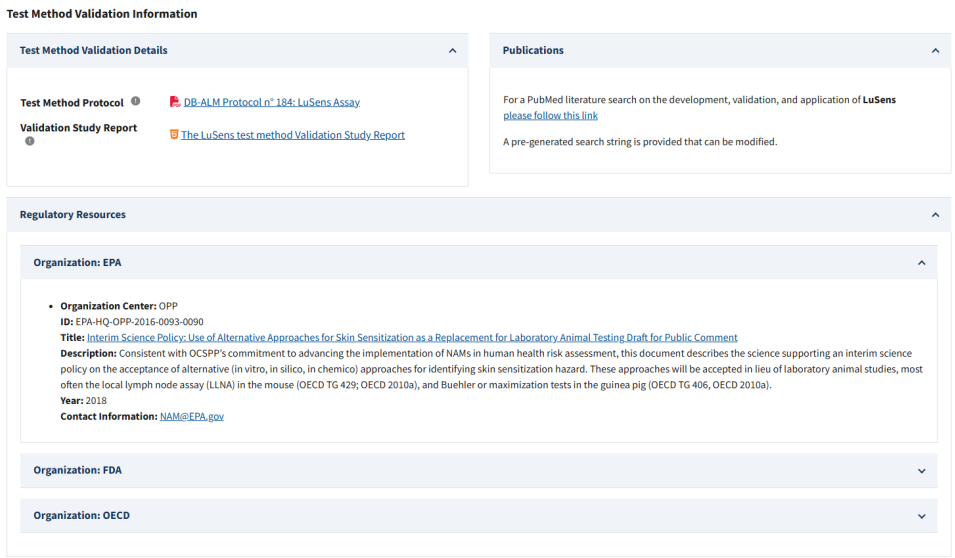
About & Resources
Explore NAMs
Smart Search
Search for NAMs, keyword or chemical name
SCROLL

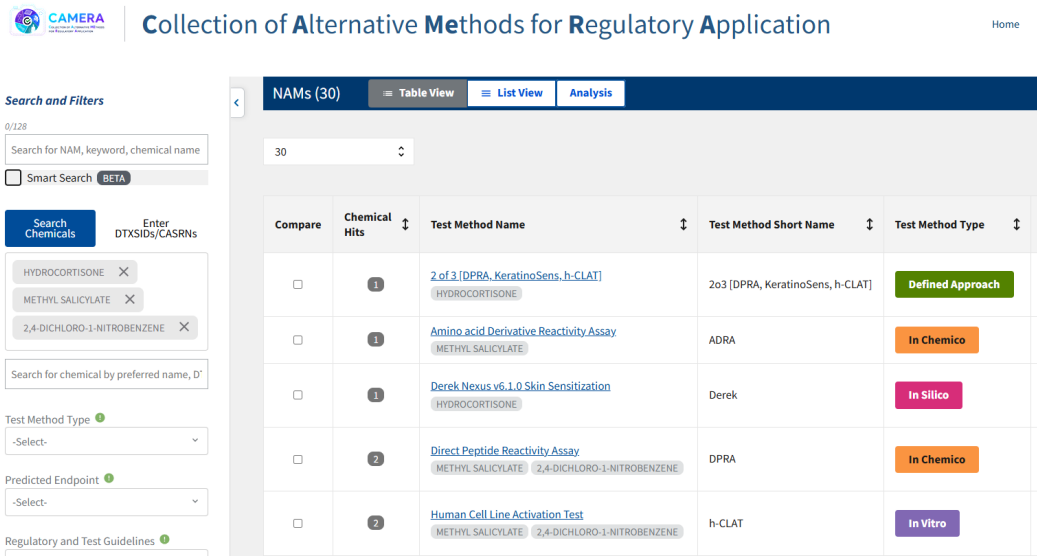
# CAMERA v2.0 (2)



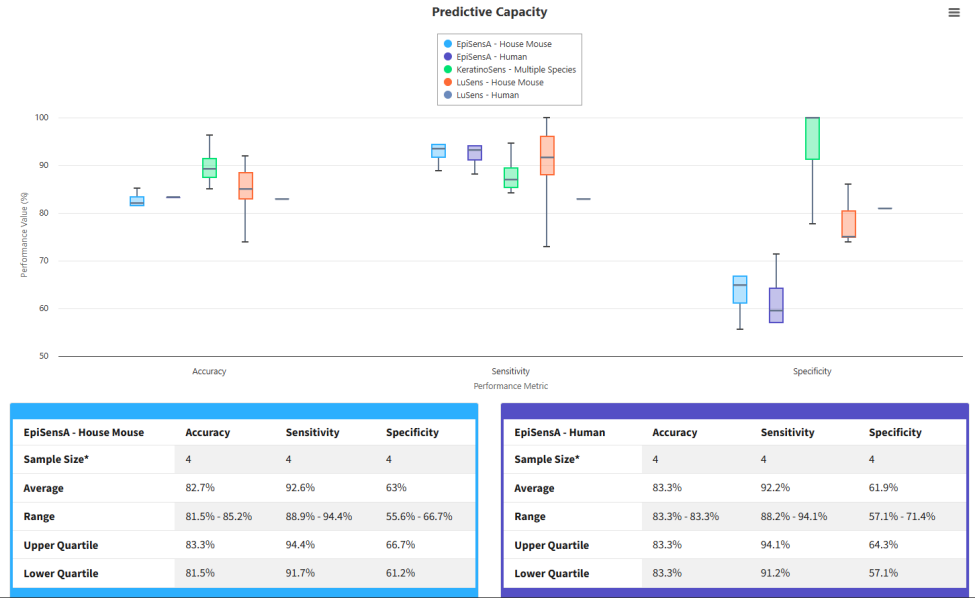




## Next

- Expand methods and predicted endpoints
- Interoperability with other databases
- Additional interactive analytical tools








| EpiSensA - House Mouse | Accuracy | Sensitivity | Specificity |
|---|---|---|---|
| Sample Size* | 4 | 4 | 4 |
| Average | 82.7% | 92.6% | 63% |
| Range | 81.5% - 85.2% | 88.9% - 94.4% | 55.6% - 66.7% |
| Upper Quartile | 83.3% | 94.4% | 66.7% |
| Lower Quartile | 81.5% | 91.7% | 61.2% |

| EpiSensA - Human | Accuracy | Sensitivity | Specificity |
|---|---|---|---|
| Sample Size* | 4 | 4 | 4 |
| Average | 83.3% | 92.2% | 61.9% |
| Range | 83.3% - 83.3% | 88.2% - 94.1% | 57.1% - 71.4% |
| Upper Quartile | 83.3% | 94.1% | 64.3% |
| Lower Quartile | 83.3% | 91.2% | 57.1% |

# Acknowledgments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## The NICEATM Group

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NIH NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

GENERAL DYNAMICS Information Technology

ARA

Sciome

DYNANET

inotiv
analyze. answer. advance.

## NIEHS/DTT Contributors

UNITED STATES ICCVAM Advancing Alternatives to Animal Testing



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